Journal of
INBORN ERRORS of METABOLISM and SCREENING

Editor-in-Chief: Roberto Giugliani

Latin American Society of Inborn Errors of Metabolism and Neonatal Screening

SPECIAL SUPPLEMENT WITH THE ABSTRACTS

XIII Congreso Latinoamericano de **Errores Innatos del Metabolismo y Pesquisa Neonatal**

PUNTA DEL ESTE, URUGUAY - OCTOBER 22-25, 2024

FOREWORD FROM SLEIMPN

Our Society is gathering again this year for the XIII Congress in Punta del Este, following the successful event in the Dominican Republic in 2022.

The main theme of our Congress is "Building Networks." Without a doubt, this meeting will foster the exchange of experiences and knowledge, as well as contact between professionals from our region and the world who accompany us.

Through the abstracts of the free communications presented, which are published in this Special Supplement of JEIMS, we can appreciate the academic growth, basic research, and incorporation of technology in our region, as well as the increase in international collaborative works, all of which benefit the better care of our patients and their families. It is a true pleasure to witness this growth.

The scientific program covers relevant topics in Inborn Errors of Metabolism (IEM) and Newborn Screening (NBS), presented by more than 30 distinguished invited professors from our Region, Europe, the USA, and Japan. We will have 3 pre-congress courses on the topics: Nutrition, NS, and IEM in adults.

We fully trust in the contribution that SLEIMPN will once again make during the event to the updating and formation of Networks among all the participants.

Aída Lemes
President of SLEIMPN
President of the XIII 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 ***13th Congress of the Latin American Society of Inborn Errors of Metabolism and Neonatal Screening*** (Punta del Leste, Uruguay, October 22-25, 2024).

In this special supplement you will find 191 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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ABSTRACTS SELECTED FOR ORAL PRESENTATION

O-001 - NEW CELLULAR MODEL FOR BASIC RESEARCH INTO CITRIN DEFICIENCY AND FOR DEVELOPMENT OF NOVEL THERAPIES

Kido J, Nakamura K

Department of Pediatrics, Faculty of Life Science, Kumamoto University

Citrin deficiency (CD) is an autosomal recessive disorder caused by a defect of the inner mitochondrial membrane transporter citrin resulting from mutations in SLC25A13. A defect of citrin primarily affects the function of the malate-aspartate shuttle but has several downstream metabolic effects impairing energy production due to hampered glycolysis, gluconeogenesis, tricarboxylic acid cycle function and beta-oxidation, and impairs nitrogen detoxification in the urea cycle. The condition is prevalent in East Asia, but also present in the Western world and hence considered a global disorder. Patients require as high-fat and low-carbohydrate diet with supplementation of medium-chain triglycerides (MCT) although this treatment has been introduced empirically without sound scientific evaluation. Especially the mechanism of action of MCT in this condition has never been systematically studied. We used skin fibroblasts from patients, which were reprogrammed into iPS cells using standard protocols prior to differentiation into hepatocytes. These cells were used for studies of energy metabolism yielding decreased ATP levels and increased NADH/NAD+ ratios confirming their usefulness as CD model cells. For control, we used cultured patient fibroblasts and the hepatoma cell line HepaRG. The MCT treatment could increase the ATP production in these CD cells. However, the NADH/NAD+ ratio in these CD cells may be not decreased. Moreover, the iPSC derived hepatocytes demonstrated these similar conditions. The usefulness of patient derived iPSCs both as disease model for CD and as a tool for studying novel treatments for this condition were demonstrated. We can use the iPSC derived hepatocytes as the new cellular model for basic research and drug screening research of citrin deficiency.

O-002 - STATE OF THE ART OF DIAGNOSED CASES AND TREATMENT WITH TYROSINEMIA TYPE 1 IN LATIN AMERICA

Cornejo V [1], Consuelo-Sánchez A [2], Reyes-Apodaca M [2], Eiroa H [3], Mahfoud A [4], Resende LR [5], Badilla-Porras R [6], Muñoz-Urribarri AB [7], Zárate MFE [8], Lemes A [9], Sanabria MC [10], Núñez-Miñana M [11], Guelbert N [12], Vallejo MA [13], Navarro S [14], Schwartz IVD [15], Ortiz-Paranza L [16], Vela-Amieva M [17], Morales M [7], Jhon R [18], Fortuna M [19], Zambrano J [20], Salazar MF [1], Arias-Pefaur C [1]

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INTRODUCTION: Tyrosinemia type 1 (Tyr-1) is an inborn error of metabolism, autosomal recessive due to deficiency of the enzyme fumarylacetoacetate hydroxylase (FAH) with a consequent increase in Tyrosine (Tyr) and succinylacetone (SUAC).in blood. Treatment includes drug 2-[2-Nitro-4-(trifluoromethyl)benzyl] -1, 3-

cyclohexanedione (NTBC=nitisinone) and diet restricted in phenylalanine (Phe) and Tyr. ***OBJECTIVE:*** To understand the situation regarding the diagnosis, treatment and follow-up of people with Tyr-1 in Latin America (LA). ***METHODS:*** The RedCAP online questionnaire was applied with 44 questions about diagnosed cases, signs and symptoms of the diagnosis, type of treatment, and treatment coverage, among others. ***RESULTS:*** Twelve LA countries participated, including 19 centers: Argentina (3), Brazil (2), Chile (1), Costa Rica (1), Colombia (2), Ecuador (2), Mexico (2), Paraguay (1), Peru (1), Dominican Republic (2), Uruguay (1), Venezuela (1), A total of 106 cases of Tyr-1 were reported. The most frequent symptoms were: hepatomegaly (94.4%), abdominal distension (83.3%) and jaundice (77.8%). The 84% of centers diagnose by clinical examination, and only about 10% by neonatal research. In the initial diagnostic approach, the majority included additional hepatic renal profile and alpha-fetoprotein (AFP) levels, 84.2% confirmed Tyr-1 with SUAC level >0.5mmol/mol creatinine in urine. Only 7/19 centers have monitoring protocols. The 70.7% of cases are treated with NTBC+diet and the cost of treatment is covered by the State in 52.6% of centers, highlighting that 31.5% of them do not have access to NTBC. Then all of them measure Tyr level in blood, 13 centers measure SUAC (blood) and only 2 centers measure NTBC in blood. The intermittent treatment with NTBC was present in 69.2% of the centers, due to lack of availability in most cases. The 25% of diagnosed cases have been transplanted due to the presence of liver nodules, increased AFP, hepatocellular carcinoma, poor adherence to treatment, or lack of access to NTBC. By the end of the year, 21 cases had died. ***CONCLUSIONS:*** The diagnosis of Tyr1 by neonatal research in LA is deficient, the evaluation and follow-up protocols as well as the availability of treatment are an urgent need for the Region.

O-003 - NEW FINDINGS SUPPORTING DIFFERENCES IN PHENOTYPE AND GENOTYPE IN LIVER GLYCOGEN STORAGE DISEASE IX PATIENTS IN ARGENTINA

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BACKGROUND: Glycogen Storage Disease IX (GSD IX) is a metabolic disorder caused by deficiency in phosphorylase kinase (PhK), affecting liver glycogen metabolism. Mutations in *PHKA2, PHKB, or PHKG2* genes lead to symptoms like hepatomegaly, elevated liver enzymes, and hypoglycemia. While symptoms generally improve with age, patients with PHKG2 mutations may face persistent symptoms and a risk of severe liver complications such as cirrhosis and hepatocellular carcinoma. ***OBJECTIVES:*** To describe clinical, molecular and biochemical data, diagnosis and long-term outcome and to compare these parameters among PHKα2 and PHKγ2 patients. ***METHODS:*** This study retrospectively collected data from 15 GSD IX patients at a highcomplexity hospital in Argentina from January 2006 to May 2024. Diagnosis was based on clinical and biochemical findings, with molecular analysis conducted using a custom NGS panel for Inborn Errors of Metabolism. The study analyzed genotype, clinical course, and outcomes. Statistical analysis was performed using IBM SPSS Statistics Software v27, with significance set at $p<0.05$. ***RESULTS:*** Median age at diagnosis was 21 months (6-46 months). Symptoms included hepatomegaly (100%), hypoglycemia (100%), and failure to thrive (80%). Median follow-up was 145 months (72-251 months). Genetic analysis revealed nine variants in *PHKA2* and *PHKB* genes, with the c.326+1G>C variant homozygous in seven patients, four from Corrientes province. Treatment improved hemoglobin ($p=0.005$), transaminases (AST $p=0.01$, ALT $p=0.008$), triglycerides ($p=0.012$), and fasting glucose ($p<0.001$). Post-treatment biochemical profiles were similar between α2 and γ2 patients, except for AST, ALT, and triglycerides ($p=0.011$, $p=0.013$, $p=0.025$). Six γ2 patients developed liver fibrosis compared to none in α2 ($p<0.001$), despite no significant age differences between groups. ***CONCLUSIONS:*** Even with treatment, GSD IXγ2 patients show persistently higher transaminases and triglyceride levels, indicative of ongoing liver issues. They also develop liver fibrosis earlier than GSD IXα2 patients. The prevalence of the c.326+1G>C variant in the *PHKG2* gene suggests a possible founder effect, but epidemiological research is needed for confirmation.

O-004 - INTEGRATING BIOCHEMICAL TESTING AND A TARGETED GENE PANEL TO DIAGNOSIS BRAZILIAN PATIENTS WITH ACUTE HEPATIC PORPHYRIAS (AHP)

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INTRODUCTION: In Brazil, analyses of clinical and laboratory features of patients with acute porphyrias are until recently limited to biochemical testing since genetic testing was expensive and not covered by national health system neither private insurance. In partnership with Brazilian Porphyria Association (ABRAPO), genetic testing was offered to patients with suspicion of an acute porphyria either by clinical features or biochemical findings. ***MATERIALS AND METHODS:*** Individuals aged ≥16 years from a Brazilian national referral center for porphyrias with a suspected diagnosis or a confirmed history of AHP that underwent genetic testing. Extracted DNA samples from saliva and buccal swabs were analyzed using a short-read next-generation sequencing gene panel. ***RESULTS:*** Overall, of the 122 unrelated individuals referred for AHP molecular diagnostic testing, 80 had an AHP mutation. Although most mutations identified were in hydroxymethylbilane synthase gene (HMBS n=43), there was an unexpected great number of pathogenic variants in protoporphyrinogen oxidase (PPOX n=31) in patients with a previous biochemical diagnosis of Acute Intermittent Porphyria (AIP). Just one heterozygous variant in *ALAD* gene was seen in our cohort in a patient with a pathogenic mutation in *PPOX* gene. Of the 250 family members of mutation-positive individuals tested for an autosomal dominant AHP, 104 (46.8%) had their respective family mutation. All patients with documented increase in aminolevulinic acid and porphobilinogen had a confirmed molecular diagnosis of AHP. ***CONCLUSIONS:*** This is the first report describing genetic variants for all four acute porphyrias in Brazilian individuals under AHP investigation. It was worthy of note that a high number of cases of VP was identified with PPOX mutations, being a frequent cause of AHP in our population. These data expand the molecular genetic heterogeneity of the AHP and document the usefulness of molecular testing to confirm the positive biochemical findings in symptomatic patients and identify at-risk asymptomatic family members. A correct genetic diagnosis allows not only better understanding of such disorders but also genetic counseling for affected and at-risk individuals.

O-005 - URIC ACID AS A BIOMARKER OF INHERITED DISORDERS OF PURINE METABOLISM: A LOCAL EXPERIENCE IN THE DIAGNOSIS OF ARGENTINEAN PATIENTS

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INTRODUCTION: Uric acid (UA) is the end product of purine nucleotide degradation. Abnormal levels of UA in serum or urine can indicate metabolic errors, such as deficiencies of hypoxanthine-guanine phosphoribosyltransferase (HPRT-d), xanthine oxidase, and molybdenum cofactor (MoCo-d). HPRT-d, with Xlinked inheritance, causes Lesch-Nyhan disease (LND) and its variants (LNV), characterized by hyperuricemia/hyperuricosuria, self-mutilation (in LND), gout, nephrolithiasis, kidney failure, and varying degrees of neurological involvement. MoCo-d is a rare autosomal recessive neurodegenerative disorder, marked by the combined deficiency of molybdenum cofactor-dependent enzymes such as xanthine oxidase, presenting with hypouricemia/hypouricosuria, microcephaly, intractable seizures, and severe developmental delay. ***OBJECTIVE:*** To characterize Argentinean patients with defects in purine metabolism in which UA levels, alongside phenotypic data, guided biochemical and molecular studies for precise diagnosis. ***MATERIAL/METHODS:*** The study included 32 male patients from 15 unrelated families with HPRT-d and 2 with MoCo-d, detailing their initial and primary clinical manifestations, and ages at onset and diagnosis. UA concentrations in serum and urine, urinary hypoxanthine and xanthine levels, enzyme activity, and genotype were determined. Metabolite quantification and activity assays were performed using liquid chromatography, while genetic studies were conducted via PCR and sequencing. ***RESULTS:*** All patients with HPRT-d presented hyperuricemia (range: 7.7-17 mg/dl; normal: 3.7-7), increased urinary UA (range: 1400-2300 µmol/mmol creatinine; normal: <1300), hypoxanthine (range: 55-778 µmol/mmol creatinine; normal: <45), and xanthine (range: 23-200 µmol/mmol creatinine; normal: <43). Deficient HPRT activity and the identification of pathogenic genetic variants in HPRT1 gene (unique to each family) confirmed the diagnosis, revealing high

phenotypic variability. Patients were classified into LND (12 patients) and LNV (20 patients). The two unrelated patients with MoCo-d had a similar clinical presentation and a fatal outcome. Laboratory findings included hypouricemia (UA <0.5 mg/dl), hypouricosuria (UA <30 µmol/mmol creatinine), increased urinary xanthine and hypoxanthine, and different pathogenic genetic variants in the *MOCS2* gene. ***CONCLUSIONS:*** Purine metabolic defects comprise a group of diseases with highly variable clinical manifestations. Altered UA levels and clinical suspicion are critical for detection, while biochemical-enzymatic and/or genetic studies enable precise nosological definition. Early diagnosis benefits patients and allows for genetic counseling for these rare or infrequent diseases.

O-006 - DISORDERS OF COBALAMIN AND FOLATE TRANSPORT AND METABOLISM PRESENTING WITH HYPERHOMOCYSTEINEMIA: CLINICAL, BIOCHEMICAL AND MOLECULAR CHARACTERIZATION IN A MULTICENTRIC SERIES OF PEDIATRICS PATIENTS

Spécola NB [1], Maxit S [2], Bindi V [3], Kleppe S [2], Durand C [4], Guelbert N [5], Eiroa HD [3], Bay LB [3], Amartino H [6], Núñez-Miñana M [1] et al.

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INTRODUCTION: Disruptions in homocysteine-related pathways can arise from genetic abnormalities affecting remethylation (or other causes of reduced methionine synthase activity), and disorders of cobalamin transport/processing. These anomalies lead to hyperhomocysteinemia, multisystemic involvement, and are amenable to treatment that modifies the course of the disease. ***OBJECTIVE:*** To describe the characteristics of a group of pediatric or adult Argentinian pati ents with hyperhomocysteinemia caused by cobalamin and folate transport and metabolism deficiency. ***METHODS:*** An online survey was conducted, inviting physicians specialized in neurometabolism from across Argentina to submit anonymized patient data. Descriptive statistics were used for data analysis. ***RESULTS:*** Only pediatric patients were reported. Thirty-four patients with a high biochemical/clinical suspicion were registered (59% male); in 30, molecular testing (nextgeneration sequencing) revealed significant variants in following genes: *MMACHC* (10/30: 9 harboring at least one c.271dupA allele and 5, in homozygosity), *CUBN* (5/30), TCN2 (5/30), *MTR* (3/30), *MTHFR* (3/30), *MTRR* (3/30), *AMN* (1/30). In 47% of the cases, symptoms started during the neonatal period, 35% within the first year of life, 12% between ages 1-5 years, and 6% between ages 5-18 years. Diagnostic delays were identified for 71% of the cases, and 75% of patients symptomatic during the neonatal period were not diagnosed at that age. Initial symptoms were predominantly neurological in 17/34 cases, mostly hypotonia (23/34), altered consciousness (10/34), seizures (9/34), neurodevelopmental delay (8/34) and weakness (8/34). In 31/34 patients homocysteine levels were available (18%, 20-50 µmol/L; 62%, >50 µmol/L). Abnormal neuroimaging was observed in 23/34. Therapeutic interventions varied, comprising dietary adjustments, intramuscular and/or oral administration of B12, folic or folinic acid supplementation, betaine or carnitine. Symptom stabilization/improvement was observed in 85% of patients; there were 3 demises despite treatment. ***CONCLUSIONS:*** This case series exhibiting hyperhomocysteinemia underscores the clinical and molecular diversity of these disorders, showcasing variable onset ages, diagnostic delays and generally positive responses to available, although heterogeneous, therapies. We emphasize the crucial role of early diagnosis through the -widely available- tool of homocysteine level assessment in patients presenting compatible symptoms.

O-007 - DETERMINATION OF TETRASACCHARIDES IN LIQUID URINE AND DRIED URINE SPOTS SAMPLES FOR SCREENING AND MONITORING OF POMPE DISEASE BY TANDEM MASS SPECTROMETRY

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INTRODUCTION: Pompe disease (PD) is characterized by a deficient activity of the enzyme acid alphaglucosidase (GAA), required for lysosomal glycogen degradation.

Tetrasaccharides (TSC) are markers increased in liquid urine (URN) of PD patients, important for disease screening and treatment monitoring. The use of URN demands some challenges for sample logistics, such as low temperature for transportation and storage, besides high shipment costs. ***OBJECTIVE:*** The aim of this work was to establish an adapted method of liquid chromatography coupled to mass spectrometry (LC-MS/MS) for quantifying TSC in samples of dried urine spots (DUS) and URN. ***MATERIALS AND METHODS:*** An aliquot of each sample of URN and DUS (previously extracted with water) was dried, normalized by creatinine (10 nmol), derivatized with 1-phenyl-3-methyl-5-pyrazolone (PMP), and analyzed by LC-MS/MS. TSC were quantified using calibration curves based on maltotetraose in samples from PD patients not on enzyme replacement therapy (ERT), compared to samples from PD patients receiving ERT, and from controls. Groups were compared using Student's t-test. ***RESULTS:*** Our results revealed levels of TSC in URN samples from PD patients not on ERT of 57.5 mmol/mol of creatinine (range: 28.1-89.6); levels of 37.0 mmol/mol of creatinine (range: 12.6-54.0) in PD patients on ERT; and of 1.12 mmol/mol of creatinine (range: 0.46-2.32) in controls. For DUS samples, levels were 65.6 mmol/mol of creatinine (range: 51.0-89.5), 23.9 mmol/mol of creatinine (range: 4.85-37.8), and 0.48 mmol/mol of creatinine (range: 0.10-0.91), respectively. The comparison between the positive and control groups showed statistical distinction for both URN and DUS samples ($p=0.00014$ and $p<0.0001$, respectively). When comparing no-ERT to ERT groups, the statistical difference occurred only for DUS samples ($p=0.01268$)**.** ***CONCLUSIONS:*** With some modifications, we demonstrated the suitability of the LC-MS/MS method of TSC measurement for PD investigation. Thus, DUS analysis can be used for the screening and/or treatment monitoring as an alternative to URN, with logistic advantages. Acknowledgements: CNPq, UFRGS, INAGEMP, FundMed, FAPERGS, IGPT.

O-008 - DARS2 DEFICIENCY: ABNORMAL BIOENERGETICS AND ANTIOXIDANT STATUS IN FIBROBLASTS AND THE POTENTIAL BENEFICIAL EFFECT OF AMINOLEVULINATE/IRON

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BACKGROUND: Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) is caused by mutations in the mitochondrial aspartyl-tRNA synthetase gene *DARS2*. Clinical presentation varies from severe infantile to slowly progressive deterioration in adolescents / adults with a distinctive brain MRI. There is no effective treatment. ***AIMS:*** 1) Characterize bioenergetic and antioxidant status of fibroblasts obtained from two affected brothers, harboring c.228-17C>G and c.492+2T>C mutations. 2) Test the effect of aminolevulinate plus ferrous iron (ALA/Fe) on enhancing energy metabolism and antioxidant defenses. ***METHODS:*** The following were analyzed in naïve DARS2 deficient cells and cells exposed to ALA/Fe (100 µM/50 µM) for 14 days: mitochondrial oxygen consumption, glycolysis, respiratory-chain enzyme activities, mitochondrial morphology, reduced and oxidized glutathione (GSH/GSSG), activities of catalase (CAT), glutathione peroxidase and superoxide dismutase (SOD), and production of reactive oxygen species. The activation of the Nrf-2 pathway, which controls cell antioxidant defenses, was also investigated using known inhibitors and activators. ***RESULTS:*** DARS2 deficient cells were characterized by energy impairment, altered mitochondrial dynamics, and increased oxidative stress. Oxygen consumption and the activities of respiratory complexes I, I-CoQ-III, II-CoQ-III, and IV were significantly compromised with increased lactate production. ALA/Fe exposure rescued these deficiencies and increased the antioxidant status by enhancing the GSH/GSSG ratio and the activities of SOD and CAT, suggesting the Nrf-2 pathway was activated. Supporting this, the main Nrf-2-regulated downstream proteins, HO-1 and NOQ1 were increased in ALA/Fe-treated cells. Furthermore, the levels of bilirubin, a product of HO-1 stimulated activity, the expression of PGC-1a, a transcription coactivator that plays a central role in the regulation of mitochondrial biogenesis and function, and the copy number of mtDNA were also increased in ALA/Fe-treated cells. The use of dexamethasone, a known Nrf-2 inhibitor, blocked the positive effects of ALA/Fe treatment. ***CONCLUSIONS:*** Altogether, this study demonstrated marked mitochondrial dysfunction and oxidative stress in DARS2 deficient fibroblasts, which could be ameliorated by the use of ALA/Fe. Mechanistically, it was demonstrated that the Nrf-2 pathway was involved in ALA/Fe effects, which gives a better understanding of the cellular pathways that can be targeted in the treatment of mitochondrial diseases.

O-009 - GENOTYPIC SPECTRUM OF ISOLATED METHYLMALONIC ACIDEMIA IN MEXICO AND IN SILICO STRUCTURAL PROTEIN MODELING

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INTRODUCTION: Isolated methylmalonic acidemia (iMMA) results from pathogenic variants in genes coding methylmalonyl-CoA mutase (MMUT, MIM*609058), methylmalonyl-CoA epimerase (MCEE, MIM* 608419) or those coding cobalamin metabolism (MMAA, MIM*607481; MMAB, MIM*607568; MMADHC, MIM*611935). These defects cause multisystemic impairment with elevated morbimortality. Despite its clinical significance, the iMMA genotypic spectrum in Mexico remains poorly characterized. ***OBJECTIVES:*** To describe the clinical and molecular spectrum in iMMA Mexican patients and perform in silico protein structural analysis of the most prevalent variants. ***MATERIALS AND METHODS:*** Clinical whole exome sequencing (WES) in 40 patients with biochemical diagnosis of iMMA was performed. To predict deleterious effect of missense variants, in silico protein structural analysis was performed using the crystallographic structure of methylmalonyl-CoA mutase. ***RESULTS:*** The mean age at symptoms onset and diagnosis was 2.7 months and 10 months, respectively. 29 pathogenic variants were identified in four genes responsible of iMMA. In 36/40 patients (90%) a biallelic genotype was documented, a monoallelic was found in 4/40, and in 2/40 a variant of uncertain significance constituted at least one variant of their genotype. 21 variants were found in MMUT, with a predominance of NM_000255.4(MMUT): c.322C>T or p.(Arg108Cys), [rs121918257], which was identified in 54.8 % of iMMA MMUT-related patients. Twenty-eight different genotypes were found, of which 42.8% were homozygous, 50% compound heterozygous and 7.2 % monoallelic. In silico modeling of MMUT p.(Arg108Cys) variant revealed that arginine 108 residue is in close contact with the substrate, if this residue is replaced by cysteine, the interaction with substrate could be lost, which would affect the catalysis and might explain the severe clinical presentation observed. ***CONCLUSION AND DISCUSSION:*** The genotypic spectrum of the iMMA studied Mexican patients is heterogenous, being pathogenic variants in MMUT the most frequently found. The high frequency of c.322C>T or p.(Arg108Cys) variant in MMUT coincides with the previously reported iMMA spectrum in Hispanic population, which is associated with a common haplotype, thus a possible founder effect should be considered. Functional studies are warranted to corroborate the in silico predicted disturbances of this variant. In monoallelic patients, further studies to discard any deep intronic variants not detected by WES are needed.

O-010 - METHYLMALONIC ACIDEMIA, PROPIONIC ACIDEMIA, AND CBLC DEFECT: COMPARING UNTARGETED URINE METABOLOMIC PROFILES ALLOWS BETTER DISEASE UNDERSTANDING

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INRODUCTION: Methylmalonic (MMA), propionic acidemia (PA) and cobalamin C deficiency (cblC) share a defect in propionate metabolism. Although presenting similarities in the biomarker profile, the clinical manifestations of the three diseases are heterogeneous. In this study we used an untargeted metabolomics approach to investigate the biochemical profiles of these conditions and their possible connections with disease pathophysiology. ***METHODS:*** Untargeted urine metabolomic profiles of 21 patients (7 MMA, 7 PA, 7 cblC), all on standard treatment, were analyzed by high resolution UHPLC-MS/MS. For each disease, the discriminating features were statistically identified ($p<0.05$; $log2FC >|1|$) and used for the annotation. Selected features were associated with different metabolic pathways, searching for possible involvement in disease(s) pathophysiology. ***RESULTS:*** Untargeted metabolomics showed different profiles among the diseases with the most affected pathways related to the metabolism of organic-acids, aminoacids, peptides and glycine conjugates. The predominant PA fingerprints were associated with glycine and its conjugates, while in cblC involved pathways included trans-sulfuration, oxidative stress (vitamin E related compound, thioproline) and numerous neuro-steroids. ***DISCUSSION:*** The untargeted metabolomics study highlighted the differences between the three diseases, pointing to the most relevant contrast of cblC profile as compared to MMA and PA. Biomarker evaluation in PA accentuated a major role of glycine and of its conjugation processes in the clearing of toxic compounds. Besides methylmalonic acid, less pronounced

abnormalities were detected in MMA. Abnormal findings in cblC, related to oxidative stress and (neuro)steroid hormones, which may have a direct connection with the development of ocular and neuronal deterioration, provided novel insights in understanding disease pathophysiology and in innovative treatment strategies.

O-011 - IMPACT OF CORTICOSTEROID ADMINISTRATION AND PREMATURITY ON NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

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INTRODUCTION: It is well known that the corticosteroids administration to the newborns prior to the newborn screening sampling (NB-CORT) or to the mother in the last month of pregnancy (MM-CORT), as well as the newborns prematurity can cause false negative results (FN) in Newborn Screening (NBS) for Congenital Hypothyroidism (CH). To avoid the risk of FN, each NBS program should establish a double sampling procedure whenever any of the above-mentioned situations occur. ***OBJECTIVE:*** To quantify the impact of the following newborns pre-analytical conditions in the NBS for CH as a cause of FN, in the period 2014-2023: NB-CORT, MMCORT and gestational age less than 32 weeks (GA<32). ***MATERIAL AND METHODS:*** For each year evaluated, the following parameters were determined: a) Number of samples received, b) First samples analyzed, c) Number of cases confirmed with CH, d) Incidence of CH, e) Percentage of NB-CORT, MM-CORT and GA<32, and f) Number of newborns confirmed with CH in a second sample after a normal result in the initial NBS sample, as a consequence of any of the above mentioned pre-analytical conditions. ***RESULTS:*** During the 10-year period under evaluation, a total of 1,664,168 newborn samples were received, of which 1,579,351 (94.9 %) were first samples. The presence of CH was confirmed in 906 newborns. A clear decreasing trend over the years was observed in these parameters. The incidence of CH was 1: 1,743 live births. The mean annual percentage [range] for NB-CORT was 0.62% [0.53-0.73]%, for MM-CORT 4.75% [3.86-5.60]% and for GA<32 0.83% [0.77-0.98]%, showing a progressive increasing trend in these indices. Of the 906 confirmed cases, 11 MM-CORT, 2 MM-CORT/NB-CORT, 1 MM-CORT/GA<32 and 1 GA<32 were detected in a second sample. ***CONCLUSIONS:*** The results obtained show an alarming and progressively increasing trend in the percentages of NB-CORT and MM-CORT, as well as an increase in the percentage of GA<32, conditions that can cause FN in NBS for CH. In this experience, the impact of these pre-analytical conditions was 1.7% of the cases, which reinforces the importance of defining precise protocols for the second samples collection to avoid the potential loss of cases.

O-012 - IMPLEMENTATION OF HEMATOCRIT CORRECTION ON NEONATAL SCREENING FOR CONGENITAL HYPOTHYROIDISM

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INTRODUCTION: Neonatal screening (NS) procedures often rely on a standard hematocrit assumption of 55%. In a previous work we established a method to estimate hematocrit by measuring hemoglobin, demonstrating significant improvements in recall rates, specificity, false positive rates, and positive predictive values in 12,758 dried blood spot (DBS). ***OBJECTIVE:*** To implement the hematocrit estimation method in our laboratory on NS for Congenital Hypothyroidism (CH) and assess its feasibility and effectiveness. To evaluate correlation and agreement between TSH results obtained in DBS and serum samples. ***MATERIALS AND METHODS:*** The methodology was implemented into our NS program (February 2022 to September 2023). TSH levels were measured in 26,335 NS samples by ELISA (Zentech) and DELFIA (PerkinElmer). Hematocrit was estimated, and TSH values were compared with and without hematocrit correction. Recall rates and percentage of samples avoiding recall, specificity, false positive rates and positive predictive values were evaluated, with and without correction (Diagnostic Utility Statistics2002). Chi square test for the comparisson of two proportions was perfomed (Medcalc v13.1.2). TSH DBS results, with and without correction, were compared to TSH serum results (chemiluminescent immunometric assay, Immulite) in endocrinology service patients (age range: 0-18.5 years, mean age: 9 years). Bland Altman analysis was conducted (Difference plot Medcalc v13.1.2). Exclusion criteria: TSH DELFIA<0.7uUI/ml whole blood (n: 67). ***RESULTS:*** Studied parameters were as follows (uncorrected/corrected, %): recall rates (1.83/1.13), sensitivity (100/100), specificity (98.56/99.08*), false positive rates (1.44/0.92*), positive predictive values (5.50/8.30*). *p<0.0001 The agreement between DBS and serum levels improved following hematocrit correction (uncorrected/corrected, uUI/ml serum): mean (-1.6/-0.2), upper limit of agreement (2.5/2.9) and lower limit of

agreement (-5.7/-3.2) ***CONCLUSIONS:*** A positive trend in the studied parameters continues with an increasing sample size. As specificity and positive predictive value of the tests increase, false positive rate reduces. The implementation of hematocrit correction markedly decreased recall rates, without loss of sensitivity, minimizing associated costs and anxiety in affected families. Furthermore, the enhanced agreement between DBS results post-correction and serum levels suggests a closer approximation to the "true values", reinforcing the validity and credibility of the obtained data. This underscores the importance of integrating hematocrit correction into NS protocols.

O-013 - COMPARATIVE STUDY OF PERCENTIL VALUES OF IMMUNOREACTIVE TRYPSINOGEN, FIXED VERSUS FLOATING VALUES

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INTRODUCTION: In Chile a pilot study in Cystic Fibrosis (CF) newborn screening were performed using fixed cutoff for Immunoreactive Trypsinogen (IRT) of 45 ng/mL (98.4th percentile). The thermal lability of this CF marker and the variations from one kit to another point to the use of floating IRT cutoff value for IRT marker, standardized procedure is in CLSI guidelines (NBS05, 2nd ed. 2019). ***OBJECTIVES:*** To calculate our daily variation in IRT results using the percentile(p), by lot and by instrument used. ***MATERIALS AND METHODS:*** A retrospective analysis was carried out on "Neonatal TIFs" software database [patent 20 2024 101 632] IRT concentrations were obtained using GSP-IRT reagent kit run in two GSP instruments (PerkinElmer); Percentile was calculated according CLSI guideline NBS05 from 37 IRT assays from period April 1 2024 to June 1, 2024 (8396 newborn samples,) and 3 IRT assays from period 2022 (1433 newborn samples, CF=3 diagnosed). Coefficients of variation (CV%), sensitivity, specificity and Positive Predictive Value (PPV) were calculated using SPSS software. ***RESULTS:*** p99th was 44.75 ng/mL (SD 4.3, CV% 26.6), lower instrument variation in p95 (9.6%), bigger in p98 and p99 (52%, 56%). A media of 2799 samples results obtained with 3 different lots show a biggest variation in p99 (CV% 26.6) and show differences by instrument used (GSP1 CV% 47.6, GSP2 CV%21.0). Results obtained in 2022 was used to calculated the sensitivity (100%), specificity (98.6% vs 98.95%) and VPP (13% vs 17%) of current fixed cutoff versus floating 99th percentile. ***CONCLUSIONS:*** CV% in p99 differs by instrument used. Analytic cutoff value used in pilot study (p95.5) can be change to p98. The use of floating cutoff value allows savings in reagents, without losing sensitivity and increasing specificity, and with an improvement in PPV. Validated protocol is in the implementation phase in our TIFs software.

O-014 - COMPREHENSIVE EXPANDED NEWBORN SCREENING PROGRAM IN THE HEALTH SERVICES OF THE MEXICAN NAVY: 11 YEARS OF EXPERIENCE

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INTRODUCTION: The expanded newborn screening (ENS) aims to detect and treat metabolic, genetic, and endocrine diseases in newborns early, thereby preventing complications. In 2012, the Naval Health Services of the Mexican Navy (SEMAR) initiated the ENS program, initially screening for 67 diseases, expanding to 78 in 2021. ***OBJECTIVE:*** To present the results of the SEMAR ENS program, detailing some performance indicators and the birth prevalence of the main detected diseases. ***MATERIALS AND METHODS:*** From July 2012 to December 2023, 27,514 ENS tests were performed on newborns using heel-prick samples at 32 naval health establishments in 18 states of Mexico. Samples were analyzed using tandem mass spectrometry (MS/MS), the GSP® automated system, isoelectric focusing electrophoresis, and high-performance liquid chromatography. Performance indicators analyzed included age at sample collection, age at result delivery, and age at start of treatment. ***RESULTS:*** The average time between birth and sample collection was five days, with the same average time for result delivery. A total of 446 cases were considered suspicious, with 91.48% of these cases successfully located for a second sample collection. Ultimately, 128 cases were confirmed. The main detected diseases included: glucose-6-phosphate dehydrogenase deficiency (77), congenital hypothyroidism (25),

congenital adrenal hyperplasia (15), cystic fibrosis (4), sickle cell anemia (3), galactosemia (2), methylmalonic acidemia (1), and isolated 3-methylcrotonyl-CoA carboxylase deficiency (1). Additionally, 431 carriers of hemoglobinopathies were identified. Confirmed patients started treatment at an average of 16 days old, and 100% of the families received genetic counseling. ***CONCLUSIONS:*** The birth prevalence of congenital metabolic and genetic defects in the studied population was 1: 215 newborns. Specific birth prevalence rates included congenital hypothyroidism (1: 1,101), glucose-6-phosphate dehydrogenase deficiency (1: 357), and cystic fibrosis (1: 6,879). The continuous efforts of the SEMAR ENS program have enabled the early detection, diagnosis, treatment, and genetic counseling of 128 newborns, thereby mitigating disability and preventing complications.

O-015 - NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY: A POPULATIONAL STUDY IN BRAZIL

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INTRODUCTION: Spinal muscular atrophy (SMA) is an autosomal recessive disorders, with an estimated incidence of 1 in 10,000 live births. The *SMN1* gene encodes the survival motor neuron (SMN) protein and alterations in this gene cause the disease. Testing for SMA has been recommended for inclusion in neonatal screening (NBS) panels, since there is greater efficacy when introduced in the pre/early symptomatic phases. In Brazil, the National Newborn Screening Program (PNTN) currently performs NBS for 6 diseases, using blood impregnated on filter paper. This test is being expanded to incorporate more diseases, including SMA. ***OBJECTIVE:*** The aim of this work was to develop a pilot study for NBS for SMA in Brazil, through the analysis of 80,000 newborns from the states of Rio Grande do Sul, Sao Paulo and Mato Grosso, by real time qPCR, to examine the possibility of implementation of this technique for the screening, providing data that would help the planning of public policies. MATERIALS AND ***METHODS:*** Samples of the conventional NBS test were collected by the Reference Services in Newborn Screening (SRTNs) of Rio Grande do Sul, São Paulo (Unicamp) and Mato Grosso states, and an aliquot was delivered at Hospital de Clínicas de Porto Alegre (HCPA). The samples were processed and analyzed with the SALSA MC002 SMA Newborn Screen kit. Further analyses of abnormal results were performed using Multiplex Ligation-dependent Probe Amplification (MLPA), considered the gold standard to diagnose SMA. ***RESULTS:*** An analysis flow was established in which the 59,045 samples screened until now were analyzed. This study enabled the identification of five suspected SMA cases. Four cases were confirmed by MLPA: two copies of SMN2 (n=1); three copies of SMN2 (n=2); and four copies of SMN2 (n=1). The other one was considered false positives. The MC002 kit seems to be a methodology that can be used by neonatal screening laboratories to detect SMA. ***CONCLUSIONS:*** This work demonstrated the feasibility of screening for SMA using samples collected for the conventional NBS test, which is extremely important for the successful expansion of the PNTN.

O-016 - TEN-YEAR EXPERIENCE OF NEWBORN SCREENING (NBS) FOR MEDIUM CHAIN ACYL CO A DEHYDROGENASE DEFICIENCY (MCADD)

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INTRODUCTION: Medium chain acyl co A dehydrogenase deficiency (MCADD) is the most common inherited defect in the fatty acid β oxidation, resulting in significant morbidity and mortality in undiagnosed patients. Newborn screening (NBS) permits the introduction of interventions that can improve MCADD outcome. ***OBJECTIVE:*** To describe the ten-year results of the MCADD NBS including the long term follow up of the detected patients. ***MATERIALS AND METHODS:*** MCADD NBS was implemented in January 2014. Blood samples were collected within 2-5 days of life. Non derivatized reagents (PerkinElmer and Chromsystem) were used on API 3200 LC-MS/MS instrument. Primary marker used was Octanoylcarnitine (C8), cut off value (CO) of 0.28 uM. Since July 2014 it was added the ratio C8/C10 with a CO of 1.0. CO for C8 was adjusted to 0.21 uM. Since July

2014 babies with C8 and C8/C10 above COs were recalled. Confirmatory studies included acylcarnitine profile, urine organic acids and molecular studies. Emergency protocol was given to the families for preventive hospitalizations for specific intercurrent illnesses. ***RESULTS:*** The number of newborns tested until December 2023 was 204810. Recalled babies were 35, global recall rate was 0.017 %. Eight patients were confirmed. The prevalence was 3.9/100000. Positive predictive value was 22.8 % The results at screening were (mean and range) C8: 6.6 uM (0.37-16.8) and C8/C10: 8.36 (1.3 - 20.9) Confirmatory results: C8: 1.56 µM (0.3-3.05) and C8/C10: 8.5 (3-17.9). Hexanoil glycine was present in the urine of every patient but one. The most frequent mutation was c.985A>G, observed in 6/16 alleles (1 homozygous and 4 compound heterozygous). Seven patients were under long term follow up. Mean follow-up time was 5.6 years (0.8 – 9 years). Six patients had preventive hospitalizations. Number of hospitalizations: 1.8 (1-3), the more frequent cause of hospitalization was fever. None of the patients suffered metabolic crisis and no complications were observed during the long follow up. ***CONCLUSION:*** The algorithm used allows having low recall rate and high specificity. The follow up of the patients and the use of emergency protocol avoided the complications of the disease in the patients detected by our program.

O-017 - NEONATAL SCREEN FOR GLUCOSE 6 PHOSPHATE DEHYDROGENASE DEFICIENCY: 2 YEARS EXPERIENCE IN A LABORATORY IN MEXICO

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INTRODUCTION: Glucose-6-phosphate dehydrogenase deficiency (G6PDd) is the most common erythroenzymopathy worldwide. The *G6PD* gene, located on the X chromosome shows polymorphism, leading to a range of G6PD activity from normal to severely deficient in males (hemizygous), while females can be homozygous or heterozygous. In heterozygous females, the erythrocyte population can be normal and/or deficient due to random inactivation of one of the two X chromosomes. Under specific conditions, G6PDd can evolve into a hemolytic crisis. ***OBJECTIVE:*** To present the results of two years of neonatal screening for G6PD deficiency in Mexico. ***MATERIALS AND METHODS:*** A retrospective study was conducted, analyzing 126,528 dried blood spot samples from newborns between January 2022 and April 2024. The samples were analyzed using the GSP Neonatal G6PD enzymatic fluorometric method by Perkin Elmer® and DNA sequencing by the Sanger method with the Big Dye® Terminator Cycle Sequencing kit from Life Technologies. Exons 3-4 (variant c.202G>A), 5 (variant c.376A>G), 6-7 (variant c.542A>T), and 9-10 (variant c.968T>C) of the *G6PD* gene, which cover 80-90% of the genotypes causing G6PDd in the Mexican population, were analyzed. ***RESULTS:*** A total of 789 suspicious samples were detected, with 277 false positives (35.11%). 145 did not receive a second sample (18.38%), 367 were confirmed (46.51%) (65 Females/302 Males). 193 cases (22 Females/171 Males) were analyzed molecularly: 123 cases (7 Females/122 Males) were the p.[Val68Met;Asn126Asp] variant (63.7%), 25 cases (2 Females/23 Males) the p.[Asn126Asp;Leu323Pro] variant (13%), and 17 cases (8.8%) were rare variants in Mexico: p.(Lys429Glu) (3), p.[Asn126Asp;Asp181Val] (2), p.(Ser184Cys) (1), p.(Arg136Cys) (3), p.(Tyr70Cys) (1), p.(Arg227Gln) (1), p.(Ile199Val) (2), p.(Asn126Tyr) (1), p.(Arg365His) (1), p.(Asn122Ser) (1), p.(Val233Leu) (1). In 28 cases (14.5%), no alterations were found, though this does not exclude pathogenic variants in exons which were not analyzed. ***CONCLUSIONS:*** A prevalence of 0.29% for G6PDd was found, with an incidence of 1: 345 screened newborns. The results are within the range reported in other studies (prevalence 0.28-6.22%). Variations in prevalence may be due to factors such as geographic area, African ancestry and the presence of indigenous groups.

O-018 - RESILIENCE IN TIMES OF PANDEMICS: STRATEGIES SUSTAINED BY THE NATIONAL NEONATAL SCREENING PROGRAM DURING COVID-19 HEALTH CRISIS

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INTRODUCTION: Costa Rica's National Neonatal Screening Program, with a 98.8% coverage, is vital to its social security system. Amidst the COVID-19 pandemic, the National Newborn and High-Risk Screening Laboratory faced several challenges regarding operational sustainability and quality standards. ***OBJECTIVE:*** The

present study outlines the challenges, perceived risks, strategies, and contingencies employed by the National Neonatal Screening Program Laboratory (LabPNT) during the COVID-19 pandemic, to ensure service provision through a process-indicator analysis. ***MATERIALS AND METHODS:*** An anonymous digital questionnaire was administered to LabPNT technicians (n=5) and laboratory professionals (n=6) regarding the challenges and obstacles faced during the pandemic as well as solutions and strategies implemented in the laboratory. Process indicators were analyzed such as coverage, sample transit time, and percentage of unsatisfactory samples. Institutional guidelines for pandemic management and health service provision reports were reviewed from 2019 to 2023. ***RESULTS:*** Since 2006, national neonatal screening coverage has exceeded 97%, reaching 98.8% in 2020. Process indicators, such as transit time and unsatisfactory samples, have improved from 2019 to 2023 despite the challenges of the pandemic. The main challenges include personnel management and communication hurdles with parents and healthcare centers. The need to prioritize service continuity, forced program advancements to stall, and communication difficulties with doctors and sample collection centers were noted. Commitment, teamwork, and communication among LabPNT staff and with health centers were mentioned as factors that helped mitigate negative impacts on service provision. According to the institutional guideline review, these actions prioritized the continuity of neonatal screening sample collection and submission, despite the interruption of other health services during this period. ***CONCLUSION:*** Despite the challenges stemming from addressing the COVID-19 emergency, the resilience and commitment of LabPNT personnel and the institution allowed for the maintenance and improvement of process indicators related to neonatal screening service provision in Costa Rica, reflecting the robustness of the program.

O-019 - NEWBORN SCREENING AND THE DIAGNOSIS OF RARE DISEASES: A RETROSPECTIVE STUDY FROM THE BRAZILIAN RARE DISEASES NETWORK

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INTRODUCTION: The newborn screening (NBS) enables early diagnosis and treatment of several rare diseases (RD). Besides red reflex, hearing and pulse oximetry screening, the Brazilian NBS Program involves a blood spot test, including Phenylketonuria; Congenital hypothyroidism; Cystic fibrosis (CF); Congenital adrenal hyperplasia; Biotinidase deficiency and Sickle cell anemia. Given the limited epidemiological data on RD in Brazil, the Brazilian Rare Diseases Network (RARAS) was established aiming to perform a national survey on RD. ***OBJECTIVES:*** To analyze the epidemiological data of RD diagnosed through NBS in Brazil using data from the RARAS network. ***MATERIALS AND METHODS:*** Retrospective data of cases with confirmed or suspected RD diagnosis in the RARAS' centers between 2018–2019 were collected using RedCap. All cases diagnosed through NBS were included. ***RESULTS:*** Out of 12,530 RARAS records, 900 (7.18%) were diagnosed through NBS. Most were born in the Southeast region (42.38%), were female (66.56%) and admixed (50.59%). The mean age at data collection was 12.97 years (±10.54). Diagnosis was confirmed in 97.71% cases; 2.29% were under investigation. The Brazilian Unified Health System funded most diagnoses (98.27%). The most frequent diagnoses were Phenylketonuria (n=454); Congenital hypothyroidism (n=145) and CF (n=117). When excluding the pathologies from the public NBS Program, the most prevalent disorders were Maple syrup urine disease (n=15), Glucose-6-phosphate dehydrogenase deficiency and Galactosemia (n=5). Familial recurrence rate was 12.20% and consanguinity rate was 11.46%. Hospitalization was reported by 201 (22.89%), with a mean of 2.37 hospitalizations/participant, mainly due to CF. The mortality rate was 0.34%, with aminoacidopathies as the leading cause of death. ***CONCLUSIONS:*** The low mortality rate of this population compared to the Brazilian infant mortality rate in 2019 (1.33%), and the reduced hospitalization rate compared to the general RARAS' rate (4.12), underline the importance of early diagnosis through NBS for better outcomes. Furthermore, the higher consanguinity rate compared to the Brazilian (1.60%) and RARAS' rate (6.40%), may be due to the autosomal recessive inheritance of most screened diseases. Data show the importance of early diagnosis of life-threatening disorders that were not diagnosed in the public NBS, highlighting the necessity of expansion of screened disorders in this program.

O-020 - ADJUSTMENT OF THE REFERENCE VALUES OF THE TESTS OF THE BASIC NEWBORN SCREENING PANEL OF THE ROOSEVELT HOSPITAL, GUATEMALA.

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INTRODUCTION: Newborn screening has been performed in Guatemala since 1991 by the Ministry of Public Health and Social Assistance. At the metropolitan level, it is performed in only two specialized fourth level hospitals. One of the two hospitals is the Roosevelt Hospital, which performs the basic panel that detects Congenital Hypothyroidism, Congenital Adrenal Hyperplasia, Cystic Fibrosis, Galactosemia and Phenylketonuria. The institutions that perform newborn screening use the reference values proposed by the parent company that manufactures and distributes the reagents, which are calculated in a population different from the Guatemalan population. ***OBJECTIVE:*** To adjust the reference values of the basic newborn screening panel. ***MATERIALS AND METHODS:*** A total of 1,304 live newborns were included, and reference values were calculated based on the non-Gaussian distribution of the population, percentiles 99, 99.5 and 99.9 were calculated. At the time of sampling, demographic data of the newborn and the mother were obtained to determine if any factors influence the values of the central panel tests. Fluoroimmunoassays developed by PerkinElmer® were used for the measurement of neonatal TSH, 17-hydroxyprogesterone, immunoreactive Trypsinogen, total Galactose and Phenylalanine. ***RESULTS:*** Factors influencing the reference values were sex, birth weight, type of feeding, time of sampling, GA and type of delivery. The reference values according to the results obtained were neonatal TSH 9.93 uIU/mL, Immunoreactive Trypsinogen 63.54 ng/mL, total Galactose 8.78 mg/dL and Phenylalanine 2.17 mg/dL. The 17-hydroxyprogesterone values were calculated based on gestational age (GA), less than 32 GA 61.38 ng/mL, 33-34 GA 33.79 ng/mL, 35-36 GA 17.13 ng/mL, 37-38 GA 19.03 ng/mL, 39-40 GA 14.45 ng/mL and greater than 41 GA 11.23 ng/mL. ***CONCLUSIONS:*** The reference values will be presented as a proposal to be implemented in the newborn screening program of the Roosevelt Hospital. The implementation of the calculated reference values could reduce the percentage of false positives and avoid false negatives, allowing for timely diagnosis, better use of institutional and state resources, and greater investment in expanding coverage to other areas of Guatemala where these specialized services are not available.

ABSTRACTS SELECTED FOR POSTER PRESENTATION (IEM)

P-001 - RESCUE OF OXIDATIVE DAMAGE WITH N-ACETYLCYSTEINE IN CLASSIC HOMOCYSTINURIA

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INTRODUCTION: Classical homocystinuria is an inborn error of metabolism of methionine caused by deficiency of cystathionine β synthetase (CBSD), an enzyme that catalyzes the transsulfuration of homocysteine (Hcy) to cystathionine. Hcy excess or cysteine deficiency would be the most probable mechanism of pathogenesis of this disease. Oxidative stress (OS) could play an important role in the pathophysiology, however, the diagnosis and treatment guidelines for CBSD do not propose using antioxidants as part of standard therapy (ST). Glutathione is a tripeptide formed by glutamic acid, cysteine and glycine that functions as a biological redox buffer. In CBSD the decrease in cysteine levels could deplete glutathione stores with the consequent accumulation of 5-oxoproline in the urine. N-Acetylcysteine (NAC) is a compound that replenishes cysteine, increasing glutathione levels and displaces thiols from their binding to proteins and forms mixed disulfides with them, increasing renal clearance of Hcy. ***OBJECTIVE:*** Describe the biochemical outcome of a case of CBSD treated with NAC. ***MATERIALS AND METHODS:*** Hcy was measured by Microparticle Chemiluminescent Immunoassay (ABBOTT). Urinary organic acids were analyzed by gas chromatography coupled to mass spectrometry (GC-MS). Amino acids in blood were processed by tandem mass spectrometry (FIA-MSMS), and plasma amino acids by ion exchange liquid chromatography with spectrophotometric detector, Biochrom30+. ***RESULTS:*** 8-year-old male patient with CBSD not responding to pyridoxine, CBS: (c.1039G>A; 1039G>A) hospitalized for metabolic stabilization due to poor ambulatory compliance is reported. He presents a marked decrease in visual acuity due to bilateral lens subluxation and marfanoid habit. Under ST, Hcy 52uM and plasma methionine 267% above the maximum reference value (AMRV) were measured, and the presence of 5-oxoproline in urine was detected. NAC was indicated and, after 15 days of treatment laboratory shows: absence of 5-Oxoproline excretion and improved values of Hcy (39uM) and methionine in blood (107%AMRV). ***CONCLUSIONS:*** The results of this work provide evidence on how NAC treatment could rescue CBSD

patients from OE and stabilize their metabolic status. We highlight the importance of searching for OS metabolites in this group of patients, and to avoid the use of medications that consume glutathione such as acetaminophen.

P-002 - AMINOTRANSFERASE DEFICIENCY TYPE 2: REPORT OF A CLINICAL CASE OF NEONATAL PRESENTATION IN CHILE.

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INTRODUCTION: Aminotransferase deficiency type 2 (BCAT2) is a rare metabolic disease that affects the metabolism of branched chain amino acids (BCAA), it is scarcely reported in the literature in pediatric age. ***OBJECTIVE:*** to describe a clinical case of BCAT2 in pediatric age. ***METHODOLOGY:*** review of clinical history from INTA, University of Chile. ***CLINICAL CASE:*** Full-term newborn, male without consanguinity. First hospitalization after 7 days due to poor weight gain, hypothermia, lethargy, irritability and sweet smell in the urine. After 72 hours he progressed to coma with epileptic encephalopathy and seizures. Maple syrup urine disease was suspected and confirmed by plasma BCAA levels: leucine 2650 umol/L, valine 600 umol/L, isoleucine 331 umol/L, alloisoleucine (+) 364 umol/L. A leucine-restricted diet and dialysis management were indicated. The patient presented an initially favorable evolution, normalizing BCAA levels and achieving resolution of the metabolic coma. During follow-up the patient developed neurological symptoms: global developmental delay, hypotonic syndrome and epilepsy, requiring gastrostomy for optimal nutritional management. A molecular study was requested and a polymorphism associated with the disease in the *BCAT2* gene was confirmed. During the last hospitalization at 4 years, pyridoxine (vitamin B6) 100 mg/day was added given the result of the molecular study and according to the expert's recommendation, the patient presented clinical stabilization of his baseline state and also a significant decrease in plasma levels of BCAA. ***DISCUSSION:*** The BCAT2 enzyme is a pyridoxine (B6)-dependent mitochondrial aminotransferase involved in the first step of BCAA metabolism. The clinical manifestations related to BCAT2 in children and adults described include a highly variable phenotype: asymptomatic forms to cases with neurodevelopmental delay, autism spectrum disorder, ataxia, spasticity, paraparesis, headaches, among others. The presentation with neonatal encephalopathy related to cases of BCAT2 deficiency has not yet been reported, so this case could contribute to broadening the clinical spectrum. ***CONCLUSION:*** In EIMs involving BCAA metabolism, BCAT2 should be in the differential diagnosis, especially regarding the potential benefit of a disease treatable with vitamin/cofactor (pyridoxine) supplements. Long term follow-up of BCAT2 patients is needed to understand the clinical phenotypic spectrum and pathophysiology of this disease.

P-003 - CHARACTERIZATION OF MAPLE SYRUP URINE DISEASE IN A CHILEAN COHORT: GENOTYPIC VARIATIONS AND METABOLIC CONTROL.

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INTRODUCTION: Maple syrup urine disease (MSUD) is caused by a defect in the branched-chain α-ketoacid dehydrogenase complex (BCKDH), leading to the accumulation of branched-chain amino acids (BCAA). Increased plasma concentrations of BCAA and the pathognomonic biomarker alloisoleucine diagnose MSUD. Treatment includes a leucine-restricted diet, BCAA-free amino acid mixtures, and supplementation (L-valine, Lisoleucine, thiamine, and L-carnitine). ***OBJECTIVE:*** To characterize the MSUD Chilean cohort's genotype, diagnostic BCAA levels, and metabolic control during follow-up. ***METHODS:*** Thirty-one patients with MSUD were analyzed. Genetic variants in four MSUD-related genes were characterized. Diagnostic plasma BCAA levels and metabolic control BCAA levels from DBS (Dried blood sample) were measured using liquid chromatography-tandem mass spectrometry. Data were presented as median with interquartile range (IQR). ***RESULTS:*** Of the patients, 61% were female, with an average age of 14±8 years. Diagnostic plasma BCAA levels were leucine 1511 µmol/L (760-1950), isoleucine 417 µmol/L (190-621), and valine 466 µmol/L (219-726), without alloisoleucine level. Genotypic analysis: 24 subjects had the *BCKDHB* gene affected, with four new

variants: c.196+5G>A (intronic), c.577dup (p.Ala193Glyfs*, frameshift), c.362dup (p.Asn121Lysfs6, frameshift), and c.397G>T (p.Gly133, nonsense). Three subjects had the *BCKDHA* gene affected, with one new variant: c.937G>C (p.Ala313Pro, missense). Two subjects had the *DBT* gene affected, with one new variant: c.51G>A (p.Leu17=, synonymous). Two subjects were homozygous for a new variant of the *DLD* gene: c.1517C>T (p.Ser506Leu, missense). The most frequent variant was c.641T>A (p.Ile214Lys), observed in 11 subjects from the central Chilean zone. Metabolic control showed leucine levels of 285.3 µmol/L (237.9-293.2) in patients ≤5 years old and 291.3 µmol/L (240.4-381.9) in those >5 years old. The isoleucine level was 293.8 µmol/L (225.8-366.5) and the valine level was 447 µmol/L (390.7-558.7). ***CONCLUSION:*** Seventy-seven percent of the *BCKDHB* gene was affected, mainly by the missense variant. Variant c.641T>A is present in 46% of the subjects and coincides in the central geographical area of Chile.

P-004 - HYPERGLYCINEMIA AND MORPHOPATHOLOGICAL ALTERATIONS IN THE OVARY AND HEART

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INTRODUCTION: Nonketotic hyperglycinemia (NKH), is an autosomal recessive inherited metabolic disease, caused by an error in the metabolism of this amino acid, and which leads to the accumulation of glycine in different body fluids, such as blood plasma, urine and cerebrospinal fluid. Several morphological and physiological alterations have been described in patients with NKH, ranging from brain malformations, peripheral neuropathies, to hypotonia. ***OBJECTIVE:*** to described two cases of non-consanguineous female patients with NKH confirmed by plasma glycine levels and with alterations in the morphology of the heart, stomach and ovaries. ***CLINICAL CASES:*** The first case was a three-day-old patient taken to the emergency room due to a clinical picture consisting of drowsiness, hypoactivity, difficulty sucking and absence of crying, with a critical condition that led to her death 10 days after admission. The second patient was three days old, who since birth has presented hypoactivity, respiratory difficulty, episodes of cyanosis during crying and died on the fourth day of life. Hyperglycinemia was diagnosed by thin layer chromatography compared to positive and negative controls. The report of the most important anatomopathological findings observed during the autopsy of both cases were: lungs with partial loss of crepitation and congestive; fibrosed ductus arteriosus, stomach, small intestine, liver and spleen with congestive mucous. Additionally, for case 2, alterations in the tricuspid valve, irregular atrial septal defect of membranous type and severe ventricular septal defect. The right ovary also had a purplish-brown mass. ***CONCLUSIONS:*** These findings allow us to speculate on the role of hyperglycinemia in the development of dysfunction of several organs other than the brain such as the heart and reproductive organs. Suggesting the need for a complete systemic evaluation in confirmed cases of nonketotic hyperglycinemia.

P-005 - A PHENOTYPIC VARIABILITY IN ORNITHINE TRANSCARBAMYLASE DEFICIENCY: SERIE OF EIGHT CLINICAL CASES

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BACKGROUND: Ornithine transcarbamylase deficiency (OTCD) is an X-linked urea cycle disorder. This rare syndrome caused by loss of function variant in *OCD* gene, which encodes OTC, responsible for catalyzing the synthesis of citrulline from carbamoyl phosphate and ornithine. The phenotype is highly variable, hemizygous males with severe neonatal onset typically exhibit life-threatening symptoms such as hyperammonemic encephalopathy (HAE), late-onset manifestations can occur in males with partial deficiency and in heterozygous females. ***OBJECTIVES:*** The aim of this report is to describe a series of Chilean patients with OTCD. ***PATIENTS AND METHODS:*** The clinical information was collect retrospectively. ***CLINICAL CASES:*** We report eight patients with OTCD, three men and five women, with current ages ranging from five months to twenty-eight years. All patients have biochemical and molecular confirmation, variants identified are variable, and include missense, nonsense and intronic variants. The age at onset ranged from first days of life to six years-old. Severe neonatal hyperammonemic encephalopathy was the clinical debut in two men, the third male patient presented the first episode of HAE at three years of age. Severe acute liver failure was the onset in three women,

intermittent episodes of HAE in another, and the youngest female patient remain asymptomatic. No patient has any known affected male relatives. All patients have been treated with a proteinrestricted diet, supplementation with citrulline, and two female patients required liver transplantation, the third female patient recovered liver function. ***CONCLUSION:*** OTCD is a condition with high clinical variability, which is evident in this group, both in male hemizygotes and in heterozygous females patients. The liver phenotype in in heterozygous females patients stands out as a form of presentation, which has led to liver transplantation in several of them, making it necessary to include it in the differential diagnosis of liver failure in women. Although diagnosis can be achieved through biochemical techniques, molecular confirmation is essential for both the patient and their at-risk relatives. Nevertheless, strict follow-up and regular health monitoring remain essential to foresee and treat potential complications in these patients.

P-006 - BACHMANN-BUPP SYNDROME: REPORT A CASE

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BACKGROUND: Bachmann-Bupp syndrome (BABS) is a very rare disorder caused by gain-of-function variants in the C-terminus of ornithine decarboxylase (ODC), a protein encoded by the *ODC1* gene, part of the polyamine pathway. This autosomal dominant disorder is characterized by alopecia, global developmental delay of varying degrees, hypotonia, behavioral issues, feeding difficulties, and dysmorphic features. Less frequent findings may include seizures and conductive hearing loss. Although there is currently no cure for this condition, a recent trial involving an OCD inhibitor has shown promising results in improving hair growth, muscle tone, and development. ***OBJECTIVES:*** The aim of this report is to describe the phenotype of a case with Bachmann-Bupp Syndrome. ***CLINICAL CASES:*** We report on a 17-year-old female, born to young, healthy, and non-consanguineous parents. She was born preterm with a normal birth weight and length (+1.02 SD and +1.98 SD), but had macrocephaly (+3.39 SD). During the neonatal period, she experienced episodes of hypoglycemia. Subsequently, in infancy, she was referred to neurology due to hypotonic syndrome, global development delay, and spastic diplegia. At 7years old, moderate intellectual disability was diagnosed (IQ 45). Initial genetic workup included a karyotype 46,XX, and chromosomal microarray analysis , which showed Xchromosome absence of heterozygosity. Brain MRI revealed bilateral subcortical white matter lesions, and signs of papilledema. Neuro-ophthalmological evaluation identifies optic atrophy. At 16 years of age, upon reassessment, physical examination showed persistent macrocephaly, high forehead, sparse eyebrows and eyelashes, hyperpigmented spots on the right side of the face, prominent eyes, and a high palate. Subsequent brain MRIs showed no progression of the lesions. NGS sequencing identified a heterozygous variant, c.1242-2A>G, in the ODC1 gene, confirming the diagnosis of BABS. ***DISCUSSION:*** BABS illustrates that not all inherited metabolism disorders are detectable through standard biochemical tests. Although this case does not have overt alopecia, it does have other recognizable phenotypic characteristics of the syndrome. Improved characterization and understanding of this disease can lead to earlier diagnosis and interventions.

P-007 - NUTRITIONAL TREATMENT AND DESCRIPTION OF A COHORT OF PATIENTS WITH GYRATE ATROPHY IN A NATIONAL REFERENCE CENTER OF MEXICO

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INTRODUCTION: Gyrate Atrophy (GA) is an autosomal recessive disorder characterized by ophthalmic, neurological, muscular manifestations and elevation of plasma ornithine levels. Different nutritional approaches, such as arginine restriction, vitamin B6, lysine, proline and creatine have been proposed to decrease ornithine levels. ***OBJECTIVE:*** To describe a cohort of patients with GA and the nutritional treatment provided. METHODS AND ***MATERIALS:*** A retrospective descriptive study was performed. Patients with confirmed diagnosis of GA were included. The following data were collected from the clinical record: place of birth, age at onset of symptoms, body mass index (BMI), plasma ornithine levels at diagnosis, vitamin B6 responsiveness trial, and the indicated dietary treatment. ***RESULTS:*** Ten patients were included from 9 families (7 females, 3 males). The mean age of first symptoms were 2.5 years (range 1-4). Mean

age at diagnosis was 25 years old (range 9 -65). 5/10 ornithine samples were taken at the National Institute of Pediatrics and the others were from external independent laboratories. The mean ornithine levels were 594 umol/L (range 43-1202). BMI at diagnosis was normal in 60% of patients, 20% were underweight, 10% overweight and 10% had obesity. Patients came mainly from the north, center and southeast of Mexico; one patient from Belize. The vitamin B6 responsiveness trial was performed in 50% of patients with 300-500 mg for two to four weeks; one was respondent with a decrease in ornithine levels of 76% (from 932 to 223 umol/L) with a one-month trial and 500 mg of pyridoxine. Diet treatment is given with restriction of natural protein (0.4-0.8 g/kg/d) and essential amino acids supplementation (0.3-0.7 g/kg/d) to achieve OMS total protein requirements for age. Patients were supplemented with lysine, proline, and creatine. ***DISCUSSION AND CONCLUSION:*** Patients with AG still have late diagnosis. In this cohort more women are affected, most patients were eutrophic at diagnosis. One patient responded to vitamin B6 supplementation; diet treatment for non-responders patients was arginine restricted diet complemented with essential amino acids, and supplemented with lysine, proline and creatine. Treatment guidelines are needed in order to standardize treatments, and biochemical biomarkers for early detection.

P-008 - 24-HOUR SAPROPTERIN DIHYDROCHLORIDE RESPONSIVENESS TEST IS EFFICIENT IN PREVENTING MATERNAL PHENYLKETONURIA SYNDROME?

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BACKGROUND: Maternal phenylketonuria syndrome occurs in women with phenylketonuria whose serum phenylalanine (PHE) levels do not remain within safe values during pregnancy. The Brazilian clinical Protocol of therapeutic guidelines for phenylketonuria (PCDT) recommends treatment with sapropterin dihydrochloride for pregnant women to reduce the risk of maternal phenylketonuria syndrome. A sapropterin dihydrochloride responsiveness test is recommended, with assessment of PHE levels 24 hours after medication overload. In the state of São Paulo, however, a 7-day (168-hour) sapropterin responsiveness test protocol was defined. ***OBJECTIVE:*** To compare the effectiveness of 24-hour and 168-hour sapropterin dihydrochloride responsiveness tests. ***MATERIAL AND METHODS:*** 168-hour sapropterin dihydrochloride responsiveness tests were carried out in post-menarcheal female patients, with blood samples taken to measure phenylalanine for 9 days (24 hours before and after the first and last administration of the medication). The dose of sapropterin dihydrochloride was 20mg/kg/day. The diet for the test was standardized according to each patient's routine. ***RESULTS:*** 10 women participated in the test, with a mean age of 21.2 years, 2 with classic phenylketonuria, 6 with mild phenylketonuria and 2 with persistent hyperphenylalaninemia. None of the patients were pregnant at the time of the test. Of these patients, 5 responded to medication 24 hours later, 3 of them diagnosed with mild phenylketonuria and 2 with persistent hyperphenylalaninemia. In addition, 2 patients with mild phenylketonuria responded after 48 hours and 1 with mild phenylketonuria after 72 hours. Also, the two patients with classic phenylketonuria responded to the test only after 96 hours. It is important to emphasize that 50% of patients were not responsive in the first 24 hours of testing. ***DISCUSSION:*** The 24-hour test does not identify all women with the possibility of better control of serum phenylalanine levels during pregnancy by using sapropterin dihydrochloride. In particular, patients with classic phenylketonuria, who would probably have more difficulty controlling phenylalanine levels during pregnancy, would not be identified. ***CONCLUSION:*** If the objective of PCDT is to prevent maternal phenylketonuria syndrome, with the use of sapropterin dihydrochloride, according to our data, the recommended test may not be efficient.

P-009 - EXPERIENCE OF SAPROPTERIN RESPONSIVENESS TEST IN MEXICAN HYPERPHENYLALANINEMIA PATIENTS.

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INTRODUCTION: Hyperphenylalaninemia (HPA) results from pathogenic variants in the phenylalanine hydroxylase (PAH, MIM*261600) gene, which encodes the enzyme phenylalanine hydroxylase (PAH). The cofactor of PAH is tetrahydrobiopterin (BH4). Sapropterin, a synthetic form of BH4 can improve the

residual activity of certain PAH pathogenic variants. This treatment has enabled responsive patients to maintain a less restricted protein diet by increasing their phenylalanine (Phe) tolerance. Additionally, PAH genotype can predict responsiveness to sapropterin. The genotypic spectrum of our potentially sapropterin-responder PAH patients is known, however, their sapropterin-responsiveness has not been completely acknowledged. ***OBJECTIVE:*** To describe the experience of sapropterin responsiveness test in mexican hyperphenylalaninemia patients. ***MATERIALS AND METHODS:*** Prospective descriptive study of nine HPA-patients with a previously described sapropterin-responder genotype. The test consisted in prescription of a 20 mg/kg/day sapropterin dose. Age at treatment start, pre- and post-sapropterin blood Phe levels, and natural protein intake were recorded and analyzed with MetabolicPro software. Data distribution was analyzed with the Shapiro–Wilk test, and pre- and post-treatment blood-Phe levels were compared using the non-parametric Mann–Whitney U test. ***RESULTS:*** The median age at treatment initiation was 6 years (range: 1-12 years). Mean blood-Phe concentration significantly decreased from 648.8 μmol/L to 245.1 μmol/L post-treatment ($p < 0.001$). During the test, natural protein intake was 0.7 g/kg/day. ***DISCUSSION AND CONCLUSION:*** The studied PAH patients showed a mean reduction of 62.2% of blood-Phe levels during sapropterin treatment, indicating positive responsiveness. The pre-selection of potentially-responder patients by their genotype for this test, allowed us to corroborate the well-known health benefits of sapropterin. The natural protein intake in these patients could be increased from 0.7 to 0.84 g/kg/day with adequate metabolic control, reducing the risk of short- and longterm complications and improving protein tolerance.

P-010 - PKU CAMP: AN INTERACTIVE EDUCATIONAL EXPERIENCE FOR PKU PATIENTS IN BUENOS AIRES, ARGENTINA

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INTRODUCTION: There is still much to be done to ensure health, educational, emotional, and social needs of patients with phenylketonuria (PKU). Fundación de Endocrinología Infantil (FEI) and the Hospital de Niños Sor Ma Ludovica (La Plata), organized the first PKU CAMP for patients with Phenylketonuria in Argentina on February 27-28, 2023, and a second one on February 28-29, 2024, in Buenos Aires, Argentina ***OBJECTIVES:*** To provide learning tools and improve treatment adherence at different stages of life, including Maternal PKU, in a warm and professionally supportive environment. ***MATERIALS AND METHODS:*** Thirteen patients and twentythree in the second Camp, were accompanied by their healthcare teams (physicians, dietitians, psychologist, social worker) and young adult PKU patients who participated as assistants. Patient selection criteria: age (11-20 years), treatment adherence, ability to interact with others, and need to incorporate self-care. Plenary educational sessions covered PKU treatment, PKU and the brain, genetics, maternal PKU, and patient-led discussions. Practical workshops included cooking and "supermarket shopping". Small group educational activities, and recreation were also included. Parents were previously informed about PKU Camp´s details and asked for authorization for activities and media usage. ***RESULTS:*** Patients learned about PKU treatment, internalized self-care concepts, shared treatment experiences, developed treatment skills, interacted with healthcare teams and peers, set future treatment goals, and enjoyed themselves. Meeting other PKU patients was very important for them socially and emotionally, helping them with treatment´s adherence. After one month, a post event survey answered by 73 % of the patients was carried out, revealing high satisfaction with Camp activities, usefulness of learned concepts and gratefulness for the possibility of sharing their experiences with other PKU. ***CONCLUSIONS:*** Self-care promotion is crucial to enhance self-esteem and adherence, transitioning responsibility gradually from caregivers to patients. Manual or Mi PKU App assisted phenylalanine/protein/exchanges calculation needs to be taught and practiced. Sharing experiences with peers is essential. PKU Camp fosters significant emotional support, sense of belonging, and security in a safe space, strengthening adherence, especially in this age group. The bidirectional nature of objectives enriched both patients and healthcare teams, generating new treatment goals for both patients and healthcare professionals.

P-011 - CASE REPORT: A CASE OF LATE EVOLUTION OF PHENYLKETONURIA

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INTRODUCTION: Phenylketonuria is an inborn error of metabolism that can be identified by newborn screening

(NBS), generally in the first days of life, after the introduction of protein foods. Early initiation of treatment is essential for preventing symptoms, mainly related to delayed neuropsychomotor development. According to the Brazilian protocol, the diagnosis is made with phenylalanine (Phe) levels above 8mg/dL in two consecutive tests or above 10mg/dL in at least one. According to the American protocol, the diagnosis is when Phe levels is above 6mg/dL. ***OBJECTIVE:*** To describe a case of late evolution of phenylketonuria. ***METHOD:*** Descriptive case study. ***RESULTS:*** Child with NBS carried out at 48 hours of life, with PHE values of 6.36mg/dL (reference range <2.49 mg/dl), considered a case of hyperphanylalaninemia according to Brazil protocol. He progressed with a decrease in PHE levels in the following months, without a protein-restricted diet, and was monitored at a reference center for neonatal screening. At 10 months of age, he presented Phe levels of 12.15 mg/dL and 13.1mg/dL and then started the treatment for PKU with Phe-restricted diet and Phe-free protein substitutes. When he was 4 years old, a brother was born to the same parents, with phenylketonuria (PHe level of 13.14 mg/dL at Newborn Screening). The case is now 10 years old and has normal global development. ***DISCUSSION:*** The late diagnosis provided challenges for the patient and his family, considering that the child was on a free diet and needed to initiate restrictions. According to the American protocol, this child would be diagnosed with phenylketonuria from the first PHE test, which suggests the need to monitor hyperphanylalaninemia to ensure that PHE levels remain safe. ***CONCLUSION:*** Monitoring children with increased PHE, even outside the diagnostic values for phenylketonuria, may be important for identifying late elevations.

P-012 - COMPARISON BETWEEN THE DETERMINATION OF PHENYLALANINE IN BLOOD ON FILTER PAPER BY TANDEM MASS SPECTROMETRY AND IN PLASMA BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY AND ITS INFLUENCE ON THERAPEUTIC DECISION-MAKING

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Phenylketonuria (PKU) is an autosomal recessive metabolic disorder. Regular and accurate monitoring of Phe concentrations in individuals with PKU is of the highest importance to make a treatment decision. Lower Phe concentrations in dried blood sample (DBS) than in plasma in paired specimens have been reported. ***OBJECTIVE:*** To determine the variability between the quantification of Phe in DBS by tandem mass spectrometry (MSMS) and in plasma by high-performance liquid chromatography (HPLC) and its influence on therapeutic decision-making in PKU patients. Also define an equation, which allows the concentrations obtained from Phe in DBS to be reliably converted into plasma concentrations and vice versa. ***METHODS:*** Phe was determined in 182 paired samples (DBS by MSMS and plasma by HPLC) from patients with hyperphenylalaninemia / phenylketonuria. The degree of correlation between the two methods was established, evaluating the differences. The medical team interpreted the results of the quantifications of both samples from a blind study and made decisions regarding whether or not to change the treatment. Statgraphics 19® was used for statistical analyses. ***RESULTS:*** Phe concentrations were highest in plasma with a median of 266 μmol/L.; in DBS, the median concentrations were 234 μmol/L. Compared the measured in DBS and plasma, there was a linear relationship with a correlation of 0.926; however, due to heteroscedasticity, we performed data power transformation to stabilize the variance, obtaining the following equation $Y=1+[(X+\lambda_2)^{\lambda 1}-1/\lambda_1 g^{\lambda 1-1}]$ in which $\lambda 1 = 0.216$, $\lambda 2 = 0$ y $g = 249$. According to clinical interpretation, in 89% of determinations, there was a coincidence in the medical decision with the results of both determinations. ***CONCLUSIONS:*** Our results confirmed previous observations on the lower Phe levels if determined by the MS/MS in DBS compared to HPLC plasma determination. DBS concentrations can be reliably converted into plasma concentrations by applying the regression equation with a data power transformation as a correction factor, in order to make an adequate medical decision.

P-013 - INCREASED CYTOKINE LEVELS IN PKU PATIENTS WITH LATE DIAGNOSIS AND THE ANTIINFLAMMATORY EFFECT OF L-CARNITINE

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INTRODUCTION: Patients with Phenylketonuria (PKU) present L-carnitine deficiency, compound that has demonstrated an anti-inflammatory role. ***OBJECTIVES:*** Evaluating the effect caused by exposure time to high phenylalanine (Phe) levels in PKU patients at early and late diagnosis, through pro-and anti-inflammatory cytokines, as well as the L-carnitine effect in treated patients. ***METHODS:*** PKU patients were classified as early diagnosis at less than 3 months of age (20 to 64 days old) and as late diagnosis at more than 1 year of age (2 years and 4 months to 44 years old). Plasma samples were obtained from: 12 PKU patients at diagnosis-7 patients at early diagnosis (mean age: 0.11±0.045 years) and 5 patients at late diagnosis (mean age: 14.16±17.58 years)-, and 12 PKU patients under dietary treatment (treatment time: 2.02±1.05 years). The 12 treated patients were submitted a Phe-restricted diet supplemented with a semi-synthetic formula of essential amino acids, vitamins and minerals, containing L-carnitine in its formulation (100-150 mg/kg/day). Control group consisted of 12 healthy individuals. The study was approved by Ethics Committee (nº2021-0618). ***RESULTS:*** We observed decrease in Phe levels in treated patients compared to patients at diagnosis [Phe(mg/dL): early diagnosis: 24.58±14.36; late diagnosis: 20.27±6.09; treatment: 5.02±1.82], and increase in L-carnitine levels in treated patients. We found increased proinflammatory cytokines levels: IL-1β, IFN-gamma, IL-2, TNF-alpha, IL-8 and IL-6 in patients at late diagnosis compared to controls, and IL-8 in patients at early diagnosis and treatment compared to controls. Increased IL-2, TNF-alpha, IL-6 levels in patients at late diagnosis compared to early diagnosis were shown, and reduced IL-6 levels in treated patients compared to patients at late diagnosis. A negative correlation between Phe versus L-car in PKU patients (r=-0.6884) and IFN-gamma versus L-car in treated patients (r=-0.6301) was found. We observed increased IL-4 levels in patients at late diagnosis compared to early diagnosis, and reduction in patients under treatment compared to late diagnosed patients. ***CONCLUSION:*** Our results demonstrate that time exposure to high Phe concentrations generates a proinflammatory status, especially in PKU patients with late diagnosis. In addition to the importance of early diagnosis and prompt start of treatment, highlighting the importance of L-car supplementation, which can improve cellular defense against inflammation in PKU patients.

P-014 - NAVIGATING NUTRITIONAL AND COGNITIVE OUTCOMES IN PHENYLKETONURIA: INSIGHTS FROM CLINICAL EVALUATIONS AT VICENTE CORRAL MOSCOSO HOSPITAL, ECUADOR

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INTRODUCTION: Phenylketonuria is the most well-known congenital metabolic error. In Ecuador, neonatal metabolic screening has been implemented since 2011 for the early detection of four pathologies, including Phenylketonuria, with 40 positive cases reported to date. ***OBJECTIVES:*** To determine the clinical characteristics and evolution of patients diagnosed with phenylketonuria in an Ecuadorian Hospital. ***METHODS:*** A cross-sectional, descriptive study was conducted with a universe of 11549 patients who attended to the pediatric nutrition assesment from January 2011 to December 2022; from theses universe we found six (6) patients diagnosed with classic Phenylketonuria through neonatal screening and through blood phenylalanine quantification outside of screening. Information was obtained from the clinical record of multidisciplinary outpatient at the Vicente Corral Moscoso Hospital. Study variables included nutritional status according to WHO classification (weight/age, height or length/age, BMI/age), IQ, psychomotor development, metabolic control (phenylalanine value) and nutritional indicators such as hemoglobin and vitamin D among others. Data analysis was performed using SPSS version 15. ***RESULTS:*** The mean age was 7 years (SD ± 6.22), 3 male and 3 female patients. In 2/6 patients, the diagnosis was made outside neonatal screening, at 20 and 16 months of age. 4/6 patients had adequate nutritional status, 1 had obesity, and one had moderate malnutrition according to WHO classification. Two patients with late diagnosis presented mild cognitive delay, particularly in language and hyperactivity, and one had a moderate delay in psychomotor development. The average phenylalanine (FA) monitoring value was 438umol/L (315-534umol/L). The mean hemoglobin value was 12mg/dl and the Vitamin D 25 OH (D3 + D2) 28ng/ml. ***CONCLUSIONS:*** Despite limitations in nutritional treatment, including the reliance on a special formula as an amino acid substitute and the absence of a national database of FA content in foods, our

patients have not experienced complications in cognitive development or nutritional status.

P-015 - PHENYLKETONURIA DIAGNOSIS IN BRAZIL: OBSERVATIONS FROM THE BRAZILIAN RARE DISEASE NETWORK

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INTRODUCTION: Phenylketonuria (PKU) is an inborn error of amino acid metabolism, with autosomal recessive inheritance. In non-treated patients, clinical signs may appear in the first months of life as hypotonia and neuropsychomotor development delay, in addition to seizures, irritability and a characteristic odor. In Brazil, PKU was one of the first genetic disorders to be included in neonatal screening, with the aim of starting early dietary treatment. ***OBJECTIVES:*** To present an overview of PKU in Brazil, using data from the Brazilian Rare Diseases Network (RARAS). ***MATERIALS AND METHODS:*** Data from individuals with a confirmed diagnosis of PKU assisted at the centers were included in this study. Cases were collected in the retrospective (2018-2019) and prospective (2022 to May 2024) survey. Data was collected and extracted from the REDCap. ***RESULTS:*** 717 individuals were included, 68.9% were female, with a mean age of 16.0 (±11.8) years at the time of data collection. Neonatal screening was responsible for 74.9% of diagnoses, while symptomatic diagnosis represented 22.5%. The largest paying source for diagnoses was the Unified Health System (SUS, 95.6%). The Southeast region had the highest number of diagnoses, with 65.2%, followed by the Northeast region, with 16.3%. ***CONCLUSION:*** Although included in neonatal screening since 2000, our data show that almost 1/4 of patients (22.5%) were diagnosed after presenting symptoms. Although the largest source of payment for diagnoses is the SUS, there is great regional inequality. Furthermore, this study corroborates the importance of diagnosis in the neonatal period to begin treatment in the first days of life. The majority of diagnoses in this registry were made through the Brazilian Unified Health System (SUS), highlighting the crucial role of the public healthcare system in neonatal screening and the diagnosis of rare diseases.

P-016 - QUALITY OF LIFE IN PKU PATIENTS RECEIVING MEDICAL ATTENTION AT THE NATIONAL INSTITUTE OF PEDIATRICS

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INTRODUCTION: Quality of life (QoL) is a multifactorial and subjective concept that varies according to the perceptions and values that each person has about health and life. Phenylketonuria (PKU) is a genetic disorder characterized by high levels of phenylalanine (PHE) in blood, due to a deficiency or absence of the enzyme phenylalanine hydroxylase. Because of the chronic nature and the need for permanent treatment, people with PKU and their families can feel alterations in the quality of life. The quality of life of these families has not been studied in Mexico. ***OBJECTIVE:*** To evaluate the quality of life of families with PKU attending the National Institute of Pediatrics by applying a specific questionnaire for the disease. ***MATERIALS AND METHODS:*** The PKU-QoL Parents questionnaire was applied in Spanish, which consists of 54 items that allows the calculation of 30 domain scores in four modules (symptoms, PKU in general, supplementation and protein restriction in the diet). ***RESULTS:*** The questionnaire was applied to mothers, fathers and when possible, to both. We studied 22 patients with classical PKU, from 7 months to 15 years. Three patients had late treatment and l9 early. 13 children were outside the control interval (>360 μM) and 9 were controlled. Responses observed a severe effect of PKU on parents' anxiety domain by PHE levels in their child, followed by a moderate emotional impact on guilt by diet carelessness, by their child's health status, and in the anxiety of the children by the routine taking of blood sample. In average 15 of the domains there was no reported impact on their quality of life. ***CONCLUSIONS:*** The present study shows that only the domain -anxiety of the father for PHE levels in his child- belonging to the module Impact of PKU on daily life, presented a severe impact and in 15 of the domains, the impact was null. These results help us to improve knowledge about the conditions,

problems, concerns and family needs of parents of children with PKU.

P-017 - PHASE 3 APHENITY STUDY RESULTS: ORAL SEPIAPTERIN FOR THE TREATMENT OF PHENYLKETONURIA

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BACKGROUND: Phenylketonuria (PKU) is caused by pathogenic variants in the *PAH* gene encoding for phenylalanine hydroxylase (PAH). PAH deficiency results in elevated phenylalanine (Phe) levels and is associated with cognitive, psychiatric, and behavioural impairments. Sepiapterin, a substrate for tetrahydrobiopterin (BH4) biosynthesis and an endogenous precursor of BH4, is an investigational oral treatment for PKU; it increases intracellular BH4 bioavailability and acts as a distinct pharmacologic chaperone, leading to increased PAH activity. ***METHODS:*** Phase 3 APHENITY (NCT05099640) trial evaluated the efficacy and safety of sepiapterin in reducing blood Phe in participants with PKU. Part 1 was a 14-day sepiapterinresponsiveness test. Participants ≥2 years with ≥15% reduction in blood Phe progressed to Part 2 (6-week, randomized, placebo-controlled, double-blind). Primary endpoint was mean change in blood Phe from baseline to Weeks 5 and 6. ***RESULTS:*** Children and adults participated in the trial [median age (min, max): 14.0 years (1, 61)]. In Part 1 (n=156), 66.0% of participants had blood Phe reduction ≥30% from baseline, with 65.3% decrease in mean blood Phe. Primary endpoint was met in Part 2 with a statistically significant ($p<0.0001$) reduction in blood Phe after 6-weeks of sepiapterin (-62.8%; Baseline blood Phe: 646 µmol/L; Weeks 5-6 blood Phe: 236 µmol/L) vs. placebo (+1.39%; Baseline blood Phe: 654 µmol/L; Weeks 5-6 blood Phe: 638 µmol/L) in participants with ≥30% reduction in blood Phe in Part 1. In Part 1, 45.7% of classical PKU (cPKU; Phe ≥ 1200 µmol/L) participants had a blood Phe reduction ≥30% from baseline. In Part 2, cPKU participants had a statistically significant ($p<0.0001$) reduction in blood Phe after 6-weeks of sepiapterin (68.95%; Baseline blood Phe: 761 µmol/L; Weeks 5-6 blood Phe: 238 µmol/L) vs. placebo (+3.45%; Baseline blood Phe: 772 µmol/L; Weeks 5-6 blood Phe: 729 µmol/L). Treatment with sepiapterin was well tolerated. ***CONCLUSION:*** Results demonstrate sepiapterin as an effective oral treatment for children and adults with PKU, including cPKU.

P-018 - AN EXPLORATORY UNTARGETED SERUM METABOLOMICS STUDY IN TREATED TYROSINEMIA TYPE 1 PATIENTS: UNCOVERING NOVEL ALTERATIONS IN METABOLIC PATHWAYS.

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INTRODUCTION: Liver disease is a significant clinical feature of Tyrosinemia type 1 (HT-1), characterized by the accumulation of toxic metabolites due to disruption in the tyrosine catabolic pathway. Nitisinone (NTBC) treatment promptly diminishes the accumulation of detrimental metabolites and restores liver function. This study aimed to characterize the metabolomic profile of patients with hereditary tyrosinemia type 1 (HT-1) undergoing active treatment with nitisinone (NTBC) to better understand the metabolic alterations in wellcontrolled patients. ***METHODS:*** High-resolution untargeted metabolomics (LC-MSMS) was performed in serum samples of 16 HT-1 Chilean patients treated with NTBC (1mg/kg/day) and 16 age- and sex-matched controls. The statistically significant ($p<0.05$; log2FC >|1|) up- and down-regulated features were annotated and associated with different metabolic pathways using MetaboAnalyst. Identification of relevant biomarkers for group classification was performed using Multivariate Exploratory ROC Analysis. ***RESULTS:*** The metabolic profile of NTBC-treated HT-1 patients differs significantly from that of control subjects. Ninety-two serum metabolites were identified as significantly increased in HT-1 patients, with the most impacted pathways being related to tyrosine, phenylalanine, and tryptophan metabolism. An increase in indole-based compounds was also observed, which has been previously described as a consequence of NTBC treatment. As a novel finding, a group of nine bile acids were elevated, including unconjugated, glycinated, and sulfated forms, as well as numerous unsaturated medium and long-chain

acylcarnitines (C10-C18). Regarding decreased metabolites in HT-1 patients, 74 were identified, predominantly from the phospholipid class. Through multivariate analysis, 15 metabolites were identified as the most significant to differentiate HT-1 patients from control ***DISCUSSION:*** This study characterized the metabolomic profile of patients under active treatment with NTBC to deeply understand the metabolic alteration in treated patients. The findings confirm previous observations regarding the disruption of tryptophan metabolism by NTBC treatment. Additionally, alterations in other metabolic pathways and biomarkers were identified, which could potentially be associated with NTBC dosage, duration of exposure to the medication, and progression of liver disease, as revealed by changes in bile acids and lipids. The impact of these metabolites on the hepatobiliary system function and their association with major liver complications, such as hepatocarcinoma, should be further evaluated.

P-019 - MACHINE LEARNING APPLIED IN TYROSINEMIA TYPE-1: IDENTIFYING LABORATORY BIOMARKERS FOR PREDICTING ALTERATION OF ALPHA-FETOPROTEIN AND THE RISK OF DEVELOPING HEPATOCARCINOMA IN CHILEAN AND ITALIAN COHORTS.

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INTRODUCTION: Hepatocellular carcinoma (HCC) is a major complication of late-diagnosed Tyrosinemia type 1 (HT-1). Alpha-fetoprotein (AFP) and liver imaging are used for HCC detection, but their efficacy in early-stage HCC is limited. This study aims to develop a machine learning (ML) approach to identify key routine laboratory variables for predicting AFP level changes and assessing HCC risk in HT-1. ***METHODS:*** A predictive machine learning (ML) model was built to assess the importance of follow-up variables in predicting abnormal levels of alpha-fetoprotein (AFP >5ng/mL). Data from HT-1 patients who either developed or did not develop hepatocellular carcinoma (HCC) were collected across three cohorts: INTA-Universidad de Chile (131 records, from 20 patients), Ospedale Pediatrico Bambino Gesù in Rome (50 records, from 6 patients), and Meyer's Hospital in Florence, Italy (38 records, from 5 patients). The analyzed variables were age at diagnosis, current age, NTBC (2-[2-Nitro-4-(trifluoromethyl) benzoyl]-1,3-cyclohexanedione) levels, succinylacetone, AFP, phenylalanine, methionine, tyrosine, transaminases (ALT, AST), GGT, prothrombin time, total bilirubin, alkaline phosphatase, and glycemia levels. Biochemical or molecular tests confirmed the diagnoses of all patients. All patients were under NTBC treatment for at least one year. Patients from the Florence cohort were the only ones diagnosed by newborn screening. ***RESULTS:*** The ML-based approach revealed that the variables transaminase ALT, alkaline phosphatase, age at the time of diagnosis, and current age were the most important clusters of variables for predicting altered AFP levels. Additionally, through the analysis of receiver operating characteristics (ROC), a cut-off value for ALT of 29 U/L (AUC 0.73) was established to discriminate the risk of developing or not HCC. ***DISCUSSION:*** In this study, we applied ML models to predict HCC progression by detecting altered alpha-fetoprotein (AFP) levels using variables collected during the follow-up of HT-1 patients. The model successfully identified previously described variables as the most influential in detecting HCC progression. Furthermore, additional variables critical for predicting elevated AFP levels were identified, potentially enhancing the early detection of HCC in patients with HT-1.

P-020 - CLINICAL, BIOCHEMICAL AND MOLECULAR CHARACTERISTICS OF PATIENTS WITH GLUCOGENOSIS ASSISTED IN THE PUBLIC MATERNAL CHILDREN'S HOSPITAL OF SALTA

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INTRODUCTION: Glycogen storage diseases (GSD) encompass a spectrum of hereditary disorders characterized by defects in carbohydrate metabolism pathways involving glycogen synthesis or breakdown enzymes. There are fifteen known types of GSD, categorized by specific enzymatic deficiencies and their target tissues—liver, muscle, or both—resulting in variable clinical presentations. The overall incidence of GSD ranges from 1: 20,000 to 1: 43,000 live births, typically following an autosomal recessive inheritance pattern, except for phosphorylase kinase deficiency (GSD type IX), which exhibits X-linked inheritance.

OBJECTIVE: This study aims to describe the clinical, biochemical, and molecular features of a case series of patients with Glycogenosis. ***MATERIALS AND METHODS:*** This observational, descriptive, and retrospective study utilized digitized clinical records and molecular analysis. ***RESULTS:*** We present the follow-up of 7 patients: 3 females and 4 males aged between 1 and 25 years. The cohort comprised 2 patients with glycogenosis type IX from native ethnic groups, and 5 other patients classified with glycogenosis type III with 2 siblings (1 male and 1 female). Clinical manifestations at diagnosis included hepatomegaly, growth retardation, and hypoglycemiarelated seizures in 2 patients. Laboratory findings indicated hypoglycemia, ketosis, hyperlipidemia, and elevated liver enzymes. Diagnostic studies encompassed general laboratory tests, glucagon tests, and molecular analysis. Regarding molecular variants, a panel of *AGL* genes (amylo-alpha-1, 6-glucosidase, 4-alphaglucanotransferase) and PHKA2 (Phosphorylase Kinase regulatory subunit alpha 2) were studied. Patient 1: AGL: c.2711_2716 delinsCAAAGGATCTGAT (p.Leu904Profs*11) - Pathogenic; AGL: c.2547-14 A>G - VUS; Patient 2: AGL: c.3216_3217delGA (p.Glu1072Aspfs*36) - Pathogenic - Homozygosity; Patient 3: AGL: c.3980G>A (p.Trp1327*) Pathogenic - Homozygosity; Patient 4 and 5 (siblings): AGL: c.3326G>A (p.Gly1109Asp) - VUS; AGL: c.2711_2717del7ins13- Probably Pathogenic; Patient 6: PHKA2: c.3373G>A (p.Glu1125Lys) - Probably Pathogenic - Hemizygosity; Patient 7: PHKA2:. c.2598-1G>A Probably Pathogenic – Hemizygosity The results found variants of uncertain significance (VUS), probably pathogenic and pathogenic and some are not described in the literature. Regarding treatment, they receive a fractionated diet, with slow reléase carbohydrates and protein supplementation. ***CONCLUSIONS:*** Glycogen storage diseases are rare in Argentina, and diagnosis remains primarily clinical, supported by suggestive laboratory findings. Molecular data provided insights into genetic variants within our population, highlighting the importance of genetic counseling.

P-021 - CONTINUOUS GLUCOSE MONITORING IN GLYCOGEN STORAGE DISEASES: THE BRAZILIAN EXPERIENCE AND LITERATURE REVIEW

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INTRODUCTION: Hepatic glycogen storage diseases (GSDs) are a group of inherited metabolic disorders characterized by deficient glycogen metabolism, leading to severe hypoglycemia with a life-threatening risk. Continuous glucose monitoring (CGM) offers a promising tool for managing these patients by providing realtime glucose levels and trends. It has been considered one of the top 10 research priorities in GSDs by healthcare providers and patient representatives. ***OBJECTIVES:*** This study aims to report the Brazilian experience with CGM in patients with GSDs and review the available evidence. ***MATERIALS AND METHODS:*** This study comprises an experience report and we reviewed existing literature and regulatory aspects on CGM in GSDs. Databases consulted included PubMed, Scopus, and Scielo, using terms “continuous glucose monitoring” and “glycogen storage disease”. We also conducted an experience report based on the multidisciplinary management of >100 Brazilian patients with hepatic glycogen storage diseases. ***RESULTS:*** In the Brazilian experience, only the flash glucose monitoring (FGM) device is available, with high costs and limited access. This FGM device was approved by ANVISA (Brazilian Health Regulatory Agency) for adults and children aged 4 to 17 years. Systematic provision through the public health system or private health insurance is not currently available, according to the National Supplementary Health Agency. Other types of CGM devices are available only in specific research contexts.. Approximately 20% of patients with GSDs in Brazil use FGM, demonstrating a concern for better metabolic control and the risk of hypoglycemia. The literature review identified only five studies published between 2014 and 2022 on the use of CGM in GSDs, with sample sizes ranging from 12 to 42 individuals. Advantages of these devices included better metabolic control, selfmanagement of care, and improved safety. Disadvantages include high cost, lack of availability, and the absence of alarms in the available FGM device. ***CONCLUSIONS:*** We highlight the importance of CGM, not only in diabetes but also for IEM with hypoglycemia, such as GSDs. However, only a small percentage of patients have access the technology, which could be an excellent adjunct in adequate nutritional management, preventing overweight and metabolic decompensation.

P-022 - GLUCOGENOSIS IN COLOMBIA, CLINICAL AND MOLECULAR ANALYSIS OF THE CASUISTICS OF A REFERENCE CENTER FOR INBORN ERRORS OF METABOLISM

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Glycogen accumulation disorders or glycogenosis present challenges in treatment due to the lack of knowledge of these disorders. This work seeks to describe and analyze the clinical and molecular characteristics of 37 patients diagnosed with glycogenosis, currently treated in a group of inborn errors of metabolism (IEM) in a reference center in Colombia. ***METHODOLOGY:*** Retrospective cross-sectional descriptive study. Inclusion Criteria: Diagnosis of glycogenosis, currently followed by 2 or more specialties of the IEM group. Exclusion criteria: Less than 3 follow-up visits, less than 2 follow-ups even if there was a molecular diagnosis, 4 or more years without follow-up. A cohort of 37 patients with glycogenosis is described, 34 of them with molecular diagnosis; 67% of the population from 0 to 15 years old. The types of glycogenosis found were: I, II, III, IV, V, IX and XI. The most frequent were IIIa and IIIb, (43%), followed by type IX a and c with 21% and type I in 4 patients, all of them type Ia. The 3 patients with glycogenosis type II received enzyme replacement therapy; 2 patients were described with glycogenosis type V, both in adulthood. One patient underwent liver transplantation, with a molecular diagnosis of glycogenosis type IV. Regarding the clinical evolution, it was found that the 3 patients with glycogenosis type XI all had the same mutation but with variable clinical presentation. Of the 25 patients between 0 and 15 years old, 88% did not have clinical or biochemical symptoms suggestive of hypoglycemia, 60% did not have height impairment and 18% present with neurological symptoms (glycogenosis type Ia, II, IIIb, IX and XIa). Of this cohort, 62% of the patients were able to receive a follow-up of less than 6 months, but among the barriers found, those of a socioeconomic nature such as difficulties in obtaining appointments and food were significant, probably in relation to the sociocultural factor.

P-023 - PHKA2-RELATED GLYCOGEN STORAGE DISEASE TYPE IXA: CLINICAL MANIFESTATIONS AND GENOTYPE OF TWO FAMILIES FROM CARTAGENA, COLOMBIA

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INTRODUCTION: Glycogen storage disease type IXa (GSD IXa) (MIM: 306000), is an X-linked genetic disorder caused by a defect in phosphorylase b kinase (PhK) due to a heterozygous mutation in the *PHKA2* gene. Patients typically present with recurrent ketotic hypoglycemia and growth retardation, but some may only exhibit simple hepatomegaly. Despite being one of the most common causes of GSD, the biochemical and genetic diagnosis of GSD IXa has been challenging due to its rarity, phenotypic overlap with other types of GSD, and genetic heterogeneity. ***OBJECTIVE:*** To identify and describe the different clinical manifestations in two families with different types of mutations in the *PHKA2* gene (GSD IXa), representing the first reported cases in Cartagena, Colombia. ***MATERIALS AND METHODS:*** Two members of one family (mother and son) and four members of another family (mother, two brothers, and one sister on the maternal side) from Cartagena, Colombia, were studied. They were initially studied in the biochemistry laboratory of the University of Cartagena, with the males mainly showing growth retardation, hepatomegaly, hypoglycemia, mixed dyslipidemia and increased transaminases, highly suspicious of having glycogenosis, while mothers and the daughter of one of them are asymptomatic. Additionally, genetic studies were conducted at the Center for Molecular Disease Diagnosis (CEDEM) in Madrid, Spain, including mass studies, sequencing analysis, bioinformatics analysis, mutation bioinformatics analysis, and confirmation by Sanger sequencing ***RESULTS:*** We present the cases of two families in which GDSIXa was confirmed. The first family exhibited the c.2746C>T mutation, a likely pathogenic variant. The other family showed the c.919-2A>G mutation in heterozygosity for the mother and daughter, and in hemizygosity for the two brothers in the *PHKA2* gene, representing a novel variant of this gene. ***CONCLUSIONS:*** GSD IXa due to phosphorylase kinase (PhK) deficiency is the most common subtype of GDS IX. Currently, the patients are asymptomatic and have not required treatment, so the GSD IXa they present is a benign condition and whose clinical manifestations improve with age. Finally, with the advent of NGS technologies, as used in this study, we have confirmed its diagnosis, avoiding the use of invasive procedures such as liver biopsy.

P-024 - BIOCHEMICAL AND MOLECULAR DIAGNOSIS OF BETA KETOTHIOLASE DEFICIENCY IN A PATIENT WITH IDIOPATHIC LACTIC ACIDOSIS

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INTRODUCTION: Beta-ketothiolase deficiency is a rare autosomal recessive disorder of isoleucine catabolism affecting ketone body metabolism. Characterized by intermittent keto acidotic episodes associated with clinical signs and symptoms of toxic encephalopathy, with an onset during infancy or toddlerhood. Enzyme deficiency is caused by mutations in the *ACAT1* gene. ***OBJECTIVE:*** To demonstrate the importance of the analysis of acylcarnitines and organic acids in the management of patients with idiopathic ketoacidosis and high lactate. ***CASE PRESENTATION:*** A 9-month-old female was taken to the emergency room due to respiratory distress, after experiencing rhinorrhea and cough, followed by vomiting, irritability, refusal to eat, weakness and flaccidity. On evaluation, she presented with Kussmaul's breathing and altered state of consciousness. The chest x-ray reported a peri-hilar reticular interstitial pattern compatible with pneumonia of viral etiology. Arterial blood gases: pH 6.8, bicarbonate 3.2 mmol/L, lactate 7.5 mmol/L, anion gap 30.1, ammonium 55 µmol/L, euglycemia (90 mg/dL). Urine test: ketones >160 mg/dL (+++). A diagnosis of lactic acidemia, with a high anion gap, ketonuria and normal blood glucose, was included. Presence of *Staphylococcus aureus* in tracheal aspirate cultures. Intubation, fluid replacement, bicarbonate infusion was decided, and fasting without improvement. She presented acute kidney injury and upper gastrointestinal bleeding. No neuroimaging study was performed. Acylcarnitines profile tandem mass spectrometry due to suspicion of organic acidemia, reporting elevation of acylcarnitines C3DC+C4OH= 0.47 µmol/L (<0.27 µmol/L) and the ratio C3DC+C4OH/C5DC+C6OH= 3.22 µmol/L (<1.80 µmol/L). The organic acids in urine by gas chromatography – mass spectrometry reported elevation of tiglilglycine, 3-hydroxybutyric, 2-methyl-3-hydroxybutyric, 3-hydroxyisovaleric and lactic acid. Both studies confirm beta-ketothiolase deficiency. The molecular study revealed 2 variants in the *ACAT1* gene, a pathogenic one c.473A>G (p.Asn158Ser) and another of uncertain significance c.826+3_826+6del (intronic, affecting the splicing site, not previously reported and in silico predictors proposed it as deleterious). After the acute episode in intensive care, on the 6th day she was extubated without incidents and the 20th day she was discharged with levocarnitine and dietary restriction. CONCLUSION. In pediatric patients with ketoacidosis, Biochemical test for the diagnosis of inborn errors of metabolism should be considered for timely treatment and genetic counseling.

P-025 - CHILEAN CASES OF MITOCHONDRIAL 3-HYDROXY-3-METHYLGLUTARYL-COA SYNTHASE DEFICIENCY: SERIE OF FIVE CLINICAL CASES

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BACKGROUND: Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2) deficiency is a very rare inherited disorder of ketone bodies synthesis. This autosomal recessive condition is cause by pathogenic variants in the *HMGCS2* gene (1p12), which encodes the enzyme that catalyzes the first irreversible step in ketogenesis by converting acetyl-CoA to acetoacetyl-CoA to form HMG-CoA. The hallmark of this disorder is hypoketotic hypoglycemia, typically triggered by catabolic episodes in infancy, which if untreated can lead to death. ***OBJECTIVES:*** The aim is to report the clinical phenotype of five Chilean patients with HMGCS2 deficiency. ***PATIENTS AND METHODS:*** The clinical information was collect retrospectively. ***CLINICAL CASES:*** We report five patients, three males and two females, with current ages ranging from four to 25 years. All cases presented with severe fasting hypoglycemia, between one to three years of age, hypoketonemia was associated in all patients, except one. Mild transient liver dysfunction was observed in two patients, low plasma free carnitine in one case. The episodes were triggered by infections associated with prolonged fasting. All patients responded to parenteral glucose administration in the initial critical episode. The molecular study identified biallelic variants in *HMGCS2* gene in all patients, one of these variants (c.1262T>G) is shared by all five patients. After the acute episode at debut, no patient has had new clinical events, including the patient with the longest follow-up of 23 years. ***CONCLUSION:*** HMGCS2 is a very rare, life-threatening disorder, however easily treatable if suspected early. Both the clinical and biochemical phenotype is nonspecific, which makes its diagnosis difficult. Therefore, it should always be considered in the differential diagnosis of hypoglycemia. This nonspecific phenotype could contribute to underdiagnosis. In our series it is evident that the first years of life are the ones with the highest risk of acute episodes, evolving asymptomatic later.

P-026 - CLINICAL AND BIOCHEMICAL IMPROVEMENT OF A PATIENT WITH SHORT-CHAIN ENOYL-COA HYDRATASE DEFICIENCY TREATED WITH TRIHEPTANOIN.

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INTRODUCTION: Short-chain enoyl-CoA hydratase (ECHS1) is involved in fatty acid and amino acids catabolism in mitochondria, and its deficiency causes Leigh syndrome. ECHS1 deficiency is a very rare inborn error of metabolism in which a valine-restricted diet and supplementation with N-acetylcysteine have been used as treatment. However, despite treatment, clinical complications continue. A recent study postulated triheptanoin (a 7-carbon oil used to treat various fatty acid oxidation disorders) as part of the treatment of ECHS1 due to its anaplerotical function. ***OBJECTIVE:*** To describe the clinical and biochemical outcomes of an ECHS1 patient treated with triheptanoin. METHODS AND ***MATERIALS:*** Retrospective descriptive analysis of one case. ***RESULTS:*** Full-term female born to non-consanguineous parents. At 3 months old, neurodevelopmental regression was observed. She presented Leigh syndrome with hypotonia, anorexia, failure to thrive, poor motor skills, and poor social interactions. A whole exome analysis showed two pathogenic variants in the *ECHS1* gene. A restricted diet started at 16 months old; valine was calculated to provide 55-60 mg/kg/d. N-acetylcysteine was supplemented at 70 mg/kg/d to avoid reduced activity of cysteine containing enzymes like pyruvate dehydrogenase (PDH) and respiratory chain enzymes. Despite treatment, she continued with multiple hospitalizations. At 48 months old, triheptanoin (Dojovi®, Ultragenyx Pharmaceuticals) was initiated at 5% of total daily energy, gradually increasing it to 14%, and divided into 3-4 doses. It was well-tolerated, and only nausea was reported. Since triheptanoin was started, the patient has remained clinically stable; she has not been hospitalized, and she is more active and reactive, with a better sleep pattern. Biochemically, a decrease in creatine phosphokinase-MB (CK-MB) levels was observed from 38 to 11.8 U/L (normal 1-16 U/L), as well as an improvement in the left cardiac ventricular ejection fraction from 42 to 63% (normal 55-70%), and in the fractional shortening from 22 to 31% (normal >28%). Her body mass index (BMI) Z-score and blood valine levels remained normal. ***DISCUSSION AND CONCLUSION:*** After triheptanoin initiation, a significant clinical improvement was observed. The cardiac ejection fraction and CK-MB levels were normalized. Due to its anaplerotical functions, triheptanoin should be considered part of the treatment of ECHS1 deficiency.

P-027 - LONG-CHAIN FATTY ACID BETA-OXIDATION DEFECTS: A CASE SERIES

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INTRODUCTION: Fatty acid beta-oxidation defects (FAOD) are a subgroup of lipid myopathies with heterogeneous presentations. Clinical presentation may manifest as muscular weakness, cramps, postexercise myalgias, and episodic rhabdomyolysis in children or adults. ***OBJECTIVE:*** to describe clinical, biochemical, anatomopathological and molecular manifestations in a series of patients with FAOD from Argentina. ***MATERIALS AND METHODS:*** A total of seven patients with carnitine palmitoyltransferase-2 (CPT II), very-long-chain acyl-CoA dehydrogenase (VLCAD) and long-chain 3-hydroxyacyl-CoA dehydrogenase LCHAD deficiency were reported. ***RESULTS:*** In this series, the mean age at diagnosis was 31.2 years and the mean time from symptom onset to diagnosis was 16 years. All patients in this series consulted pediatricians, general practitioners, rheumatologists, and orthopedists for years, underscoring the need to disseminate these presentation patterns across various medical specialties. In 6 out of 7 patients, muscle pain occurred some hours after starting physical activity, and rhabdomyolysis episodes were precipitated by prolonged exercise, fasting, cold weather, or fever. CPK peak level (media) during rhabdomyolysis episodes was 30.000 UI (range 6000-112000 UI). Just 2 out of 7 (VLCAD and LCHAD deficiency) showed fixed weakness, the other cases presented normal physical examination out of rhabdomyolysis episodes. Even though CPTII and VLCAD deficiency are recessive disorders, in 2 cases we could find just one pathogenic variant, but the presence of typical clinical manifestations, pattern of acylcarnitine profile and muscle biopsy confirmed the diagnoses. ***CONCLUSIONS:*** The definite diagnosis of metabolic myopathies due to FAOD requires an understanding of clinical, biochemical, neurophysiological, and muscular imaging/biopsy patterns. Early diagnosis and treatment using traditional

diets and new pharmacological strategies not only enhance quality of life but also improve survival in these patients.

P-028 - NUTRITIONAL MANAGEMENT OF AN INFANT DIAGNOSED WITH AND SUCCESSFULLY TREATED FOR CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY (CPT-II)

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BACKGROUND: Carnitine Palmitoyltransferase II (CPT-II) deficiency is an inherited metabolic disorder that affects the mitochondrial oxidation of long-chain fatty acids (LCFA). Nutritional treatment is based on adapting the profile and type of fats: total fats 20-30%, LCFA ≤ 10% of total caloric value, and the rest consisting of medium-chain fatty acids (MCT). Prolonged fasting should be avoided and carnitine supplementation is advised. ***CASE REPORT:*** We present a full-term female infant with a suspected CPT-II diagnosis on newborn screening, and later confirmed. Birth weight was 3.614 kg (77th percentile), height 49 cm (41st percentile), and head circumference 34 cm (45th percentile). Both parents were of Moroccan origin, non-consanguineous, and the mother spoke only Arabic. Feeding was initiated with Monogen-8 bottles daily- and MCT (4 doses), supplemented with breast milk. The dietary characteristics were explained to the father, and bi-monthly checkups were scheduled. At 6 months, weaning began with vegetables, tubers, cereals, fruits and animal protein. At 8 months, the patient required hospitalization for metabolic decompensation due to a viral infection. Nutritional history revealed that the prescribed diet was not strictly followed, as the mother did not understand the disease and dietary information was translated by the father. In response, the diet was reformulated: 1000 kcal, 10.6% protein, 28% total fat (MCT: 27.16g, LCFA: 5g), 61.4% carbohydrates. The new regimen included 5 daily meals and 2 nighttime feedings (Monogen) along with four doses of 5 ml MCT. A pictogram-based diet was designed to enhance the understanding of the foods to be provided at each meal. Nutritional education for the mother was conducted using images, and the father's understanding was verified. Currently, the diet is strictly followed and there have been no further hospitalizations. Moreover, the patient's growth is appropriate for her age. ***CONCLUSIONS:*** Individualizing the diet and educational materials provided to parents is crucial for effective metabolic control in pediatric patients, especially when dealing with patients from a different cultural

P-029 - SEARCH FOR NEW DIAGNOSTIC TOOLS IN MEDIUM-CHAIN ACYL COA DEHYDROGENASE DEFICIENCY

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INTRODUCTION: Medium-chain acyl CoA dehydrogenase deficiency (MCAD) is an autosomal recessively inherited disorder of mitochondrial fatty acid oxidation characterized by a rapidly evolving metabolic crisis. Treatment is to avoid fasting and medium chain triglycerides. The diagnosis is made by the characteristic abnormal pattern of acylcarnitines (increased C6, C8 and C8/C10 ratio) and metabolites in the urine. Confirmation is obtained by analyzing the variants. Currently, it is included in neonatal screening programs. ***OBJECTIVE:*** Analyze the acylcarnitines and relationships currently used for the diagnosis of MCAD and propose new relationships (NR) as diagnostic tools. ***MATERIALS AND METHODS:*** 84 acylcarnitine profiles were analyzed from 18 MCAD patients (pMCAD) with molecular confirmed diagnosis, 58 patients with normal profiles (NP) and 28 doubtful profiles (DP) whose selection criterion was C6, C8 and/or C10: 1 above the cut-off value. Using traditional profiles and relationships and incorporating long-chain acylcarnitines, relationship of Wang et al. (C8/C14: 1) is evaluated and 5 NR are proposed to analyze their possible diagnostic power. Ratios: (C6+C8+C10: 1)/C14: 1; (C6+C8+C10: 1)/(C14: 1+C10); (C6+C8+C10: 1)/C10; (C6+C8+C10: 1)/(C12+C10) and (C6+C8+C10: 1)/(C14: 1+C10+C12). ***RESULTS:*** In the pMCAD, 71.4% had elevated C6, 97.6% elevated C8 and 85.7% C10: 1, all with elevated C8/C10 and C8/C12 ratios. No acylcarnitine was elevated in the NP, 67.2% had an elevated C8/C12 ratio. In DP, 21.4% C6, 82.1% C8 and 75% C10: 1 were elevated, with 7.1% C8/C10 ratios elevated and 75% C8/C12. Using the NR, the NP did not exceed the minimum values, except for the elevated C6+C8+C10: 1/C10 ratio in 6 patients (10.3%). In the DP population, 3 of the NR did not exceed the minimum

values, with the ratio (C6+C8+C10: 1)/(C14: 1+C10+C12) having the best predictive and statistical value. ***CONCLUSION:*** MCAD deficiency can be misdiagnosed based on primary markers of acylcarnitine or the C8/C10 ratio. Wang et al propose using C8/C14: 1 which was not shown to differentiate the populations. The analysis of the NR excludes some of them as a possible diagnostic tool for MCAD. It is necessary to use other populations to validate use of the NR (C6+C8+C10: 1)/(C14: 1+C10+C12) as a complementary secondary marker of MCAD.

P-030 - ARTIFICIAL INTELLIGENCE APPLIED TO THE INTERPRETATION OF DE NOVO AND UNREPORTED GENETIC VARIANTS: A CASE REPORT OF FAMILIAL HYPERCHOLESTEROLEMIA DUE TO APOB

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INTRODUCTION: Familial Hypercholesterolemia (FH) is a genetic metabolic disorder characterized by elevated levels of low-density lipoprotein (LDLc) in the blood and an increased risk of premature atherosclerotic disease. It is caused by pathogenic variants in autosomal dominant inheritance genes such as *LDLR, APOB, LDLRAP1*, and *PCSK9*. New genes have been described, including *APOE, LIPA, STAP1, ABCG5*, and *ABCG8*, with autosomal recessive inheritance, as well as de novo cases. It has a prevalence of 1 in 300 individuals. Most patients do not present clinical manifestations, which complicates diagnosis. ***OBJECTIVE:*** To promote, through the report of a clinical case of hypercholesterolemia, the application of artificial intelligence for the classification of unknown or reported variants as uncertain. CLINICAL CASE We describe the case of a 15-year-old female with a non-consanguineous background, non-syndromic phenotype, on physical examination without signs of insulin resistance, no signs of metabolic syndrome and absence of xanthelasmas, corneal arcus, or xanthomas, but with screening indicating LDLc levels >450 mg/dl in 3 samples; ; no known family history of severe hypercholesterolemia or cardio-cerebrovascular diseases; suspected alteration in genetic lipid metabolism, molecular study via NGS + CNV sequencing detected a variant in the *APOB* gene, previously reported in ClinVar with a single entry as uncertain, not reported in ClinGen or other databases; with only 4 individual predictors, in-silica with uncertain, moderate, and strong benign meanings; with very low population frequency given by gnomAD v.4.0, ExAC, TOPMed, reinforces the need to search for other tools supporting the interpretive process, through data integrators, annotations, genomic browsers in other species, protein, genetic, ontological studies, and artificial intelligence, learning that the substitution occurs in a highly conserved position within the APOB protein, suggesting functional and structural implications, interaction with lipoproteins, effects on secretion and metabolism. ***CONCLUSION:*** The application of artificial intelligence as an ally to different genetic diagnostic tests expands our knowledge about de novo variants or variants of uncertain significance, in addition to enabling us to apply the concept of 7P medicine that is personalized, predictive, precise, preventive, participatory, and proactive for potential population-level application.

P-031 - FIRST CASE REPORT: WOLMAN DISEASE WITH COMPOUND HETEROZYGOUS GENOTYPE IN COLOMBIA

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INTRODUCTION: Wolman's disease is caused by pathogenic variants in the *LIPA* gene, resulting in decreased or null activity of the acid lipase enzyme. This condition leads to the accumulation of cholesterol esters, causing organomegaly, renal calcifications, and malabsorption. Clinical presentation includes steatorrhea, abdominal distension, adrenal insufficiency, and lipid deposits in the intestinal tract. ***OBJECTIVE:*** To describe the first case of Wolman disease with a compound heterozygous genotype in Cali, Colombia, and to analyze the genotype-phenotype correlation using molecular and AI tools. ***CLINICAL CASE:*** A 15-year-old patient had hepatomegaly since the first year of life, with persistent increased echogenicity of the parenchyma, portal vein, and patent suprahepatic artery, hyperthyroidism, hyperlipidemia, chronic hepatitis, vasculitis limited to the skin, splenomegaly, frequent hematomas, and epistaxis. Whole exome sequencing was conducted. The study identified variants in the LIPA gene: c.894G>A (p.Gln298Gln) and c.398delC (p.Ser133fs) in compound heterozygosity of the transcript NM_000235.4. The p.Gln298Gln variant was reported in ClinVar with multiple pathogenic presentations and in databases like

gnomAD (*f*=0.000762), with bioinformatics softwares (Combined Annotation Dependent Depletion, dbscSNV, MaxEnt Scan) predicted a moderate pathogenic effect. AI tools (GenAI, VarChat, AlphaFold) described splicing alterations resulting in enzymatic activity of only 3-5%. The p.Ser133fs variant was reported in ClinVar with 6 pathogenic presentations and was listed in gnomAD (*f*=0.0000723). AI described the early termination of the amino acid sequence, giving rise to a truncated protein causing loss of enzymatic function. ***CONCLUSIONS:*** We reported a female patient carrying two pathogenic variants in compound heterozygosity not previously described. One copy of the gene produced a minimal amount of functional enzyme due to the c.894G>A variant, while the other copy produced a truncated and non-functional protein due to the c.398delC variant, resulting in extremely low or no enzymatic activity of acid lipase. This is the first case report of a patient with these variants in compound heterozygosity presenting an attenuated clinical manifestation. The penetrance of these variants explains the variability in symptom severity from mild to moderate. The genotype-phenotype correlation facilitates early detection programs and targeted treatments, reducing morbidity and mortality, moving towards precision medicine.

P-032 - NOVEL HOMOZYGOUS MUTATION IN DGAT1 GENE AS CAUSE OF CONGENITAL DIARRHEA

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INTRODUCTION: Diacylglycerol-acyltransferase 1(DGAT1) deficiency is a rare inherited disorder causing congenital diarrhea. It has been associated with mutations in the *DGAT1* gene. The enzime catalyzes intestinal formation of triacylglycerol from diacylglycerol and acyl-CoA. Diarrhea seems to be related to abnormal fat absorption and buildup of *DGAT1* substrates in the intestinal mucosa. Characterized by early-onset vomiting and/or chronic, noninfectious, nonblood watery diarrhea associated with protein-losing enteropathy that produces hypoalbuminemia and hypogammaglobulinemia. ***OBJECTIVES:*** To describe a case of DGAT1 deficiency diagnosed in our institution. ***MATERIAL AND METHODS:*** We describe the clinical and biochemical findings of the first case of DGAT1 deficiency managed at Rebagliati Hospital of Lima, Peru. ***RESULTS:*** A 6-month-old male was brought to our hospital, owing to diarrhea, vomiting and poor weight. He was the first child of unrelated parents born by caesarean section due to preeclampsia, weighed 3,7 kg at birth. Three days after birth, he developed vomiting and non-bloody, watery diarrhea, daily that have persisted until admission to the hospital. Due to the predominance of vomiting, it was suspected intestinal subocclusion and underwent correction of partial gastric volvulus, however the symptoms persisted. Severe allergic enteropathy was suspected, so an amino acid-based formula was started. Given the persistence of symptoms and the difficult progression of the oral route, he received parenteral nutrition. Subsequently, he exhibited protein-losing enteropathy, with stool α1 antitrypsin >112ng/ml (normal, < 26,8), hypoalbuminemia, hypogammaglobulinemia and vitamin D deficiency. He required prolonged parenteral nutrition and intermittent infusions of albumin. Stomach, duodenum, and colon biopsies were negative for chronic granulomatous disease, autoimmune enteropathy, and food protein-induced enterocolitis. Given the persistence of severe intractable diarrhea with malnutrition a genetic panel for primary immunodeficiencies was performed. A novel homozygous pathogenic variant c.530_531del (p.Cys177Phefs*10) was identified in the *DGAT1* gene which we attributed the cause of the diarrhea. The transition to a formula containing 85% medium-chain triglyceride reduced the stool frequency. He died at 33 months of age from complications of malnutrition and sepsis. ***CONCLUSIONS:*** We identified a patient with a novel homozygous mutation in *DGAT1* gene as cause of congenital diarrhea.

P-033 - SJÖGREN'S SYNDROME - LARSSON: ANALYSIS OF TWO PEDIATRIC CLINICAL CASES.

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INTRODUCTION: Sjögren-Larsson syndrome is a rare autosomal recessive inborn error of lipid metabolism, with a prevalence ≤0.4 per 100,000, caused by mutations of the *ALDH3A2* gene that codes for the fatty aldehyde dehydrogenase. Deficiency of this enzyme causes an

accumulation of fatty alcohols and fatty aldehydes, leading to altered cell-membrane integrity. Clinically, is a neurocutaneous disorder usually characterized by congenital ichthyosis, intellectual disability and spasticity. It may be associated with ocular alterations. The diagnosis is carried out through the determination of FALDH activity in cultured fibroblasts or mutation analysis of the *ALDH3A2* gene. ***OBJECTIVE:*** To report two cases of Sjögren-Larsson syndrome with pathognomonic clinical signs but differences in their clinical-neuroimaging presentation. Clinical case 1. A 7year-old, male patient, with ichthyosis with hyper-linearity in the neck and wrists, pruritus, and spastic paraparesis. Developmental evaluation at 4 years of age detected neurocognitive development within normal limits, with motor impairment with speech and oral praxis compromised. Magnetic resonance imaging (MRI) showed increased intensity in bilateral periventricular frontal and parieto-occipital white matter on T2/FLAIR sequences. Optical coherence tomography exhibited punctiform hyperreflectivities that corresponds with macular crystals. Genetic study identified two variants in the *ALDH3A2* gene: exon7: c.1047delA; exon10: c.1443+1G>A. Clinical case 2: A 17-year-old, male adolescent with congenital ichthyosis, nocturnal pruritus, delayed motor development, moderate intellectual disability, spastic paraparesis. Eye fundus showed retinal abnormalities. MRI at 2 years of age evidenced increased intensity in the white matter on T2/FLAIR sequences, which were difficult to appreciate in a new MRI at 10 years of age. Genetic study identified c.1094C>T mutation in homozygosis in the *ALDH3A2* gene. ***CONCLUSIONS:*** In these clinical cases of Sjögren-Larsson syndrome, certain atypical manifestations could be identified: case 1 presented a normal level of neurocognitive development at 4 years of age; case 2, presented minor alterations in the neuroimaging. The diagnosis makes it possible to address the associated clinical manifestations, possible comorbidities and genetic counseling.

P-034 - OLIGOGENIC DISEASE AND SYNERGISTIC HETEROZYGOSITY IN A CASE OF FAMILIAL INTRAHEPATIC CHOLESTASIS AND ERYTHROPOIETIC PORPHYRIA.

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INTRODUCTION: Congenital metabolic errors can represent a diagnostic challenge, next-generation sequencing, through exome or whole-genome analysis, frequently reveals the etiology of a human condition, however, molecular tests can be inconclusive. We present a case of both familial intrahepatic cholestasis (FIC) and erythropoietic porphyria (EP) where molecular analysis partially explains the diagnosis. We hypothesize a possible case of cholestasis due to oligogenic and complex synergistic heterozygosity in cooperation with an autosomal recessive disease. ***CASE:*** A 12-month-old infant born to consanguineous parents after an uneventful pregnancy and vaginal delivery at 38 weeks, debuted at 2-days-old with neonatal jaundice due to direct hyperbilirubinemia. Laboratory tests showed: direct bilirubin: 16.7 mg/dL, indirect bilirubin: 7.4 mg/dL, and alpha-1-antitrypsin: 96.6 mg/dl. Neonatal management included phototherapy, hydrolyzed formula, ursodeoxycholic acid, vitamins D, E, K, and zinc supplementation. At 3-months-old, liver biopsy revealed abundant chronic inflammatory infiltrate with hepatocanalicular cholestasis, extramedullary hematopoiesis, and intrahepatic iron deposits, indicating alpha-1-antitrypsin deficiency. Cholestasis multigene panel identified heterozygous variants of uncertain significance (VUS) in *UGT1A1* c.211G>A and *CFTR* c.601G>A genes. At 7-months-old, liver transplant was performed due to coagulopathy with good tolerance, which improved jaundice however, resulting in purple-colored urine and erythrodontia. Trio-based whole-exome sequencing (WES) detected homozygous VUS in gene UROS c.50A>G (Asp17Gly). Follow-up tests showed elevated serum total porphyrins at 1.148,7 µg/L. ***CONCLUSIONS:*** This case involves two rare and nowadays undiagnosed metabolic diseases, presenting clinically as FIC and EP which were caused by three genes: two heterozygous variants for *UGT1A1* and *CFTR* genes and a third homozygous variant for *UROS* gene, all of them classified as VUS. We hypothesize, for FIC oligogenic inheritance and synergistic heterozygosity in two functionally related proteins with liver metabolic dysfunction and EP as a second concomitant diagnosis with elevated serum porphyrins. We recommend expanding these causal hypotheses towards either the widely segregation analysis, reclassification of these genetic findings by bioinformatic or functional analysis under oligogenic disease (biallelic or triallelic) hypothesis, where different synergizing genes acting on the same functional pathway and causing FIC phenotype and EP as

a second disease, which is supported by purple-colored urine, erythrodontia and elevated porphyrins.

P-035 - UNRAVELING PHENOTYPES IN GENETIC CUTANEOUS PORPHYRIAS: THE IMPACT OF NEXT GENERATION SEQUENCING SHORTENING THE DIAGNOSTIC ODYSSEY

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INTRODUCTION: Cutaneous porphyrias are a heterogeneous group of both acquired and genetic disorders whose diagnosis rely on clinical features and specific biochemical testing. In Brazil, biochemical testing for acute porphyrias become more accessible in the last years, nevertheless the same was not seen for cutaneous porphyrias, so most of the key laboratory testing are performed only abroad, increasing the costs for analysis. In this context, Next Generation Sequencing (NGS) became an important tool in the investigation of patients with genetic cutaneous porphyrias. ***MATERIALS AND METHODS:*** Prospective data of 50 Brazilian patients with suspicion of a genetic cutaneous porphyria were collected by a national referral center for rare diseases over a 2-year period. Extracted DNA samples were analyzed using a short-read next-generation sequencing gene panel. ***RESULTS:*** Mutations were identified in 45 patients. All patients with clinical features of erythropoietic protoporphyria (EPP) showed a FECH mutation on one allele trans to a hypomorphic FECH IVS3-48C allele, being classified as having pseudodominant EPP. No compound heterozygotes (recessive EPP) neither ALAS2 mutations were identified in our patients. Biallelic UROS mutations were present in three unrelated patients with features of Congenital Erythropoietic Porphyria (CEP). No UROD mutations were found in 3 patients with a strong family history for Porphyria Cutanea Tarda (PPOX and CPOX mutations were not identified as well). Two pediatric patients born to unrelated families showed biallelic mutations in *UROD* gene, confirming the diagnosis of hepatoerythropoietic porphyria (HEP) – one of the patients had a previous diagnosis of CEP and was referred for bone marrow transplant that was put on hold after the genetic diagnosis. ***CONCLUSIONS:*** This is the first report describing genetic variants for all cutaneous porphyrias in a sample of Brazilian patients. A genetic diagnosis allowed not only family genetic counseling but also changes in the management of patients whose clinical features could overlap, such as HEP and attenuated CEP patients. Our results also suggest that a comprehensive clinical history and physical exam can better guide the genetic testing, avoiding unnecessary and expensive laboratory tests which many times become a barrier to families in the pursuit of a rare disease diagnosis.

P-036 - ATYPICAL PRESENTATION OF A PATIENT WITH PYRIDOXINE-DEPENDENT EPILEPSY (PDE) Torres J, Suarez N, Mabe P

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INTRODUCTION: PDE is an autosomal recessive condition characterized by neonatal-onset seizures with developmental encephalopathy that responds to pyridoxine. Caused by pathogenic variants of ALDH7A1 gen, which encodes the α-aminoadipic semialdehyde dehydrogenase enzyme, responsible for lysine oxidation. We present a patient with an unexpected PDE diagnosis due to an atypical clinical presentation of this disease. ***CASE REPORT:*** Female patient with no relevant perinatal or family history. Non- consanguineous parents. Since the 4th day she presented focal seizures that only partially responded to phenobarbital and levetiracetam. A brain magnetic resonance imaging (MRI) at the 7th day showed bilateral T2 hyperintensities of the globus pallidus. This finding is present in many metabolic disorders. During the first month she presented focal seizures daily, despite treatment with three antiepileptic drugs. Her psychomotor development was normal. Electroencephalographic study (EEG) showed multifocal epileptic discharges. At 2 months of age we received the result of genetic epilepsy panel, with 1 patogenic variant (c.589C>T) of ALDH7A1 gen and another likely pathogenic variant (c.122G>A), not described before in the medical literature. With this result we indicated pyridoxine, incremental doses until 30 miligram per kilogram daily, plus l-arginine 250 miligram per kilogram daily. The patient had a very good response, with complete seizure remission. At age of 2 years she has normal EEG and normal psychomotor development. Control brain MRI showed no lesions. ***CONCLUSION:*** This case highlights an atypical presentation of PDE, with

no developmental delay at the beginning and bilateral lesions in globus pallidus (not described before in the literature). These findings were a pitfall for the correct diagnosis and the timely treatment of our patient. Despite this, she presents now a very good evolution. This case highlights the importance of the clinical suspicion of PDE in every early seizures presentation, even if the patients do not have encephalopathy.

P-037 - CASE DESCRIPTION: RESPONSE TO PYRIDOXINE IN NEWBORN WITH REFRACTORY EPILEPSY.

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INTRODUCTION: Neonatal seizures represent a neurological emergency and may be the initial manifestation of a rare and serious neurological disorder such as pyridoxine-dependent epilepsy. It is characterized by being difficult to control and responds only to pyridoxine hydrochloride. The family history becomes important in the diagnostic and therapeutic approach of these patients, in relation to genetic causes. ***AIM:*** To present a clinical case of a newborn with refractory epilepsy that responds to pyridoxine. ***MATERIALS AND METHODS:*** Description of sociodemographic and clinical characteristics and response to treatment of a case of a newborn with difficult-to-manage epilepsy treated at a Level III referral hospital in Colombia. For its presentation, the informed consent signed by the legal representative of the minor was required. ***CASE DESCRIPTION:*** We present a case of a full-term newborn, with no history of consanguinity, with a history of a brother who died due to status epilepticus at 4 months without clear etiology. During the first hours of life he presented a generalized clonic seizure, without response to usual anticonvulsants, until the initiation of pyridoxine. Among relevant studies, it has a simple brain magnetic resonance imaging that shows active communicating hydrocephalus, corpus callosum thinning, and electroencephalogram of spontaneous sleep with sporadic epileptiform paroxysmal discharges of interictal bitemporal left frontal spikes. The genetic test reports a homozygous pathogenic variant in the *ALDH7A1* gene c.1093+1G>A, which confirms pyridoxinedependent epilepsy. ***DISCUSSION AND CONCLUSIONS:*** Neonatal seizures pose a significant risk of morbidity and mortality, particularly in cases that do not respond to standard anticonvulsant treatment. When considering the background, clinical history, and lack of response to conventional anticonvulsant therapy, it is important to consider the potential for a genetic cause. This is exemplified by a case in which a pathogenic variant disrupts neuronal lysine catabolism, leading to the accumulation of alpha-piperidine-6-carboxylate and inactivation of pyridoxal 5′-phosphate (P5P). The latter serves as a cofactor and plays a role in neurogenesis and neuronal migration, as evidenced by imaging and electroencephalographic findings. Prompt initiation of high-dose pyridoxine treatment can prevent the progression of these events and significantly influence the patient's outcomes and prognosis.

P-038 - CLINICAL, BIOCHEMICAL AND MOLECULAR FINDINGS ON 9 URUGUAYAN PATIENTS WITH WILSON DISEASE

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INTRODUCTION: Wilson disease (WD) is caused by autosomal variants affecting the *ATP7B gene*, resulting in alterations in physiological copper homeostasis and copper accumulation. The clinical manifestations of copper accumulation are heterogeneous and include symptoms of central nervous system (CNS), liver, cornea and kidney. If left untreated can lead to cirrhosis and death. The standard treatment is decided according to the form of presentation and includes a low copper diet and zinc or a copper chelator. ***AIM:*** To present our experience on 9 Wilson disease cases, regarding clinic, diagnosis, treatment and follow up. Clinical Cases: From the clinical point of view, only one patient started in the pediatric age, four in adolescence and four in adulthood. With regard to gender/sex, five of them are male and four female. Two cases presented as an isolated hepatic form, two with pure neurological symptoms and five with multiple organ compromise. Biochemically all of them presented low ceruloplasmin and cupremia as well as high excretion of urine cooper in 24 hours sample. This last marker presented the expected elevation after beginning chelation therapy. Molecular confirmation with the sequencing of the *ATP7B* gene was performed in all patients. Mutation detected were: c.1934T>G, c.2336G>A, c.2292C>T, c.1369C>T, c.3061-12T>A, c.3402del, c.1285+5G>T, c.3207C>A, c.3809A>G, c.2930C>T, c.3955C>T. There was no correlation between mutations and individual clinical manifestation. The initial treatment in most of the

cases was diet and D-penicillamine with pyridoxine. Stabilization or clinical improvement was observed in all patients. No serious severe effects were reported with the use of D-penicillamine. ***CONCLUSION:*** Our series of cases of Wilson disease represents a broad spectrum of the clinical onset and evolution of this genetic disorder.

P-039 - NON-PROGRESSIVE ENCEPHALOPATHY IN CHILDHOOD ASSOCIATED WITH DISABILITY: A CASE REPORT OF BETA-PROPELLER PROTEIN-ASSOCIATED NEURODEGENERATION (BPAN)

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INTRODUCTION: Neurodegeneration with cerebral iron accumulation constitutes a group of rare genetic disorders characterized by progressive neurological degeneration. One of these disorders is beta-helix proteinassociated neurodegeneration syndrome (BPAN), which is associated with mutations in the *WDR45* gene. Pathogenic variants in this gene affect the function of cellular autophagy, leading to the accumulation of iron and other toxic materials in neurons. This disorder manifests in childhood as developmental delay, including delayed language and motor skills, and unlike other subtypes of neurodegeneration with brain iron accumulation (NBIA) that can manifest early, the presentation of developmental delay remains relatively static until adolescence/young adulthood. ***OBJECTIVE:*** To present a clinical case of non-progressive encephalopathy associated with a mutation in the WDR45 gene. ***CASE REPORT:*** We describe the case of a 13-year-old adolescent girl with non-progressive encephalopathy and intellectual developmental disorder. She had a history of global developmental delay and focal epilepsy. Neuroimaging studies revealed bilateral hypointensity on T2 and susceptibility weighted imaging (SWI) sequences at the pallidal level and substantia nigra. Genetic confirmation by exome showed the presence of a pathogenic variant in the *WDR45* gene. The diagnosis of neurodegeneration with X-linked brain iron accumulation type 5 was confirmed. ***CONCLUSION:*** Consider mutations in the *WDR45* gene in a clinical case characterized by global developmental delay, with neurocognitive impairment in early childhood remaining static for years, and worsening neurocognitive changes occurring in adolescence or early adulthood, and the development of progressive, Levodopa-resistant parkinsonian features suggest the diagnosis of beta-helix protein-associated neurodegeneration (BPAN), which is the only X-linked subtype of neurodegeneration with brain iron accumulation (NBIA). Neuroimaging and genetic testing are essential for diagnosis.

P-040 - WILSON DISEASE WITH NEUROLOGICAL ONSET: REPORT OF 2 URUGUAYAN CASES

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INTRODUCTION. Wilson's Disease (WD) is a rare disorder affecting copper transport, initially described in 1912 and characterized by variable clinical presentations including liver, neurological, and ophthalmic manifestations. Despite progress in its understanding, delayed diagnosis remains common, contributing to increased morbidity and mortality. Neurological symptoms can be difficult to link to this disease, especially when there is no liver involvement at the beginning. ***OBJECTIVE:*** This study aims to expand understanding of WD's neurological presentations based on the description of 2 cases. ***CLINICAL CASES:*** The cases involve a 32-year-old male and a 20-year-old female, both initially presenting with neurological symptoms. The female also exhibited liver involvement, while the male presented solely with neurological phenomenology. Both experienced progressive onset with severe movement disorders, parkinsonism, behavioral changes, and cognitive decline. MRI findings showed diffuse brain parenchymal atrophy, cerebellar involvement, bilateral basal ganglia hyperintensities and caudate atrophy consistent with WD. Biochemical tests showed in both cases decreased ceruloplasmin and serum copper, while increased 24-hour urinary copper levels. In the female case, liver results where abnormal (High total bilirrubine, LDH, GPT and GOT) while the female patient showed normal results. Genetic testing identified mutations in the

ATP7B gene, confirming the diagnosis identifying a c.3207>A; (p.His1069GIn) variant in homozygosis in the male, and a variant c.2930C>T;p.(Thr977Met) and c.3955C>T;p.(Arg1319*) both considered pathogenics, in the female. Treatment responses varied: the female's symptoms stabilized, while the male showed improvement. Diagnosis was delayed by one year in the first case and two and a half years in the latter, underscoring the challenge of timely recognition. ***CONCLUSIONS:*** This report contributes to understanding WD's neurological manifestations, highlighting cases with severe adult-onset neurological symptoms and absence of familial history. Notably, one case presented neurological involvement without liver disease, further emphasizing the need for heightened clinical suspicion in such scenarios to enable timely treatment initiation, which remains crucial for optimizing clinical outcomes in WD.

P-041 - BONE HEALTH AND 25OH-D LEVEL IN 15 CHILEAN PATIENTS WITH GLUT1 DEFICIENCY ON KETOGENIC DIET THERAPY

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BACKGROUND: The ketogenic diet (KDT) is treatment in patients with Glucose transporter type 1 deficiency syndrome (GLUT1DS) with bone health being a long-term concern. ***OBJECTIVE:*** To evaluate bone status in patients with GLUT1DS in KDT in 2 consecutive periods. ***METHODS:*** Bone Mineral Density (BMD) was evaluated in 15 GLUT1DS; 13 have a variant in the *SLC2A1* gene and 2 cases only hypoglycorrhachia and clinical symptoms, all of them on KDT. Period 1 (P1) October 2021-March 2022 and Period 2 (P2) November 2023-March 2024. Dual-energy X-ray absorptiometry (DEXA) was used to measure spinal and femoral BMD, expressed the results in <5 years old as a density (g/cm3) and z-score to total BMD (zBMD) in >5 years old. To determine calcium (mg/day) and vitamin D (IU/day) intake, a 24-hour recall record was used, compared with recommendations (RDI). Average standard±deviation (SD), and median and interquartile range (IQR) were applied. ***RESULTS:*** The age average is 12±6 years old and a median of 6 years (5-8 years) in KDT. Fast ketonemia in: P1=2.32±0.73 mmol/L and glycemia=76±7.9 mg/dL and P2=2.6±0.85 mmol/L and 78±8.3 mg/dL respectively. P1=<5 years old, femoral BMD was 0,520 g/cm3, and spinal BMD was 0,5280 g/cm3; P2= > 5-year-old, the zBMD was -0.47±1.6 SD. One GLUT1DS < 5-year-old in P2, femoral BMD was 0,486 g/cm3, and spinal BMD was 0,553 g/cm3. In subjects >5 years- old, a zBMD was -0.65±1.8. Regarding calcium intake, P1=1118 mg/d (952-1841 mg/d) and P2=1475 mg/d (988-1815 mg/day), complying with the RDI. With vitamin D intake, P1= 680 IU/d (480–1280 IU/d) and P2 = 560 IU/d (400 – 810 IU/d). The average of 25-OHvitaminD(25OH-D) was: P1=38.7±14.3 ng/mL and P2=41.7± 7.9 ng/mL. Twenty percent of subjects (n=3) in P1 presented insufficient 25OH-D (between 10-29 ng/mL) but got better in P2, observed in 7% (n=1). ***CONCLUSION:*** No significant difference between zBMD in P1 and P2. DEXA evaluation is recommended, as a slight decrease in zBMD was observed after 2 years on KDT.

P-042 - CAPILLARY ELECTROPHORESIS AS A CDG SCREENING METHOD

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INTRODUCTION: Congenital disorders of glycosylation (CDG) are a group of inborn errors of metabolism that affect the synthesis of glycans and glycoconjugates in proteins and lipids, resulting in variable clinical manifestations. Phosphomannomutase 2 (PMM2)-CDG, a type of N-glycosylation disorder is the most common form of CDG. Traditionally, transferrin has been used in screening tests due to its high concentration in serum, with Isoelectric Focusing established as the standard method for separating sialylated glycoforms. Since 2016, the Newborn screening laboratory in Uruguay (LPN) has been performing transferrin isoelectric focusing (IEF) as a screening test for patients with suggestive symptoms. Recently, due to the lack of availability of some resources in Uruguay, necessary to carry out IEF studies, it has forced the use of an alternative method to continue with this study. So this, LPN has incorporated Capillary Electrophoresis (CE), with the commercial kit for Carbohydrate deficient transferrin (CDT). ***OBJECTIVE:*** Compare the performance of CE with IEF and determine the reference values of a non-CDG pediatric population using CE. ***MATERIALS AND METHODS:*** CDG type I (PMM2) and non-CDG samples were performed by IEF (BIORAD) as qualitative analysis and CE with CDT kit (Sebia, Minicap) for qualitative and relative percentages analysis. To determine the relative percentages of

sialotransferrins, 44 serum samples of both sexes from non-CDG subjects under 15 years of age were used. ***RESULTS:*** The qualitative analysis was consistent using both methods for a patient sample with CDG- tipe I profile. Reference values calculated as a range between 2.5 and 97.5 percentiles was pentasialotransferrin: 10-18%. tetrasialotransferrin: 78-86%, trisialotransferrin: 1.1-5%, disialotransferrin: 0.3-1.2, monosialotransferrin: 0% and asialotransferrin: 0%. Ratio disialotransferrin/trisialotrasnferrin was between 0.1-0.7. ***DISCUSSION AND CONCLUSIONS:*** CE with CDT kit is a good alternative method to performe CDG selective screening. Although CE requires a greater amount of sample than IEF, is an automatic system that provides rapid and easy results with relative quantification of the different sialotransferrins reducing probability of operator errors. Our results are in agreement with previously reported studies.

P-043 – CCDC115-CDG – A NEW CASE REPORT OF A RARE CONGENITAL DISORDER OF GLYCOSYLATION CHARACTERIZED BY COMBINED DEFECT OF N- AND O-GLYCOSYLATION DUE TO GOLGI DISTURB

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INTRODUCTION: Congenital Disorder of Glycosylation are inherited metabolic disorders due to altered glycosylation pathway. CCDC115-CDG is an autosomal recessive disease characterized by infantile onset of progressive liver failure, hypotonia, and delayed psychomotor development. Cell hypoglycosylation is caused by Golgi vesicular trafficking and lumen disturbances due to increasing pH acidification. Laboratory abnormalities include elevated liver enzymes, coagulation factor deficiencies, hypercholesterolemia, and low ceruloplasmin levels. Serum isoelectric focusing of proteins reveals a combined defect of N- and Oglycosylation, indicative of a Golgi apparatus dysfunction. Currently, specific treatment for this condition is unavailable. ***OBJECTIVE:*** To report a clinical presentation and diagnosis difficulties associated with a severe phenotype. ***CLINICAL CASE PRESENTATION:*** We present a female patient born to a healthy nonconsanguineous couple, with two healthy siblings. During pregnancy severe maternal cholestasis was diagnosed and, despite treatment with ursodeoxycholic acid, liver function worsened, requiring delivery at 36 weeks of gestation. Birth was uneventful, but on day 2 she developed jaundice due to direct hyperbilirubinemia. At three months of age, petechiae and bleeding associated with coagulation disorders, vitamin K deficiency, elevated transaminase enzymes, and hemolytic anemia developed. Liver biopsy showed chronic liver disease with moderate necroinflammatory activity and complete cirrhosis stage. Genetic testing identified compound heterozygous variants in the *CCDC115* gene: NM_032357.392T>C;p.(Leu31Ser) and NM_032357.3.1A>G;p.(Met1?), associated with CDG2O. Hypercholesterolemia and low ceruloplasmin levels were also detected. Results of ongoing investigations include reanalysis of liver biopsy for copper deposits and further isoelectric focusing of serum proteins to explore N- and O-glycosylation defects. The patient is currently 2 years and 6 months old, showing normal growth and neurodevelopmental progression. ***CONCLUSIONS AND DISCUSSION:*** Only eight cases have been reported, which restricts our understanding of its complete phenotypic range. This patient presents a unique case, showing similar biochemical characteristics to others, but to date maintains satisfactory liver function and developmental milestones. Continued longitudinal followup will yield deeper insights into her clinical trajectory.

P-044 - CLINICAL INVESTIGATION FOR INBORN ERRORS OF METABOLISM IN BRAZIL OVER A DECADE OF THE NATIONAL POLICY FOR COMPREHENSIVE CARE OF RARE DISEASES

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INTRODUCTION: The National Policy for Comprehensive Care for People with Rare Diseases (RD), established in Brazil in 2014, aims to reduce morbidity and

mortality and improve the quality of life for patients with RD in the Unified Brazilian Health System (SUS). This ordinance outlines procedures for diagnosing and managing RD. One focus is Clinical Evaluation for Diagnosis of Inborn Errors of Metabolism (IEM), therefore twelve different biochemical and molecular diagnostic procedures were incorporated into SUS. This study analyzes these diagnostic procedures from January 2014 to December 2023, as recorded in federal databases. ***MATERIALS AND METHODS:*** A retrospective analysis was conducted using data from January 2014 to December 2023. The dataset included information on clinical diagnostic procedures for IEM in various municipalities, the implementation timeline, geographical distribution of centers, and the number of procedures performed. Data were collected using the DATASUS TABNET Win32 3.2 platform, maintained by the Ministry of Health. ***RESULTS:*** By December 2023, of 29 centers licensed as RD centers, 24 (82.7%) were designated for EIM procedures. The first clinical diagnostic procedures for IEM were recorded in January 2017 in Brasília, Federal District. In February 2017, Porto Alegre, Rio Grande do Sul, began operations as the second center. Since then, 9,516 procedures have been performed across all centers. From January 2017 to December 2023, the average monthly number of procedures was 113.3. Seventeen municipalities, plus the Federal District, performed at least one procedure. The highest numbers were observed in Brasília (n=1,990, 20.9%), Porto Alegre (n=1,937, 20.4%), and Curitiba (n=1,333, 14.0%). The highest annual production was observed in 2023 (n=2,184) and the lowest in 2021 (n=778). ***DISCUSSION AND CONCLUSIONS:*** Despite the policy's publication and implementation beginning in January 2014, the first center was not licensed until 2016, with procedures starting in January 2017. This three-year delay highlights initial challenges in operationalizing the policy. The expansion of diagnostic centers has been slow, with new centers gradually becoming operational over several months. This underscores the need for sustained efforts to expand diagnostic capabilities and ensure access to specialized care for patients with rare metabolic disorders.

P-045 - DIAGNOSIS OF INBORN ERRORS OF METABOLISM IN ELDERLY PATIENTS: A SYSTEMATIC LITERATURE REVIEW

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INTRODUCTION: Inborn errors of metabolism (IEM) are a group of genetic disorders mostly diagnosed in newborns, infants or children. However, either due to the increasing life expectancy or due to the later onset of symptoms, the number of young adult patients diagnosed with IEM is increasing. Nevertheless, until now, there is no data about the diagnosis of IEM in elderly patients. ***OBJECTIVES:*** This study aims to characterize the IEM diagnosed in elderly patients (>=65 years old), including the age of onset of symptomatology and the most frequent symptoms and organs involved. ***MATERIALS AND METHODS:*** A systematic review of the literature (SRL) was performed, following the current guidelines. PubMed, Embase, Lilacs and Web of Science were searched, until March 2023, using MESH terms for "IMDs" and "elderly people". The inclusion criteria encompassed: 1) case reports, case series, cohort studies, systematic reviews; 2) IEM being diagnosed above 65 years old; 3) languages (English, Italian, French, Portuguese or Spanish). Studies about common metabolic diseases, such as diabetes, gout, hemochromatosis, hypercholesterolemia and amyloidosis, were excluded. ***RESULTS:*** A total of 28,168 articles were identified, and 272 were included, with 310 patients. The five more frequent diagnoses were Fabry disease; Alkaptonuria; Mitochondrial diseases; Gaucher disease; and Mc Ardle disease. Many other IEM have been identified, including some very rare disorders. The age of onset of the first symptoms was below 65 years old for most of the patients. ***DISCUSSION:*** This SLR points out the diagnostic odyssey of IEM patients, and identifies a significant number of IEM that can be diagnosed in elderlyhood. Our data underscores the importance of not limiting the metabolic investigation only to younger patients, and it draws attention to the fact that health professionals who care for adult and elderly patients should be able to identify the main clinical manifestations of IEM. The question of some specific clinical presentations of IMDs in elderly patients has to be further elucidated.

P-046 - IMPLEMENTATION OF EXOME SEQUENCING FOR THE MOLECULAR DIAGNOSIS OF INHERITED METABOLIC DISORDERS: PIONEERING EXPERIENCE IN AN ARGENTINIAN SINGLE CENTRE

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INTRODUCTION: Inherited metabolic disorders (IMD) are monogenic defects with great phenotypic variability; the evaluation of patients with clinical suspicion of IMD includes biochemical studies, enzymatic and/or genetic analysis. This phenotype-to-genotype diagnostic strategy is effective when the clinical features are highly suggestive and associated with specific biomarkers. However, in diseases without specific biochemical alterations, exome sequencing is emerging as an effective diagnostic tool. ***OBJECTIVE:*** to present the first local experience of the implementation of exome sequencing in the diagnosis of IMD. ***MATERIAL/METHODS:*** The study included 50 patients with clinical and/or biochemical suspicion of IMD (CEMECO, April-2022/March-2023); three of them with a reported consanguineous family history. Genomic DNA was purified from whole blood using the Roche MagNA kit; sequencing and exome data analysis were performed by 3billion company (South Korea). Identified variants were classified according to American College of Medical Genetics and Genomics guidelines. ***RESULTS:*** The first-stage diagnosis rate was 54% (27/50): 22/27 patients with IMD (10 with high clinical-biochemical suspicion and 12 with non-specific clinicalbiochemical findings) and 5/27 with other genetic diseases. Two coexisting genetic diseases were detected in 2 patients and incidental findings related to risk factors were identified in 3 patients. Identified IMDs included: aminoacidopathies (33.3%), organic acidurias (19.0%), mitochondriopathies (19.0%), fatty acid β-oxidation defects (14.4%), cofactor/vitamin defects (9.5%), urea cycle defects (4.8%), and CDG defects (3.7%). At a later stage, the results of patients without diagnosis were re-analyzed and the diagnostic rate increased to 58% (29/50). Two genetic disorders (no IMD) were diagnosed. Forty-four genetic variants were identified in 25 genes, classified as: pathogenic (51.2%), probably pathogenic (23.2%), and of uncertain significance (25.6%). ***CONCLUSION:*** The experience allowed the diagnosis of patients with non-specific clinical and/or biochemical expression. Clinical exome re-analysis allowed to increase the diagnostic rate. Exome sequencing is an effective method in the diagnosis of IMD (especially in complex or inconclusive cases). Exome re-analysis should be a routine clinical practice, as it may provide additional diagnoses, mainly due to novel gene-disease discoveries, updated clinical features, and improved bioinformatics tools.

P-047 - MOLECULAR CHARACTERIZATION OF INBORN ERRORS OF METABOLISM IN PATIENTS LESS THAN ONE YEAR OF AGE WITH CRITICAL STATE OF HEALTH AND RECURRENT HOSPITALIZATIONS, AT ROBERT REID AND ARTURO GRULLÓN CHILDREN'S HOSPITALS, DOMINICAN REPUBLIC.

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INTRODUCTION: Inborn Errors of Metabolism (IEM) are a group of genetic, monogenic diseases due to a defect of an enzyme or a transport protein that leads to a blockage in a metabolic pathway. The overall incidence of 1: 800 live births vary depending on the population. ***OBJECTIVES:*** To molecularly characterize the IEM in patients < 1 year of age, with critical state of health and recurrent hospitalizations at Robert Reid Cabral of Santo Domingo and Arturo Grullón Children's Hospital of Santiago. ***METHODOLOGY:*** A descriptive, prospective and cross-sectional study was carried out between November 15, 2022, and March 15, 2024. A sample of 100 patients was proposed. Participants signed an informed consent, and a Form was filled out with the following data: birth region, perinatal history, consanguinity, death of siblings, miscarriages, clinical and laboratory findings at the patient's admission. Laboratory Tests: complete blood count, glycemia, arterial gases, anion Gap, electrolytes; urea, creatinine, uric acid, alanine and aspartate aminotransferase, gamma glutamyl transpeptidase, total proteins, prothrombin and partial thrombin time, ammonium, lipid profile, creatine phosphokinase, lactic acid, calcium, phosphorus, alkaline phosphatase, amino acids in blood, organic acids and special qualitative tests in urine. Expanded Newborn Screening and molecular study were performed. ***RESULTS:*** A total of 31 participants were detected. Seven participants were discarded, staying 24 participants from different regions of the country and Haiti. 11 out of 24 died (45.8%). 2 out of 24 had an IEM (8.33%), that were Classic Galactosemias. The molecular results are still pending. ***CONCLUSIONS:*** Two cases of Classic Galactosemia have been detected. This study shows an important presence in the population of this disease. EIM PROJECT / FONDOCYT COD. 2020-2021-2A3-106 Keywords: inborn errors of metabolism, rare diseases, Neonatal Screening.

P-048 - THE NEED FOR A "ASOCIACIÓN ARGENTINA DE ERRORES CONGÉNITOS DEL METABOLISMO" (AAECM)

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INTRODUCTION: Patients with rare diseases, particularly inborn errors of metabolism(IEM) face significant challenges in accessing care. Improving this situation is imperative, given the expansion of newborn screening(NBS) and clinical suspicion. The existence of specialized working groups for IEM are crucial. ***OBJECTIVES:*** 1-Evaluate Argentina's resources for IEM diagnosis and treatment 2-Justify the creation of a AAECM by defining it´s main objectives. ***METHODS:*** Information from the National Ministry of Health's Newborn Screening Strengthening Program, EIM-related laboratories and treatment centers was compiled. Data about the number of laboratories, level of complexity, geographic distribution and their healthcare professionals were collected. ***RESULTS:*** Argentina has 21 NBS laboratories nationwide and only 9 of them have a group trained in IEM. Regarding the confirmation centers, they are located in the following cities: Córdoba, La Plata, Bahía Blanca and the Ciudad de Buenos Aires. Data on private NBS were not available. After diagnosis patients are followed in one of the 15 Hospitals, 7 of them located in Buenos Aires province or in the Ciudad de Buenos Aires. Only four of them had both the laboratory equipment and medical expertise in the same center. ***DISCUSSION:*** The National Ministry of Health has a program to strengthen newborn screening, a coordination area, an advisory group on rare diseases and information on a web page in this regard. It is important to emphasize that from our experience, NBS tests in private centers lack systematic control and there is no accessible information about them. An EIM-focused scientific society could improve Argentina's situation by integrating national and international efforts, disseminating knowledge, training personnel, and supporting research, families and authorities. The lack of local healthcare professionals nationwide, forces patients to travel long distances to access proper medical care. ***CONCLUSION:*** The establishment of the AAECM in 2024 will enhance EIM patient care and family support by integrating healthcare professionals worldwide, while supporting health authorities, through our objectives: The integration of work at the National and International level, awareness of EIM, training of health personnel, information, formation of a national network, support for research, support for authorities and family associations and training of specialists.

P-049 - GUARITA INDIGENOUS TERRITORY: EXPLORING CLASSICAL GALACTOSEMIA AND BUILDING COLLABORATIVE PARTNERSHIPS

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INTRODUCTION: The Guarita Indigenous Territory (IT), located 461 km from the capital of Rio Grande do Sul, Brazil, is home to over 8,000 inhabitants, primarily from the Kaingang group. This vulnerable population has recently seen an alarming increase in diagnoses of classical galactosemia (CG). CG is a rare inborn error of galactose metabolism that, without treatment, can lead to life-threatening clinical manifestations. Developing effective healthcare policies for this population is imperative. Here we report the results of the first expedition to the Guarita IT. ***OBJECTIVE:*** To establish communication with the Kaingang community, provide comprehensive information about CG and acquire tools for planning and developing healthcare initiative strategies and future research by attentively listening and considering their specific concerns. ***METHODS:*** The expedition took place between April 15-19, 2024 with a group from the Federal University of Rio Grande do Sul, including Kaingang students, and the Clinical Hospital of Porto Alegre (HCPA), linked to the National Institute of Rare Diseases (InRaras). An assembly was convened during the Indigenous Week, involving local authorities, healthcare professionals and residents to exchange information and experiences. Graphic materials (folders and posters) about CG were distributed among the community, and the families of three patients with confirmed diagnosis were interviewed, with nutritional formulas donated. ***RESULTS:*** The reception from the community was positive, culminating in their approval for the development of collaborative projects. The assembly provided valuable insights into their major needs and cultural perspective on genetic conditions. During interviews, all families highlighted common challenges related to diagnosis and treatment: time and distance required to reach the HCPA, unfamiliar concepts during medical consultations, and the city's environment. The vital role of onsite healthcare personnel (including Kaingang) became evident, serving as the primary contact and offering crucial insight into community needs for future collaborative research efforts. ***CONCLUSION:*** This expedition underscored the importance of proactive healthcare engagement for early diagnosis and treatment, integrating their culture while enhancing understanding of CG in the Kaingang community. Furthermore, it was crucial for planning and developing healthcare and research initiatives aiming early

diagnosis and follow-up, such as molecular screening and regular medical visits.

P-050 - LANDSCAPE OF INBORN ERRORS OF METABOLISM IN BRAZIL: RESULTS OF THE BRAZILIAN RARE DISEASE NETWORK

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BACKGROUND: Inborn errors of metabolism (IEM) present significant challenges in diagnosis and management. The Brazilian Rare Diseases Network (BRDN) is a consortium of 40 healthcare centers from all five regions of Brazil established in 2020, designed to perform an epidemiological survey on rare diseases (RD). This study aims to present comprehensive data on patients with IEM assisted in the centers of BRDN, including their clinical profiles, diagnosis, and treatments applied. ***METHODS:*** We conducted a comprehensive review of all cases with confirmed or suspected IEM in BRDN. Selection criteria were established using the Rare IEM classification from Orphadata (v. Dec 4, 2023, https: //www.orphadata.com/classifications/), incorporating ICD-10, OMIM, and Orpha diagnostic codes. A retrospective (2018-2019) and prospective (2022-2024) data collection was conducted using a RedCap standard form. ***RESULTS:*** Of 19,307 total records at BRDN, 2,667 (13.8%) IEM cases were registered (retrospective phase: 1,798/12,285; prospective phase: 870/7022). Most participants (32.4%) lived in the Southeast region of Brazil. The mean age at inclusion was 18.0 years (±15.5), and 1,402 (52.6%) were female. Diagnosis of IEM was confirmed in 88.3% and suspected in 11.7%. For RD coding, Orpha was mostly (71.4%) used. The most frequent diagnoses were Phenylketonuria (PKU, n=762), Mucopolysaccharidosis (MPS) type 2 (n=102), Fabry disease (n=95), MPS type 6 (n=89) and Gaucher disease (n=86). Biochemical diagnosis was performed in 66.6% of cases, molecular diagnosis was conducted in 25.7%, and the remaining cases were categorized as Others. Only 26.2% were diagnosed through newborn screening. The most recorded Human Phenotype Ontology were: Reduced phenylalanine hydroxylase level, Seizure, and Hyperphenylalaninemia. Positive family history was registered in 27.1% and 16.5% reported consanguinity. In the retrospective phase, specific treatment for IEM was reported in 71.6% of cases. Within the overall cohort, 41.2% received diet therapy. Previous hospitalizations were documented in 88.3%. The mortality rate was 1.8% during the retrospective phase. ***CONCLUSIONS:*** This study shows the first Brazilian nationwide data on IEM, demonstrating the importance of networking between specialized RD centers. PKU is included in the Brazilian Newborn Screening Program, leading to higher diagnostic prevalence. This data may contribute to improving the assistance of IEM in Brazil.

P-051 - SPECTRUM OF INBORN ERRORS OF METABOLISM TREATED AT IRMANDADE SANTA CASA DE MISERICÓRDIA, BRAZIL: A RETROSPECTIVE ANALYSIS OF 2023.

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INTRODUCTION: Inborn Errors of Metabolism (IEM) are single-gene disorders characterized by deficient activity of specific enzymes, structural proteins, or transporter molecules within metabolic pathways. However, diagnosing IEM can be challenging due to diverse clinical presentations. The current prevalence of inborn errors of metabolism is 50.88 per 100,000 live births, with 51% of diagnosed cases associated with consanguinity. ***OBJECTIVE:*** This study aims to analyze the profile of patients treated at our center in São Paulo and initiate a discussion about the patients with inborn errors of metabolism within our service. ***METHOD:*** A retrospective data collection involved reviewing the medical records of all patients with suspected IEM treated in the pediatric neurology department in 2023. ***RESULTS:*** In 2023, 30 patients with suspected inborn errors of metabolism were evaluated. Among them, 8 did not have a confirmed etiological diagnosis as they did not undergo adequate genetic or metabolic evaluation. Of the total patients, only 4 reported consanguinity. The diagnoses found in the data collection were, in descending order: galactosemia (7), mitochondrial disorders (4), mucopolysaccharidosis (4), arginase deficiency (3), gangliosidosis (specifically Tay-Sachs disease) (2), orotic aciduria (1), and maple syrup urine disease (1). The other 8 patients are still under investigation. Confirmatory studies for patient diagnoses included exome genetic testing and serum metabolic tests collected on filter paper, conducted at the Metabolic Disorders Laboratory of Hospital das Clínicas de Porto Alegre. The age range of

the evaluated patients varied from 3 years to 28 years old. During the data analysis, it was noted that two patients treated in 2023 had died: one with Tay-Sachs disease and another with Kearns-Sayre syndrome. ***DISCUSSION:*** In Brazil, despite the availability of diagnostic resources within the Unified Health System (SUS) and comprehensive protocols for neonatal screening, testing is limited to a panel screening of treatable diseases, thereby delaying the diagnosis of inborn errors without proposed specific treatments. Access to genetic diagnostic tests or enzymatic analyses of blood and urine remains a challenge for many. Additionally, referrals to our clinic, primarily led by pediatric neurology specialists, may introduce biases, as patients typically present symptoms related to central nervous system disorders.

P-052 - COCKAYNE SYNDROME, A DISORDER OF NUCLEIC ACID METABOLISM. WHY IT IS NOT INCLUDED IN THE INTERNATIONAL DATABASE IEMBASE?

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INTRODUCTION: Cockayne Syndrome (CS) is a rare multisystemic disorder caused by pathogenic variants in the CSA (*ERCC6*) or CSB (*ERCC6*) genes which develop, in CS cells, inefficiency to nucleotide excision repair of DNA damage, and to recover RNA synthesis upon stress, leading to permanent transcriptional arrest of many genes with reduced levels of ERCC6 or ERCC8 protein expression, which may serve as molecular markers. Mitochondrial dysfunction in the form of decreased mitophagy may also be involved in its pathophysiology. CS is inherited as an autosomal recessive genetic trait and is characterized by failure to thrive, microcephaly, cutaneous photosensitivity, neurodevelopmental delay, pigmentary retinopathy, neurosensory hearing loss, dental caries. CS has a wide spectrum of clinical severity, with at least a CS type I "classic" form, type II "severe, neonatal" form, and type III "mild" form. ***OBJECTIVE:*** To present a clinical case of type II CS with a progressive clinical disease and significant brain atrophy and typical calcifications. ***CLINICAL CASE:*** A fouryear and six-months old male patient, born of non-consanguineous parents, presented with congenital microcephaly, intrauterine growth restriction and global developmental delay. Cranial MRI at nine months of age showed moderate mega cisterna magna without any other abnormalities. On the evolution, he exhibits severe global developmental delay, microcephaly, facial dysmorphisms, enophthalmos, leukocoria, cachectic dwarfism with severe chronic malnutrition, spastic quadriparesis, swallowing disorder, erythema in sunexposed areas, dental abnormalities and bilateral cryptorchidism. A recent MRI showed severe whole brain atrophy with significant diffuse leukoencephalopathy and a lactate peak on spectroscopy, with calcifications in the basal ganglia and in the sulcal depth of the cerebral cortex, confirmed with computed tomography. Once major and minor criteria were obtained, we genetically confirm our suspicion identifying heterozygous variants c.3445G>T; p. (Glu1149*) classified as likely pathogenic and c.2839C>T; p. (Arg947*) classified as pathogenic in the *ERCC6* gene. ***CONCLUSIONS:*** Considering its pathophysiology and clinical and neuroimaging features, illustrated by this clinical case, with progressive whole brain atrophy and calcifications and demyelination (clearly not hypomyelination as it has been proposed), we suggest that this syndrome should be included in IEMbase in the category of disorders involving nucleic acid metabolism.

P-053 - COEXISTENCE OF TWO ORPHAN PATHOLOGIES AND THEIR CLINICAL IMPACT

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INTRODUCTION: Orphan diseases affect a low percentage of the population, however the coexistence of two of them is a possible event. The diagnosis of this coexistence is difficult because interaction between them can modify their clinical presentations. ***OBJECTIVES:*** To report 4 patients with 2 orphan diseases, including an inborn error of metabolism. Patient 1: Boy, diagnosed at age of 6 months with DiGeorge Syndrome (DGS), due to typical facial and cardiac dysmorphias. He presented severe malnutrition, recurrent vomiting and severe hypertriglyceridemia in non-lipemic blood. Glycerol kinase deficiency (GKD) was confirmed (c.259+1G>A gene variant). Treatment for GKD improved nutritional status and decreased vomiting events. Patient 2: Girl, born with facial dysmorphias and arthrogryposis. She presented seizures since the first day. Since the 9th day of life she

presented apneas and progressive neurologic deterioration. Metabolic study suggested a Maple Syrup Urine Disease (MSUD). Despite specific treatment, she died at age of 6 months. Genome analysis confirmed CLIFAHDD syndrome and MSUD (*NALCN* gene with c.1733A>G variant; *BCKDHA* gene with c.109-15T>A and c.137C>A variants). Patient 3: Boy, consanguineous parents. He presented malnutrition since infancy. He developed exocrine pancreatic insufficiency, impaired renal function, protein aversion and hyperammonemia. Genetic panel for exocrine insufficiency confirmed cystic fibrosis (CF) and lysinuric protein intolerance (*CFTR* gene with c.3454G>C variant; *SLC7A7* gene with c.455dup variant, both in homozygosis). Treatment for CF, and protein restriction and carnitine supplementation, normalized ammonium and nutritional status. Patient 4: Girl, with hepatomegaly and hypoglycemia detected during the first year of life, associated with increased transaminases, dyslipidemia, and hyperCKemia. A glycogenosis type 3 (G3) was proposed. Despite adequate treatment, she developed mild liver cirrhosis. Genetic panel for liver dysfunction demonstrated G3 and Wilson disease (*AGL* gene with c.3216_3217 variant; *ATP7B* gene with c.3139G>T variant, both in homozygosis). We planned to add penicillamine or trientine to the treatment. ***DISCUSSION:*** In our patients, the coexistence of 2 orphan pathologies was suggested by the atypical clinical evolution of the most evident disease. The diagnosis was made by extensive genetic studies. The correct diagnosis allowed the adjustment of the treatments and improved the clinical course in ¾ of the patients.

P-054 - GENOMIC IMPACT ON THE HEREDITARY GENETIC COLLAGEN DISEASE IDENTIFICATION AND CHARACTERIZATION

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INTRODUCTION: Imperfect Osteogenesis (IO) is an autosomal dominant disorder caused by pathogenic variants in multiple genes, with 90% of cases linked to variants in COL1A1-A2. The extracellular matrix of connective tissue primarily consists of type I collagen. The *COL1A1* and *COL1A2* genes encode the three alpha chains required for the formation of type I procollagen. After these molecules are folded and packaged into transport vesicles, they are delivered to the Golgi apparatus. There, procollagen undergoes modifications before being secreted into the extracellular space, where it is converted into functional collagen. IO is classified IEM because of disruptions in this signaling pathway within the Golgi apparatus lead to alterations in collagen composition, ultimately impacting bone formation. ***OBJECTIVE:*** We present a case report to highlight the importance of genomics in the diagnosis of hereditary collagen diseases. ***MATERIALS AND METHODS:*** A review of the patient's medical history was carried out to extract all the clinical data of interest in our research. ***RESULTS:*** 35-year-old female patient, with six fractures and five dislocations, and blue sclera. Maternal family history with predisposition to similar symptoms and a history of multiple diagnoses as spondyloarthritis, rheumatoid arthritis with pharmacological treatment as sulfasalazine, methotrexate, folic acid, and biologics without confirmatory studies. The patient is the mother of an 8-year-old child diagnosed with OI, suggesting the possible presence of inherited genetic disease, with the son becoming the index case. Using Next Generation Sequencing (NGS) and Copy Number Variants (CNV) analysis, a targeted panel of genes associated with collagenopathies revealed in the child a heterozygous pathogenic missense variant c.3652G>A (p.Ala1218Thr) in the *COL1A1* gene (NM_000088.4), reference rs72656337. This variant confirms the diagnosis of OI type I. ***CONCLUSIONS:*** The availability of advanced genetic testing methods allows high-throughput DNA sequencing, enabling accurate diagnoses and individualized therapeutic approaches. In addition, genetic testing facilitates cascade screening, identifying affected, oligosymptomatic carriers, and at-risk family members through pedigree. Precision medicine enhances treatment outcomes through proactive management strategies involving prevention, prediction, follow-up, and prognosis. It also establishes guidelines for early detection in family members. This underscores the transformative potential of genetic testing in shaping personalized medicine's future.

P-055 - IMPORTANCE OF OMIC SCIENCES AND ARTIFICIAL INTELLIGENCE IN THE CLASSIFICATION OF CLINICAL SIGNIFICANCE OF NEW AND DE NOVO VARIANTS ASSOCIATED WITH MODY2: PRECISION MEDICINE

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INTRODUCTION: Maturity-Onset Diabetes of the Young (MODY), is a rare and heterogeneous group of genetic disorders characterized by dysfunction of

pancreatic β cells, leading to chronic hyperglycemia. Glucokinase (GCK) variants are known as GCK-MODY2. In the ClinVar database, there are 1093 variants reported for *GCK* gene. ***MATERIALS AND METHODS:*** We present a case of a 7-year-old male patient with polyuria, pollakiuria and weight loss. Non-consanguineous parents, with paraclinical tests with elevated blood glucose and HB1AC, negative antibodies. Given the clinical and paraclinical suspicion of MODY a targeted study was requested, whole exome sequencing + variants number of copies of genes related to MODY. ***RESULTS:*** A nucleotide variant was identified c.1022G A in heterozygosity in exon 8 of the *GCK* gene (NM_033507.3). At the protein level it produces the missense change from a Serine to an Asparagine at amino acid 341 (p.Ser341Asn). ***CONCLUSIONS:*** The heterozygous variant in the *GCK* gene generates the change of a guanine for an adenine in position 1022 of the cDNA. Compromising insulin secretion and glucose homeostasis. MODY type 2 is associated with pathogenic variants in the *GCK* gene. The variant identified is located at a splice site and has not been reported in the principal databases: National Center for Biotechnology Information (NCBI); Medical Genomics (MedGen), Online Mendelian Inheritance in Man (OMIM), ClinGen. High-performance bioinformatics algorithms (MetaScore) and individuals predict a deleterious effect. This variant's effect is classified as pathogenic, as found in biological and molecular bases, genomic annotations, proteomics, protein structure and function, functional studies, and some artificial intelligence tools (GenAI, VarChat, Alphafold, Mastermind, Alliance of Genome Resources Version: 7.1.0). It is important to establish a genotype/endotype/phenotype correlation with related ontological platforms (Human Phenotype Ontology (HPO), OMIM, Gene Ontology (GO), and Orphanet) in a patient without a related family history, which confers a de novo inheritance mechanism. The early identification of this new and de novo diseases through multimodal approach, omics, algorithms, and artificial intelligence, could achieve precise diagnoses, establish targeted treatments, proper genetic counseling, monitoring of the disease, and determine prognos

P-056 - THE EXHAUSTIVE ROAD TO ARRIVE AT A CONGENITAL DISORDERS OF GLYCOSYLATION (CDG) DIAGNOSIS: WHAT HAPPENS IN ARGENTINA?

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INTRODUCTION: Here we present not only a report of a cohort of Congenital Disorders of Glycosylation (CDG) patients but also a road map of countless efforts to arrive at a CDG diagnostic in Argentina. The complexity of this algorithm requires coordinated efforts to overcome the obstacles of a fragmented system. During the last 20 years, a group of research and healthcare professionals has been encouraged to grow according to the exponentially emerging CDG classes. ***OBJECTIVE:*** To communicate the multidisciplinary efforts necessary to detect a broad spectrum of CDG patients in a collaborative "ARG-CDG Community" to make appropriate health decisions and facilitates access to emergent or palliative therapies in Argentina. ***METHODOLOGY:*** Multisystem clinical presentations lead the healthcare and research professionals to work to enhance the methodological algorithm. Study altered glycosylation in biomarkers, such as transferrin isoelectrofocussing (Tf-IEF) or capillary electrophoresis (Tf-CE), remain insufficient. It must be necessary to access powerful tools as high-performance liquid chromatography/mass spectrometry (HPLC-MS) and genetic tests including massive sequencing to diagnose CDG. The exome (WES) or genome (WGS) sequencing was necessary to detect the affected gene. Cell models are useful in identifying biological processes and molecular mechanisms to assess protein functionality in N- or O-glycosylation disorders. ***RESULTS:*** CDG casuistic include 15 patients with a broad spectrum of affected genes, 3 detected by Sanger studies and 12 by massive sequencing (8 WES and 4 WGS): PMM2-CDG (n: 7), ALG2-CDG (n: 2), ALG1-CDG (n: 1), ATP6AP2-CDG (n: 1), SLC39A8-CDG (n: 1), MAN1B1-CDG (n: 1), CCDC115-CDG (n: 1), CCDC115-CDG (n: 1) and a

compounds ALG13/PIGN-CDG patient in study. The knowledge of the cell pathogenesis due to CDG is necessary when Variant of Uncertain Significance (VUS) is detected. In relation to this, we managed to establish two cell models (661W and HEK) to test it that could also allow us to evaluate the follow-up in future therapies. ***DISCUSSION:*** The challenge is to engage families and professionals, to make evident a collective vision of the translational medical research necessary to provide responses to the patients. This work proposes a new perspective on CDG teamwork in our region (CONICET; FONCYT; UCC).

P-057 - THE POTENTIAL OF WHOLE EXOME SEQUENCING IN THE DIAGNOSIS OF INBORN ERRORS OF METABOLISM

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INTRODUCTION: Inborn errors of metabolism (IEM) are complex genetic disorders with a wide range of clinical manifestations. Molecular diagnosis of these disorders is challenging because different genes can cause similar phenotypes, and the same variant can cause multiple clinical phenotypes. Whole exome sequencing (WES) has revolutionized the diagnosis of IEM by providing a comprehensive view of all coding regions of the genome, enabling efficient and accurate identification of genetic variants responsible for these diseases. ***OBJECTIVES:*** To improve the genetic diagnosis of pediatric patients suspected of having IEM using WES and to provide a comprehensive analysis of the genetic data obtained. ***MATERIALS AND METHODS:*** Genetic analysis using WES was conducted in a cohort of 50 pediatric patients with suspicion of an IEM based on clinical, biochemical and imaging findings. Coding exons and exon-intron junctions of IEM-associated genes were analyzed. Variants were classified according to the American College of Medical Genetics and Genomics guidelines. ***RESULTS:*** We demonstrated the clinical utility of WES in our patient cohort, achieving a diagnostic yield of 70%. Specifically, the yield was 100% in patients with a clear monogenic disease identified by neonatal screening (n=5), 74% in patients with moderate certainty of IEM (n=26), and 12% in those with low certainty (n=4). The positive group included 13 patients with autosomal dominant disease and 22 with autosomal recessive disease. Variants were classified as pathogenic (n=21) and likely-pathogenic (n=14), with 11 being novel. Additionally, 12 variants were classified as variants of uncertain significance. ***CONCLUSIONS:*** WES has proven to be an invaluable tool in clinical practice for the diagnosis of rare genetic diseases, especially in patients suspected of IEM with normal targeted biochemical screening. The versatility of WES to detect abnormalities in any gene favors its application as a routine diagnostic procedure. Molecular diagnosis not only provides definitive clinical confirmation but also enables genetic counseling for families and improves patient management by anticipating disease progression and selecting appropriate therapies. Our results emphasize the importance of comprehensive analysis of candidate variants and recommend WES as a first-line diagnostic tool in cases without a clear differential diagnosis to expedite medical care.

P-058 - EVALUATING THE IMPACT OF MEASUREMENT UNCERTAINTY ON THE ACCURACY OF ENZYMATIC ALPHA-GALACTOSIDASE A QUANTIFICATION USING FILTER PAPER

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INTRODUCTION: Monitoring laboratory assay performance to detect errors is crucial for ensuring the reliability and validity of reported results, which is a significant responsibility within the context of patient safety. Common statistical tools such as the coefficient of variation and total analytical error are wellestablished indicators for evaluating measurement precision and accuracy. However, these tools do not account for all variables that may influence a measurement. Estimating uncertainty encompasses sources such as the reading equipment, the method's performance, and the laboratory

technician's proficiency, providing comprehensive information about the result, which is ultimately used for patient diagnosis and treatment monitoring. ***OBJECTIVE:*** This study aims to present the results of uncertainty estimation using the enzymatic assessment of alpha-galactosidase A on filter paper as a model. The goal is to evaluate the impact of this uncertainty on the accuracy of the results and the clinical decision limits. ***MATERIALS AND METHODS:*** The uncertainty in measuring alpha-galactosidase A was estimated by quantifying the enzyme in control population samples. Two laboratory technicians conducted the quantifications over a specified period under consistent analytical conditions. Statistical tools such as Fisher's F test, one-way analysis of variance (ANOVA), Student's ttest for bias, and the z-Score for bias were applied to the results. The uncertainty estimation considered contributions from the fluorescence reader, the method's performance, and the laboratory technicians' performance. ***RESULTS:*** Over the study period, each laboratory technician performed 40 determinations on the control sample. The repeatability for each technician was evaluated at 4.5% and 4.3%, respectively. The method's repeatability was 0.028 nmol/ml/h, its intermediate precision was 0.06 nmol/ml/h, and the fluorescence reader's contribution was 0.01 nmol/ml/h. The expanded uncertainty (U) was calculated to be 8.9%. ***DISCUSSION:*** The measurement uncertainty for alpha-galactosidase A indicates that the accuracy of the result and the clinical decision limits are not significantly affected. While the determination of this enzyme in DBS serves as a screening method, uncertainty estimation serves as a tool to monitor method performance, significantly reducing both false positives and false negatives in the test.

P-059 - INBORN ERRORS OF METABOLISM "TRANSCOBALAMIN II DEFICIENCY: A CASE REPORT

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INTRODUCTION: Transcobalamin II (TC-II) deficiency is considered a rare autosomal recessive genetic disease. It appears in early childhood caused by mutations in the *TCN2* gene. TC-II is a transport protein for vitamin B12 and facilitates its cellular uptake by receptor-mediated endocytosis. TC-II deficiency results in a lack of vitamin B12 entry into cells, this leads to depletion of intracellular cobalamin. Patients with this disorder present the following clinical characteristics: growth retardation, diarrhea, pancytopenia, neurological abnormalities, and infections due to immunodeficiency. ***OBJECTIVES:*** Present a clinical case with a definitive molecular diagnosis of Transcobalamin II Deficiency. ***METHODOLOGY:*** It was performed a descriptive and analytical case of a 10-month-old boy with gastrointestinal symptoms, recurrent infections, cyclical pancytopenias, severe anemia, neutropenia, thrombocytopenia, plus low B lymphocyte count secondary to transcobalamin deficiency due to pathogenic variants identified in the *TCN2* gene. The paraclinical tests from the initial admission showed pancytopenia, leukopenia, anemia (hemoglobin and hematocrit HG 7.5 - HTO 20.8) and severe thrombocytopenia, for which correction was performed, with transfusions of red blood cells, plasma and platelets on several occasions. Broad spectrum antibiotic coverage for rare microorganisms was performed; viral serology determinations were negative. The immunological profile showed hypoganmaglobulinemia. Initially, primary immunodeficiency was suspected due to the clinical presentation and characteristics. Because of the clinical presentation of this patient, it was carried out a Next Generation Sequencing (NGS) panel for the sequence analysis of 894 genes associated with genetic disorders. ***RESULTS:*** The sequence analysis of the *TCN2* gene by NGS identified two homozygotic variants, c.497_498del (p.Leu166Profs*7), which have been previously classified as pathogenic. This result was consistent with a diagnosis of transcobalamin II deficiency, which is a rare disorder causing intracellular cobalamin depletion. ***CONCLUSIONS:*** When observing signs that could suggest a primary immunodeficiency, it is important to think about inborn errors of metabolism that share a very similar clinical presentation, but the definitive diagnosis will be made by the identification of the genetic variant implicated. The definitive diagnosis enable to apply the specific treatment, reducing hospitalizations and continuous transfusions, considerably improving the quality of life and neurological development of this pediatric patient.

P-060 - REVIEW OF THE MANAGEMENT OF CRITICAL RESULTS AND DIAGNOSTIC RECORDS IN THE LABORATORY OF METABOLIC DISEASES AFTER 5 YEARS SINCE NATIONAL ACCREDITATION IN CHILE.

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INTRODUCTION: Inborn errors of metabolism are diseases of mostly autosomal recessive inheritance. Most of these pathologies manifest with non-specific signs and symptoms in the pediatric age. The strategy for implementing the national accreditation system is establishing a system of registration guidelines and timely notification of the results considered critical and/or highly diagnostic detected in the laboratory. Accreditation means that we operate under the quality standards set and regulated by the Ministry of Health, ensuring our patient's access, opportunity, financial protection, and quality of our services. ***OBJECTIVE:*** To retrospectively analyze the critical and diagnostic results of metabolic pathologies since the implementation of the Chilean national accreditation system between January 2019 and December 2023. ***MATERIALS AND METHODS:*** A search was carried out in the clinical laboratory's computer system for all altered test results; Organic Acids, Alpha-Galactosidase, Alpha-Iduronidase, Arylsulfatase A and B, Beta-Galactosidase, Beta-Glucuronidase, BetaGlucosidase, Quantification of Amino Acids, Hexosaminidase A, Total Hexosaminidase, Iduronate-2-sulfatase, Nacetylgalactosamine-6- sulfatase, Profile of Amino Acids and Acylcarnitines and Succinylacetone in urine recording the diagnostic results in the period from January 2019 to December 2023. The diagnoses were grouped by pathologies: Aminoacidopathies, Organic Acidurias, b-oxidation Defects, Lysosomal Storage Disease, and Urea Cycle Defects for each year. ***RESULTS:*** The total number of diagnoses per year was; 2019: 60 pathologies, 2020: 39 pathologies, 2021: 45 pathologies, 2022: 36 pathologies and 2023: 53 pathologies detected. The frequencies of the diseases diagnosed in the 5-year retrospective period correspond to 60.5% to Aminoacidopathies, 22.3% to Organic Acidurias, 12.4% to Lysosomal Storage Diseases, 1.7% to B-Oxidation Defects, 1.7% to Cycle Defects of Urea and 1.3% to other inborn errors of metabolism. 74.2% of patients are referred from public healthcare centers, while 25.8% are referred from private healthcare centers. CONCLUSIONS AND/OR DISCUSSION: Implementing the Chilean national accreditation system allows the clinical laboratory to maintain a structured and continuous evaluation program of compliance with relevant aspects of the safety of services. The maintenance of diagnostic records by groups of pathologies helps to know the distribution of patients at the national level, allowing the generation of diagnostic strategies and determining the need to implement new confirmatory tests.

P-061 - TRIGLYCERIDES LIE, BUT THEY GUIDE

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INTRODUCTION: X-linked glycerol kinase deficiency (GKD) has been reported as an isolated deficiency or as part of a contiguous gene deletion syndrome(CGDS). CGDS Xp21 a rare genetic metabolic disorder resulting from the deletion of a chromosomal fragment containing several loci, including glycerol kinase. The presence of elevated plasma triglycerides(TG) together with the urinary organic acids profile(UOA) (excretion of urinary glycerol and other metabolites depending on the deletion) can suggest the diagnosis. Traditional laboratory methods for TG use a lipase transforming them into glycerol; In the presence of free-glycerol in the patient sample we will obtain pseudotriglyceridemia. ***OBJECTIVE:*** To describe four cases of GKD diagnosed because of elevated TG. ***CLINICAL CASES:*** Case 1: 6-month-old male, admitted for hypotonia and repeated bronchoobstruction symptoms. Suspected cystic fibrosis due to altered screening with a normal sweat test. CPK 23015, ammonium and normal lactic acid. AOU: marked presence of glycerol (GKD), without orotic. TG: 425mg/dL, ACTH: 426pg/mL; cortisol 8.06 mg/dL. Dystrophin gene deletion. Primary adrenal insufficiency. CGDS diagnosis. Currently 8 years old, under medical supervision. Case 2: 3-month-old male from Salta. Hospitalization 16 days of life. Suprarrenal insufficiency. Persistent hyponatremia. Increased transaminases, anemia. TG: 729mg/dL. No ammonium. AOU: Marked presence of glycerol. CGDS diagnosis. Nutritional treatment. Case 3: 4-year-old male, native of Salta. No personal medical history until the age of 2 years, episode of hypoglycemia secondary to prolonged fasting. At 3 years old with paleness and drowsiness. Third current episode. Laboratory: Ketotic hypoglycemia. TG: 441mg/dL. AOU: marked presence of glycerol. GKD diagnosis. Case 4: Male, 7 years old, native of Salta. He was admitted due to dehydration secondary to vomiting with a history of several admissions. Ammonium and normal lactic acid. TG: 418mg/dL. Urine and blood samples are sent for metabolic evaluation. AOU: Marked presence of glycerol. GKD diagnosis. ***CONCLUSION:*** Suspected GKD in patients with a profile of pseudotriglyceridemia should be confirmed with AOU in search of the presence of glycerol (search for orotic acids in cases of CGDS). The marked phenotypic heterogeneity is evident. Although the outcome of isolated GKD is

favorable, (improve with age and nutritional treatment) the presence of CGDS requires multidisciplinary follow-up.

P-062 - INTERIM RESULTS FROM THE FIRST-IN-HUMAN INTRACISTERNAL DOSING OF RGX-181 INVESTIGATIONAL *AAV9* GENE THERAPY IN A CHILD WITH LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (CLN2)

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INTRODUCTION: CLN2 Batten disease is a lysosomal storage disorder caused by biallelic mutations in the *CLN2* gene encoding tripeptidyl peptidase 1 (TPP1), resulting in progressive neurological degeneration. Treatment involves biweekly intracerebroventricular (ICV) enzyme replacement therapy (ERT) with recombinant human TPP1 (cerliponase alfa) via an indwelling port. While ERT slows progression of motor loss, it does not stop or reverse most manifestations of the disease. ***OBJECTIVE:*** RGX-181 is an investigational gene therapy comprised of a recombinant NAV® AAV9 vector containing a human CLN2 expression cassette (AAV9.CB7.hCLN2) designed to induce sustained secretion of TPP1 enzyme in the central nervous system. ***CLINICAL CASE:*** We report a 5-year-old brazilian child with a genetic diagnosis of CLN2 that received intracisternal with 5 RGX-181 at a dose of 1.25 x 1011 genome copies/g brain mass under a single-patient investigator-initiated study. He started symptoms at 3,4 years and was diagnosed at 3.7 years. TPP activity was 16 nmol/h/mg protein (NR: 93 - 521). Pathogenic mutations in TPP1 identified were c.622 C>T and c.509-1G>C. Assessments included safety and tolerability, seizure frequency, anti-epileptic medication use, ERT use, CLN2 Clinical Rating Scale Expanded Language and Motor (CLN2 CRS-LX and -MX), and Mullen Scales of Early Learning (MSEL). Cerebrospinal fluid (CSF) was collected via indwelling ICV port immediately before ERT infusions 34 days prior to RGX-181 administration, immediately prior to the RGX-181 administration procedure, and at regular intervals following RGX-181 administration. All CSF samples were measured for TPP1 using electrochemiluminescence immunoassay. The procedure had been well tolerated with no serious adverse events. After 12 months, RGX-181–derived CSF TPP1 expression was 27- to 55-fold higher than measured ERTderived concentrations (14 days post-ERT) prior to RGX-181 administration. This elevated, sustained TPP1 expression was associated with 89% reduction in seizure frequency through 12 months, leading to withdrawal of two anti-epileptic medications and increased intervals between ERT infusions. Small but meaningful improvements in fine motor and expressive language skills on MSEL were also observed at 6 months. ***CONCLUSION:*** First-in-human administration of RGX-181 has been well tolerated without drug- or procedure-related AEs and the expression was sustained over 12 months.

P-063 - USE OF PP6D5 POLYMER AS A GENE THERAPY DELIVERY SYSTEM FOR TAY-SACHS DISEASE

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INTRODUCTION: Tay-Sachs disease (TSD) is a severe neurodegenerative disorder caused by a deficiency of the enzyme β-hexosaminidase A that results in the accumulation of partially degraded molecules, particularly in the central nervous system. ***OBJECTIVE:*** This study explores new therapeutic strategies, such as gene therapy using CRISPR-nCas9 and the non-viral vector PP6D5 polymer, to overcome the limitations of traditional viral vectors that induce adverse immune responses. ***MATERIALS AND METHODS:*** Polymer cytotoxicity, transfection efficiency, and enzymatic activity were evaluated in GM00515B fibroblasts in the short and medium term. Three plasmids (dHEXA, dHEXB, and CRISPR-nCas9) were used, and on-target release was confirmed by T7 endonuclease assay and donor insertion (dHEXA) in HEK 293 cells. Lysosomal mass, reactive oxygen species, and lipids were also evaluated. T-student, one-way, and two-way ANOVA statistical tests were performed with a significant difference of $P < 0.05$. ***RESULTS:*** The results showed that the PP6D5 polymer had an IC50 of 33.49 µM with a transfection efficiency of 8.1%, which was higher compared to lipofectamine (6.6%). Enzyme activity increased from 7 to 15 days post-transfection by 1.9% for dHEXA and 2.4% for dHEXA/dHEXB with Lipofectamine 3000. For the polymer, transfection increased 2.6% with dHEXA and 6.2% with dHEXA/dHEXB at 15 days. The activity stabilized up to 30 days, but decreased for the polymer to 2.9% for dHEXA/dHEXB, while cells transfected with Lipofectamine 3000 showed a further increase of 2.8% and

11.2% at 30 days post-transfection compared to untreated cells. However, the wild-type levels were not reached. There was a decrease in lysosomal mass and reactive oxygen species when cells were transfected with the polymer, although an increase in lipids was observed compared to untreated cells. ***DISCUSSION/CONCLUSIONS:*** This study demonstrates the potential of PP6D5 polymer and CRISPR-nCas9 for gene therapy in TSD due to its higher transfection efficiency compared to Lipofectamine 3000. It also provides the basis for future research in animal models and the correction of genetic abnormalities in the central nervous system for this disease, another lysosomal storage disorders.

P-064 - ENZYMATIC ALPHA-MANNOSIDASE ASSESSMENT ON LEUKOCYTES AND DRIED BLOOD SPOT (DBS) FOR THE DETECTION OF ALPHA MANNOSIDOSIS. THE COLOMBIAN EXPERIENCE.

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INTRODUCTION: Alpha mannosidosis is an inherited lysosomal metabolism storage disorder (OMIM 248500) characterized by autosomal recessive inheritance and a deficiency in alpha mannosidase (MAN2B1) activity. This deficiency leads to the intracellular accumulation of partially degraded mannose-rich oligosaccharides. The disease's natural progression displays the typical progressive and systemic clinical features common to lysosomal storage disorders, including mental retardation, coarse facial features, hearing loss, skeletal deformities, immunological defects, and central nervous system impairment. The phenotypic expression of these symptoms can vary widely, often correlating with the level of residual enzyme activity, which typically ranges from 5 to 15% of normal levels in the classic form of the disease. The clinical approach to diagnosing alpha mannosidosis requires differentiating it from other lysosomal storage disorders that present with Hurlerlike features, such as mucopolysaccharidosis, sialidosis, and mucholipidosis. Identification of the specific enzyme deficiency confirms the diagnosis, with molecular studies serving as complementary support for family studies. ***OBJECTIVES:*** To present the first reports in Colombia and by extension to the Andean region, of leukocyte and DBS reference values for the enzymatic activity of MAN2B1 in a population cohort under preliminary screening for mucopolysaccharidosis. ***MATERIALS AND METHODS:*** Two micro methods were standardized for analyzing MAN2B1 in leukocytes and DBS (1.2 mm cut) using an endpoint fluorometric assay that measures the enzyme's action on the substrate 4MU-Alpha-D-mannopyranoside. Beta-galactosidase was used as the control enzyme. RESULTS/ DISCUSSION. The reference range for MAN2B1 activity in leukocytes in the control population (n=80) was 70.3 - 428.4 nmol/mg protein/hour. For DBS in the control population (n=170), the reference range was 20.6 - 99.5 nmol/ml/hour. The age range for both control populations was 10-50 years. The DBS method was applied in a population screening of individuals with phenotypic traits compatible with mucopolysaccharidosis between 2021 and 2024. A total of 2,236 patients were screened, resulting in the identification of two cases with atypical deficiencies (residual activity ~ 20%) and 13 individuals with overexpression (2 - 6 times the maximum reference value). These findings directed the diagnosis towards other types of lysosomal disorders.

P-065 - ESTABLISHMENT OF A METHOD FOR THE DETECTION OF GLYCOSAMINOGLYCANS USING LIQUID CHROMATOGRAPHY COUPLED TO TANDEM MASS SPECTROMETRY (LC-MS/MS) IN COLOMBIA

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INTRODUCTION: Mucopolysaccharidoses (MPS) are part of the group of lysosomal storage disorders caused by deficiencies in lysosomal enzymes necessary for the degradation of glycosaminoglycans (GAGs). There are 12 distinct MPS disorders, each dependent on the type of accumulated GAG. To date, five GAGs have been identified: heparan sulfate (HS), dermatan sulfate (DS), chondroitin sulfate (CS), keratan sulfate (KS), and hyaluronic acid. In Colombia, the incidence is estimated to be 3 per 100,000 live births. Given that GAGs are the primary molecules accumulated in MPS, they have become key biomarkers for diagnosis and pharmacotherapeutic monitoring. In Colombia, local methodologies for diagnosis include the quantification of total GAGs using colorimetric methods, which have low specificity and

sensitivity. ***OBJECTIVE:*** To evaluate a method based on liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) for the characterization of glycosaminoglycans (GAGs) dermatan sulfate (DS) and chondroitin sulfate (CS) in urine and blood samples from Colombian patients with mucopolysaccharidosis (MPS) and in vitro cultured fibroblasts. ***MATERIALS AND METHODS:*** The Shimadzu LCMS-8060 chromatograph was used to analyze the samples. Calibration curves were obtained by enzymatic digestion of DS and CS polymers, along with blood and urine samples. Finally, Chondrosine was used as an internal standard. The cohort of MPS individuals was 7, and the cohort of healthy individuals was 35. ***RESULTS:*** Calibration curves were generated for the disaccharides of CS and DS with a linearity range of 1000 to 12000 ng/mL for CS and 2000 to 20000 ng/mL for DS, along with the identification of a cutoff point for healthy individuals and MPS patients of twice the standard deviation, with a value of 38,115.19 ng/mL for DS and 4,007.191 ng/mL for CS. ***CONCLUSIONS:*** These results will contribute to the accurate diagnosis of potential MPS patients in our country. Additionally, they will provide a tool for monitoring the development of potential gene or enzyme replacement therapies currently being developed by our research group.

P-066 - GENERATION OF CELLULAR MODELS FOR MUCOPOLYSACCHARIDOSIS IIIB GENERATED BY CRISPR/CAS9

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INTRODUCTION: Mucopolysaccharidosis IIIB (MPS IIIB) is an inborn error of metabolism caused by mutations in the *NAGLU* gene. These mutations result in the accumulation of heparan sulfate (HS) in the lysosome and cell membrane, leading to apoptosis, tissue damage, and organ dysfunction. MPS IIIB is a predominantly neurodegenerative disease that causes motor dysfunction, developmental delay, sleep disturbances, and dementia, among other symptoms. Occurs at 3-4 years of age with an overall incidence of 1/200,000 births. The study of physiological defects at the cellular level has focused on cells of the central nervous system, particularly neurons, but the effects of this disease on other cell types, such as astrocytes, are unknown. ***OBJECTIVE:*** To generate cell models deficient in the NAGLU enzyme in the HEK 293FT, neuroblastoma SHSY5Y, and astrocytoma U-87MG lines was proposed, using the CRISPR/Cas9 gene editing system to generate a knockout of the *NAGLU* gene. ***MATERIALS AND METHODS:*** A vector with a gRNA targeting exon 1 of the *NAGLU* gene was designed and constructed. Then, functional assays were performed to determine the changes caused by the mutations generated in the cellular models, leading to the identification of alterations in lysosomal mass, cell proliferation, glycosaminoglycans accumulation, oxidative stress, and autophagy. ***RESULTS:*** A vector with a gRNA targeting exon 1 of the gene was obtained which caused a reduction in enzymatic activity of more than 70% of the NAGLU enzyme in mutant cell populations. These populations have a broad spectrum of mutations, demonstrating the randomness of non-homologous cell repair systems when using this editing technique. In addition, the models showed increased lysosomal mass, cell proliferation, glycosaminoglycan accumulation, and autophagy relative to healthy cells. ***CONCLUSIONS:*** MPS IIIB models of astrocytes and neurons were generated with a significative reduction in NAGLU enzymatic activity, and the models show a similar phenotype to the MPS IIIB cell patients. These results will subsequently contribute to the understanding of the physiopathology of the disease, as well as its use in the search for therapeutic targets, treatments, and the development of capabilities for the generation of cellular models for other pathologies.

P-067 - IDENTIFICATION OF THREE DISTINCT NEUROCOGNITIVE TRAJECTORIES IN MPS II: CHALLENGES AND IMPLICATIONS FOR THERAPEUTIC APPROACHES

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INTRODUCTION: MPS II or Hunter syndrome patients traditionally are classified into severe/ neuronopathic and attenuated/ non-neuronopathic phenotypes based on the presence or not of progressive intellectual impairment with a cognitive decline starting before age 6. However, some recent evidence suggests the presence of a minority of patients with marked cognitive or behavioral impairment but not declining over time. The lack of recognition of this subgroup and its different natural course was a critical confusing factor for the design of clinical trials that evaluated the efficacy of new treatments for MPSII on CNS manifestations. ***OBJECTIVE:*** To characterize the phenotypic trajectories of MPS II patients older than age 6 from a cross sectional, four-dimentional neuropsychological evaluation, identifying potential indicators that could differentiate the 3 groups:

neuronopathic, "pseudoneuronopathic" and non-neuronopathic. ***METHODS:*** We performed a longitudinal cluster analysis of 1) intellectual level (IQ), 2) adaptive behavior (AB), 3) language development and 4) functional independence (FIM) in 18 MPS II patients aged 7 to 24 years evaluated with neuropsychological assessments as part of a home infusion program in Argentina between 2020 and 2021. ***RESULTS:*** The analysis revealed three clear distinct clusters: - Neuronopathic Group (n=11): Severe intellectual disability (IQ < 45), poor adaptive behavior, minimal language development (parent-reported levels 1-2), and high dependency (FIM scores indicating need for moderate to full assistance). "Pseudoneuronopathic" Group (n=3): Wide range of IQ (moderate to normal disability), better adaptive behavior than intellectual ability, significant language impairment (levels 3-5), and need for moderate assistance (FIM scores indicating need for supervision). - Non-Neuronopathic Group (n=4): Intellectual and adaptive scores close to normal (IQ and CDA around 82), age-appropriate language skills, and greater independence (FIM scores indicating modified independence). ***CONCLUSION:*** Our findings support the hypothesis that these three distinct neurocognitive trajectories in MPS II could be also identified without the need to confirm the decline with multiple assesments since early childhood. Although the N is too small to draw definitive conclusions, we can observe a trend towards the existence of three groups with different profiles. Early identification and personalized support are crucial for effective management for each phenotype.

P-068 - IMPROVING THE DIAGNOSIS OF LYSOSOMAL STORAGE DISEASES (LSDs) IN BRAZIL AND LATIN AMERICA THROUGH THE LSD BRAZIL NETWORK

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INTRODUCTION: To overcome the challenges related to the diagnosis of lysosomal storage diseases (LSDs), we created the LSD Brazil Network (LBN), which started activities in 2013. ***OBJECTIVES:*** The LBN aims to make largely available tools to enable diagnosis of lysosomal storage diseases, especially in Brazilian regions with difficult access to diagnostic facilities. ***METHODS:*** The LBN headquarter is located in Porto Alegre, and can be accessed via website, email, toll-free telephone, or WhatsApp. The LBN coordinating center raises unrestricted grants from several sources to maintain its infrastructure and provide the diagnostic service free of charge. The requester, who usually is a medical geneticist, metabolic pediatrician, or another specialist who suspect a LSD in a patient, fills a form with basic clinical information and send it to the LBN by courier, along with an Informed Consent Form, and the appropriate samples (DBS, plasma, urine, CSF, etc.). During the period 2013-2022 (10 years), samples from 26,489 subjects were received and processed, coming from all Brazilian regions, from some other countries, mainly Latin American. ***RESULTS:*** A total of 1,320 cases of LSDs were diagnosed (yield of 4.98%). The ten most frequent diseases were Mucopolysaccharidosis II (166), Gaucher (140), Mucopolysaccharidosis IVA (127), Mucopolysaccharidosis VI (121), Ceroid Neuronal Lipofuscinosis 2 (91), Mucopolysaccharidosis I (90), Acid Sphingomyelinase Deficiency (75), GM2 gangliosidosis/Tay-Sachs (73), Krabbe (72), and Mucopolysaccharidosis IIIB (57). This distribution may not reflect the actual relative prevalence of LSDs, as testing for some diseases are more frequently requested due to the availability of therapies (examples: Gaucher, MPS, CLN2). Also, some diseases (such as Fabry) have several other diagnostic services available in the region, and so the cases identified by LBN may represent only a fraction of the total diagnoses. Interestingly, the age at diagnosis decreased for some diseases (probably related to improved test availability) but increased for others (possibly related to atypical phenotypes identified in older patients). ***CONCLUSION:*** In summary, the LBN demonstrated to be a useful tool to enable the diagnosis of LSDs, especially in a region with scarce facilities as Brazil and Latin America.

P-069 - MUCOPOLYSACCHARIDOSIS VII (MPS VII) IN LATIN AMERICA: RESULTS FROM A NOVEL, LONGITUDINAL, MULTICENTER DISEASE MONITORING PROGRAM (DMP)

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Netherlands; (9) Centro Hospitalar do Porto, Porto, Portugal; (10) Hospital Británico, Buenos Aires, Argentina.

INTRODUCTION: MPS VII is an ultra-rare, autosomal recessive, debilitating, progressive lysosomal storage disease caused by beta-glucuronidase (GUS) enzyme deficiency. Vestronidase α (VA; recombinant human GUS) enzyme replacement therapy is approved in multiple regions worldwide for MPS VII treatment. ***OBJECTIVE:*** Describe patient characteristics and VA safety and efficacy among Latin American patients in the DMP. ***METHODS:*** The DMP is an ongoing, multicenter observational study collecting real-world data from patients with MPS VII (N≈50 planned). ***RESULTS:*** As of 17Nov2023, 36 patients were enrolled in the DMP. Sixteen (44%) had a history of suspected non-immune hydrops fetalis (NIHF). Mean (SD) age at enrollment was 13.9 (11.1) years (range 1.5-50.2 years). Twenty-three patients (64%) were treated with VA prior to DMP enrollment, 5 (14%) were initially treated during the DMP, 7 (20%) had not received VA, and 1 was unknown. Among patients treated prior to enrollment, dermatan sulfate (DS) was reduced >80% from pre-treatment baseline levels. All treatment-related adverse events were consistent with the known VA safety profile. Fourteen patients were from Latin American countries and have up to 3.2 years of DMP data and 8.6 years of VA treatment. Age at enrollment ranged from 1.5-25.8 years. Nine (64%) had a history of NIHF. Ten (71%) had cardiomyopathy and/or cardiac valve abnormalities, and 8 (57%) had hepatomegaly and/or splenomegaly. Ten (71%) had severe to profound intellectual disability, and four (29%) had mild to moderate intellectual disability. Six (43%) were treated with VA prior to DMP enrollment, 4 (29%) were initially treated during the DMP, and 4 (29%) had not received VA. Pre-treatment DS levels (n=10) ranged from 8.2-24.8 times the upper limit of normal (ULN). DMP baseline levels for those who had previously received VA (n=6) ranged from 1.2-6.5xULN; levels for those who had not yet received VA (n=8) ranged from 8.2-11.6xULN. ***CONCLUSION:*** Baseline characteristics and reductions in DS levels were similar to overall data, though access to VA may be more limited. Long-term follow-up resources needed in remote regions.

P-070 - SLY SYNDROME, A RARE BUT TREATABLE DISEASE: A CASE REPORT

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INTRODUCTION: Sly Syndrome, also known as mucopolysaccharidosis (MPS) type VII, is an extremely rare, life-threatening, progressive disease caused by genetic mutations affecting lysosomal function. The estimated worldwide prevalence is <1: 1,000,000, accounting for <3% of all MPS diagnoses. In Brazil, from 1982 to 2019, only 21 cases were confirmed. Although mucopolysaccharidosis type VII is very rare, some cases may go undiagnosed. Given that it is a treatable disease, it cannot be ignored. Treatment with enzyme replacement therapy is available and is generally beneficial, especially for patients with minimal or no cognitive involvement. ***OBJECTIVE:*** The objective of this report is to disseminate knowledge about Sly Syndrome through a clinical case recently diagnosed in our service, aiming to increase medical community awareness regarding similar cases and prevent undiagnosed cases. ***METHOD:*** The chosen method was a clinical ***CASE PRESENTATION: CASE REPORT:*** A 7-year-old male patient, the first child of a non-consanguineous couple with a possibility of hidden consanguinity, presented with numerous perinatal complications including jaundice, cholestasis, blood dyscrasias, and respiratory distress, necessitating neonatal intensive care. Over the years, he developed physical deformities, abnormal neuropsychomotor development, and significant behavioral disorders, diagnosed as autism by an external physician. Due to interference of his behavioral issues with therapies, he was referred to our neuropediatric evaluation at 6 years old. Our examination revealed dysmorphic facial features, prompting an etiological investigation with enzyme assays for treatable MPS using dried blood spots. This revealed low β-glucuronidase enzyme activity, along with elevated levels of glycosaminoglycans (GAGs) in urine, leading to a diagnosis of MPS VII, later confirmed genetically. Currently, the patient is receiving specific treatment with intravenous enzyme replacement therapy (ERT) without reported side effects. ***DISCUSSION:*** As clinicians, our tendency is to suspect diseases with which we are familiar. Therefore, increasing awareness among clinicians about the early signs of MPS is crucial for timely diagnosis and the initiation of appropriate treatments like enzyme replacement therapy (ERT) as early as possible.

P-071 - THERAPEUTIC EFFECTS OF LOSARTAN ON AORTIC PATHOLOGY IN MUCOPOLYSACCHARIDOSIS I MICE

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INTRODUCTION: Mucopolysaccharidosis type I (MPS-I) results from a deficiency in alpha-L-iduronidase, causing an accumulation of glycosaminoglycans. Aortic dilatation and cardiac abnormalities are common characteristics in MPS-I patients and, also, are observed in mouse model. Our previous research demonstrated that losartan treatment improves cardiac function and reduces aortic diameter in MPS-I mice. ***OBJECTIVE:*** In this study, we further evaluated the impact of losartan on the aortic structure in MPS-I mice and explored the underlying mechanisms responsible for its beneficial effects. ***METHODOLOGY:*** Three groups of animals were used in this study: (1) wild-type mice (WT; n=10), (2) untreated MPS-I mice (n=8), and (3) MPS-I mice treated with losartan from 2 months of age (0.6g/L in water; n=9). At 6 months, all animals were euthanized, and their aortas were collected for analysis. Histological were performed to quantify elastin breaks per millimeter and aortic thickness. Immunohistochemistry was conducted to assess levels of pSMAD2/3, pSTAT3, and pERK1/2. Additionally, TGF-β gene expression was measured using RT-qPCR. Cathepsin and metalloproteinase (MMP) activities were evaluated through fluorometric assays. Statistical comparisons were performed using one-way ANOVA with Tukey's post-hoc. All animals' studies were approved by local ethical committee. ***RESULTS:*** A significant increase in elastin breaks was observed in untreated MPS-I mice, while losartan treatment normalized this parameter ($p<0.01$). We observed an increase in pSTAT3, pERK1/2, and mRNA level for TGF-β, coupled with a reduction in pSMAD2/3 in aortas from untreated MPS-I mice. Cathepsin and MMP activity also increased significantly ($p<0.05$). Losartan treatment reduced pSTAT3 levels and increased pSMAD2/3 levels but did not affect pERK1/2 levels. Furthermore, losartan had no effect on cathepsin activity but reduced TGF-β mRNA levels and MMP activity. ***CONCLUSION:*** These findings reveal a potential mechanism by which losartan reduces aortic dilatation in MPS-I and support its potential as a promising adjunctive therapy for MPS-I, which is currently being evaluated in clinical trials.

P-072 - CERLIPONASE ALFA FOR THE TREATMENT OF CLN2 DISEASE IN A PATIENT COHORT INCLUDING CHILDREN LESS THAN 3 YEARS OLD

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INTRODUCTION: Open-label studies in children 3 to 16 years of age with CLN2 disease showed that biweekly intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa slowed deterioration in motor and language function. ***OBJECTIVES:*** We report findings from a study to assess safety and efficacy of cerliponase alfa in an expanded cohort including children <3 years. ***MATERIAL AND METHODS:*** Subjects received ICV cerliponase alfa biweekly; dosage was based on age (subjects ≤2 years receive <300 mg). Safety was assessed by adverse event (AE) frequency. The primary efficacy endpoint was rate of decline in score on the motor and language (ML) domains of the CLN2 Clinical Rating Scale, comparing treated subjects with matched historical controls. ***RESULTS:*** A total of 14 subjects were enrolled (8 female, 6 male). Mean (SD) baseline ML score was 4.6 (1.7); mean (SD) age at baseline was 3.1 (1.5) years (range: 1.1-6.0). Subjects received cerliponase alfa for a mean (SD) of 140.4 (6.0) weeks. Twelve subjects were matched to historical controls: mean (SD) rate of decline in ML score was 0.15 (0.24) points/48 weeks for treated subjects and 1.30 (0.86) points/48 weeks for matched controls (mean difference: 1.15; 95% CI: 0.80, 1.50). Among subjects <3 years of age at baseline (n=8), 7 subjects had a baseline ML score of 6 and remained at an ML score of 6 at end of study. For the older subjects (n=6), four had baseline ML score of 4 and two had ML score of 2. All subjects experienced ≥1 AE; the most common drug-related AEs were pyrexia and hypersensitivity. Twelve subjects experienced ≥1 serious AE; there were no deaths or discontinuations due to AEs. ***CONCLUSIONS:*** ICV-administered cerliponase alfa slowed the decline in motor and language function in children with CLN2 disease, including those <3 years of age, with a safety profile consistent with prior studies. Additionally, these results may suggest that early initiation of treatment can delay symptom onset.

P-073 - COMPARISON OF LYSOSOMAL FUNCTION AMONG DIFFERENT IN-VITRO CELL MODELS: RELEVANCE IN THE STUDY OF LYSOSOMAL STORAGE DISEASES

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INTRODUCTION: To study lysosomal storage diseases (LSDs), in-vitro cellular models can be employed. Currently fibroblasts are the most used model, however macrophages (a monocyte derived lineage) constitute an important representative of the reticuloendothelial system and are characterized by their capacity for endocytosis and degradation of substrates associated with LSDs, thus representing an intersting model for LSDs which has been poorly explored so far. ***AIM:*** To compare in-vitro lysosomal function of three cellular models, macrophages, monocytes and fibroblasts, in terms of lysosomal mass and intracellular enzymatic activity in basal state and under specific substrate stimulation. ***METHODS:*** The evaluated cell populations included: WT fibroblasts (n=1), MPS IV fibroblasts (Coriel GM00593), WT mononuclear cells (n=2), WT monocytes (n=2), WT macrophages (n=2), and MPS VI monocytes (n=1). The enzymatic activities of βgalactosidase, β-hexosaminidase, and β-glucuronidase were performed using artificial fluorescent (4-MU) substrates. Additionally, lysosomal mass was evaluated through microscopy and flow cytometry using Lysotracker. Comparisons of these parameter were performed under basal conditions and under a "challenge assay" suplementing cell culture media with chondroitin sulfate and heparin at a final concentration of 80 µg/mL for 3 hours. Results were analyzed using non-parametric statistics (P-value <0.05) with Graphpad prism. ***RESULTS:*** Significant differences were found in basal enzymatic activity between WT-macrophages and WT-fibroblasts for β-galactosidase (P=0.0011) with average values of 99 and 54 nmol/h/mg respectively and βglucuronidase (P=0.001) with values of 29 and 10 nmol/h/mg for WT macrophages and WT-fibroblasts. Cell viability with the "challenge assay" was >80%. Non-significant differences were observed in basal enzymatic activities compared to activities of cells exposed to the challenge assay for any cell population, except for WTmonocytes. Flow cytometry showed no significant differences in lysosomal mass at 3h. ***CONCLUSIONS:*** Our results showed that WT-macrophages appear to have higher basal lysosomal activity compared to WTfibroblasts, although this behaviour seems to vary depending on the parameter evaluated. In addition, a protocol was established for challenging cell in culture with a lisosomal substrate like GAGs which could be extrapolated to other lisosomal substrates. However, further improvement on substrate concentrations and time of exposure are required for triggering significant changes in lisosomal function.

P-074 - FIRST CONFIRMED CASE OF THE SAPOSIN B PROTEIN ACTIVATOR DEFICIENCY PRESENTING AS METACHROMATIC LEUKODYSTROPHY IN THE DOMINICAN REPUBLIC: A CASE REPORT

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INTRODUCTION: Metachromatic leukodystrophy (ML) is a rare autosomal recessive lysosomal storage disorder characterized by the deficient activity of arylsulfatase A (ARSA), leading to the pathological accumulation of cerebroside sulfate within the central and peripheral nervous systems. In exceedingly rare instances, ML may also be attributed to pathogenic variants in the *PSAP* gene, which encodes the Saposin B (Sap-B) protein activator. This case represents the first confirmed diagnosis of Sap-B deficiency in the Dominican Republic, underscoring the geographical and diagnostic challenges associated with this disorder. ***OBJECTIVE:*** To document the first confirmed case of Sap-B deficiency manifesting as ML in our medical facility, with emphasis on the diagnostic methodology, genetic findings, and clinical implications. ***CASE PRESENTATION:*** A 5-year-old male patient with an unremarkable medical history presented with new-onset generalized tonic-clonic seizures. Initial evaluations, including routine hematological and biochemical tests, cerebrospinal fluid analysis via lumbar puncture, and electroencephalography, yielded normal results. Computed tomography imaging revealed cerebral edema. The patient's clinical course was marked by progressive gait ataxia, culminating in an inability to ambulate. Additionally, the patient exhibited a marked decline in speech, characterized by dysarthria and eventual regression to babbling. Due to the constellation of seizures, spasticity, and global psychomotor regression, a cranial magnetic resonance imaging was performed, revealing cortico-subcortical atrophy without the typical white matter and corpus callosum changes associated with ML. Molecular genetic analysis performed by the Neurology and Genetics departments identified a homozygous deletion in the *PSAP* gene (c.679_681del), resulting in an in-frame deletion (p.Lys227del) consistent with Sap-B deficiency, a rare variant of ML. Additionally, the patient exhibited pseudodeficiency alleles for *ARSA* and *GALC* genes. The patient received conservative management but succumbed to diseaserelated complications following a two-month hospitalization in the pediatric intensive care unit. ***CONCLUSION:*** Although there is no definitive cure for ML, allogeneic hematopoietic stem cell transplantation may offer therapeutic benefits in early-stage patients. This case emphasizes the critical need for heightened global

awareness and precise diagnostic capabilities for rare genetic disorders. Early implementation of genetic testing, particularly in underrepresented regions such as the Dominican Republic, is paramount for timely and effective therapeutic interventions, ultimately enhancing patient outcomes.

P-075 - HEXOSAMINIDASE UP, HEXOSAMINIDASE DOWN!

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INTRODUCTION: β-hexosaminidase is a lysosomal hydrolytic enzyme constituted by the α and/or β subunits, which participates in the catabolism of sphingolipids. When these enzymes present deficiencies and/or alterations, diseases of lysosomal origin develop.β-Hexosaminidase A is built up of alpha subunit (*HEXA* gene) and β subunit (*HEXB* gene), β-hexosaminidase B made up of 2 β subunits and the always forgotten βhexosaminidase S built up of 2 alpha subunits.If affected gene is *HEXA*, decreased fraction is β-hexosaminidase A with normal values of β-hexosaminidase B and total (Tay-Sachs disease). Both fractions and total are decreased when the affected gene is *HEXB* (Sandhoff disease). Like in many inherited diseases, a blood test can determine enzyme activity. ***OBJECTIVE:*** To describe 2 different biochemical profiles from the enzymatic activity of β-Hexosaminadase and to highlight the importance of a correct interpretation. ***CLINICAL CASES:*** Case 1: 1-year-old male patient, with no relevant prenatal history, hospitalized for 36 hours in neonatology due to abnormal movement and possible bradycardia. Studied for the presence of hypotonia, respiratory problems and the presence of a cherry red spot at an ophthalmological level. Result of the activity of β-Hexosaminidase Total, β-Hexosaminidase B and A in both leukocytes and plasma were decreased. Sandhoff disease is suspected. Genetic study pending. Case 2: 12-year-old female patient, without family or prenatal history. He presents skeletal malformations suggestive of lysosomal storage disease. Oligosaccharides in TLC with the presence of nonspecific abnormal bands. Three enzymatic activities of different hydrolases are carried out, being elevated with respect to the reference values. Panel of skeletal dysplasias with 2 VUS for the *GNPTAB* gene. Plasma β-Hexosaminidases elevated 2 times compared to the reference value. Probable diagnosis of Mucolipidosis with inconclusive genotype due to VUS variants. The families will be analyzed for possible reclassification of variants. ***DICUSSION OR CONCLUSION:*** Both cases highlight the importance of both decreased and elevated β-hexosaminidase values. When there is clinical suspicion of a lysosomal storage disease, laboratory tests support, confirm and rule out the suspicion. The correct interpretation of the enzymatic activities of the different fractions by the laboratory is critical for the correct diagnosis.

P-076 - JUVENILE PRESENTATION OF TAY SACHS DISEASE: A CASE REPORT

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INTRODUCTION: Tay-Sachs disease is a progressive neurodegenerative disorder with autosomal recessive inheritance caused by a deficiency of the enzyme β-hexosaminidase A, leading to an accumulation of GM2 (a type of ganglioside) in lysosomes, thus classified as a lysosomal storage disease. It results from mutations in the hexosaminidase A gene located on chromosome 15q23-q24. Three forms of presentation are described based on age and enzymatic activity: Infantile, juvenile, and adult. The juvenile form is the rarest, manifesting subacutely in the preschool stage with developmental regression and progressive neurological deterioration; patients typically succumb in adolescence mainly due to respiratory or infectious complications. Cherry-red spot in the retina, gait abnormalities, and speech impairments are characteristic features. ***OBJECTIVE:*** To present a case of a 5-year-old patient diagnosed with juvenile Tay Sachs disease, presenting as progressive encephalopathy since the age of two. ***CLINICAL CASE:*** The patient exhibited normal neurodevelopment until age two, after which she progressively developed gait abnormalities with frequent falls, loss of language and social interaction, severe swallowing disorder, deceleration in head circumference growth, spastic quadriparesis, and difficult-to-control epilepsy. The cranial MRI showed alterations in the white matter and signs of cerebral atrophy. The diagnosis of Tay-Sachs disease was confirmed by finding a pathogenic

variant c.566G>A (p.Arg189His) in heterozygosis and a likely patoghenic variant c.1570>T (p.Gln524*) in heterozygosis of the *HEX-A* gene in exome sequencing and determining decreased enzymatic activity of β hexosaminidase A in leukocytes. ***CONCLUSIONS:*** Developmental regression is always a warning sign, and inborn errors of metabolism should be considered in diagnostic suspicions. The juvenile form of Tay-Sachs disease is very rare and should be taken into account in cases of developmental regression between the ages of 2 and 6. Genetic testing and measurement of β hexosaminidase enzyme levels confirm the diagnosis. New treatments, such as the administration of Acetyl-L-leucine, aim to slow down the progression of the disease.

P-077 - LABORATORY STUDIES FOR LYSOSOMAL DISEASES: 20-YEAR REPORT

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INTRODUCTION: Lysosomal diseases (LD) are a group of more than 70 diseases caused by alteration of the function of a lysosomal protein and are generally associated to substrate accumulation. Laboratory analysis for diagnosis include substrate determination, enzyme assays and/or genetic tests. ***OBJECTIVES:*** The aim of this study is to report 20-year results of lab studies in DIEL laboratory for diagnosis of Argentine patients with clinical suspicion of a LD. ***MATERIALS AND METHODS:*** In the period between 2002 and 2022 urine and/or blood samples from patients with clinical suspicion of a LD were received. Lab tests specific for each pathology were carried out, including substrate detection, enzyme assays in dried blood spots and leukocytes, and genetic tests. All the patients signed the informed consent form. ***RESULTS:*** A total number of 17652 samples were received at DIEL. More than half of the samples were from patients with clinical suspicion of Fabry disease, followed by Gaucher and MPS. The proportion of positive results were 7, 6 and 13%, respectively. Regarding MPS samples, the major percentage of positives were for MPS II, with a proportion of 20%. ***CONCLUSIONS:*** As a conclusion, it is of recognition the high rate of confirmatory diagnosis among these group of rare diseases, revealing a good relationship with the clinical suspicion targeted for this group of diseases.

P-078 - POSSIBLE ANTITUMOR EFFECT OF CYSTEAMINE IN PATIENTS WITH NEPHROPATHIC CYSTINOSIS.

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INTRODUCTION: Nephropathic cystinosis (NC) is a lysosomal storage disease with autosomal recessive inheritance. This study presents the long-term follow-up of a patient managed for NC who developed a selflimited intracranial neoplasm. ***CASE:*** Male is 28-years-old who was diagnosed with nephropathic cystinosis during childhood. He has been treated with cysteamine (CysA) since the age of 4 and received an allograft kidney transplant from his mother at 9 years old. He has not received (CysA) for the last 2 months which is confirmed by the high level of cystine in leukocytes: 4.79 nmol/cystine/mg. At the age of 26, he experienced seizures and hyperglycemia which were corrected. A neurology/neurosurgery medical board requests CT and brain MRI. Neuroimages revealed a lesion in the right middle occipital region, adjacent to the occipital horn of the right lateral ventricle, suspicious for a glial tumor. The patient refused a biopsy. After 18 months, he presented with altered consciousness due to hyponatremia and hypokalemia. New diagnostic imaging studies were performed. New diagnostic imaging studies were performed, including videoelectroencephalography and brain magnetic resonance imaging, which were reported as normal. ***CONCLUSIONS:*** The association between NC and glial tumors has not been reported in the medical literature (Pubmed, scopus and DOAJ). We propose that the patient had an occipital brain tumor that spontaneously resolved 18 months later. Cysteamine is known to cross the blood-brain barrier; Jeitner et al. proposed its use as a promising antitumor thiol for neural neoplasms in vitro. Yao et al. demonstrated significant tumor reduction in vivo by injecting Cu-CysA (copperCysA) followed by 5 minutes of microwave irradiation. We hypothesize that the remission of the brain mass could be attributed to the radiation dose administered during computed tomography 18 months prior to the recent neuroimaging. This radiation could have acted as a photosensitizer for cysteamine, explaining the observed antineoplastic effect.

P-079 - BETA-GLUCOSIDASE LEVELS IN DBS USING A 5 MM PAPER PUNCHED DISC. FIVE YEARS' EXPERIENCE IN HIGH-RISK SCREENING FOR GAUCHER DISEASE.

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INTRODUCTION: Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by mutations in the *GBA* gene (1q2.1), leading to deficient Beta-glucosidase activity (D-glucosyl-acylsphingosine glucohydrolase, EC 3.2.1.45). This disease is likely the most prevalent sphingolipid metabolism disorder globally, with an estimated incidence ranging from 0.39 to 5.8 per 100,000 live births. The phenotype of the disease exhibits a broad spectrum of clinical manifestations, including hepatosplenomegaly, anemia, leukopenia, thrombocytopenia, and bone lesions of varying severity, highlighting the critical importance of enzymatic assessment studies. ***OBJECTIVE:*** To report the results of a 5-year (2019-2024) high-risk screening program for individuals with clinical characteristics of Gaucher disease using 5 mm diameter dried blood spots (DBS), approximately 10 µL of blood. This specific cut was chosen to minimize the impact of low blood counts typically seen in these often anemic patients, which could otherwise increase the likelihood of false positive results. METHODS/MATERIALS The Beta-glucosidase enzymatic activity in patients and controls was assessed by eluting the specified cut in 300 µL of 0.5% Triton X-100 and using an endpoint fluorometric method with 4-methylumbelliferyl-β-D-glucoside as the substrate. Beta-galactosidase was used as the control enzyme. ***RESULTS:*** During the specified period, 801 controls were analyzed, showing a Beta-glucosidase activity range of 3.56 - 12.82 nmol/ml/h (Mean: 5.29). Additionally, 3,634 patients with clinical suspicion of GD were assessed, with Beta-glucosidase activity range of 0.5 - 55.64 nmol/ml/h. After subsequent confirmation enzymatic assays of the 3,634 evaluated patients, it was determined that 92 patients (2.5%) had Gaucher disease, with DBS values ranging from 0.66 to 3.36 nmol/ml/h (Mean: 1.9). Notably, 90% of these confirmed patients exhibited values ≤ 2.8 nmol/ml/h. ***DISCUSSION:*** Compared to the protocol previously used in our laboratory (slice: 1.2 mm, ≈ 0.52µL of blood), which were directly eluted in reaction buffer-substrate, the current assay offers a 53% reduction in false positives (62 cases / 1.4% of the total). This is because the described cut provides a more homogeneous sample in the elution, which is less affected by leukopenia or lack of impregnation. Additionally, there was an improvement in the intra/inter-assay variability coefficients (Mean: 4.5% and 4.9%, respectively).

P-080 - EVALUATION OF CELLULAR MODELS FROM ASTROCYTOMA AND NEUROBLASTOMA CELL LINES FOR THE STUDY OF TAY-SACHS PATHOPHYSIOLOGY

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INTRODUCTION: Beta-N-acetyl-hexosaminidase A (Hex A) is a heterodimeric lysosomal enzyme formed by alpha and β subunits coded by the *HEXA* and *HEXB* genes respectively. Mutations in the HEXA gene cause reduced enzymatic Hex A activity which produce accumulation of non-degraded GM2 ganglioside in the lysosomes. Accumulation of GM2 is the primary cause of the Tay Sachs disease, an autosomal recessive condition with a significant neuronal involvement. Although it is known that the accumulation of GM2 ganglioside is the main cause of neurodegenerative deterioration, the exact mechanism that promotes neuronal death in patients is not totally clear. Therefore, the development of two Tay-Sachs models from neuroblastoma and astrocytoma cell lines (U87-MG and SH-SY5Y) using CRISPR-Cas9 to induce mutations in the first exon of the *HEXA* gene would allow the expand in the knowledge about the disease pathophysiology. ***OBJECTIVES:*** To develop two cellular models that replicates the classical phenotype of the Tay-Sachs disease using the cell lines SH-SY5Y and U87MG. ***MATERIALS AND METHODS:*** By transfecting CRISPR-Cas9 plasmids, we knocked out the *HEXA* gene in SH-SY5Y and U87MG cell lines (Which are neuroblastoma and glioblastoma like cell lines respectively). After proliferation of single clones selected by cell sorting, we sequenced a region of the first exon of the HEXA gene. Clones that showed reduced Hex A activity were selected for lysosomal mass accumulation by Lysotracker deep red staining, neutral lipids accumulation by Nile Red staining, and increase in reactive species of oxygen by H2DCFDA staining. One-way ANOVA was used for statistical significance evaluation among different conditions. $p<0.05$. ***RESULTS:*** Cell populations selected by cell sorting and screened by low Hex A enzymatic activity also showed increased lysosomal mass. These clones also accumulated neutral lipids. Overall, this suggest accumulation of lipid-based molecules in the cell lysosomes. Finally, contrary to expectations, increase in reactive species of oxygen was not observed. ***CONCLUSIONS:*** The cellular models generated showed a phenotype similar of what have been reported for Tay Sachs disease and could be an important tool for the study of cellular mechanisms related with the disease

progression and the evaluation of future and current therapeutic approaches.

P-081 - BASELINE CHARACTERISTICS OF FABRY DISEASE "AMENABLE" PATIENTS TO ORAL TREATMENT IN ARGENTINIAN COHORT.

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INTRODUCTION: Fabry disease (FD) is a multisystem lysosomal storage disorder induced by genetic variants in the *GLA* gene. Some FD patients have GLA variants with a reduction in overall αGalA enzymatic activity due to mutated proteins with reduced stability, caused by protein misfolding and premature degradation, but the αGalA catalytic activity remains conserved. To correct this misfolding and to prevent premature degradation, an oral small iminosugar molecule was developed. ***OBJECTIVE:*** We report the clinical characteristics of FD "amenable" cohort patients from Argentina, prior to starting oral treatment. ***MATERIALS AND METHODS:*** Seventeen Fabry adult patients were recruited from 13 Argentinian Centers; 8 males were included. Inclusion criteria were as follows: FD patients with confirmed diagnosis by the genetic test and "amenable" GLA variants. The study of the genetic variant was carried out by PCR amplification and sequencing of all coding exons and franking intronic regions from previous DNA extraction from Dried Blood Spot. ***RESULTS:*** All genotypes included were missense-type "amenables" mutations. Some classic FD typical early manifestations were more frequent in patients with "classic" versus "late-onset" FD phenotype (pain, p=0.002; cornea verticillata, p=0.019). There was a statistically significant difference in estimated glomerular filtration rate in the "classic" versus "late-onset" phenotype (p=0.026) but no difference between genders (p=0.695). Left ventricular mass was similar between genders and phenotypes. In patients who started "de novo" oral treatment, the main indications were (i) heart disease, (ii) kidney damage and (iii) pain, while in "switched from prior IV treatment" patients, the most frequent indication was "patient decision;" this coincides with publications by other authors. Contrary to expectations, in our population, plasma Lyso-Gb3 was similar between both phenotypes, probably due to an effect of the subjects included distribution, with more patients in the "late-onset" group and within the "classical" population, a greater number of females. ***CONCLUSIONS:*** Among Fabry "amenables" patients from Argentina, NOT all major clinical disease manifestations are more frequent among "classic" versus "late-onset" phenotypes.

P-082 - BIOTECHNOLOGY FOR LYSOSOMAL DISORDERS: A COLOMBIAN EXPERIENCE IN DEVELOPING RECOMBINANT PROTEINS AS POTENTIAL ENZYME REPLACEMENT THERAPIES

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INTRODUCTION: One of the most important challenges in Inborn Errors of Metabolism is to find a novel and effective treatment. Lysosomal storage disorders are one of the groups where just 11 of 70 diseases have approved a therapy, and not all are totally effective. ***OBJECTIVE:*** In Colombia, during the last 25 years, the Institute for the Study of Inborn Errors of Metabolism has worked in the study of enzyme replacement therapy. ***MATERIALS AND METHODS:*** The process has reached to the production of six lysosomal enzymes on bacteria (Escherichia. coli/Lactobacillus plantarum) and yeast (Pichia pastoris/Komagataella phaffii). All proteins have been produced at different scales, as well as purified and characterized for biological activity, stability, cell uptake, lysosomal delivery, and substrate reduction. ***RESULTS:*** At

first iduronate-2-sulfate sulfatase (IDS) and N-acetyl-galactosamine-6-sulfate-sulfatase (GALNS) were assessed in E. coli, with successful production, biological activity (2.82 to 34.2 U/mg to IDS and 0.078 to 1.2 U/mg to GALNS), recombinant proteins were partially secreted and stable at pH and temperature but were not internalized. Several efforts were focused to improve the activity and allowed the production of a N-glycosylated GALNS in E. coli, leading to cell internalization in fibroblasts and substrate reduction. L. plantarum, was assessed to produce an active phenylalanine hydroxylase (PAH), showing a 28% reduction of L-Phenylalanine. The yeast Pichia pastoris has been assessed to obtain active recombinant proteins at different production scales as IDS (up to 7.3 U/mg), GALNS (16.7 U/mg), Hexosaminidase A and B (12,364 and 10,340 U/mg respectively), Nacetyl-alpha-glucosaminidase (NAGLU, 0.4 to 0.74 U/mL), and arylsulfatase B (ARSB, 879 to 3,335 U/mg). All of them have shown high stability, proper cellular uptake by skin fibroblasts, HEK293, U87MG (astrocytoma) or SHSY5Y (neuroblastoma), lysosomal delivery, and substrate reduction, in some cases reaching normalization. Finally, P. pastoris, was modified to obtain glycoengineered protein with N-glycans like those of human proteins, achieving higher levels of activity, stability, and uptake, as well as lower immunogenicity compared to proteins obtained in the non-modified yeast. ***CONCLUSION:*** The findings presented here offer a significant contribution to the field of health sovereignty, providing a foundation for further research into other disorders.

P-083 - NEURONAL CEROID LIPOFUSCINOSIS TYPE 2: ENZYME REPLACEMENT THERAPY (ERT) AND NATURAL HISTORY OF THE DISEASE AMONG 3 SIBLINGS

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INTRODUCTION: Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is a rare rapidly progressive neurodegenerative disease that results in early-onset, severe, progressive, neurological disabilities, leading to death in late childhood or early adolescence. Intracerebroventricular enzyme replacement therapy (ERT) with cerliponase α has been shown to delay disease progression in symptomatic patients. ***OBJECTIVES:*** We describe the clinical evolution of 3 siblings diagnosed with classic CLN2, 2 of which are receiving ERT. ***MATERIALS AND METHODS:*** Medical report of 3 siblings with biochemical and molecular diagnosis of CLN2. ***RESULTS:*** Patient 1: a 22 year old male patient who began with language delay, drug-resistant epilepsy and ataxia, with a late diagnosis of CLN2 at 7 years of age, prior to the advent of ERT. He develops a rapidly progressive disease with total loss of walking and language at age 8, demonstrating the natural evolution of the disease. He currently presents a severe commitment with a requirement for home hospitalization. Patient 2: his 9-year-old brother who began with language delay at age 2. Given his family history, an early diagnosis of CLN2 was made, starting ERT at 30 months of age. He progressed slowly with epilepsy onset at age 6, reaching literacy at age 7. He showed retinopathy at age 8 and preserved independent gait. Patient 3: the 2 years and 8 months old brother with presymptomatic diagnosis of CLN2, initiation of TRE at 20 months of age. He currently shows speech delay as the only symptom. The diagnosis was made by molecular study that showed the variant c.827A>T (p.Asp276Val) in homozygosis in the *TPP1* gene, described as pathogenic in the literature. ***CONCLUSION:*** In our patients, early-onset ERT has shown to slow the appearance of symptoms compared to the natural evolution of the disease, therefore, we emphasize the relevance of an early diagnosis based on the aknowledge of clasical CLN2. However, we must consider the importance of conducting a longterm follow-up study in a larger cohort of patients

P-084 - ONE YEAR OF FOLLOW-UP DATA FROM THE NATURAL HISTORY STUDY OF JUVENILE GM1 AND GM2 GANGLIOSIDOSES (PRONTO).

Giugliani R [1,2,3,4], Harmatz P [5], Héron B [6], Patterson M [7], Schneider SA [8], Bourchany A [9], Hahn A [10], Do Valle DA [11], Barone R [12], Chabrol B [13] et al.

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BACKGROUND: PRONTO is a prospective natural history study assessing neurological disease progression in juvenile GM1 and GM2 gangliosidoses using three different approaches to identify the most accurate assessment for disease follow-up. ***METHODS:*** The inclusion/exclusion criteria were based on age at baseline (2-20 years), age at onset (>1st birthday), and genetic diagnosis. Patients receiving any treatment that, in the investigator's judgment, could influence disease progression, were not eligible. The Scale for Assessment and Rating of Ataxia (SARA) was performed quarterly, and a swallowing questionnaire was biannual. Seizure, respiratory, and choking events were recorded daily on an e-diary. Caregivers were biannually asked to answer questionnaires such as Vinland. ***RESULTS:*** Thirty participants (14 GM1 and 16 GM2) were recruited in 12 sites (EU, US, and Brazil). Twenty-one have been monitored for 12-months. The mean age at diagnosis and baseline was 6.7 and 12.6 years, respectively. Analyzed by groups, GM1 participants were older (7 years at diagnosis and 12.6 at baseline) than GM2 (6.3 and 9.4 years at diagnosis and baseline, respectively). After 12 months, the mean SARAtotal score increased by 1.1 points. The evolution was faster in the GM2 group (4.7 GM2 worsening vs 0.6 GM1 worsening), being SARAgait (worsening of 0.8) and SARAspeech (worsening of 1.1) the most affected domains. No change in swallowing could be detected within one year. Four participants reported daily seizures at baseline but only two of them recorded the episodes on the e-diary. After one year, an increase in seizure frequency was detected in both participants but with high variability among months. Regarding VABS, a worsening of 4 scores on the ABC score was reported after one year of follow-up, with a more severe worsening in GM2 particiants than in GM1 (6 points vs 1 point) and with socialization as the most affected domain. ***DISCUSSION:*** These data will serve as a basis to accurately identify the most suitable outcome measures for clinical trials, to establish well-defined cut-off scores for a subsequent phase 3 study and reinforce the need to randomize GM1 and GM2 diseases separately due to the difference in the speed of disease progression.

P-085 - UNBLINDED SAFETY DATA OF NIZUBAGLUSTAT PHASE 2 STUDY FOR GM2 GANGLIOSIDOSIS AND NPC DISEASE.

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BACKGROUND: Nizubaglustat (AZ-3102) is an orally available, brain-penetrant, highly potent, highly selective inhibitor of glucosylceramide synthase (GCS) and non-lysosomal-neutral-glucosylceramidase. It is a small molecule that is being developed for the treatment of neurodegenerative glycosphingolipidoses. ***OBJECTIVE:*** The primary objective of this phase 2 study (RAINBOW) is to determine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of nizubaglustat as a disease treatment for GM2 gangliosidosis and Niemann-Pick type C (NPC) patients. ***METHODS:*** RAINBOW is a 1: 1: 1 randomized, doubleblind clinical study with two doses of nizugablustat and placebo. The main study duration was 12 weeks (monthly visits) with an extension where placebo patients were randomized to nizubaglustat (biannual visits). To be eligible, patients had to be ≥12yr, on stable antiepileptic treatment, if needed, and must discontinue miglustat at least 1 month before baseline. The extension phase is ongoing and also, collecting clinical data. ***RESULTS:*** Thirteen patients with genetic confirmation (7 GM2 and 6 NPC) were recruited with a mean age of 19yr and a body mass index of 17. The total score at baseline for the scale for the assessment and rating ataxia was 23.8 and all patients could swallow. Two NPC patients withdrew due to gaining access to an approved drug. No death or serious adverse events (AEs) occurred, all AEs were mild or moderate and not study drug-related.

67, Drug-related AEs were associated with skin disorders. Patients with daily seizures at baseline (3 participants) reported a reduction in seizures after 6 months of nizubaglustat. One patient without a seizure history at baseline and receiving a placebo reported seizures during the first week of the study. No new onset of seizures was reported. A consistent PK profile was seen in all patients at the highest dose and glucosylceramide concentration showed a dose-dependent reduction of >80%. No significant changes in disease biomarkers were observed. ***DISCUSSION:*** Nizubaglustat was safe and well tolerated in treated NPC and GM2 patients. In line with previous studies, it was not associated with gastrointestinal AE, common with other GCS inhibitors. More safety and clinical data will be assessed during the extension phase.

P-086 - A GLIMPSE INTO THE COMPLEXITY OF RARE DISEASES: THE INITIAL EXPERIENCE OF CASA DOS RAROS

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INTRODUCTION: Casa dos Raros (CDR) in Porto Alegre, Rio Grande do Sul, provides comprehensive and multidisciplinary care for patients with rare diseases. This innovative approach includes teleconsultations followed by in-person multidisciplinary assessments. Patients are evaluated by various specialists simultaneously, following international protocols tailored to individual cases. All cases are discussed in multidisciplinary meetings to determine diagnoses and individualized management plans. ***OBJECTIVES:*** To present the sociodemographic and clinical profiles of cases managed at CDR from June 2023 to April 2024. ***MATERIALS AND METHODS:*** Data were collected through direct telephone calls to patients and/or their legal guardians and recorded in a standardized form. Informed consent was obtained from all participants. ***RESULTS:*** During the evaluated period, CDR managed 347 patients with a mean age of 17.5 years (range: 0-82 years), predominantly male (54.9%). About 45% received social benefits, and only 19.2% were affiliated with patient organizations. At first contact, 54.1% of patients were either illiterate or of preschool age. Prematurity was reported by 18.3% of patients. Clinically, most patients exhibited neurodevelopmental delay (52.4%) and/or speech delay (50.7%). Abnormal neuroimaging was reported in 113 patients (32.5%), while 28.5% had a history of seizures. Regarding diagnosis, 40.8% had a confirmed clinical or laboratory diagnosis, 35.1% had a suspected diagnosis, and 24.1% were undiagnosed. Prior genetic testing was reported by 48.6% of patients, with the most common tests being karyotyping (17.5%) and exome sequencing (13.5%). Family recurrence was disclosed in 42.4% of cases, with consanguinity reported in 4.9%. Patients reported an average of 3.8 previous hospitalizations. According to the Brazilian Economic Classification Criteria, the majority of families were classified as C2 (lower-middle economic class). ***CONCLUSION:*** The results highlight the diversity and complexity of conditions managed by CDR. Alongside clinical challenges resulting in high morbidity, socioeconomic factors such as dependence on social benefits and low representation in patient organizations emphasize the need for a comprehensive, patientcentered approach to rare disease management.

P-087 - A PATIENT´S JOURNEY TOWARDS THE DIAGNOSIS OF FUCOSIDOSIS.

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INTRODUCTION: Fucosidosis is a rare lysosomal storage disease, caused by autosomal recessive mutations in the *FUCA1* gene, leading to alpha-L-fucosidase deficiency. As a result, incomplete catabolism of N- and Oglycosylproteins results in excessive accumulation of fucose-containing glycolipids and glycoproteins in various tissues and urine, which eventually leads to dysfunction in multiple tissue systems. Fucosidosis is a neurodegenerative disorder which progresses inexorably. A wide spectrum of manifestations, with variable age of onset, speed of progression and severity of different clinical features may be observed. Most affected patients have neurologic deterioration. Other manifestations including developmental delay, coarse facial features, hepatosplenomegaly, dysostosis multiplex, kyphoscoliosis, skin abnormalities (angiokeratomas, telangiectasia) eye abnormalities, seizures, visceromegaly, hearing loss and visual impairment. However, there are cases with no obvious facial coarsening, skeletal or skin abnormalities. ***OBJECTIVE:*** To elucidate some of the

diagnostic challenges and methodologies involved in the diagnosis of fucosidosis. ***CLINICAL CASE:*** A 14-year-old female patient, born form non-consanguineous parents, with no family history of neurodegenerative disease, with an uneventful perinatal history and normal psychomotor milestones until the age of 4, began experiencing difficulties in fine motor skills and, by age 9 frequent falls progressing to gait impairment and slow neurologic deterioration. She exhibits intellectual disability, emotional lability, limited language, nystagmus, dystonia in upper and lower limbs, global extrapyramidal hypertonia, hyperreflexia in all four limbs, and a rigid gait. Brain magnetic resonance imaging revealed signal abnormalities in the external and internal globus pallidus and substantia nigra. The neurodegeneration with brain iron accumulation (NBIA) gene panel did not identify any pathogenic variants. Whole exome sequencing showed compound heterozygous variants in the *FUCA1* gene: the variant c.563G>A; p.(Trp188Ter), classified as probably pathogenic, and the variant c.424T>G; p.(Phe142Val), classified as a variant of uncertain significance. Leukocytes alpha-L- fucosidase enzyme assay showed null activity. Urine oligosaccharides profile was suggestive of fucosidase deficiency. ***CONCLUSIONS:*** Fucosidosis is a rare condition with a wide spectrum of clinical symptoms that require careful attention to neuroimaging, biochemical studies, and genetic testing for an accurate diagnosis. Early treatment with hematopoietic-stem-cell transplantation may be effective in terms of symptoms stabilization in some cases.

P-088 - ALLANN-HERNDON-DUDLEY SYNDROME: DIAGNOSTIC ORIENTATION IN MALE INFANTS WITH HYPOTONIA WITHOUT A DETERMINED CAUSE.

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INTRODUCTION: Allann-Herndon-Dudley syndrome (AHDS) is an X-linked disorder caused by deficiency of the monocarboxylate transporter 8 (MCT8), a specific syndrome for thyroid hormones at the brain, with mutation in the *SLC16A2* gene. AHDS clinical features include a severe neurological disorder with an early onset, characterized by hypotonia, global developmental delay and drug resistance epilepsy. ***OBJECTIVE:*** Report of two cases of Allann-Herndon-Dudley Syndrome. CLINICAL CASE 1. A 8 years-old male patient, with complicated pregnancy with retroplacental hematoma, was born at term by cesarean section due to fetal distress. No perinatal problems were reported. He was referred at 2 months of age to pediatric neurologist for axial hypotonia and generalized tremors since birth. Subsequently he presented severe global developmental delay, dystonia, hypotonia, hyperreflexia. At 6 months hypothyroidism was diagnosed due to decreased free tetraiodothyronine (T4) and increased thyroid stimulating hormone (TSH). Magnetic resonance imaging (MRI) at 9 months showed hypomyelination. At 11 months, complete thyroid profile was requested with increased free triiodothyronine (free T3). Genetic study identified a likely pathogenic variant c.1428C>A (p.Tyr476X) in the *SLC16A2* gene. Nowadays, he has a severe global developmental delay, failure to thrive, dystonic quadriparesis. CLINICAL CASE 2. A 5 years-old male patient, whose pregnancy was complicated with urinary tract infection, was delivered vaginally at term. The perinatal period was unremarkable. At 5 months of age, developmental delay with incomplete head support, axial hypotonia, convergent strabismus and swallowing disorder was detected. At 9 months of age thyroid profile was performed: normal TSH, slightly decreased free T4 and increased free T3. At 10 months of age epilepsy with epileptic spasms was diagnosed. MRI at 12 months showed hypomyelination. Genetic study detected a variant of uncertain significance c.1025T>C (p.Leu342Pro) of the *SLC16A2* gene. ***CONCLUSIONS:*** MCT8 deficiency is a rare genetic disorder, and its knowledge is important to raise diagnostic suspicion in a male infant with compatible symptoms. Early diagnosis is accessible and should be guided by a complete thyroid profile. Mutations in the *SLC16A2* gene confirm the diagnosis.

P-089 - CEREBRAL CREATINE TRANSPORTER DEFICIENCY: FIRST CASE REPORTED IN URUGUAY.

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INTRODUCTION: Cerebral creatine deficiency syndrome is a group of neurometabolic disorders that include two diseases involved in its synthesis (guanidinoacetate methyltransferase (GAMT) deficiency and L-arginine glycine amidinotransferase (AGAT) deficiency), and creatine transporter (CRTR) deficiency. Among the 3 disorder, CRTR is the only one with X-linked inheritance. ***OBJECTIVE:*** To present the first case of a patient diagnosed with CRTR deficiency in Uruguay. CLINICALl CASE: A 10-month-old male patient, born from nonconsanguineous parents, was admitted due to global developmental delay and ocular movements characterized by brief episodes of upward eye deviation. Brain magnetic resonance imaging (MRI) showed thinning of the corpus callosum and bilateral hyperintense signal in T2/FLAIR with diffusion restriction in periventricular white matter, with a significant decreased creatine peak in magnetic resonance spectroscopy. An elevated urine creatin concentration of 10792 nmol/mL (reference range: 200 – 9210 nmol/mL) and urine creatine/creatinine ratio of 4.47 (normal range 0.04-1.75) were detected. A hemizygous mutation was identified in the *SLC6A8* gene (c.1392+14_1392del), described as a variant of uncertain significance as has not been previously reported. With supplementation with creatinine, arginine and glycine, he has shown a relative positive neurodevelopmental response. ***DISCUSSION AND CONCLUSIONS:*** CRTR deficiency is a rare condition, often underdiagnosed as it can present with nonspecific findings, with a highly compromised functional and vital prognosis. However, early diagnosis and treatment can modify the natural course of the disease. Early diagnosis also allows screening for the disease in presymptomatic stages in family members and genetic counseling for the family. This case report adds information related to MRI features, as bilateral hyperintense signal in T2/FLAIR with diffusion restriction in periventricular white matter, to the best our knowledge, has not been previously described, and also identifies a new variant in the *SLC6A8* gene that acquires pathogenic value.

P-090 - CLINICAL MANIFESTATIONS AND THERAPEUTIC APPROACH IN RARE METABOLIC DISORDER CAUSED BY MUTATION IN THE TANGO2 GENE: A CASE REPORT

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INTRODUCTION: The condition called MECRCN (Recurrent metabolic crises with rhabdomyolysis, cardiac arrhythmias and neurodegeneration) - OMIM 616878, was first described in 2016 as a rare metabolic disorder, caused by a recessive mutation in the *TANGO2* gene (chromosome 22q11.21), which acts on the functions of the golgi complex, endoplasmic reticulum and mitochondria. The aim of this study is to describe the case of two siblings with compatible clinical manifestations and identification of a pathogenic mutation in *TANGO2*, who are taking vitamin B5 to keep their condition stable. ***METHODOLOGY:*** chart and literature review. ***RESULTS:*** In July 2015, an Exoma was performed on WTSF, a 4-year-old male patient, based on the following clinical presentation: first child of a non-consanguineous couple, previously healthy child, with regression of neurodevelopment from 13 months old, after a metabolic crisis in the context of infection. The child developed spastic tetraparesis and epilepsy, as well as primary hypothyroidism and adrenal gland insufficiency. MRI showed diffuse, non-progressive brain volume reduction. Laboratory tests showed mild hyperammonemia, a slight and non-sustained increase in aldolase, liver enzymes and CPK. Initial metabolic investigation no alterations. Muscle biopsy not compatible with mitochondrial disease and ophthalmological examination within normal limits. Exome was normal at this point. In July 2018, her sister MJSF, 15 months old, previously healthy, developed a metabolic crisis similar to her brother's, with regression in neurodevelopment, hypothyroidism and epilepsy. This prompted a review of her brother's exome to look for new mutations and her exome, a mutation was found in the TANGO2 gene: c.728+1G>A in homozygosity, pathogenic in both siblings, whose parents carried the mutation. Since 2018, both have been supplemented with B-complex, coenzyme Q10 and riboflavin, and after 2023 they have been taking vitamin B5 exclusively, keeping their condition stable. ***DISCUSSION:*** Current studies suggest a significant improvement in metabolic crises related to MECRCN, especially in the mental state and rhabdomyolysis, after administration of a combination of vitamin B5 and B3, as well as stability of the pathology with restricted use of vitamin B5. Reports such as ours can corroborate and aid the study of this rare and challenging pathology.

P-091 - EVALUATION OF DBS CHITOTRIOSIDASE IN MEXICAN PATIENTS WITH NEPHROPATIC CYSTINOSIS.

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INTRODUCTION: Nephropathic cystinosis (NC) is a rare lysosomal disease due to absence of cystine transporter protein and causes an abnormal accumulation intra-lysosomal of cystine. Diagnosis is confirmed by observation of cystine crystals in cornea, by elevated cystine levels in leucocytes or by presence of mutations at the *CTNS* gene. Chitotriosidase is a human chitinase produced by leucocytes and it is elevated in more than 40 conditions including lysosomal disorders. It is used as a screening biomarker and for monitoring therapeutic goals in Gaucher disease. ***OBJECTIVE:*** To evaluate chitotriosidase levels in DBS and presence/absence of 24-pb duplication polymorphism at the *CHIT* gene in treated Mexican patients with NC and to correlate with adherence treatment. ***METHODS:*** DBS chitotriosidase activity was measured in 19 Mexican patients with NC using the 4-MU-triacetylchitotrioside (Chamoles et al, 2002), DNA was extracted by Single Lysis Salting Out (Shaik et al, 2016), PCR amplification of a fragment of the *CHIT* gene was done to determine the presence/absence of 24-pb duplication polymorphism (Juarez-Rendón et al, 2012). ***RESULTS:*** 19 patients (12M/7F) were measured basally on Chit; 8 were heterozygous for dup24 pb, none was homozygous for 24-pb dup; 15 of 19 patients were under treatment (14 with Cystagon and 1 with Procysbi), all the 4 patients with no treatment showed elevated levels of chitotriosidase. In 13 of 19 patients, chitotriosidase were elevated compared with normal individuals. Measure of Chit in at least two times was obtained in 11/19 patients: two shown elevation of Chit measurements, five shown no significative Chit variation and four shown diminutions of the biomarker. It was noteworthy that all the patients with tendency to diminution of Chit were on the group of adherence to treatment (11 of the 19). Unfortunately, the Chit evaluations were not realized every 6 months in any patient. ***CONCLUSIONS:*** This study indicates that chitotriosidase activity can be a practical and useful marker to measure response and treatment adherence in patients with Nephropatic Cystinosis.

P-092 - FIRST NAXD DEFICIENCY PATIENTS IN ARGENTINA: TWO AFFECTED SIBLINGS, TWO OUTCOMES. WHEN TREATMENT MAKES THE DIFFERENCE.

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INTRODUCTION: Nicotinamide adenine dinucleotide (NAD) and NAD-phosphate (NADP) are required for essential biochemical reactions. Nicotinamide repair system consists of two enzymes: epimerase (NAXE) and dehydratase (NAXD). NAXD deficiency (MIM 618321) was recently described by Van Bergen et al (2019). This autosomal recessive disorder is caused by biallelic pathogenic variants in the *NAXD* gene. The commonest feature is a lethal infantile encephalopathy triggered by febrile illness, and severe pellagra-like cutaneous lesions. As these defects are expected to deplete intracellular NAD+ in stress-related episodes, a treatment of niacin (precursor of NAD+) was recently proposed by Manor et al (2022). The aim of this presentation is to communicate the first NAXD deficient patients from Argentina and to alert about the benefits of an early recognition and treatment. ***CLINICAL CASES:*** Patient LR, 2 y-o boy was admitted to the hospital due to severe acute ataxia and irritability. 20 days before admission he had COVID. Brain MRI was normal, as well as ophthalmologic, hematologic and laboratory tests. Metabolic workout results were non-conclusive. His older sibling (patient TR) developed many febrile-triggered acute encephalopathies since he was 15 months-old. At 20 months, he was admitted due to an acute encephalopathy and progressive multisystemic disease with severe skin, oral and perianal ulcers. Brain MRIs revealed white matter involvement, lactate and DWI abnormalities. He died at 23 months in 2018, without diagnosis. LR started mitochondrial drug cocktail. Partial improvement was noticed. After each febrile episode he got worse with motor and cognitive impairment. Leukodystrophy genetic panel reported two variants in *NAXD* gene: c.1112 C>T (p.Ser371Leu) and c.848_852dup (p.Val285Serfs*21) Retrospective genetic test in patient TR confirmed the same result. Niacin treatment was started at 3 years of age, with good response. After a short period, he recovered motor and cognitive skills with progressive improvement. He is now 5 yo. He had many febrile episodes, but no new encephalopathic crisis or worsening. ***CONCLUSIONS:*** *NAXD* deficiency is a fatal multisystemic disease. Prominent features are progressive neurological deterioration after fever, skin

lesions, and premature death. As in our patients, niacin treatment could dramatically improve the outcome, due to an early recognition and treatment.

P-093 - GLUTATHIONE SYNTHETASE DEFICIENCY: A CASE REPORT

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INTRODUCTION: Glutathione synthetase deficiency (GSSD) is a ultra-rare autosomal recessive genetic disorder, with only 90 cases reported worldwide, which may present a variable and not yet fully characterized phenotype. In its early form, it may manifest as hemolytic anemia, metabolic acidosis, progressive neurological symptoms, recurrent bacterial infections, and characteristically 5-oxoprolinuria. Currently, diagnosis relies on clinical findings, 5-oxoprolinuria, and analysis of variants in the glutathione synthetase (*GSS*) gene. It is important to identify 5-oxoprolinulinuria in hemolytic anemias once more common causes have been ruled out and to initiate appropriate treatment to achieve a better quality of life. ***OBJECTIVES:*** To describe a clinical case of glutathione synthetase deficiency with systemic involvement and its evolution over time. ***CASE DESCRIPTION:*** A 3-month-old patient from Paraguay presented to Hospital Juan P. Garrahan (HJPG) for a second opinion due to metabolic acidosis, hemolytic anemia, and epilepsy. The child, with no significant personal history, developed respiratory distress within the first 20 hours of life, with transfusion requirements at 48 hours and 18 days of life in the context of severe hemolytic anemia and metabolic acidosis. He also developed epilepsy and developmental delay during his first two months of life. Previous laboratory tests showed hematological abnormalities, metabolic acidosis, and hyperbilirubinemia. Evaluation at HJPG, with samples sent to the inborn errors of metabolism´s laboratory, revealed 5-oxoprolinuria in urinary organic acids. The clinical presentation and the laboratory finding led to the diagnosis of a glutathione disorder, which was confirmed by molecular biology, identifying two variants described as pathogenic (c.491G>A) and probably pathogenic (c.706C>T) in the *GSS* gene. After 2 years and 6 months of follow-up under treatment with antioxidants and bicarbonate, the patient has shown stable and increasing hemoglobin values without hemolytic crises or epileptic episodes. He presents a developmental delay, predominantly in gross motor skills, which has improved favorably with physiotherapy and occupational therapy, showing similar progress in expressive communication with speech therapy. ***CONCLUSION:*** Early metabolic suspicion and specialized laboratories are crucial for timely treatment, improving quality of life, and fostering optimal development.

P-094 - INRARAS & BRAZILIAN RARE DISEASES NETWORK: MITIGATION OF THE ENVIRONMENTAL DISASTER IN RIO GRANDE DO SUL, BRAZIL

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INTRODUCTION: Rare Diseases (RD) are complex chronic conditions, usually of genetic origin, with a prevalence of less than 65: 100,000 inhabitants - in Brazil. The RD community faces various vulnerabilities, such as the lack of specific and expensive treatments, diagnosis and medical attention concentrated in specialized centers, need for continuous therapies, and absence of support networks. Similar to the challenges experienced during the SARS-CoV-2 pandemic, the environmental disaster that occurred in Rio Grande do Sul (RS), the southernmost state of Brazil, in May 2024, increased the vulnerability of this patients. Heavy rains caused the main rivers of the state to overflow, flooding entire cities and hindering the transportation and distribution of medicines due to roadblocks. ***OBJECTIVE:*** To describe the assistance provided to the RD community by the National Institute of Science and Technology (INCT) for Rare Diseases - InRaras, and the Brazilian Rare Diseases Network (RARAS), during the flood period. ***METHODOLOGY:*** Through the virtual networks of InRaras and RARAS, informative bulletins were disseminated, alongside the establishment of a 24-hour WhatsApp hotline. ***RESULTS:*** Eight posts containing health guidelines for the general population were published, including information on locations for distributing special medications. On Instagram, over 14,000 accounts were reached, and more

than 50% of them directly interacted with the page, sharing the posted content. On WhatsApp, 52 contacts were received, mainly requesting medications and metabolic formulas. In partnership with the Special Medications Logistics Center (CELME) of RS, 250 units of formulas/medications were distributed. ***CONCLUSION:*** The data underscore the necessity for more decentralized care and medication distribution systems for patients with RD in RS. Telemedicine emerges as a crucial tool in addressing these needs.

P-095 - METAB-LATAM: SHARING SCIENTIFIC KNOWLEDGE ABOUT INBORN ERRORS OF METABOLISM IN LATIN AMERICA

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INTRODUCTION: Metab-Latam is a multidisciplinary initiative designed to bring together experts in inborn errors of metabolism (IEM) from around the world through an online mailing list and Instagram account. ***AIM:*** To foster discussion and facilitate accessible information sharing through social media platforms in Latin America. ***METHODS:*** The mailing list started in April 2020, with participation initially requested via email: candidates agreed to the rules and answered a questionnaire about demographic data and conflicts of interest. In April 2021, a public content creator profile was created on Instagram. Since then, bilingual posts (Portuguese and Spanish) about scientific publications on IEM featuring Latin American authors, as well as posts on related events and ongoing studies, have been published. Currently, participation in the mailing list is initiated by accessing a link in the Instagram bio. ***RESULTS:*** In May 2024, the mailing list had 156 participants from 16 countries. Most participants were from Brazil (48.0%), Argentina (14.7%), Colombia (8.3%), and Mexico (8.3%). Between April 2020 and April 2024, 697 emails were exchanged, covering the promotion of events and discussion of clinical cases, among other topics. On Instagram, from February to May 2024, 10 posts were created. The one with the most engagement was about neonatal screening for lysosomal storage diseases. During this period the profile reached 644 accounts, most Brazilian (81.3%). The main age group of Instagram visitors ranged from 35 to 44 years old (36.0%). ***CONCLUSION:*** Social media has become a crucial tool in disseminating scientific knowledge in developing countries and bridging gaps in education and access to information. Since its creation, Metab-Latam social media profile and mailing list have enabled broader, more accessible, and democratic access to clinical and laboratory knowledge related to the diagnosis, treatment, and care of patients with IEM in Latin America.

P-096 - NEW DELETION OF MULTIPLE GENES IN THE PATHOGENIC SUBTELOMERIC REGION IS RELATED TO THE PHENOTYPIC HETEROGENEITY OF PATIENTS WITH POLYMALFORMATION SYNDROME

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INTRODUCTION: Genomic testing has significantly advanced, enabling the identification of changes from specific locus modifications to genomic structural alterations. This progress has enhanced the diagnosis of diseases and the understanding of little-known genetic disorders. ***OBJECTIVE:*** To describe the case of an adolescent with no consanguineous parents or family history of genetic variants, presenting with cognitivebehavioral impairment, epilepsy, hypothyroidism, tall stature, and minor facial dysmorphisms suggestive of an overgrowth syndrome. Due to the complex phenotype affecting multiple organs and systems, the patient underwent aCGH analysis to identify deletions or duplications. ***METHODS:*** Genomic DNA was extracted from a peripheral blood sample of the patient, labeled, and hybridized using the Agilent®

SurePrint G3 Human CGH array 4x180K. Data were scanned and analyzed with Agilent CytoGenomics v5® software. ***RESULTS:*** aCGH analysis identified a sub-telomeric pathogenic heterozygous deletion in the chromosomal region 5q35.2q35.3. Databases including Online Mendelian Inheritance in Man, Clinical Genome Resource, and GeneScout revealed 12 out of 74 genes associated with medical conditions, with 9 having autosomal recessive inheritance mechanisms and 3 autosomal dominant (AD). A Human Phenotype Ontology search linked the deletion to conditions such as hematological malignancy predisposition syndrome, hereditary angioedema, infantile hypercalcemia 2, Fanconi renotubular syndrome 2, nephrolithiasis/hypophosphatemic osteoporosis 1, Lewy body dementia, and Sotos syndrome. This deletion is associated with a complex phenotype including autism spectrum disorder and various physical anomalies. DISCUSSION AND JUSTIFICATION: Although not a classic hereditary metabolic disorder, the identified deletion affects genes involved in key metabolic pathways. Genes related to calcium and phosphate metabolism (e.g., infantile hypercalcemia, nephrolithiasis/hypophosphatemic osteoporosis) and steroid metabolism (hereditary angioedema) highlight the intricate relationship between genetic deletions and metabolic processes. ***CONCLUSIONS:*** Genetic tests like aCGH are essential for diagnosing congenital anomalies and neurodevelopmental disorders. Identifying deletions in the 5q35 region enhances understanding of polymalformative syndromes, aiding genetic counseling and improving patient prognosis and family plannin.

P-097 - IMPROVING THE DIAGNOSIS OF MITOCHONDRIAL DISEASES: IMPLEMENTATION OF HIGHTHROUGHPUT SEQUENCING OF THE MITOCHONDRIAL GENOME

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INTRODUCTION: Mitochondrial diseases (MD) can be caused by variants in either mitochondrial DNA (mtDNA) or nuclear DNA. The mtDNA exhibits unique characteristics, making its study complex and requiring the use of different methodologies and tissues. The implementation of next-generation sequencing (NGS) has revolutionized the genetic diagnosis of MD, enabling comprehensive analysis of mtDNA. ***OBJECTIVE:*** To describe the implementation of NGS of the entire mtDNA for the diagnosis of patients with suspected MD in a public pediatric hospital. ***PATIENTS AND METHODS:*** DNA samples (n=108) from blood and other tissues were analyzed in five independent runs (Twist Bioscience, NGS-mtDNA). To evaluate the performance of the implemented method and the detection capacity of the bioinformatics pipeline, 29 positive controls [22 single large-scale mtDNA deletions and 7 single nucleotide variants (SNV)] and 2 negative controls were included. Additionally, 65 samples from 56 patients with suspected MD were included, along with 12 samples from 10 mothers for segregation studies. ***RESULTS:*** An average depth of ≥700X was achieved for 87% of the samples, with a minimum coverage of 400X for 97% of the entire mtDNA. In controls, 100% of SNVs and 82% of mtDNAdeletions were detected, with no relevant variants found in the negative controls. Regarding the 56 patients with suspected MD: 12 presented pathogenic/likely pathogenic variants (10 SNVs involving 7 genes and 2 mtDNA-deletions), heteroplasmy levels 3-92% and one in homoplasmy; 9 showed variants of uncertain significance, 6 in homoplasmy; and in the remaining 35 patients no relevant variants were found. In 8 patients, the study of additional tissues was useful to evaluate heteroplasmy and to confirm or rule out the molecular diagnosis. Maternal inheritance was established in 5/10 patients. ***CONCLUSION:*** The implementation of NGS was achieved with optimal sequencing quality metrics, although it showed limitations for detecting mtDNAdeletions. Analyzing variants in different tissues from patients and their mothers allowed for accurate classification according to mtDNA guidelines, providing precise molecular diagnosis and appropriate genetic counseling. These results highlight the advantages of high-throughput NGS for studying patients with suspected MD to avoid missing rare variants in mtDNA.

P-098 - A CASE OF SEVERE BCS1L RELATED MITOCHONDRIAL DISEASE: GRACILE SYNDROME.

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INTRODUCTION: The most frequent cause of mitochondrial CIII deficiencies is due to defects in the *BCS1L* gene encoding BCS1 protein located at the mitochondrial inner membrane. The two major clinical phenotypes which are well known to be associated with disease causing variants in *BCS1L* are GRACILE and Bjornstad syndromes. Some pathogenic variants were associated with significantly worse survival and exclusively found in those with disease onset within the first month of life. GRACILE syndrome is a rare autosomal recessive disease characterized by Growth Restriction, Fanconi type Aminoaciduria, Cholestasis with Iron overload in the liver, profound Lactic acidosis and Early death. No available treatments have changed the fatal course of the disease. It has been described mostly in newborn infants with parents of Finnish origin. ***OBJECTIVE:*** To present our first case of GRACILE syndrome. ***CASE:*** A 12 days old female newborn was referred to our clinic because of intractable metabolic acidosis. She was product of the first normal pregnancy and delivery of a young non consanguineous couple with no Finnish ancestries. Physical examination revealed failure to thrive hypotonia, and hepatomegaly. The laboratory examinations showed severe lactic acidosis, hypobicarbonatemia, hypoglycemia, increased blood alanine, alanine aminotransferase and aspartate aminotransferase levels, cholestasis, hyperferritinemia, generalized aminoaciduria, glucosuria, and phosphaturia. The first symptoms had started at 18 hours of life when she showed abnormal deep breath. Metabolic acidosis and hypoglycemia were detected. She was unresponsive to bicarbonate replacement. Despite intensive care and alkali therapy she died at 7 months of age. Sequencing of *SLC2A2* gene of Fanconi Bickel syndrome, showed no mutations. After that, whole exome sequencing revealed heterozygous pathogenic variants at *BCS1L* gene. ***CONCLUSION:*** Patients with BCS1L mutations should be considered in the differential diagnosis of severe tubulopathy and lactic acidosis in the newborn period. Although there is still no specific treatment available for this disease, early recognition is very important for genetic counseling of the family.

P-099 - ATYPICAL PRESENTATIONS IN MITOCHONDRIAL DISEASES - CASE REPORT.

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INTRODUCTION: The diagnosis of mitochondrial diseases is challenging due to the variable spectrum of their clinical manifestations, often resulting in a delayed diagnosis. The organs typically affected are those with a higher energy demand; however, any organ can be compromised, necessitating a high index of suspicion. ***OBJECTIVES:*** To expand the spectrum of possible initial presentations of mitochondrial diseases.***MATERIALS AND METHODS:*** We report two cases of mitochondrial diseases with atypical symptom onset. ***RESULTS:*** Case No. 1: A 5-month-old male infant, who was born at 36,5 weeks, presented with a cyanotic episode and cardiomegaly, suspected to be a cyanotic congenital heart disease. Echocardiogram showed a 5 mm diameter patent ductus arteriosus (PDA) with right cavity dilation and indirect signs of pulmonary hypertension. He was discharged with a pulmonary vasodilator and anti-congestive management. He was readmitted a month later due to oral intolerance and metabolic acidosis, evolving into respiratory failure with refractory pulmonary hypertension, shock, and multiple organ dysfunction. He required nitric oxide, vasoactive support, and ECMO. PDA closure was performed; he tolerated withdrawal of circulatory support but persisted with severe hyperlactatemic metabolic acidosis, severe hyperglycemia, and multiple organ dysfunction. A ketogenic diet (1: 1) resolved the acidosis. A pathogenic homozygous variant in the *NFU1* gene was identified. He died at 9 months. Case No. 2: A 4-month-old male, who was born of a full-term pregnancy, presented with cyanotic spells that worsened over time, with difficult recovery from episodes. Two months later, he was hospitalized due to a loss of motor skills with vertical nystagmus, frequent emesis, and very severe cyanotic spells. Brain MRI showed supra- and infratentorial lesions with restricted diffusion and a lactate peak in the spectroscopy. He died 19 days after hospitalization. A pathogenic homozygous variant in the *NDUFAF5* gene was identified. ***DISCUSSION AND CONCLUSIONS:*** Mitochondrial diseases have highly variable clinical presentations, and typical manifestations of frank multisystem involvement from onset are not the rule, even in severe cases. Neurological, pulmonary, or cardiac atypical manifestations should raise suspicion of these

entities. The ketogenic diet can help to control de metabolic acidosis.

P-100 - CLINICAL AND DIAGNOSTIC DESCRIPTION OF MITOCHONDRIAL DISEASES IN PEDIATRIC PATIENTS: A CASE SERIES AND ITS PHENOTYPIC VARIABILITY

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INTRODUCTION: Mitochondrial diseases (MD) are a heterogeneous group of genetic disorders affecting mitochondrial function and cellular energy metabolism. Their dual genetic etiology leads to great phenotypic variability and diagnostic challenges, especially in pediatric patients. ***OBJECTIVES:*** To describe and compare clinical manifestations, biochemical, imaging, and molecular findings in MD patients. ***MATERIALS AND METHODS:*** Seventeen MD patients were analyzed, comparing clinical and paraclinical findings between those with mitochondrial (47%) and nuclear gene alterations (53%) ***RESULTS:*** Among the 17 pediatric MD patients (53% male, aged 1-27 years, mean 11.4), the average age of symptom onset was 34 months, with a mean diagnosis age of 8 years. Most patients presented neurological manifestations as a cardinal symptom suggesting a neurogenetic or metabolic condition: Psychomotor development delay (41%), movement disorders (41%), developmental regression (30%), hypotonia (30%), and epilepsy (47%). Patients with mitochondrial variants (mainly MT-TL1 and MT-ATP6) showed developmental regression and abnormal movements (dystonia 37%, chorea 25%). Those with nuclear mutations (mainly PDAH1 and PDHX) exhibited psychomotor delay, hypotonia, and movement disorders (predominantly ataxia and spasticity), with earlier symptom onset (9 vs. 62 months); 94% had neuroimaging abnormalities; alanine and lactate elevation was more prevalent in the mitochondrial gene group. In terms of comorbidities and additional symptoms, the most common were hearing disorders, swallowing disorders, gastrointestinal symptoms, vitamin D deficiency, scoliosis, and pain; 70% of patients have a functional assessment with Gross Motor Function Classification System (GMFCS) between III and V; 71% of caregivers experienced burden given the cognitive impairment and functional dependence of the patients. ***DISCUSSION/CONCLUSIONS:*** Mitochondrial diseases show significant clinical and genetic variability depending on the detected mutations. The findings highlight the importance of a comprehensive diagnostic approach, including clinical, biochemical, imaging, and molecular evaluation, to achieve an accurate and timely diagnosis. Likewise, there is an emphasis on the need for a multidisciplinary approach that provides comprehensive and personalized management to each patient, considering their specific needs and those of their family environment.

P-101 - CLINICAL CASE: IMPLICATIONS OF A DE NOVO NDUFAF6 VARIANT IN MITOCHONDRIAL DISEASE

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INTRODUCTION: NADH dehydrogenase (ubiquinone) complex I assembly factor 6 (NDUFAF6) is involved in the assembly of mitochondrial complex I, crucial for mitochondrial function and associated with several metabolic disorders. ***OBJECTIVE:*** To identify and characterize a novel de novo variant in the *NDUFAF6* gene in a patient with clinical features of mitochondrial disease, and determine its pathogenicity and clinical implications using advanced omics and AI tools. ***CLINICAL CASE:*** A 17-year-old male with consanguineous parents presented a 10-year history of gait stiffness, frequent falls, language disorders, spastic paraparesis, and acute lesions in the putamen region on brain MRI, with no related family history. A complete exome sequencing trio study was requested using NGS+ CNVs methodology. The study reported a germline missense variant NM_152416.4 in the *NDUFAF6* gene (Chr 8q22.1): c.371T>C; p.Ile124Thr. This variant has conflicting pathogenicity classifications in ClinVar. It is identified in ClinGen as CA325074; gnomAD 0.00003; TOPMed 0.00003; ExAC 0.00007; 1000 Genomes Project 0.00020; dbSNP: rs201732170; UniProt-Q330K2. It is widely expressed, with lower expression in lung and kidney compared to heart, muscle, and liver. In silico predictors suggest moderate pathogenicity. According to Franklin by Genoox, the suggested classification is "Likely Pathogenic". ***DISCUSSION:*** The c.371T>C variant results in the substitution of isoleucine for threonine at position 124 of the NDUFAF6 protein. This variant is associated with Leigh syndrome, characterized by loss of mental and

movement abilities, bilateral lesions in the basal ganglia, dystonia, psychomotor regression, and other neurological deficits.AI tools (GenAI, VarChat, AlphaFold, Mastermind, Alliance of Genome Resources Version 7.1.0) report that functional studies show the variant is associated with loss of NDUFAF6 protein expression, reduced activity, and assembly of mature complex I in fibroblasts, with deleterious effects on mitochondrial function. Genetic complementation assays showed that the introduction of the wild-type *NDUFAF6* gene restored normal function. ***CONCLUSIONS:*** Multimodal studies, including omics techniques and AI, enable accurate diagnoses, targeted treatments, genetic counseling, monitoring, prognosis, reverse phenotyping, and 7P Medicine. These multimodal studies following current recommendations on variant interpretation allow for precise and comprehensive clinical management.

P-102 - IDENTIFICATION OF TWO NEW VARIANTS IN EARS2 GENE ASSOCIATED WITH A MILD EARLYONSET PHENOTYPE: CLINICAL CASE REPORT

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INTRODUCTION: Patients with EARS2-related mitochondrial disease become symptomatic in infancy with characteristic MRI findings of diffuse white matter changes and symmetrical signal abnormalities in the thalamus and brainstem (leukoencephalopathy with thalamus and brainstem involvement and high lactate). There are two possible phenotypes described. Presentation before 6 months of age with marked neurological regression followed by clinical stagnation and later onset in infancy with neurological regression, but recovery with stable clinical course thereafter. ***OBJECTIVE:*** Reclassification of a VUS in the *EARS2* gene associated with a mild phenotype of the disease but early onset. ***CASE PRESENTATION:*** We present a patient referred to our hospital at 6 months of age with an Infantile Apparent Life Threatening Event (ALTE). He associated low muscle tone from birth and evolved to loss of motor maturation patterns with greater difficulties for feeding and weight loss. MRI of the brain showed thinning of the corpus callosum and increase in the ventricular spaces without thalamic involvement. Metabolism laboratory was performed showing metabolic acidosis , increased GAP anion, increased hepatic transaminases, lactic acidosis, hyperketosis, mild hyperammonemia and Krebs cycle intermediates in urinary organic acids. Whole exome with CNV and mitochondrial DNA sequencing were performed. Two variants were obtained in heterozygosity in the *EARS2* gene: c.1277_1279dup in frame variant, Likely Pathogenic; c.244C>T unreported missense variant, classified as VUS. The patient, after treatment with riboflavin, coenzyme Q10, thiamine, carnitine and a diet rich in carbohydrates, improved muscle tone, swallowing and made good weight progress. Laboratory parameters improved with persistence of Krebs cycle intermediates in organic acids in urine. ***DISCUSSION:*** The c.244C>T variant in EARS2 is found at an extremely low frequency in the population, which gives it a prediction of moderately pathogenic. There is no further evidence described for this variant. As the patient presents a phenotype compatible with the disease, it could be suggested as a functional model to reclassify the VUS in EARS2. It could correspond to a milder phenotype of the disease, with an early presentation but better evolution with the treatment established for mitochondrial disease.

P-103 - PYRUVATE DEHYDROGENASE DEFICIENCY, REPORT OF 3 CLINICAL CASES WITH PHENOTYPIC VARIABILITY

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BACKGROUND: Primary deficiency of the pyruvate dehydrogenase complex (PDCD) is a rare mitochondrial disorder, with a low prevalence of <1/1,000,000 live births. The nucleus encoded PDHC contains of 5 enzymes, 3 catalytic (PDHA1-E1, E2, E3) and 2 regulatory, as well as 3 cofactors and an additional protein (E3-binding protein). The phenotypic spectrum is extremely wide and includes cases with severe congenital lactic acidosis with neonatal death, encephalopathy with hypotonia, developmental delay and/or seizures, to less severe cases of childhood-onset intermittent ataxia or dystonia, or peripheral neuropathy with normal cognitive functioning. Treatment focuses on correcting the energy deficit and preventing metabolic acidosis. The ketogenic diet and supplementation with thiamine have shown benefits in some cases. This study highlights the complexity in PDCD

77diagnosis. ***OBJECTIVE:*** We report 3 clinical cases of pyruvate dehydrogenase complex deficiency with diverse clinical phenotypes and imaging findings. Clinical cases: Three cases of pyruvate dehydrogenase complex deficiency (PDCD) are analyzed. Cases 1 and 2 are two sisters, born to nonconsanguineous parents. The elder sister had neonatal lactic acidosis, microcephaly with brain malformations with lactic peak in magnetic resonance spectroscopy. PDCD was suspected but enzymatic assay in fibroblasts showed PCDC normal enzymatic activity; genetic testing was not performed. The younger sister exhibited severe global developmental delay, hypotonia progressing to spastic quadriparesis, pharmaco-resistant epilepsy, brain malformations that evolved to hydrocephalus, with genetic study that identified a pathogenic variant in *PDHA1* gene: (Xp22.12): NM_001173454.1: exon 10: c.969_970insACTT (p.Q323fs). Both sisters' conditions followed a chronic and progressive course, and they passed away at the age of 4 years. Case 3. A 2 years 5 months-old female patient, with global developmental delay (assisted gait, simple words, social interaction), with hypotonia, showed multifocal subcortical and profound white matter leukoencephalopathy in MRI. Whole exome sequencing identified a probably pathogenic variant in PDHA1 gene: c.379C>T; p.(Arg127Trp) ***CONCLUSION:*** This study underscores challenges in molecular diagnosis and complexity in managing PDCD deficiency patients. As PDHA1 is X-linked, PDCD enzyme activity may vary between tissues. Diagnosis is important to consider specific treatment options and genetic counseling.

P-104 - PYRUVATE DEHYDROGENASE DEFICIENCY: MOLECULAR CHARACTERIZATION IN FOUR PEDIATRIC PATIENTS.

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INTRODUCTION: Pyruvate dehydrogenase (PDH) deficiency is a rare genetic disorder that affects mitochondrial function and energy production, primarily caused by variants in *PDHA1* gene on the X chromosome. This condition results in metabolic dysfunction and severe neurological symptoms with a wide phenotypic variability. Early molecular diagnosis is crucial for clinical intervention. ***OBJECTIVE:*** To report the molecular insights in four patients with PDH deficiency due to variants in the*PDHA1* gene. ***PATIENTS AND METHODS:*** We analyzed data from four patients with PDH deficiency within a cohort of 168 mitochondrial disease patients treated at Garrahan Pediatric Hospital (August 2014-December 2023). Molecular data were obtained by massive parallel sequencing (panel or exome). ***RESULTS:*** Four patients were diagnosed with PDH deficiency: one girl and three males (age-onset: 2-7 months) within a subgroup of 43 patients with Leigh/Leighlike syndrome. Two presented with severe encephalopathy with lactic acidosis and two with atypical Leigh syndrome, one of them initially manifested as Guillain-Barré syndrome. The plasma and/or CSF lactate levels were elevated in all patients. They all presented pathogenic/likely-pathogenic missense variants in the *PDHA1* gene (NM_000284.4), coding for E1-subunit of PDH complex. Patient 1, the female, presented the c.482A>Gp.(Tyr161Cys) variant in heterozygous state. Patient 2, showed the c.260T>C-p.(Ile87Thr) variant, and patient 4 the c.491A>G-p.(Asn164Ser) variant, both in hemizygous state. Patient 3 presented the c.905G>Ap.(Arg302His) variant as a mosaic (29%). All variants were located in critical protein motifs. The p.Ile87Thr variant is novel and first reported here (ClinVar-ID: 3062013). It is located in the α2β2-tetramer interface region of the PDH-complex; bioinformatic tools predict a strong deleterious effect. ***CONCLUSION:*** We identified four patients with PDH deficiency due to missense variants at highly conserved residues in the E1-subunit of the PDH complex, consistent with most reported pathogenic variants. Additionally, we report a novel variant with a strong deleterious predictive effect. Our findings contribute to expanding the list of known variants of the *PDHA1* gene. Early molecular diagnosis is important to establish a prompt treatment, such as a ketogenic diet, to avoid progressive neurological damage.

P-105 - THIAMINE RESPONSIVE PYRUVATE DEHYDROGENASE ENZYME COMPLEX DEFICIENCY IN A PATIENT WITH RECURRENT MUSCLE WEAKNESS.

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INTRODUCTION: Pyruvate dehydrogenase enzyme complex (PDHC) plays an important role in aerobic energy metabolism. Its deficiency has a broad clinical spectrum ranging from severe brain malformations with neonatal lactic acidosis to chronic neurologic dysfunction without lactic acidosis, and rarely, paroxysmal neurologic problems such as ataxia, weakness, exercise-induced dystonia or recurrent demyelination. ***AIM:*** To report a patient with PDHC deficiency with recurrent episodes of muscle weakness who dramatically improved after thiamine supplementation. ***CLINICAL CASE:*** Male, 21 years-old, born form non-consanguineous parents, normal pregnancy and perinatal period. Learning difficulties were detected from the beginning of scholarship. At 4-, 6- and 7-years of age, he developed intermittent episodes of mainly inferior limb paresis, after usual physical exercise, with recovery after a few hours. By 9 years-old, he was admitted with paresis of upper limbs, with hypotonia and areflexia, with shoulder amyotrophy and pes cavus as signs of chronic evolution. Three days later, paresis of inferior limbs and bilateral facial palsy were detected. Laboratory tests revealed slightly elevated creatine-kinase, plasmatic lactate and ammonia. Cerebrospinal fluid showed normal proteins, glucose and no cells, with elevated lactate level of 6,9 mmol/L. Brain and spinal magnetic resonance imaging showed bilateral and symmetric hyperintense T2/Flair images in mesencephalon and in globus pallidus. Nerve conduction studies showed motor-sensorial polyneuropathy. Electromyography showed myopathic profile. Deltoid muscular biopsy exhibited features that suggested neurogenic changes. Treatment with mitochondrial cofactors, included thiamine 100 mg/day. Progressive improvement with functional recovery after 3 months was observed. Clinical course was stable for 10 years, including 2 years without any medication, when he developed a similar episode of limb paresis. Molecular genetic analysis revealed a hemizygote mutation in *PDHA1* (Xp22.12) gene: NM_000284: exon 3: c.C262T (Arg88Cys) which should be considered pathogenic given current evidence. Low protein levels of PDH-E1alpha and respiratory rates, indicative of mitochondrial bioenergetic dysfunction, were detected in patient's platelets. High doses of thiamine (800 mg/day) were prescribed. Muscle power recovered within one month. The clinical status has remained stable for 2 years. ***CONCLUSIONS:*** The need for identifying unusual neurological presentations of this rare disorder is emphasized as simple treatment may be extremely effective.

P-106 - TYPE 1 PEDIATRIC ACUTE LIVER FAILURE SYNDROME ASSOCIATED WITH A NEW VARIANT IN THE LARS1 GENE: CLINICAL CASE REPORT

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INTRODUCTION: Pediatric Acute Liver Failure Syndrome is a rare entity is a rare entity with a high morbidity and mortality rate. Variants in the *LARS1* gene are related to Pediatric Acute Liver Failure Syndrome, with crises of intermittent liver failure triggered by catabolic events such as physiological stress or disease. ***CLINICAL CASE:*** This study presents a 16-month-old male patient that developed acute gastroenteritis. At 72 hours of evolution, he presented elevated liver enzymes, nodular images and signs of steatohepatitis that appeared to be previous to this event in the abdominal TC. The patient evolved with signs of acute liver failure. Secondly, he evolved with worsening of the basal anemia, thrombocytopenia and presented with seizures followed by 2 cardiorespiratory arrests that were reversed with resuscitation maneuvers. The patient evolved with acute renal failure, generalized edema and petechial or maculopapular skin lesions. With the suspicion of a metabolic disease, laboratory tests were ordered. These showed several elevated plasma lactic acid results, with a maximum value of 8 mmol/L, hyperammonemia with a maximum of 300 µg/dL. Urinary organic acids showed marked elevated lactic acid, liver dysfunction metabolites and Krebs cycle metabolites. No other representative laboratory results were found. The patient was started on mitochondrial cofactors empirically (coenzyme q10, thiamine, rivoflavin, idebenone, carnitine). The liver failure seemed to have not progressed since the initiation of treatment, nor did the seizures reappear. Unfortunately, due to the advanced nature of the multiorganic commitment, the patient died of multiple organ failure and cardiorespiratory arrest.The exome result was obtained post-mortem: two variants in the *LARS1* gene, one with a stop codon,

c.676A>T and a previously unreported missense variant in heterozygous c.1312G>A. ***CONCLUSION:*** This study presents a patient who triggered by an infectious event, presents Pediatric Acute Liver Failure Syndrome. Given the establishment of mitochondrial cofactors, the patient's symptom improvement could be explained by the role of *LARS1* in mitochondria. We believe that this treatment should be studied in depth.

P-107 - GLUTARIC ACIDURIA TYPE 1 ASSOCIATED WITH CATAPLEXY IN A CHILD: RARE PRESENTATION WITH GOOD OUTCOME

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INTRODUCTION: Cataplexy is defined as the sudden and uncontrollable onset of paralysis or weakness in skeletal muscles during wakefulness. It can be triggered by everyday situations such as strong emotions and laughter. Cataplexy primarily occurs in the context of narcolepsy or as a late sign in Niemann-Pick type C disease. There are no reported cases in other metabolic diseases. ***OBJECTIVE:*** To present the first described clinical case of a patient with gelastic cataplexy and a diagnosis of glutaric aciduria type 1. ***CLINICAL CASE:*** Female, 15 years old. No prenatal history. Diagnosed with glutaric aciduria type I (GA1), detected through neonatal screening. Development: CIT 60, significant expressive language impairment, assisted walking. At 5 months, she suffered a metabolic decompensation, resulting in spastic-dystonic tetraparesis (GMFCS III) since then. Cranial MRI: Mild signs of frontotemporal atrophy with enlargement of the Sylvian fissures. Signal alteration in the basal ganglia and white matter. Plasma amino acids: increased glutaric acid and decreased lysine. Since the age of 9, she has experienced sudden episodes of loss of muscle tone with falls triggered by laughter, which limit her functionality; no loss of consciousness. No sleep disorders. Methylphenidate treatment was attempted but discontinued due to adverse effects. Venlafaxine was initiated with a good therapeutic response, which is currently maintained. Other current treatments: trihexyphenidyl, CoQ10, and arginine. ***CONCLUSIONS:*** Although the incidence of the conjunction of these two entities is unknown, based on this case, we should inquire about the presence of cataplexy in patients with GA1, as it is a condition that can contribute to functional deterioration in this group of children. Various treatments have shown efficacy, thereby improving the quality of life for these patients.

P-108 - MOLECULAR INSIGHTS OF GLUTARIC ACIDURIA TYPE-1: UNRAVELING GENETIC VARIANTS AND DIAGNOSTIC IMPLICATIONS

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INTRODUCTION: Glutaric aciduria type-1 (GAI) is an autosomal recessive disorder caused by glutaryl-CoA dehydrogenase deficiency, encoded by *GCDH* gene. Affected patients typically present in infancy or early childhood with macrocephaly and an acute encephalopathic crisis often caused by a catabolic state, resulting in an irreversible, mostly dystonic movement disorder with limited life expectancy. Glutaric, glutaconic and 3hydroxyglutaric acid in urine and increased glutarylcarnitine (C5DC) in blood are present in high excretory forms, while low excretors (LE) may show normal concentration of these metabolites. Some GSDH genotypes correlate with biochemical phenotype, but not with the clinical course. ***OBJECTIVE:*** To describe molecular findings of *GCDH* gene in patients with clinical diagnosis of GAI, and to compare biochemical parameters among GSDH genotypes. ***PATIENTS AND METHODS:*** Molecular analysis was performed on 13 GAI patients through a customized next generation sequencing panel for Mitochondrial Disorders and Inborn Errors of Metabolism. Biochemical data was collected: C5DC and acetylcarnitine (C2) in dried blood spots, and organic acids in urine. C5DC/C2 ratio was calculated, and analyzed among genotypes by ANOVA. ***RESULTS:*** In 13 patients with

GAI (8 females, 5 males), 7 different variants in GCDH were detected. The most frequent one was c.1098G>A, p.(Met363Ile), accounting for 8 of 24 unrelated alleles, followed by c.1204C>T, p.(Arg402Trp) in 7 of 24. Two patients homozygous for c.1098G>A or c.740C>T, p.(Ala247Val) had an average C5DC/C2 ratio of 0.008, whereas in 7 c.1098G>A heterozygous patients it was 0.034 and in the remaining 3 patients (excluding LE known genotype) was 0.160 (p=0.031). At least one C5DC measurement was normal in 5 of 9 patients bearing c.1098G>A or c.740C>T, and characteristic urinary organic acids were absent in 3. ***CONCLUSION:*** In this cohort, two previously uncharacterized variants, c.1098G>A and c.740C>T, were detected in GAI patients with normal or borderline glutarylcarnitine levels, or absence of marker urine metabolites. Even more, c.1098G>A variant showed a high allele frequency among patients with GAI. This study highlights the advantages of including the genetic analysis in the diagnostic algorithm of GAI in our population.

P-109 - NUTRITIONAL STATUS AND REQUIREMENTS ADEQUACY IN CHILEAN PATIENTS WITH GLUTARIC ACIDURIA TYPE 1, BEFORE AND AFTER RELAXATION OF DIETARY RESTRICTIONS

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INTRODUCTION: Glutaric aciduria type 1 (AG1) is caused by glutaryl-CoA dehydrogenase enzyme deficiency, leading to an accumulation of metabolites from lysine, hydroxylysine, and tryptophan. AG1 can result in encephalopathic crisis and cognitive disability. Treatment includes a restrictive lysine diet, lysine-free protein substitute (PS), and L-carnitine supplementation, with dietary relaxation after age six. ***OBJECTIVE:*** Compare nutritional status and requirements in subjects with AG1 before and after relaxing the diet and without using PS. ***METHODS:*** A retrospective study of 12 Chilean AG1 subjects was conducted, comparing data before diet relaxation (AG1-1) and after age six (AG1-2). Intake was calculated using a 24-hour recall. Data was represented as average±standard deviation or median with interquartile range (IQR). Paired comparison and Spearman correlation were used. ***RESULTS:*** The median age at diagnosis was eight months (5-14 months), and none was diagnosed by newborn screening. The 4/12 of subjects experienced an acute encephalopathic crisis (AEC) at six months. Five cases had an insidious start with neurological sequelae, and 3 had normal development. Regarding the clinical picture before diagnosis, ten patients presented macrocephaly, nine delayed psychomotor development, and eight abnormal movements. In total, 41% had gastrostomy. An increase in malnutrition was observed in AG1-2, but not significant. AG1-1 met protein requirements with 26% (IQR: 22-37) from high protein value (HPV) and 37% (IQR: 31-49) from PS. AG1-2 met 71% (IQR: 63-78) of protein needs from HPV sources, including dairy (62%), eggs (29%), and meat (17%). Energy intake was better in AG1-1 than AG1-2 without gastrostomy, but there was no significant difference. In patients with gastrostomy, AG1-2 had better energy intake. Lysine intake increased significantly in AG1-2 ($p<0.01$). Lcarnitine in AG1-2 was 55±26 mg/kg. AG1-1 showed better adequacy in critical minerals and vitamins than AG1-2, except in patients with gastrostomy. No correlation was found between HPV and plasma Lys, free carnitine, or esterified carnitine. ***CONCLUSION:*** The relaxed diet in AG1-2 did not affect lysine plasma levels or free and esterified carnitine, but it highlighted the need for continued dietary monitoring to prevent nutritional deficiencies.

P-110 - INSIGHTS FROM SIXTEEN YEARS EXPLORING ORGANIC ACIDURIAS. METABOLIC PROFILES IN HIGH-RISK POPULATION.

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INTRODUCTION: The urinary organic acid profile(OAp) is the gold standard for organic acidurias (OA) diagnosis, moreover, it is a targeted metabolomic approach that allows the identification of a wide variety or metabolic intermediaries. The OAp is also informative for other inborn errors of metabolism and also reflects physiological metabolic changes, interactions with gut microbiota and fluctuations due to diet, medication, or age. In our laboratory this technique has been available for high risk population since 2007. Here, we present a summary of our findings for 16 years. ***METHODOLOGY:***

Retrospective analysis OAp in our laboratory from 2007-2022. ***RESULTS:*** We have processed near 4000 samples. Most of our population is over one year of age (55%) versus only 10% of newborns. We have observed metabolic profiles of 20 different IEM: 16 different OA, aminoacidopathies (Tyrosinemia, and UCD) and Fatty acids disorders (mostly MADD). In our population Glutaric acidemia type I (GA1), is the most frequent diagnosis (24%) followed by Propionic (21%) and Methylmaloic Acidemias (13%). Outstandingly, in our cohort 22% of cases correspond to OA, classified as rare diseases: Piroglutamic (8%), 2-Hydroxyglutaric (6%) methylglutaconic (3%), and mevalonic (1%) acidurias. In addition, in 4% of samples metabolic profiles suggestive of multiple carboxylase deficiency due to holocarboxylase deficiency were observed. We also observed a high rate of unspecific profiles (around 30%) and we have found basal excretion in specific age groups of previously considered pathological metabolites like isovalerylglycine, methylmalonic and methylcitric acids. On the other hand, we observed medication derived metabolites in around 20% of samples. ***CONCLUSION:*** Our experience contrast with incidences of GA1 and classical OA reported in literature. In addition, we observed an unexpected high incidence of rare OA. Our findings might be influenced by the particular genetic background of Colombian population which deserved further studies. In addition, our results point out a delayed diagnosis which might be related to the lack of expanded newborn screening. However, our results highlight the importance of increase awareness of OA in Colombia and the importance of having experienced diagnostic centers in order to improve OAp interpretation.

P-111 - WHEN LESS IS MORE: THE IMPORTANCE OF A PROPER BALANCE OF BRANCHED-CHAIN AMINO ACIDS IN MANAGING ORGANIC ACIDEMIAS

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INTRODUCTION: Propionic acidemia (PA) and methylmalonic acidemia (MMA) are common among inherited metabolic disorders. Their nutritional management is based on protein restriction to prevent endogenous intoxication, improving growth and cognitive outcomes. Specific amino acid-free formulas are used to supplement protein intake along with other micronutrients and vitamins. However, the ratio of branched-chain amino acids (AA) must be carefully monitored to avoid iatrogenic imbalances that can have long-term health impacts on patients. ***OBJECTIVES:*** To highlight the importance of a proper balance between natural proteins and specialized AA mixtures in the management of organic acidemias. ***MATERIALS AND METHODS:*** A case of MMA is presented before and after a change in nutritional management. ***RESULTS:*** Male patient presenting at 4 months of age with vomiting, lethargy, and metabolic acidosis after vaccination. He was diagnosed with mut0 MMA (MMUT c.1808G>C homozygote) and began external nutritional management. At 22 months, he was receiving a total protein intake of 2.5 g/kg/day, including 1.1 g/kg/day of natural protein and 1.4 g/kg/day of a specific AA mixture. His parameters were: weight/age (W/A): -0.72 SD, height/age (H/A): -1.74 SD, weight/height (W/H): 0.25 SD, and AA profile: valine 69 mmol/L (72-272), isoleucine 27 mmol/L (13-122), and leucine 233 mmol/L (41-160). After modifying the nutritional parameters, the total protein intake was adjusted to 1.4 g/kg/day, with 0.9 g/kg/day of natural protein and 0.5 g/kg/day of a specific AA mixture. Seven months later, his growth parameters were W/A: -0.59 SD, H/A: -0.66 SD, W/H: -0.40 SD, and AA profile: valine 65 mmol/L, isoleucine 35 mmol/L, and leucine 51 mmol/L. ***DISCUSSION AND CONCLUSIONS:*** A iatrogenic imbalance of branched-chain AA with excessive leucine values compared to valine and isoleucine levels, due to the overuse of specific AA formulas, can lead to poorer growth outcomes without significant clinical benefits, as observed in the presented case and previously described by Dr. Manoli, Myles et al. (2015). Improvement was achieved by reducing the specialized formula to ensure a better balance of these AA. It is important to conclude that specific AA formulas for PA and MMA can have deleterious iatrogenic effects if used excessively, negatively impacting ponderal growth.

P-112 - EFFECT OF L-CARNITINE SUPPLEMENTATION ON PROPIONATE METABOLISM DISORDERS

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INTRODUCTION: Methylmalonic acidemia and propionic acidemia (MMAcidemia and PAcidemia) are genetic diseases characterized by the accumulation of 3-hydroxypropionic acid and methylmalonic acid in biological fluids. L-carnitine (LC) levels may be decreased in patients with MMAcidemia and PAcidemia due to treatment with a low-protein diet and because of conjugation and excretion of metabolites accumulated in these diseases. Therefore, supplementation with LC is highly recommended. ***OBJECTIVES:*** The aim of the study was to evaluate the effectiveness of LC supplementation in patients with MMAcidemia and PAcidemia. Free LC levels in urine and plasma were evaluated at diagnosis and during treatment. ***METHODS:*** Patients with MMAcidemia and PAcidemia were recruited from the Medical Genetics Service of the Hospital de Clínicas de Porto Alegre (HCPA), Brazil. This study was approved by the Ethics Committee (n° 2023-0157). Urine and blood samples were collected from healthy individuals. Urine samples were obtained from 26 patients at diagnosis (median age of 3 months) and from 5 patients under treatment (median age of 12 months and median of treatment duration was 4 months). Blood samples were obtained from 12 patients at diagnosis (median age of 7 months) and also from 10 patients under treatment (median age of 1.3 years and the median of treatment duration was 11 months). The treatment groups were receiving LC supplementation (100 mg/kg/day) and a lowprotein diet. ***RESULTS:*** Reduced levels of free LC were observed in urine and plasma of patients with MMAcidemia and PAcidemia at diagnosis. It was observed that urinary and plasma free LC levels were increased in patients who were receiving LC supplementation compared to patients at diagnosis. ***DISCUSSION/CONCLUSIONS:*** The literature shows that LC has an important antioxidant and antiinflammatory effect and is responsible for the excretion of toxic metabolites. It was observed that our patients with MMAcidemia and PAcidemia present secondary LC deficiency at diagnosis and that LC supplementation was able to reverse this condition. LC supplementation at the recommended dose is effective in increasing urinary and plasma free LC levels. It is suggested that LC may be fundamental in improving the prognosis of patients with MMAcidemia and PAcidemia.

P-113 - NUTRITION-BASED TREAMENT FOR THE OPTIMAL MANAGEMENT OF ADULT PROPIONIC ACIDEMIA. A CASE REPORT.

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BACKGROUND: Propionic academia (PA) is a genetic disorder caused by the deficiency of propionyl-CoA carboxylase, which affects branched-chain amino acids and odd-chain fatty acids metabolism, leading to accumulation of toxic organic acids. Without treatment, it can lead to neurological disorders. Chronic nutritional is the paramount of treatment in order to control symptoms, avoid complications and improve overall health status. ***CASE REPORT:*** We report a 41-year-old woman with recently diagnosed PA after multiple hospital admissions in psychiatric wards for confusional syndrome, depression and autolytic attempts non- responding to usual treatments, MRI was requested and showed hyperintensity in the cerebral basal ganglia therefore, suggesting, among others, inborn errors of metabolism. Urine organic acid and plasma propionylcarnitine levels suggested PA that was confirmed with genetic test. Her medical history included type 2 diabetes mellitus, obesity, hypertension, cardiomyopathy, dyslipidaemia, kidney transplant, vitamin B12 and folic acid deficiency. Family history showed a brother died at 21yo from cardiomyopathy. After diagnosis, she was referred to our unit for nutritional management. We adjusted diet energy and protein intake to BMI of25 kg/m² (weight 72kg, height 1.51m). Total protein intake resulted in 36-40 g/d (0.5 g/kg/d of current weight, and 0.6- 0.7 g/kg adjusted weight) allowing 12-14g/d of high-biological-value protein from eggs and salmon and free consumption of vegetables and fruits (except tubers and avocados). We also supplemented with medical food of amino acid formula (15 g protein equivalent). During semi-annual follow-up, good adherence to the diet was observed, with a weight loss of only 3 kg, maintaining good and stable diabetes mellitus control and no significant blood biochemical tests alterations. ***CONCLUSIONS:*** In patients diagnosed with metabolic disorders in the adulthood, it is still essential to adjust the diet according to the previous eating habits to obtain good results and allow for a progressive adaptation to nutritional treatment. Given the good response to nutritional treatment, it is inferred that most of her pathological history might have been caused by a lack of diagnosis in childhood.

P-114 - PHENYLKETONURIA IN LATIN AMERICA. A BIBLIOMETRIC ANALYSIS

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INTRODUCTION: Phenylketonuria (PKU) is a genetic condition most often caused by missense mutations in the gene encoding phenylalanine hydroxylase (PAH), which catalyzes the hydroxylation of phenylalanine (Phe) to generate tyrosine (Tyr). In PKU phenylalanine levels build up in body. Newborns with PKU can appear normal at birth with the first signs appearing after several months. If left untreated, phenylketonuria can affect a person's cognitive development. There are very few bibliometric reviews on the scientific production in Inborn errors of metabolism (IEM) in Latin America (LATAM) and none in phenylketonuria that can guide the research needs on the topic. ***OBJECTIVE:*** of this bibliometric review was to know the scientific production and dissemination of PKU research in Latin America (LATAM). ***METHODS:*** For this purpose, a bibliometric review was carried out in the Scopus database, with the search algorithm: [(phenylketonuria) OR (hyperphenylalaninemias)], to know the trend, collaboration, quality and contents in the research work in PKU in LATAM. ***RESULT:*** in 107 documents published, the top 10 Latin American countries were identified (Brazil, Chile, Argentina, Cuba, Mexico, Costa Rica, Colombia, Uruguay Ecuador y Panamá) which were analyzed from the parameters of production volume, relationship between generators and research topics. Regarding production, with Brazil being the country with the highest number of publications (43 in total), followed by Chile with 18 and Argentina and Cuba with 10 each. For the analysis of the citation, the VOSviewer 1.6.13 software was used, with which maps of the relationships between the resulting documents were generated and it was obtained that Brazil, Chile, Argentina, Mexico, Colombia and Cuba are the LATAM countries that they have more collaborations with each other, with Brazil being the most generator of collaborations. Among the findings, it was found that the most frequent topics in the publications are about neonatal screening (43.7%), followed by topic reviews and collaborative studies (17.9%) and original researches (10.3). Very little research in molecular biology and mutations (7.5%), nutrition and treatment (5.6%) standardization of diagnostic methods and case reports (1.9%). Thus, this review provides the general overview of scientific production in phenylketonuria in LATAM.

P-115 - PHENYLKETONURIA IS THE MOST PREVALENT INBORN ERROR OF METABOLISM IN BRAZIL...BUT DO WE HAVE RELIABLE DATA? A STUDY BASED ON DATASUS.

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INTRODUCTION: Phenylketonuria (PKU) appears to be the most prevalent inborn error of metabolism in Brazil. However, studies on this population are scarce. Carvalho et al. (2007), using data from the National Neonatal Screening Program (PNTN) from 2001 to 2005, estimated a PKU incidence of 1: 25,326 newborns. ***OBJECTIVES:*** To characterize the epidemiology of PKU in Brazil using data from the Department of Informatics of the Brazilian Unified Health System (DATASUS). ***METHODS:*** Retrospective study. Data were obtained from DATASUS for the period 2019-2022. The International Classification of Diseases (ICD) codes analyzed were E70.0 (Classical Phenylketonuria) and E70.1 (Other hyperphenylalaninemias), as well as High Complexity/High Cost Procedures Authorization (APACs) related to dispensation of metabolic formulas for PKU and sapropterin dihydrochloride. ***RESULTS:*** In 2019 and 2020, PNTN covered 80.08% and 82.53% of live newborns in Brazil, respectively. We identified 4,454 PKU patients in Brazil (prevalence: 2.2 per 100,000 inhabitants; male: 52.3%), originating from Southeast (54.7%), Northeast (15.8%), South (14.3%), Midwest (9.4%), and North (5.8%) regions. The mean age was 14 years. The state with the highest number of patients was São Paulo (n: 1,319); no patients were identified in Amapá and Roraima. Treatment information was available for 2,568 patients (57.6%); of these, 2,507 (56.2%) used metabolic formula and 61 (1.4%) used sapropterin dihydrochloride. The found incidence of the disease was 1: 30,826 newborns, with the highest rate in the Southeast region (1: 20,534) and the lowest in the North region (1: 97,087), and Paraíba had the highest incidence rate (1: 11,640). Data indicating registration issues were also found, such as the existence of 120 PKU patients in

Paraíba. ***DISCUSSION/CONCLUSION:*** The frequency of PKU found is consistent with the Brazilian definition of a rare disease, and its incidence is similar to the study by Carvalho et al. The relatively small number of adult PKU individuals is explained by the start of the PNTN in 2001. However, the data should be used cautiously because ICD E70.1 also includes BH4 deficiencies, for which sapropterin is also used as treatment. The importance of DATASUS for generating data on rare conditions, and its proper completion, should be emphasized at all levels involved.

P-116 - ACCESS TO DIAGNOSIS AND TREATMENT FOR UREA CYCLE DISORDERS IN A COHORT OF PATIENTS FROM ARGENTINA

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INTRODUCTION: Urea cycle disorders (UCDs) are a group of genetic conditions that result in the inability to convert ammonia into urea, leading to hyperammonemia and severe neurological damage. Early diagnosis and timely treatment are critical for improving patient outcomes. Access to these essential services can vary significantly across different regions and healthcare systems. In Argentina the healthcare system is marked by significant disparities that affect both the accessibility and quality of care. The disparity is exacerbated by differences in insurance coverage, with a portion of the population lacking health insurance. This inequity is particularly pronounced for rare diseases like UCDs, where specialized diagnostic tools and treatments are often unavailable or inaccessible to many patients. ***OBJECTIVE:*** This study aims to evaluate the accessibility of diagnostic services and treatment for patients with UCDs in Argentina, identifying potential gaps and barriers within the healthcare system. ***METHODS:*** A retrospective analysis was conducted on a cohort of patients diagnosed with UCDs in Argentina from 2010 to 2023. Data were collected from medical records, including demographic information, time to diagnosis, access to diagnostic laboratories, and access to specialized treatments such as dietary management, ammonia scavengers, and control laboratories. ***RESULTS:*** The study included 135 patients diagnosed with UCDs. 33,3% had bad and 66,5% had good access to diagnostic labs; 19,1% had bad and 80,9% good access to treatment. We show a correlation between death and bad accessibility to diagnostic labs p0,002, to treatment p0,033 and access to special foods p0,001 as with the number of decompensations. Variables that affect death are also parental education p0,011 and disease comprehension p0,044 and having health insurance p<0,001. ***CONCLUSIONS:*** This study highlights the impact of access to diagnosis and treatment on outcomes of UCDs in Argentina. Despite advances in medical knowledge and technology, many patients face delays and barriers that hinder optimal care. Efforts should be directed towards improving accessibility to biochemical testing and treatment for all patients with UCDs.

P-117 - ATYPICAL CLINICAL MANIFESTATION WITH CHOREODYSTONIA IN A UREA CYCLE DISORDER DUE TO N-ACETYLGLUTAMATE SYNTHASE (NAGS) DEFICIENCY

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INTRODUCTION: N-acetylglutamate synthase (NAGS) catalyzes the formation of N-acetylglutamate (NAG), which activates carbamoyl phosphate synthetase 1 (CPS1), the first enzyme in the urea cycle. Deficiency of NAGS or CPS1 leads to a similar biochemical phenotype, including elevated ammonia and glutamine levels, reduced citrulline, and normal orotic acid. Clinically, it manifests as encephalopathy with or without associated epilepsy. ***OBJECTIVE:*** Present a clinical case of a patient with N-acetylglutamate synthase deficiency (NAGSD) with an uncommon clinical-radiological manifestation. ***CLINICAL CASE:*** Male, 5 years old. History of consanguinity. No prenatal history. Onset at 6 days of life with vomiting, lethargy, feeding difficulties, and

respiratory distress. Progressed to acute encephalopathy requiring mechanical ventilatory assistance. Notable hyperammonemia 1390 µmol/L. Brain MRI (18 days): Severe signal alteration in the caudate nuclei, medial putamen, and central pallidum bilaterally (T2). Peripheral pallidal signal alteration (T1). Global signal alteration in deep white matter and insular cortex. At 4 years: T2 signal alteration persists without significant changes. Atrophy of caudate nuclei and putamen. Clinical exome guided by HPOs: NAGS (NM_153006.2): c.916-2A>G: homozygosity (pathogenic). Currently presents global developmental delay with absence of expressive language, but predominant movement disorder (choreodystonic). Current treatment: arginine, carnitine, carglumic acid, citrulline, protein-controlled diet. ***CONCLUSIONS:*** A child with a rare pathology that also presents an atypical phenotype is reported. NAGSD is an autosomal recessive inherited disease, in which its early detection is crucial given the existence of targeted pharmacological treatment.

P-118 - MRI FINDINGS AND CLINICAL CORRELATION IN A COHORT OF PATIENTS WITH NEONATAL ONSET UREA CYCLE DISORDERS

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INTRODUCTION: Urea cycle disorders (UCDs) are inborn errors of nitrogen detoxification due to defects in five enzymes: carbamoylphosphate synthetase 1(CPS1), ornithine transcarbamylase(OTC), argininosuccinate synthetase(ASS), argininosuccinate lyase(ASL) and arginase 1(ARG1). Complete deficiencies usually present with hyperammonemic coma promptly after birth. Magnetic resonance imaging(MRI), including diffusionweighted imaging(DWI), may reveal abnormalities with a variable pattern and should ideally be performed within first 4 days after a hyperammonemic episode. Certain regions of the brain, particularly the insular and peri-rolandic cortices and basal ganglia are mostly involved. Correlation between the initial MRI findings and the neurological outcome in UCDs has not been fully studied. ***OBJECTIVES:*** We describe the initial MRI findings in a cohort of patients with neonatal onset UCDs and evaluate some biochemical and clinical parameters, correlating these data with the neurocognitive outcome. ***MATERIALS AND METHODS:*** We evaluate the brain MRIs of 7 patients (1 CPS1D; 1 OTCD; 1 ASSD and 4 ASLD), diagnosed in a tertiary care center. Only those patients with a first MRI performed during the neonatal period were included. Laboratory findings, time to normalization of ammonia, requirement of extracorporeal detoxification, number of hospital admissions, requirement of liver transplantation and neurocognitive status at the last outpatient visit were collected from medical records. ***RESULTS:*** The median of ammonia peak concentration was 957.5 ug/dl. Abnormal coagulation was observed in 4 patients (3 required extracorporeal detoxification). Developmental delay was observed in all patients and patient 3 developed a disabling movement disorder. Pathological findings related to hyperammonemia on MRI were observed in 1 CPS1D and 2 ASLD patients. ***DISCUSSION AND CONCLUSION:*** The median of ammonia peak concentration was significantly higher in patients with pathologic brain MRI (2.543 ug/dl) and the neurocognitive profile showed a trend towards a worse outcome in this subgroup. The first MRI was performed at a lower age in patients with pathologic findings. The timing at first MRI could be a key factor and DWI, looking for diffusion restriction, must always be performed in the initial evaluation of a patient with hyperammonemia. Due to the heterogeneity of this group of disorders, clinical decision-making based on neuroimaging results should be done with caution.

P-119 - OXIDATIVE PROFILE OF UREA CYCLE DISEASES IN PATIENTS FROM A REFERENCE CENTER IN BRAZIL

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INTRODUCTION: Urea cycle diseases (UCD) are a group of genetic disorders that result from a deficiency in the urea cycle, a metabolic process essential for eliminating excess ammonia from the body. Ammonia is a byproduct of protein metabolism and is normally converted to urea by the liver and excreted by the kidneys. UCD leads to accumulation of ammonia (hyperammonemia), causing extreme toxicity. Literature indicates that oxidative stress may be one of the mechanisms involved in UCD. ***OBJECTIVES:*** We aimed to investigate the presence of oxidative stress in patients with UCD to better understand

its pathophysiology. ***METHODS:*** Reactive species to thiobarbituric acid (TBARS), carbonyl content and nitrogen reactive species (RNS) were analyzed in plasma samples from 14 patients (mean age: 5.25 ± 9.86) with UCD, diagnosed at a reference center in Brazil (study approved by the Ethics Committee). Results from dosages were compared to healthy individuals levels (n: 13; mean age: 4.91 ± 9.58). ***RESULTS:*** The UCD patients group consisted of individuals affected with ornithine transcarbamylase deficiency (n =8), carbamoyl phosphate synthetase deficiency (n = 2), argininosuccinate synthetase deficiency (n = 2); arginase deficiency (n = 1) and argininosuccinate lyase deficiency (n =1). A significant reduction in RNS were observed in patients when compared to controls and TBARS and carbonyl content were significantly increased, indicating lipid peroxidation and oxidative damage to proteins, respectively. ***DISCUSSION/CONCLUSION:*** Our results demonstrate that oxidative stress occurs in UCD patients, and it can be associated with the presence of hyperammonemia. Hyperammonemia can decrease endogenous antioxidants and provoke accumulation of toxic metabolites, such as glutamate and glutamine, increasing the production of reactive species of oxygen (ROS) and causing several cellular modifications. Our group of patients consisted mostly of ornithine transcarbamylase deficiency, which is associated with decreased citrulline. Literature demonstrated decrease in nitrite and nitrate in these patients, a fact associated with disruption in the de novo arginine synthesis pathway, due to the decrease in citrulline levels, explaining the low RNS levels found. All this evidence together helps us to better understand the pathophysiology of UCDs and help in the search for new therapeutic strategies.

P-120 - UREA CYCLE DISORDERS: CASE SERIES OF THE BRAZILIAN RARE DISEASES NETWORK

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INTRODUCTION: Urea cycle disorders (UCDs) represent a group of rare diseases (RDs) characterized by impaired ammonia detoxification, leading to significant challenges in diagnosis and management. The Brazilian Rare Diseases Network (RARAS) aims to conduct an epidemiological surveillance of RD in 40 health centers from all regions of the country. ***OBJECTIVE:*** Present the epidemiological profile of UCDs cases in RARAS Network. ***MATERIALS AND METHODS:*** Data from patients with suspected and confirmed UCD diagnoses were extracted from RARAS REDCap database, from retrospective (2018-2019) and prospective (2022-2023) approaches. ***RESULTS:*** Fourteen individuals were identified with a UCD diagnosis of almost 20 thousand cases registered in the RARAS database. One case had suspected diagnosis (waiting for confirmatory tests), two were diagnosed through neonatal screening and 11 were diagnosed postnatally. The most prevalent disorders were Argininemia (n=4), Ornithine transcarbamylase deficiency (n=3), and Citrullinemia type I (n=3). Diagnoses were either biochemical (69.2%) or molecular (30.8%). Unified Health System (SUS) funded 69.2% of diagnoses. The interval until diagnosis ranged from 36 days to 27 years and 4 months (median of 3 years and 3 months). Also, 78.5% patients reported receiving treatment, of which 64.2% relied on private sources. The most consulted medical specialties were neurology or pediatric neurology (77.7%), followed by gastroenterology and hepatology (44.4%). The most common signs and symptoms, registered through the Human Phenotype Ontology, were hyperammonemia (n=5); jaundice; vomiting; seizure and intellectual disability (n=3). Nine patients (64.3%) registered hospitalizations (mean: 2.22 per patient), mainly due to UCD (ICD-10 E72.2). No death was reported in the studied period. ***CONCLUSION:*** Currently, in Brazil, the Neonatal Screening Program does not encompass tests for UCDs; nevertheless, a few states have implemented expanded neonatal screening. The two cases in this study were born in these locations. This study highlights the need to support UCD diagnosis through neonatal screening as early diagnosis is essential to therapeutic interventions and patient outcomes improvements. These results show the importance of public policies with SUS as the main funding source for diagnosis and management of UCDs patients.

ABSTRACTS SELECTED FOR POSTER PRESENTATION (NS)

P-121 - ANALYSIS OF THE LAST 10 YEARS IN THE CONFIRMATION OF BIOTINIDASE DEFICIENCY DETECTED IN NEONATAL SCREENING.

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INTRODUCTION: Biotinidase is responsible for the recycling of biotin, from biocytin or small biotinylated peptides produced in the degradation of carboxylases, and release of the vitamin bound to dietary proteins. Biotinidase enzyme deficiency (BTD) is inborn error of metabolism of autosomal recessive origin, included in the mandatory neonatal screening in Argentina with a frequency of 1: 60000. The phenotype of disease can be very variable. Patients show a great difference in the age of presentation as well as in clinical expression. The onset of symptoms, in the absence of treatment, occurs during the first trimester of life although it can be delayed up to 2 years. Some patients increase enzymatic activity over time, allowing treatment to be changed or discontinued. ***OBJECTIVES:*** Describe the results of biotinidase enzymatic activity (BEA) in the last 10 years and evaluate the enzyme activity with increasing age. ***MATERIALS AND METHODS:*** 203 results of BEA were analyzed in the period 2014 to April 2024. Colorimetric method was used whose substrate is biotinyl-4-aminobenzoic acid. Classification was according to BEA: total deficiency (<0.7 nmol/min/mL), partial deficiency (0.7 – 2.0 nmol/min/mL), heterozygous (2.1 – 5.0 nmol/min/mL) and normal (>5.0 nmol/min/mL). The results of the 13 patients in whom BEA was repeated over time were analyzed. ***RESULTS:*** Of the 203 BEA results, 15 showed total deficiency (7.4%), 54 partial deficiency (26.6%), 79 heterozygous (38.9%) and 55 normal (27.1%). 13 patients underwent a second evaluation of the BEA, 1 total deficiency, 3 heterozygous and 9 partial deficiency. 2 patients with partial deficiency recovered enzymatic activity when they were repeated at 18 months on both occasions. ***DISCUSSION/CONCLUSION:*** The amount of plasma BEA performed shows the low incidence of false positives in neonatal screening, evidencing good practices. Two patients with partial deficiency who increased their enzymatic activity with age demonstrates the importance of measuring it again with the consequent impact on treatment. We will continue the practice of monitoring BEA over time following the recommendation of Forny et al.

P-122 - BIOTINIDASE DEFICIENCY IN THE INTERIOR CITIES OF SÃO PAULO STATE, BRAZIL

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INTRODUCTION: Biotinidase deficiency (BD) is an inborn error of metabolism with an autosomal recessive inheritance pattern. The symptoms of BD can vary widely among affected individuals, ranging from mild to severe forms. Due to the variability of clinical manifestations, there is a significant risk of delayed diagnosis. Since 2001, the Brazilian Federal Government has implemented a national neonatal screening program to diagnose rare diseases, including BD. Biotinidase activity is measured from dried samples of whole blood spotted on the same filter papers used in neonatal screening, using fluorometric methods. A second measurement with the same sample and technique is performed if the initial results are below the normal rate. If the abnormal result persists, a new plasma sample is collected to confirm the activity using colorimetric techniques. The Clinics Hospital of Ribeirão Preto at the School of Medicine of Ribeirão Preto, University of São Paulo (HCFMRP-USP), Brazil, serves as one of the reference centers for follow-up and treatment of patients with rare diseases. ***OBJECTIVES:*** To calculate the annual incidence of BD in cities covered by the neonatal program at HCFMRP-USP. ***MATERIAL AND METHODS:*** This study involves a quantitative, retrospective review of medical records extending from 2001 to 2021, focusing on patients with either a partial or complete diagnosis of BD. The annual incidence of BD was calculated using data from newborn children available from the Brazilian Institute of Geography and Statistics. ***RESULTS:*** The study observed a total of 42 patients—15 females and 27 males—with either total (4 patients) or partial BD (38 patients) from 20 cities in the interior of São Paulo state. The combined incidence of partial and total BD was estimated at 1 in 55,766 live births. ***CONCLUSIONS:*** Our results confirm the worldwide combined incidence estimate of BD at 1 in 60,000, derived from neonatal screening procedures. Due to the ethnic diversity of Brazil's population, there is significant variation in the incidence of cases across different states.

P-123 - NEWBORN SCREENING FOR BIOTINIDASE DEFICIENCY: EXPERIENCE FROM THE 5 YEARS OF THE IMPLEMENTATION IN THE NEWBORN SCREENING REFERENCE SERVICE IN ESPÍRITO SANTO.

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INTRODUCTION: Biotinidase deficiency (BD) is a hereditary metabolic disease with varied phenotypic expression, in which there is a defect in the biotin metabolism. The disease is manifested with neurological and cutaneous symptoms, with the possibility of irreversible neurological sequelae in patients not treated early. Due to the variability and non-specificity of clinical manifestations, there is a great risk of delay in the diagnosis when it is not made through newborn screening. ***OBJECTIVES:*** Describe the results of the last five years of the implementation of newborn screening for Biotinidase Deficiency (BD) at the Newborn Screening Reference Service (SRTN) in Espírito Santo (ES). ***RESULTS:*** 224,778 newborns were screened between January 2018 and December 2022 at SRTN-ES. 7 patients diagnosed with BD, indicating a prevalence of 1: 32,288. The study showed that 6 patients were diagnosed with partial deficiency and 1 with total deficiency. The methodology of analysis used for newborn screening was quantitative colorimetric enzymatic and the diagnostic confirmation quantitative by the analysis of serum activity of biotinidase enzyme. ***CONCLUSION:*** The inclusion of Biotinidase Deficiency in ES Newborn Screening indicated a higher prevalence than that observed worldwide (1: 60,000), which reinforces the need for new research on the topic. Early diagnosis, with treatment starting in the first months of life, ensured adequate development for patients, free from sequelae and better quality of life, reiterating the benefit of including this pathology in the National Newborn Screening Program.

P-124 - CONGENITAL ADRENAL HYPERPLASIA: TWO SIDES OF THE COIN IN NEONATAL SCREENING

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INTRODUCTION: Congenital adrenal hyperplasia (CAH) is a genetic disorder with enzyme deficiency characterized by insufficient or excessive production of one or more adrenal steroids, resulting in glucocorticoid insufficiency with or without changes in mineralocorticoid production and/or or sex steroids. Greater than 90% of CAH is due to 21-hydroxylase deficiency, which is caused by mutations in the *CYP21A2* gene ***OBJECTIVE:*** To report 2 cases of siblings with congenital adrenal hyperplasia diagnosed in our country, one of them detected by neonatal screening and the other by clinical suspicion in childhood with a pathogenic variant in the *CYP21A2* gene. ***METHOD:*** Retrospective review of the clinical records of 2 patients with CAH. ***RESULTS:*** We report a pair of siblings with a pathogenic variant in the *CYP21A2* Gene in which one of them debuted with ambiguous genitalia and electrolyte imbalance in the neonatal stage and the other patient was diagnosed due to clinical suspicion and family history of a younger sister with this variant. ***DISCUSSION:*** Congenital adrenal hyperplasia is a condition that can be diagnosed by neonatal screening and is supported by molecular diagnosis (massively parallel sequencing). In this case, a patient was detected with a suggestive neonatal screening who subsequently underwent genetic counseling that supported her brother's approach with clinical data of precocious puberty, and this variant could be detected through molecular tests. In this way, it was shown that it is a same variant with variable expressibility.

P-125 - MULTIPLEX PCR FOR MOLECULAR DIAGNOSIS IN PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA

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INTRODUCTION: Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder caused by deficiency of several enzymes of adrenal steroid synthesis, the most common being 21-hydroxylase (21-OH), the synthesis of cortisol is prevented and increases the androgen production. ***OBJECTIVE:*** To develop a molecular test to simultaneously detect four mutations in the *CYP21* gene and establish correlation with the clinical diagnosis. ***METHODS:*** A multiplex-PCR method was established for the P30L, I235N, I2G and Q318X mutations. The amplification product of the *CYP21* gene was used to simultaneously detect the point mutations with a mixture of allele-specific primers for the previous mutations. The multiplex PCR reaction was carried out in a final volume of 25 µl containing preamplified product, 25 µM/L of each primer, dNTP's, reaction buffer, magnesium chloride, taq polymerase, the amplification program was 30 cycles with 30sec at 95ºC, 35sec at 58ºC and 1min at 72ºC. The PCR product was observed in a 2% agarose gel stained with ethidium bromide, bands of 2.7,

1.5, 2.2 and 0.8Kb were obtained respectively. ***RESULTS:*** 9 patients were evaluated, with a previous diagnosis of CAH supported by 17-OHP analysis. The average age of the patients was 14 years and the average age of diagnosis was 4 years. The average 17-OHP levels were 13.7ng/dL, higher than the reference values (2.5 and 5 ng/dL); The most frequent clinical characteristic was hirsutism, which occurred in 55.5% of cases. The most frequent mutation was P30L with 72%, the I235N and Q318X mutations occurred in 11% of patients. In patients with simple virilizing forms of CAH, the frequency of the I235N mutation was 100%; In the Non-Classical form of CAH the causal mutation P30L was identified in 100% of the patients, while the highest levels of 17-OHP corresponded to the I2G mutation. ***CONCLUSION:*** The methodology used in this study for the direct molecular analysis of the 21-hydroxylase gene has made it possible to detect the causal mutation in 98.5% of the cases, presenting this methodology as an alternative in the diagnostic support of this pathology.

P-126 - NEWBORN SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA IN FEDERAL DISTRICT, BRAZIL: TEN YEARS SAVING LIVES

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INTRODUCTION: Congenital adrenal hyperplasia (CAH) is a genetic metabolic disorder. More than 95 percent of the cases are attributed to mutations in the *CYP21A2* gene that cause a deficiency in the 21-hydroxylase (21OH) enzyme activity. The main goal of newborn screening for CAH (CAH-NBS) is to prevent death in the first year of life, due to life-threatening adrenal crises. The overall incidence of classic CAH-21OHD is approximately 1: 10,000 to 1: 20,000 live births. About 75% are present with the salt-wasting (SW) form. Many countries have incorporated CAH-NBS into NBS programs. Federal District (FD) was one of the first to implement this in Brazil. ***OBJECTIVES:*** to describe the confirmatory cases of CAH detected by NBS in FD ***MATERIALS AND METHODS:*** A cross-sectional study included all consecutive CAH-NBS tests performed on newborns from public healthcare service units in the FD from January 2012 to September 2022. Suspicion of CAH-21OHD was triggered by neonatal 17OHP (N17OHP) levels exceeding the percentile 99 (P99) cutoff adjusted for birth weight. The confirmatory diagnosis for CAH-21OHD was established by increased serum 17OHP and androstenedione levels. The Ethics Committee approved the study. ***RESULTS:*** Among the 433.248 newborns, CAH-21OHD was confirmed in 22, nineteen of whom had a SW form (86,3%). CAH incidence was 1: 19.693. The average weight was 3.220g. No confirmed cases of CAH were detected for BW ≤ 1500 g. The ratio of females to males was 1.2 to 1. All females had ambiguous genitalia, with nine classified as Prader stage IV. The average time for the first sample collection (1.93 + 36,5 days) and age at diagnosis (7.92 + 42,8 days) were the lowest among children born in public hospitals in FD. The average N17OHP level (314 ± 185,63 ng/ml) and serum 17OHP level (100 ± 62 ng/ml) were higher in the SW form. ***CONCLUSION:*** The efficiency of CAH-NBS in FD was demonstrated by detecting all cases in the first sample, most of which were collected before the newborns were discharged from the maternity ward, thus preventing deaths. Our study included one of the largest sample sizes compared to previous studies in Brazil.

P-127 - NEWBORN SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA: EVALUATING CLINICAL OUTCOMES IN CHILDREN WHO TESTED POSITIVE.

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INTRODUCTION: Congenital Adrenal Hyperplasia (CAH) is a genetic disorder caused by a lack of enzymes that are needed to produce adrenal steroids. CAH can manifest in traditional forms, such as salt-wasting and simple virilizing, as well as non-classical forms. The salt-wasting form of CAH can be life-threatening if not promptly diagnosed and treated. In dry blood spot testing, newborn screening (NBS) can detect CAH by analyzing the levels of 17-hydroxyprogesterone. ***OBJECTIVE:*** Analyze and describe the characteristics of children diagnosed with CAH upon admission to the NBS Reference Service. ***MATERIALS AND METHODS:*** This observational population-based study used a retrospective approach to analyze data obtained between 2018 and 2022. The sample included all children diagnosed with CAH through NBS upon admission at the "Associação de Pais e

Amigos dos Exepcionais" in Salvador, Bahia, Brazil. ***RESULTS:*** From 2018 to 2022, 814,914 newborns were screened, and 54 children were diagnosed with CAH, resulting in a screening rate of 1: 15,000. Most of the cases (61%) were male, with more than 90% classified as salt-wasting. At the initial visit to the reference service, the median (IIQ) age was 32 (25–42) days. There were a median (IIQ) of 4.0 (1,9–4,9) follow-up visits per year. Furthermore, one out of every five children admitted to the service showed signs and symptoms of severe illness, such as dehydration (19%) and virilization (18%). The anthropometric evaluation was appropriate, revealing a median (IIQ) Z score of height for age of -0,62 (-1,46–+0,3). ***CONCLUSION AND DISCUSSION:*** This research emphasizes the clinical aspects of children recently diagnosed with CAH. It was possible to demonstrate excellent aspects of the NBS care center that supported the maintenance of the infants' ideal nutritional status, including height, in addition to the utilization of high-quality indicators such as visit intervals. However, the service continued to admit these babies at unfavorable times, with the majority exhibiting significant symptoms of clinical disease decompensation, a situation that could benefit from improvement. Furthermore, recommending additional research in this field is crucial as it positively impacts public health, especially by enhancing the quality of life and prognosis for individuals diagnosed with this disease.

P-128 - TRANSIENT 170H PROGESTERONEMIA: A NEWBORN SUBGROUP DIAGNOSED BY NEONATAL SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA

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INTRODUCTION: Newborn screening for congenital adrenal hyperplasia (CAH) is associated with a high falsepositive rate, particularly among preterm infants wich can significantly impact the families of affected patients. ***OBJECTIVE:*** This study aims to characterize the clinical and biochemical features of a subset of infants with transient hyper-17-hydroxyprogesteronemia identified through the Buenos Aires City Government Neonatal Screening Program, and to describe their follow-up. ***MATERIALS AND METHODS:*** We conducted a retrospective analysis of clinical data from newborns with positive CAH screening results referred to Ricardo Gutierrez Children Hospital from January 2014 to May 2024. These infants underwent clinical evaluation (including physical examination and weight progression) and blood tests to assess extracted serum 17-hydroxyprogesterone and electrolyte levels upon recall. Extracted serum 17-OHP measurements were performed using RIA and adjusted for gestational age and sampling age. Infants with elevated serum 17-OHP levels were followed longitudinally. ***RESULTS:*** Among 210383 screened newborns, 162 initially tested positive for elevated 17-OHP and were recalled. Subsequent analysis revealed normal 17-OHP serum levels in 133 infants upon reevaluation. Eleven infants were diagnosed with CAH (9 Salt-Wasting and 2 Simple Virilizing subtypes), with a median 17-OHP concentration of 122 ng/ml (range: 18.8-243.5). Eighteen infants (11 male) exhibited transient hyper-17-OHP, of whom 12 were born preterm (33-36 weeks gestational age). The median age at first abnormal 17-OHP sample was 14.5 days (range: 7-67). Perinatal stressful events were reported in 15 patients (83.3%). All infants showed normal physical exam, weight gain, and electrolyte levels. Median 17-OHP concentration was 6.9 ng/ml (range: 4.6-9.7) in preterm infants and 4.9 ng/ml (range: 3.9-7.2) in term infants. 17-OHP levels normalized at a median age of 38.5 days (range: 13-116). ***CONCLUSIONS:*** We identified a cohort of newborns with transient hyper-17-hydroxyprogesteronemia who lacked clinical or biochemical signs of CAH. A significant proportion were born preterm and/or experienced perinatal stress. Extracted serum 17-OHP levels normalized spontaneously before four months of age. Until more accurate methods are available to evaluate the steroidogenic profile, close follow-up until normalization is essential for these infants.

P-129 - DISTRIBUTION OF TOTAL THYROXINE (TT4) IN NEWBORN SCREENING (NBS) SAMPLES IN PRETERM (PTN) AND TERM NEWBORNS (TN) IN THE EVALUATION OF CONGENITAL HYPOTHYROIDISM (CH)

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INTRODUCTION: Measurements of Total T4 (TT4) and TSH in newborn screening (NBS) have been used for the detection of congenital hyphothyroidism (CH). In patients with central congenital hypothyroidism (CCH), TSH is not useful, demonstrating the necessity of measuring TT4 for its detection. TT4 can be affected mainly due to immaturity and the presence of non-thyroid illness. ***OBJECTIVES:*** To evaluate TT4 in preterm newborns (PTN) and term newborns (TN), newborns with primary congenital hypothyroidism (PCH) and CCH. To compare TT4 in paired samples of PTN with ≤30 weeks of gestational age (GA),. To correlate birth weight with TT4 in PTN. ***MATERIALS AND METHODS:*** 145 NBS samples in PTN of 25wGA (n=20), 30wGA (n=27), 35wGA (n=32), TN (n=49), newborns diagnosed with PCH (n=13) and CCH (n=4) obtained 48 hours after birth were retrospectively analyzed. In newborns with 25wGA (n=2) and 30wGA (n=7) second samples were obtained at 15 days of life. TT4 was measured with the Neonatal T4 ELISA AP BIOTECH Kit. Mann Whitney and KruskalWallis tests were used for statistical analysis. ***RESULTS:*** TT4 was expressed according to GA, as median and range in µg/dL serum: 25wGA 3.0 (< 1.2-5.5), 30wGA 5.0 (3.0-7.0), 35wGA 6.75 (4.5-9.5), TN: 10.6 (7.0-16.0), PCH: 2.9 (<1.2-6.5) and CCH: 2.35 (1.2-5.5). When comparing the medians of TT4 between consecutive groups in PTN and TN, statistically significant differences were observed (P<0.0001). No statistically significant difference was observed between TT4 in ≤30wGA PTN and CCH. Statistically significant differences were observed between 30wGA PTN and PCH. In the paired samples, an increase in the concentration of TT4 was observed in the second sample, with an average of 119% for 25wGA and 46 % for 30wGA. TT4 and weight correlation in PT<2500 g (n=59) was r: 0.66. ***CONCLUSIONS:*** TT4 values in ≤30wGA PTN are similar to those observed in CCH. TT4 levels increase as GA increases. A strong correlation was found between TT4 and birth weight in PTN. TT4 in the first sample is limited to ≤30wGA PTN. However, the detection of CCH could benefit from a strategy that considers delayed sampling in order to improve the specificity in this population.

P-130 - THE EVOLUTION OF CONGENITAL HYPOTHYROIDISM SCREENING IN URUGUAY: 30 YEARS OF HISTORY

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INTRODUCTION: Congenital Hypothyroidism (CH) is an endocrinopathy, the detection of which is carried out through the determination of TSH (Thyroid Stimulating Hormone) in cord blood. Without early treatment, the condition progresses rapidly, causing irreversible neurological damage. ***OBJECTIVE:*** To show the evolution of CH screening in Uruguay. ***MATERIALS AND METHODS:*** A retrospective analysis of data obtained from CH newborn screening at the Uruguayan Neonatal Screening Laboratory was conducted. ***RESULTS:*** In 1990, Uruguay began a pilot program using cord blood samples from babies born in Social Security maternity hospital. The first case of CH was detected in 1991. In 1994, the mandatory requirement to perform cord blood screening for all newborns was approved by decree 430/94. The country was divided into 2 regions, with the north collecting cord blood on filter paper and the south collecting cord serum. This practice continues to date. Since 2012, healthcare providers have started performing TSH tests for their newborns in their own laboratories. As a result, the Neonatal Screening Laboratory achieved a coverage of 95% of births in 1995, which decreased to 32% by 2023. Over these 30 years, our institution has processed 1,016,852 cord blood samples, detecting 495 confirmed cases of CH. Since 2022, we have implemented a pilot program where all heel blood samples from preterm, low birth weight, and/or twin children are tested at 20 days of life. ***DISCUSSION AND CONCLUSIONS:*** Over the past 30 years, the CH screening program has evolved to ensure maximum coverage and provide early results, leading to the development and implementation of screening for other diseases. The decentralization of samples, associated with the easy and cost-effective availability of technology for TSH determination, offers the advantage of rapid CH diagnosis but presents the disadvantage of greater difficulty in collecting complete data on confirmed cases nationwide. Another challenge identified with decentralization is that repeat tests at 20 days are not performed for premature, low birth weight, and/or twin newborns. Therefore, the Neonatal Screening Laboratory has resolved to test TSH on all repeat heel blood samples received to avoid false negatives.

P-131 - CYSTIC FIBROSIS DIAGNOSIS. SWEAT TEST BY GIBSON&COOKE/SCHALES&SCHALES METHOD IMPLEMENTATION IN CHACO PROVINCE

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INTRODUCTION: The quantitative measurement of chloride in sweat is used to confirm the diagnosis of cystic fibrosis (CF). It is an autosomal recessive disorder

characterized by viscous secretions that affect the exocrine glands, primarily in the lungs and pancreas. Patients with CF have an increased concentration of chloride in their sweat. The criteria for the diagnosis of CF include the presence of one or more characteristic phenotypic features or a history of CF, or a positive newborn screening (NBS) test result; and an increased sweat chloride concentration by pilocarpine iontophoresis on two or more occasions, or identification of two CF-causing mutations or demonstration of abnormal nasal epithelial ion transport. ***OBJECTIVE:*** To assess results of sweat test (ST) method implemented. ***MATERIALS AND METHODS:*** Retrospective study between April 2020 and December 2023. Sweat samples from 165 patients with positive NBS (81), compatible symptoms (63), family history (7) and with a diagnose of CF (14) were analised to initiate and follow-up treatment with triple therapy. Sweat production was stimulated through iontophoresis with pilocarpine. Samples were collected by using gauze (Gibson&Cooke method). The samples collected were weighted (mg) and the chloride (Cl^-) concentration in the sweat was measured (Schales&Schales method with mercury nitrate). CF diagnostic criteria: $Cl^- \leq$ 29 mmol/l normal; Cl^-=30-59 mmol/l intermediate and $Cl^- \geq$60 mmol/l indicative of CF. ***RESULTS:*** 10 out of 81 positive NBS patients showed Cl^- values ≥60, 62 had normal range and 9 intermediate values.1 2 out of 63 patients with compatible symptoms presented $Cl^- \geq$60, 49 had normal range and 12 intermediate values. 5 out 7 patients with family history had normal range of values of Cl^-, 1 intermediate and 1 ≥60. Patients with CF presented $Cl^- \geq$60 values similar to those obtained at the time of diagnosis. ***CONCLUSION:*** 13 patients had diagnosis confirmed during the research period. The ST is still the gold standard method to diagnose CF, even if it is not always conclusive. In our country, the implementation of the NBS has faced us with new diagnostic challenges of the disease. Therefore, the province needs to have validated techniques as a reference methodology to measure Cl^- in sweat.

P-132 - CYSTIC FIBROSIS: MUTATIONS IDENTIFIED IN NON-CLASSICAL URUGUAYAN CASES

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INTRODUCTION: Cystic fibrosis (CF) is the most common autosomal recessive genetic disease. It is a multisystem disease caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene. More than 2000 mutations of the *CFTR* gene have been documented. These mutations are categorized based on their molecular impact into Class I to VI. Considering the severity of the disease, they are classified as follows: causing CF variants, non-CF causing variants, variants with variable clinical consequences, and variants of unknown significance. Classic CF is defined by a sweat test result of greater than or equal to 60 mEq/L along with two mutations. ***OBJECTIVE:*** To analyze the genetic results obtained between 2012 and 2022 in patients with abnormal neonatal screening but normal or intermediate sweat test results. ***METHODOLOGY:*** A retrospective study was conducted on genetic results obtained genetic analysis performed for the 50 most common mutations using the CF-EU2v1 Kit (Elucigene) on an ABI 310 sequencer. In instances of negative results, complete gene sequencing was carried out by an external laboratory. ***RESULTS:*** During the study period, 9 patients were diagnosed with CF, 2 with normal sweat test results and 7 with intermediate sweat test results, all of them having 2 mutations. Eleven different variants were identified. The most common mutation found in heterozygosity was DF508 (3 times), which is a variant causing CF and is classified in Class II. In total, there were 5 Class II variants, 4 Class IV variants, 4 polymorphisms, and others with lower frequency. Among these, 6 variants causing CF can be classified, along with four associated with variable clinical consequences, and one variant of unknown significance. So far, 44% of the cases presented with pseudomonas aeruginosa sp development, and 100% of them debuted with at least 1 year of life. ***CONCLUSION:*** The combination of benign mutations or polymorphisms with class II or class IV mutations can lead to patients with symptoms but borderline or normal sweat test results. In all cases, abnormal neonatal screening was present. Therefore, over the 10 years studied, the diagnosis of these patients has required closer clinical monitoring for confirmation.

P-133 - CYSTIC FIBROSIS: VISION OF MORE THAN A DECADE IN NEONATAL SCREENING IN SALTA, ARGENTINA

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INTRODUCTION: Cystic fibrosis (CF) is an autosomal recessive condition characterized by chronic lung disease,

pancreatic insufficiency, elevated sweat chlorides, and male infertility. This pathology is caused by the presence of more than 2000 mutations in the *CFTR* gene that codes for a chloride channel called transmembrane conductance regulatory protein (CFTR). ***OBJECTIVE:*** evaluate the frequency of CF in our population, present mutation and clinical presentation at the time of diagnosis. ***MATERIALS AND METHODS:*** Retrospective and descriptive analysis of program data. Determination of Immunoreactive Trypsinogen (IRT): quantitative enzyme immunoassay, sandwich ELISA, ZenTech. Cut-off point: 70 ug/l. Sweat test: stimulation by Iontophoresis with Pilocarpine (Gibson and Cooke technique) and chloride assessment using the Schales and Schales method. Values greater than 60 mEq/l: pathological. Extended CF Mutation Study: ARMS- Elucigene CF-EU2v1 ***RESULTS:*** 276,075 newborns (NB) were investigated from 2010 to 2023, corresponding to children born in the public and private sectors; 5 newborns with CF were detected and confirmed in this period, calculating a frequency of 1: 55215. Of the patients with CF, 60% obtained a Trypsin with values greater than 100 ug/l in the first sample. The results of the sweat test reflected 30% of chlorine values greater than 100 mEq/l. 2 of the CF patients had a homozygous ΔF508 mutation, 2 of them had a heterozygous ΔF508 mutation, and 1 had a different variant: 1677Ddel. 40% of diagnosed newborns started treatment before two months of age. ***CONCLUSIONS:*** in Argentina there are different prevalences associated with the regions. The incorporation of CF in the screening program began in 2010; although the frequency is not high, the importance for the prevention and growth of NBs is highlighted. Knowing the type of predominant mutation and their clinical features allows for improved treatment. The objective is early diagnosis and improving the prognosis of patients.

P-134 - FIVE-YEAR EVALUATION OF NEWBORN CYSTIC FIBROSIS SCREENING USING THE IMMUNO-REACTIVE TRYPSIN/PANCREATITIS-ASSOCIATED PROTEIN (IRT/PAP) ALGORITHM

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INTRODUCTION: Cystic Fibrosis (CF) is the most prevalent lethal hereditary disease in the Caucasian race, with an estimated prevalence of 1: 3000 newborns. The IRT/IRT strategy in two samples and IRT/PAP strategy in a single sample are two of the possible strategies used in newborn screening for cystic fibrosis in order to reduce false positive results for the IRT first test. Our program had performed previously a prospective twoyear pilot study comparing both strategies. ***OBJECTIVE:*** to evaluate the results of the cystic fibrosis screening with the IRT/PAP algorithm in the period 2018-2022. ***MATERIALS AND METHODS:*** All newborns in the program born between January 2018 and December 2022 were included. IRT was measured from 36 hours of life by immunofluorometric method (Perkin-Elmer), cut-off value 60 ng/ml and PAP by ELISA method (Dynabio) cut-off value 1.6 ng/ml for samples with IRT values between 60 and 99 ng/ml and 0.5 ng/ml for values ≥100 ng/ml in a single dried blood sample. Sweat Tests (ST) were performed using the Gibson and Cook method to confirm the diagnosis and molecular studies (50 mutations) were performed for all the detected and died patients. ***RESULTS:*** A total of 102280 newborns were screened, of which 853 had high IRT values (0.83 %). A total of 319 patients with elevated IRT/PAP were recall to perform ST. Recall rate was 0.31%. 15 patients with CF were detected, 33 patients died without being able to perform ST, but molecular studies were negative for all of died patients. The prevalence of CF was 1/6819. The homozygous ΔF508 mutation was detected in 58% of those affected. The IRT value (x ± SD) in those affected was: 192 ± 78.4 ng/ml. The age (x ± SD) at the final report of confirmed patients was 78 ± 115 days of life ***CONCLUSIONS:*** The prevalence of cystic fibrosis of 1: 6819 live births in our population is lower than that reported for the Caucasian population. The recall rate was acceptable, optimizing the newborn screening of cystic fibrosis in our program in this five-year evaluation.

P-135 - LABORATORY DIAGNOSTIC ALGORITHM FOR THE DETECTION OF CYSTIC FIBROSIS USED AT COSTA RICA'S NATIONAL CHILDREN'S HOSPITAL

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INTRODUCTION: In Costa Rica the laboratory diagnosis of Cystic Fibrosis (CF) dates back to 1966, when the sweat chloride test was performed in patients with clinical

suspicion of the disease. In 2014, the immunoreactive trypsinogen test (IRT) was successfully implemented within the National Screening Program, which changed the paradigm of CF detection. Because it has been ten years since the implementation of IRT, there is a need to review the protocols to determine whether they comply with the recommended international guidelines with the aim to establish opportunities for improvement. ***OBJECTIVE:*** to compare the current diagnostic algorithm for CF used at the National Children´s Hospital with the parameters recommended by the Cystic Fibrosis Foundation (CFF). ***MATERIALS AND METHODS:*** a review of the Clinical and Laboratory Standards Institute (CLSI) C34-A2 guideline and the CFF consensus guidelines was carried out and compared with the local working protocol. ***RESULTS:*** It was determined that the laboratory complies with most of the points established in both guidelines; however, some discrepant issues were identified. Regarding the C34-A2 guideline, it was found that the laboratory does not apply the recommended reference intervals for the neonatal population and uses the conductivity technique (Nanoduct®) instead of the quantitative confirmatory test (Macroduct®) as the method of choice. In relation to the CFF consensus guideline, it was found that the laboratory does not perform the sweat test bilaterally, and does not have additional tests that directly measures CF transmembrane conductance regulator (CFTR) function, such as nasal potential difference (NPD) and intestinal current measurement (ICM). Moreover, the current algorithm does not allow for the detection of CFTR-related metabolic syndrome (CRMS)/ CF Screen positive inconclusive diagnosis (CFSPID) condition as genetic analysis is not part of the initial diagnostic process. ***CONCLUSION:*** Although the comparison of the current working model showed general agreement with the recommendations of the CFF guidelines, the need to optimize the diagnostic algorithm is evident. A new algorithm in agreement with international recommendations is proposed to provide a faster and more efficient laboratory diagnosis.

P-136 - NEWBORN SCREENING OF CYSTIC FIBROSIS USING IMMUNOREACTIVE TRYPSINOGEN AND PANCREATITIS ASOCIATED PROTEIN IN THE SOCIAL SECURITY INSTITUTE OF PANAMA.

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INTRODUCTION: Cystic fibrosis is a genetic disease with an autosomal recessive inheritance. Newborn screening of this condition is performed using immunoreactive trypsinogen (IRT) with several protocols; but those using only this analyte have not the best specificity, leading to a lot of screened positive babies with no cystic fibrosis. This situation has led to using second tier analytes to increase the specificity of the screening. The pancreatitis associated protein (PAP) has been used in those babies with elevated IRT for increasing specificity with low cost and in one sample. ***OBJECTIVES:*** To present the results of the implementation of newborn screening of cystic fibrosis with IRT and PAP using enzyme-linked immunosorbent assay (ELISA) in the Institute of Medical Genetics and Genomics of the Social Security Institute of Panama.***MATERIALS AND METHODS:*** Descriptive and observational study of the results newborn screening for cystic fibrosis using IRT and PAP in samples of dried blood spots (DBS) from January to July 2023. ***RESULTS:*** A total 3291 DBS samples were analyzed. 293 (8.9%) were positive for IRT (> 50 ug/L). Of this IRT positive test, 48 (16.4%) were positive for PAP (PAP > 1.8 ug/L if IRT is between 50 – 99.9 ug/L; PAP > 1.0 ug/dL if IRT > 100 ug/L) and 245 resulted negative (83.6%). 1.45% of the newborn screened had a positive newborn screening for cystic fibrosis using this protocol. ***CONCLUSION:*** There was reduction of newborn screen positive patients using the protocol of IRT/PAP. This protocol appears to be a useful and cost-effective strategy for newborn screening of cystic fibrosis. There were some advantages using this protocol like using the same sample for second tier screening, saving time in reporting results.

P-137 - UPDATE IN CYSTIC FIBROSIS NEWBORN SCREENING IN URUGUAY: A TWO-YEAR REVIEW

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INTRODUCTION: Cystic Fibrosis (CF) is a severe autosomal recessive disease, the incidence is between 1/2,500 and 1/6,000 in newborns. The gene responsible encodes a protein called cystic fibrosis transmembrane

conductance regulator (*CFTR*), which acts as a channel for chloride in the respiratory, digestive and reproductive systems, as well as in sweat and saliva glands. In Uruguay, the diagnostic algorithm for CF begins with newborn screening using dried blood spot tests for immunoreactive trypsin (IRT) and Pancreatitis Associated Protein (PAP). Confirmation tests include the Sweat Test (ST) and genetic studies. ***OBJECTIVE:*** Describe and analyze the results obtained from Cystic Fibrosis newborn screening over a two years period. ***MATERIALS AND METHODS:*** A retrospective study was carried out on the samples received in the newborn screening program in Uruguay between January 2022 and December 2023. IRT was performed by Perkin Elmer AutoDelfia reagent kit, MucoPAP II DYNABIO reagent to perfome PAP and Macroduct Kits were used for ST. The commercial Kit CF-EU 2V1 kit (Elucigene) was used for 50 most common CF mutations panel. ***RESULTS:*** During the period studied, 71,642 samples were processed. 673 patients (0.94%) had high IRT. Of which, 248 (36.8%) had the conditions to continue with the algorithm and perform ST. Finding 223 with normal ST (89.90%), 14 (5.65%) with intermediate ST, and 11 (4.44%) with high ST. 14 cases were diagnosed by molecular study, representing 56% of the STs out of normal range. The most frequent mutation found in 10 patients was DF 508, with 4 of these cases being homozygous for this mutation. ***DISCUSSION AND CONCLUSIONS:*** To our knowledge, no false negatives have been reported. Less than 1% of the samples required confirmation studies, and 56% of the samples received for genetic testing are diagnosed. All of this allows us to conclude that this diagnostic strategy is a good option. The most common mutation found is in accordance with what is expected for our population. The incidence calculated from these results is 1 in every 5,000 births, as expected.

P-138 - NURSES ARE PIONEERS IN BRAZIL IN GENETIC GUIDANCE IN A REFERENCE SERVICE IN NEONATAL SCREENING: EXPERIENCE REPORT

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INTRODUCTION: Genetic counseling is a crucial process where trained multidisciplinary teams convey the meaning of laboratory test results to families affected by genetic alterations related to hemoglobin. By understanding the genetic inheritance perspective, family members gain insights into the disease's origin and their right to informed family planning. In Brazil, hemoglobinopathies and traits are identified through the Newborn Screening Test, commonly known as "Teste do Pezinho." ***OBJECTIVE:*** Sharing nurses' experience in genetic counseling for parents of newborns with traits or hemoglobinopathies and quantifying test collection adherence and genetic counseling. ***METHOD:*** In 1992, our service in Campinas, São Paulo state, initiated a program for individuals with Sickle Cell Disease, enabling early diagnosis and follow-up for newborns with hemoglobinopathies. We screened umbilical cord blood, and since then, nurses have been the trained professionals responsible for genetic counseling. Theoretical study, updating courses, and guided practice were the necessary conditions for the training of nurses. Accredited as a Neonatal Screening Reference Service (SRTN) in 2002, we started to use the newborn's heel prick for test collection. Through active outreach, we provide individualized counseling sessions for 12 to 15 family members daily. Parental genetic counseling involves four stages: (1) Welcoming and Assessing Knowledge: Parents' prior understanding is evaluated. (2) Education-Based Counseling: we use illustrative materials and heredograms. (3) Key Concepts Reinforcement: traits don't cause symptoms in children; only at-risk couples can have an affected child. (4) Referring parents for test collection and providing an explanatory brochure. ***RESULTS:*** Between 1992 and 2023, we screened 1,954,553 samples, identifying 813 newborns with hemoglobinopathies and 65,204 with different traits. Nurses provided genetic counseling in 28,512 cases. Regrettably, we were unable to track family decisions following counseling. ***CONCLUSION:*** Despite low parental adherence, informed family planning decisions were facilitated. Our team aims to implement strategies such as collecting samples in the couple's hometown, telenursing genetic counseling, and training nurses in hospitals and primary care units. This account of nurses' practices could serve as a model to be implemented in other health care services, thus contributing to reduce the incidence of newborns with hemoglobinopathies.

P-139 - 16 YEARS OF IMPLEMENTING A COMPREHENSIVE EXPANDED NEWBORN SCREENING PROGRAM IN YUCATÁN, MEXICO

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INTRODUCTION: For 16 uninterrupted years, the Health Services of Yucatán (SSY) in Mexico have implemented a comprehensive expanded newborn screening program (CENSP) to detect 67 congenital metabolic diseases (CMDs) in newborns (NBs). The program includes institutional follow-up for confirmed cases up to five years of age. ***OBJECTIVE:*** To present the key performance indicators and the birth prevalence of CMDs detected by the CENSP in Yucatán. ***MATERIALS AND METHODS:*** A retrospective analysis of SSY's neonatal screening database was conducted. All samples were obtained via heel prick, deposited on Guthrie cards, and analyzed using Auto DELFIA®/GSP®, tandem mass spectrometry, isoelectric focusing, or highperformance liquid chromatography. ***RESULTS:*** From January 2008 to May 2024, 238,344 newborns were screened in Yucatán (90.83% coverage). Of these, 99.97% of samples were adequate, with 91.74% taken between the third and seventh days of life. A total of 2,459 NBs were considered suspicious cases, of which 99.15% were located within 24 hours (1.04% repeat rate). There were 461 confirmed cases (1: 519 NBs) and 1,943 false positives (0.81%). Unfortunately, 21 newborns did not have the opportunity for timely diagnosis (0.85%). The average delivery time for results was 5 days. Currently, 162 children under five years are under follow-up. Confirmed cases include: congenital hypothyroidism (184) (1: 1,301 NBs); glucose-6-phosphate dehydrogenase deficiency (dG6PD) (128) (1: 1,870 NBs); congenital adrenal hyperplasia (42) (1: 5,698 NBs); cystic fibrosis (19) (1: 12,597 NBs); galactosemia (6) (1: 39,890 NBs); hemoglobinopathies (9) (1: 26,594 NBs); aminoacidopathies (14) (1: 17,096 NBs); and organic acidemias (22) (1: 10,879 NBs). Additionally, 37 cases of transient hyperthyrotropinemia (1: 6,469 NBs) and 1,160 carriers of hemoglobinopathies (1: 206 NBs) were detected. ***CONCLUSIONS:*** The CENSP in Yucatán has proven highly effective for the early detection of congenital diseases. The prevalence of birth defects in Yucatán was 1: 519 NBs, with the most common being endocrinopathies and dG6PD. All confirmed NBs received timely evaluation and treatment, starting on average at 17.8 days of age.

P-140 - DIAGNOSIS OF LEIGH SYNDROME MT-ATP6 RELATED TO C5OH ACYLCARNITINE ELEVATION BY EXPANDED NEONATAL SCREENING IN COSTA RICA

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INTRODUCTION: In Costa Rica, expanded newborn screening for organic acidemias and beta-oxidation defects began in January 2006 with the use of mass tandem spectrometry as part of the National Newborn Screening Program. Clinical experience of more than 15 years showed a series of cases in which, despite the persistent elevation of C5OH, a diagnosis of some related inborn error of metabolism could not be defined. As of 2021, studies begin to relate elevated C5OH and low citrulline in metabolic newborn screening with pathogenic variants in *MT-ATP6* gene with high heteroplasmy associated with Leigh syndrome, a neurodegenerative mitochondrial disease. Since then, a new differential diagnosis was added. ***OBJECTIVES:*** The main purpose of the study was to determine the genetic cause and clinical implications of extended Newborn screening positive patients with persistent elevation of C5OH acylcarnitine.***MATERIALS AND METHODS:*** A 15-year retrospective review of cases with C5OH elevation and low citrulline, from our National Newborn Screening Program, was performed. From all positive cases, without a confirmed diagnosis, one case who had developed epilepsy, cognitive limitation and behavioral problems appeared to have a pathogenic mutation in the MT-ATP6 gene. With this evidence, targeted analysis revealed 3 retrospective cases and 4 prospective cases with the same diagnostic confirmation. ***RESULTS:*** All retrospective cases (total of 4) and 3 out of 4 of the prospective cases showed the same m.8993T>G (p.Leu156Arg) pathogenic mutation in *MT-ATP6* gene. A new likely pathogenic mutation was found in the latest case m.9176T>G (p.Leu217Arg). There is a wide clinical spectrum among cases ranging from epilepsy, behavioral problems, cognitive impairment to asymptomatic. ***CONCLUSIONS:*** Leigh Syndrome is an important differential diagnosis in positive patients with elevation of C5OH in expanded Newborn Screening Retrospective evaluation of all undiagnosed cases is underway to expand the clinical phenotype of the condition. Further evaluations and precise determination of the level of heteroplasmy is important for clinical correlations

P-141 - DUAL DIAGNOSIS OF MAPLE SYRUP URINE DISEASE (MSUD) AND PHENYLKETONURIA (PKU) IN A SINGLE PATIENT BY EXPANDED NEWBORN SCREENING: CLINICAL CHALLENGES IN MANAGEMENT AT PRESENTATION

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INTRODUCTION: Newborn Screening in Costa Rica started in 1990 with 4 diseases and in 2006 it was expanded to 28 different diseases with the use of mass tandem spectrometry. Over 34 years a large series of isolated Phenylketonuria (PKU) and Maple Syrup Urine Disease (MSUD) cases was documented. This is the first case report of both conditions occurring in the same patient in our Program ***OBJECTIVES:*** To present the first dual diagnosis case of PKU and MSUD in a single patient, over 34 years of biochemical newborn screening. To demonstrate clinical challenges in the acute management of a patient with two different inborn errors of metabolism and limited oral formulas. ***MATERIALS AND METHODS:*** One patient from our newborn metabolic screening program showed an initial combined leucine-isoleucine level over 3000 umol/L. Initial Phenylalanine level was under 200 umol/L but retrospectively the ratio Phenylalanine/Tyrosine was in 2.7. Admitted on day 8, her clinical response was poor, brain US showed edema, epilepsy started, and baseline leucine was 5880 umol/L. Ammonia was 750 umol/L; all findings were suggestive of Maple Syrup Urine Disease (MSUD) Aggressive intra venous fluid management with ammonia scavengers was initiated according to international guidelines. Clinical improvement was noted on day 13. Oral feeding was started using branched chain amino acid free formula for MSUD. Phenylalanine levels progressively increased up to 780 umol/L. On day 15 shock signs appeared with multiorgan dysfunction, cardiac arrest and death related to a multiresistant Escherichia coli sepsis. ***RESULTS:*** Molecular testing revealed two homozygous mutations: c..853C>T (p.R285*) in *BCKDHB* gene and c.722G>A (p.R241H) in *PAH* gene. Leucine levels raised with oral formula. Acute septic shock caused the death of the patient. ***CONCLUSIONS:*** Incompatibility of oral special formulas is a management challenge in PKU and MSUD dual diagnosis. Long term management with exclusively oral feeding will force clinicians to choose one special formula over the other to avoid acute decompensation versus long term brain damage. Cases like ours should consider a special parenteral nutrition free of Valine, Leucine Isoleucine and Phenylalanine that was not available in our country and non-sustainable over time.

P-142 - BIOCHEMICAL AND MOLECULAR CHARACTERISTICS OF GALACTOSEMIA IN NEWBORN SCREENING (NBS) REFERENCE SERVICE OF THE JÔ CLEMENTE INSTITUTE

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BACKGROUND: Galactosemia is an autosomal recessive disorder classified as an inborn error of metabolism. It is caused by the deficiency or absence of one of the three main enzymes involved in galactose metabolism: Galactose-1-phosphate uridyl-transferase (GALT), Galactokinase (GALK), and UDP-glucose-4-epimerase (GALE). Recently, GALM deficiency, involving Galactose mutarotase, has also been described. ***OBJECTIVE:*** To evaluate the biochemical and molecular characteristics of galactosemia cases in the population of São Paulo city from December 2020 to February 2024. ***MATERIALS AND METHODS:*** A total of 275,030 newborns were screened through NBS at the Jô Clemente Institute. Total galactose and GALT enzyme levels were analyzed using the Fluorimetry method on the GSP/Revvity equipment. For all cases with altered biochemical analysis, a molecular panel was performed with DNA extracted from buccal swabs. ***RESULTS:*** Three cases of classic galactosemia were observed, where enzyme activity was less than 20% (0.38 to 1.74 U/dL; reference value (RV) > 4.2 U/dL) and total galactose values (GAOS) ranged from 25.00 to >100.00 mg/dL (RV < 8.0 mg/dL). The common molecular variant identified was p.Gln188Arg, found in compound heterozygosity with three other variants: p.Arg258Cys, p.Phe171Ser, and a complex deletion and insertion event encompassing the entire *GALT* gene. Four cases of GALE deficiency were noted, with GAOS ranging from 11.5 to 23.0 mg/dL. The p.Gly319Glu variant was identified in homozygosity, and in three other cases, a variant of uncertain significance with pathogenic variants was identified. The two cases of GALK1-related galactosemia had the p.Arg256Trp variant in common, in heterozygosity with variants classified as variants of uncertain significance (VUS). One of these cases had a GAOS of >100.00 mg/dL. One case of GALM deficiency was detected, with a GAOS of 9.44 mg/dL, and molecular study revealed the variants

c.654_668delinsACTT and p.Ala198Gly in heterozygosity. All cases were referred to the Reference Center for clinical follow-up. ***CONCLUSION:*** This study highlights the importance of NBS for the detection of galactosemia and underscores the need for molecular tests for diagnostic confirmation.

P-143 - DETECTION OF TYPE IV GALACTOSEMIA IN COSTA RICA

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INTRODUCTION: Galactosemia is an inborn error of galactose metabolism, with autosomal recessive inheritance, caused by deficient activity of one of the following enzymes: galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), uridine diphosphate galactose-4-epimerase (GALE), or the recently described galactose mutarotase (GALM). ***OBJECTIVE:*** To determine the prevalence of GALM deficiency in the Costa Rican population between 2002-2023 and highlight the importance of its molecular detection. ***METHODOLOGY:*** GSP® Neonatal Total Galactose kit from Perkin-Elmer was used to quantify total galactose from neonatal samples, considering a result ≥12.8 mg/dL as positive. GALT, GALE, GALK, and GALM deficiencies were confirmed by Sanger sequencing of all the coding regions. ***RESULTS:*** Between 2002 and 2023, 1,474,662 newborns were screened. Molecular biology analyses were conducted on 47 suspected cases of galactosemia. The prevalence of GALK deficiency was 1: 98,311 (n=15), GALT was 1: 163,851 (n=9), and GALE was 1: 294,932 (n=5). Seventeen negative samples were determined (11 without variants and 6 with a single variant present in any of these genes). Following the publication of Wada et al. (2018), which linked the *GALM* gene with galactosemia, *GALM* gene analysis was standardized, and negative samples were reanalyzed, resulting in five positive samples due to pathogenic variants (two homozygotes and three compound heterozygotes). Variants found in the *GALM* gene (NM_138801.3) were c.985delG p.(Glu329ArgfsTer18), c.424G>A p.(Gly142Arg), and c.602A>G p.(Tyr201Cys), which have been described previously as pathogenic. GALM deficiency prevalence in Costa Rica was of 1: 294,932 (n=5), similar to that reported at the population level in another study (1: 228,411). The total prevalence of galactosemia was 1: 43,372. ***CONCLUSIONS:*** Molecular analysis GALM allowed for the reclassification of patients with previously negative genetic reports (GALE, GALK1 and GALT). Due to the scarcity of information on the clinical presentation of GALM deficiencies, the need for appropriate molecular classification by the laboratory and timely clinical follow-up of confirmed patients is emphasized.

P-144 - NEWBORN SCREENING FOR GALACTOSEMIA IN FEDERAL DISTRICT - BRAZIL, FROM 2014 TO 2023.

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INTRODUCTION: The Federal District has been screening for galactosemia since 2012. In Brazil, the galactosemia mandatory testing requirement dates 2021 but has not yet been implemented by most federative units. ***OBJECTIVES:*** To describe the Federal District galactosemia neonatal screening program. ***MATERIALS AND METHODS:*** Descriptive, retrospective study of galactosemia Federal District neonatal screening program from 2014 to 2023. Total galactose was assayed by fluorimetry, cut-off was set at 9 mg/dL. Galactose-1-phosphate uridyltransferase (GALT) was also assayed by fluorimetry (normal value >37 micromol/h/gHb). The study was approved by the Ethics Committee. ***RESULTS:*** Screening was carried out for 413,158 newborns and 1,574 were recalled (1/263). 662 female (42%), 886 male (56.3%) and 26 no sex available (1.7%). The average birth weight was 3,060g ±539g, 201 (12,7%) the birth weight was <2500g and 83 was premature (5,3%). Newborn screening dried blood sample were collected at day 3,1 ±3,7, the first total galactose average value was 11.14mg/dl ±5,2. All patients were recalled and 237 (15.06%) showed abnormal results. The average second sample value was 5.8mg/dl ±7,6. These children were referred to the newborn screening reference center to a clinical evaluation, at 21,6±9,3 days after deliver. The average GALT value was 38.6± 13,6 micromol/h/gHb. 70

patients were diagnosed (1/5902 newborns): including 48 with Duarte variant, 19 with clinical galactosemia, 1 lost to follow-up, and 2 type III galactosemia (deficiency of uridine diphosphate (UDP)-galactose 4-epimerase - GALE) by molecular biology. ***CONCLUSION:*** The Federal District was the first brazilian federation unit to screen galactosemia. It provided early intervention in clinical galactosemia children as its complications are significant and preventable. The Federal District galactosemia neonatal screening program still doesn't offer molecular biology to confirm galactosemia diagnosis but we hope it soon comes true.

P-145 - HEMOGLOBINOPATHIES NEWBORN SCREENING FROM PILOT TO HEALTH PROGRAM: TECHNICAL AND ETHICS IMPLICATION

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INTRODUCTION: Hemoglobinopathies are one of the most frequent genetic disorders. Sickle cell disease, Hemoglobin (HB) S/C and S/ β thalassemia are recommended to be include in a newborn screening program since early detection could prevent morbility and mortality. Technology used to screen these diseases allows not only finding pathology cases but also traits and rare hemoglobin, being always necessary molecular confirmation. Therefore, with the incorporation of hemoglobinopathies arises the ethical problem weather traits should or not be reported considering that they may not be in accordance with traditional screening criteria. Uruguay worked in a pilot program since 2013, and in 2023 national authorities decided to incorporate hemoglobinopathies as mandatory screening. ***OBJECTIVE:*** Analyze the data collected since hemoglobinopathies were included as universal program from September 2023 to March 2024 using two technologies. ***MATERIALS AND METHODS:*** Dry blood spot samples from babies born in Uruguay were analyzed in the Newborn Screening Laboratory. Samples were processed alternately by High-Performance Liquid Chromatography (HPLC)- Variant nbs (Biorad) and Capillary electrophoresis (CE) –Capillaris 3 (Sebia). ***RESULTS:*** 10523 samples were processed by HPLC and 9996 by CE. No pathologic cases were found, but 151 carriers of some hemoglobin variant, with results concordant by both methodologies, were determinated. Using HPLC methodology, 325 samples with a high but not specifically fast peak were found, usually attributed to alpha thalassemia trait or elevated bilirubin. Out of these 325 samples only 12 presented Hb Barts peak by CE. In all cases, the percentages corresponded to silent alpha thalassemia (Hb barts between 0.6 -2.8%). ***CONCLUSIONS:*** During this period all the altered results found were from carrier patients. Discrepancies between both methods were found when probable alpha thalassemia carriers were detected. These results do not represent health risk, but it could generate concern and anxiety in parents, could be interpreted as information about ethnic origins, represents a ethic dilemma in a system with no genetic counseling or prevention program incorporated. It is important that national programs define in detail the scope of a hemoglobinopathies screening program to ensure funds to cover not only screening, but also diagnostic confirmation and counseling of families.

P-146 - IDENTIFICATION OF COMPOUND HETEROZYGOSIS FOR HB PORTO ALEGRE AND HB S BY NEONATAL SCREENING

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INTRODUCTION: Hemoglobinopathies are hereditary diseases resulting from mutations in hemoglobin (Hb) genes, in homozygosis or heterozygosis, which can lead to various complications. Early diagnosis and treatment can prevent/avoid postnatal disorders. ***OBJECTIVES:*** This paper describes a case of compound heterozygosis of an indeterminate hemoglobin (HbInd) and HbS, whose diagnosis was possible due to use of two different methods in neonatal screening. ***RESULTS:*** Sample from a male newborn was collected on filter paper 48 hours after birth. In the qualitative isoelectric focusing (IEF) method the sample showed a "FAS" profile, and repetition by quantitative newborn screening (NBS) high performance liquid chromatography (HPLC) system showed a "FS" profile. Difference between results led us to suspect the presence of HbInd (electrophoretic profile as HbA and chromatographic profile as HbF). Second sample collected in 35 days (whole blood) showed a different result, "FAS" profile for both techniques, however the quantification of HbA in HPLC was higher than in IEF, increasing suspicion

of HbS/HbInd sickle cell disease. New blood samples from the child (6 months after birth) and his parents were send to the laboratory specializing in hemoglobinopathies for elucidation. Electrophoresis at alkaline pH and HPLC (cation exchange) revealed "A2SFInd" profile in the child, "A2SA" in his mother and "A2AInd" in his father, with HbInd migrating/eluting concomitantly with HbA. Reversephase HPLC revealed the globins βS+βX in child, β+βS in his mother and β+βX in his father. Sequencing of the β gene (*HBB*) confirmed the mutation in the 6th codon, corresponding to HbS [NM_000518.5(HBB): c.20A>T(p.Glu7Val), child and mother] as well as in the 9th codon corresponding to HbPorto Alegre [NM_000518.4(HBB): c.29C>G(p.Ser10Cys), child and father], both in heterozygosis. Child was forwarded to the reference service for follow-up. At 10 months he presented painful crises, Hb 9.5g/dL, VCM 48.5fL and then hydroxyurea therapy was introduced, with clinical improvement. ***CONCLUSIONS:*** There are few reports of HbPorto Alegre in Brazil and, to our knowledge, this is the first report in association with HbS in this country. Considering that the concomitance of variants is rare, follow-up through age will be essential to determine the clinical and hematological aspects of this association.

P-147 - NEONATAL SCREENING FOR HEMOGLOBINOPATHIES: A TWO-YEAR EXPERIENCE IN A LABORATORY IN MEXICO

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INTRODUCTION: Hemoglobinopathies are a group of genetic disorders affecting the structure and function of hemoglobin, the protein responsible for oxygen transport in the blood. These conditions can be asymptomatic, cause anemia, fatigue, shortness of breath or even result in death. The frequency of hemoglobinopathies varies according to geographic region and racial ancestry, representing a public health issue in Mexico, with a prevalence ranging from 0.6% to 13.7%. ***OBJECTIVE:*** To present the results of a two-year study conducted by a laboratory specialized in processing neonatal screening samples, focusing on the prevalence of hemoglobinopathies at birth in Mexico. ***MATERIALS AND METHODS:*** A total of 89,432 dried blood spot samples from newborns (NB) were analyzed between January 2022 and December 2023. The samples were obtained by heel prick between the third and seventh day of life from all 32 Mexican states. The samples were analyzed using the isoelectric focusing technique with the RESOLVE® Systems Hemoglobin kit from Perkin Elmer, high-performance liquid chromatography with the Variant kit from Bio-Rad®, and DNA sequencing by the Sanger method with the Big Dye® Terminator Cycle sequencing kit for the *HBB* gene (11p15.4, MIM+141900). ***RESULTS:*** A total of 626 hemoglobin variants (Hb) were confirmed. This included 3 cases of homozygous sickle cell disease (HbSS) (1: 29,811 NBs), with HbS carriers (521) having the highest incidence (1: 172 NBs). Other variants included HbG-Philadelphia (43) (1: 2,080 NBs), HbD (23) (1: 3,888 NBs), HbC (31) (1: 2,885 NBs), and HbE (5) (1: 17,886 NBs). Additionally, one carrier of the beta-thalassemia trait (1: 89,432 NBs) and one carrier of the alpha-thalassemia trait (1: 89,432 NBs) were detected. Molecular studies were conducted on 34 patients, identifying the following carriers: HbAS (17), HbD (6), HbAC (4), HbG (3), betathalassemia trait (2), Hb KHARTOUM (1), and Hb Korle-Bu (1). ***CONCLUSIONS:*** This study provides information on the birth prevalence of hemoglobinopathies in Mexico. Since these conditions are not included in the Mexican basic neonatal screening panel, our findings suggest that the presence of hemoglobinopathies at the national level is significant enough to consider their inclusion in the mandatory neonatal screening panel in the future.

P-148 - NEWBORN SCREENING OF SICKLE CELL DISEASE AND OTHER HEMOGLOBINOPATHIES USING CAPILLARY ELECTROPHORESIS IN THE SOCIAL SECURITY INSTITUTE IN PANAMA.

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INTRODUCTION: Sickle cell disease and hemoglobinopathies are together as a group the most detected condition through newborn screening in Panama. Since newborn screening for these conditions was initiated, several technologies were used based on dried blood spots samples. High performance liquid chromatography (HPLC) is one of the most widely used methods to screen hemoglobinopathies; but other emergent techniques such as capillary electrophoresis have been used with good results. ***OBJECTIVES:*** To present

the results of the implementation of newborn screening of hemoglobinopathies using capillary electrophoresis. ***MATERIALS AND METHODS:*** Retrospective review of the results newborn screening for hemoglobinopathies using capillary electrophoresis in the years 2022 and 2023 in Institute of Medical Genetics and Genomics of the Social Security Institute of Panama. ***RESULTS:*** A total 7118 dried blood spot (DBS) samples were analyzed using SEBIA Capillarys 2 Neonat Fast™ equipment. There were 708 (5.7%) samples positive tests. The most common hemoglobin type detected was FAS hemoglobin with 606 cases (85.6%), followed by FAC with 92 cases (13%) and FS with 4 cases (0.6%). There were other types of hemoglobin less common such as Korle-Bu/S and AD hemoglobin that have only a few cases described in literature and that were detected with this technique. In all positive results, familial studies were performed using capillary electrophoresis and in case of rare hemoglobin types such as Korle Bu/S hemoglobin, molecular analysis was performed. ***CONCLUSION:*** The hemoglobinopathies are a major health issue worldwide with a high burden of disease. The early detection of these conditions allows us to avoid major complications and to provide genetic counseling to parents. The capillary electrophoresis is a technology that can be used for newborn screening of hemoglobinopathies. It allows us to detect not only the most common types of hemoglobinopathies; but also the less common types such as Korle-Bu/S and AD.

P-149 - ARGININOSUCCINIC ACID LYASE DEFICIENCY DIAGNOSIS BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY WITH POST-COLUMN DERIVATION COUPLED WITH SPECTROPHOTOMETRIC DETECTION

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INTRODUCTION: Argininosuccinic acid lyase (ASL) deficiency is an autosomal recessive disorder of the urea cycle. Clinical characteristics include hyperammonaemic coma, intellectual disability, seizures, episodic unconsciousness, hepatomegaly, skin lesions, and dry and brittle hair, showing trichorrhexis nodosa. Treatment includes dietary protein restriction, arginine supplementation and administration of nitrogen scavengers. ASL is an enzyme in the urea cycle that cleaves argininosuccinic acid (ASA) to produce arginine and fumarate. In addition to the presence of ASA, most individuals with ASL deficiency also have mild to moderate elevations of citrulline. ***OBJECTIVE:*** To describe the laboratory procedure to identify argininosuccinic acid in plasma by High-performance liquid chromatography (HPLC). ***MATERIALS AND METHODS:*** A plasma sample from a patient with citrulline elevation detected by newborn screening was referred to the Biochemistry Laboratory. The sample was deproteinized and subsequently analyzed by ion-exchange HPLC, with post-column derivation and spectrophotometric detection. To confirm the presence of ASA, deproteinized plasma was placed in a water bath at boiling point for an hour, and then re-analyzed by HPLC. ***RESULTS:*** On the first run, two atypical peaks were observed, one between leucine and tyrosine and the other just before gamma-aminobutyric acid, as well as elevated concentrations of homocystine and citrulline. Elevated homocystine was not compatible with the results obtained on the newborn screening test but rather with the presence of anhydride ASA, which coelutes with this amino acid. Free ASA has also been described to elute between leucine and tyrosine. After boiling the sample, the free acid was converted to its anhydrides which led to the disappearance of the free ASA peak, and the increment of the other two peaks, confirming the presence of ASA in the sample. The diagnosis was confirmed afterwards by genomic sequencing and deletion/duplication analysis, two variants were found in heterozygous state, one pathogenic and the other likely pathogenic. ***CONCLUSIONS:*** HPLC with post-column derivation and spectrophotometric detection proved to be an efficient technique for the detection of ASA in plasma samples. It is an effective method for the diagnosis of ASL deficiency, which immediately allowed pediatricians to start treating the patient.

P-150 - EVALUATION OF ENZYMATIC STABILITY OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE AND BIOTINIDASE IN DRIED BLOOD SPOTS FROM HEEL PRICKS IN TWO REFERENCE HOSPITALS IN GUATEMALA

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INTRODUCTION: Glucose-6-Phosphate Dehydrogenase (G6PD) is a crucial enzyme in the oxidative pathway of the hexose monophosphate shunt in red blood cells, while the

enzyme Biotinidase (BTD) plays an essential role in recycling biotin, a water-soluble B-complex vitamin that acts as a coenzyme in four carboxylases. The stability of these enzymes is influenced by factors that affect their enzymatic activity and their quantification. The storage time before sample processing can impact enzyme quantification due to red blood cell degradation and genetic variations among patients. ***OBJECTIVE:*** To determine the in vitro stability of Glucose-6-Phosphate Dehydrogenase and Biotinidase enzymatic activities in dried blood spots.***MATERIALS AND METHODS:*** 249 newborns were screened by dried blood spots for G6PD and 259 for BTD, during April and May 2024 at Roosevelt Hospital and General San Juan de Dios Hospital. Samples were stored for different times: 1, 3, 5, and 7 days after collection at 19-21 degrees Celsius, without direct light and without contact with each other to prevent contamination. Desiccants were not used for storage. Enzymatic activity of BTD and G6PD were performed using a fluorometric assay with the Victor 2D fluorometer. ***RESULTS:*** A gradual decrease in the means of G6PD and BTD was observed over the storage time: (Day 1) 8.71 ± 0.058, (Day 3) 7.59 ± 0.058, (Day 5) 7.52 ± 0.058, and (Day 7) 6.01 ± 0.058 U/g Hb for G6PD, while for BTD, the values were (Day 1) 150.42 ± 1.815, (Day 3) 154.57 ± 1.815, (Day 5) 138.88 ± 1.815, and (Day 7) 120.22 ± 1.815 U/g Hb. The Pearson correlation coefficients for G6PD and BTD were <0.0001 and 0.0080, respectively. ***CONCLUSIONS:*** Variability in enzymatic activity were demonstrated by fluorometric assay. Pearson correlation coefficients indicated a negative and statistically significant relationship between time and enzyme activity, suggesting that as time passes, the enzymatic activites of G6PD and BTD tend to decrease, which can affect the accuracy and reliability of clinical results and increase false-positive rates.

P-151 - VERIFICATION OF COMMERCIAL KITS FOR EXPANDED NEONATAL SCREENING; IMMUNOREACTIVE TRYPSIN (IRT), 17-OH-PROGESTERONE (17OHP), BIOTINIDASE (BIO), TOTAL GALACTOSE (GAO) AND GALACTOSE 1-PHOSPHATE-URIDYL TRANSFERASE (GALT).

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INTRODUCTION: Neonatal screening plays a crucial role in the early detection and management of congenital disorders in newborns. The reliability and accuracy of the screening techniques used are paramount to ensure proper diagnosis and timely intervention. ***OBJECTIVE:*** To verify the reliability and performance of commercial kits used in neonatal screening techniques supplied by Labsystems company. ***MATERIALS AND METHODS:*** A minimum of 250 samples were processed and verified by fluorometry for each kit. The parameters verified were precision, accuracy, and linearity. Two samples with known concentrations were selected. One run per day was analyzed with three replicates for each of the two quality control concentrations, daily for five days. The daily quality control samples normally used were included, and calibration was performed as specified in the manufacturer's instructions for operators. The repeatability defined by the manufacturer was compared with that calculated by the laboratory, and verification limits were calculated to evaluate accuracy. For linearity assessment, five concentration levels were used, including a blank, from calibrators with assigned values. The mean concentrations or activities were obtained for each standard, and the equation of the line of best fit was calculated, along with the correlation coefficient. ***RESULTS:*** The IRT, 17OHP, and BIO kits demonstrated precision; refers to the consistency or reproducibility of measurement results, accuracy; refers to the closeness of measurement results to the true or accepted value and linearity; refers to the method's ability to provide results that are directly proportional to the analyte concentration in samples within a specified range. The GAO kit lacked precision but exhibited accuracy and linearity. The GALT kit showed a lack of precision at the level 1 control, while maintaining accuracy and linearity with the EP15-A2 verification criteria used by the laboratory. ***CONCLUSIONS:*** The implementation of these kits in their current state is not recommended without first addressing the issues of high recall rates and stability. Although they offer advantages in terms of cost and ease of implementation, the potential negative effects (increased false positives, additional costs due to repeat testing, and impact on families) outweigh these benefits.

P-152 - COMPARING TWO MASS SPECTROMETRY METHODS IN URUGUAY: AN ANALYTICAL EXPLORATION

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INTRODUCTION: Tandem mass spectrometry allows for the simultaneous analysis of a wide range of amino acids (AAs) and acylcarnitines (ACs) extracted from dried blood spots (DBS), facilitating the detection of various aminoacidopathies, organic acidemias, and fatty acid oxidation disorders. Sample preparation involves butyl-esterification (derivatization) of AAs and ACs, enhancing the versatility of the technology despite its lower sensitivity. ***OBJECTIVE:*** To compare two analysis methods for the determination of AA and AC in DBS using mass spectrometry. ***MATERIALS AND METHODS:*** A total of 521 DBS samples from anonymous newborns in Uruguay were processed by the butylated derivatized method (D) and the non-derivatized method (ND). The ND was adapted from the one used by La Marca and collaborators. All samples were processed using the API 3200 mass spectrometer and the data obtained were analyzed with Chemoview Software. Both methods were compared using a statistical test for the determination of the amino acids phenylalanine (Phe) and tyrosine, as well as the acylcarnitines C8 and C5DC. A Student's t-test assuming unequal variances was applied to compare both methods using Microsoft Excel, with a significance level of 0.05. ***RESULTS:*** For the study of a sample size (n) of 521, the mean values compared for the derivatized (D) and non-derivatized (ND) methods are as follows in umol/l: Phe 35.44 (D), 35.11 (ND); Tyr 53.15 (D), 51.58 (ND); C8 0.073 (D), 0.079 (ND); C5DC 0.061 (D), 0.056 (ND). All calculated t-values for each analyte are lower than the critical t-values. ***DISCUSSION AND CONCLUSIONS:*** The statistical test applied confirms that the means of the evaluated methods are comparable, suggesting that they can be used interchangeably in processing samples for the selected analytes. Additionally, the benefits of the non-derivatized method have been demonstrated in the daily routine of the laboratory, with observed reductions in processing time and elimination of exposure to corrosive reagents. Despite the API 3200 not being as sensitive as newer technology, this comparison demonstrates its excellent performance for this application.

P-153 - SECONDARY MARKERS IN NEWBORN SCREENING OF MAPLE SYRUP URINE DISEASE. IMPACT ON RECALL RATE

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INTRODUCTION: With the implementation of the mass spectrometer, in 2014, new diseases were incorporated into the Newborn Screening (NS) Program of Buenos Aires City. Starting in 2017, newborn screening for Maple Syrup Urine Disease (MSUD) was implemented, using Leucine and Valine as primary markers. One of the main drawbacks when screening this disease is its high recall rate, mainly due to parenteral nutrition. The use of informative relationships between amino acids can be used as secondary markers in newborns (NB) with elevated primary markers that receive parenteral nutrition at the time of sampling. To improve the NS process, together with the medical area, different secondary markers were established in order to exclude false positive results in the MSUD screening. ***OBJECTIVE:*** To evaluate the impact of the use of informative amino acid ratios on the recall rate in the NS of MSUD.***MATERIALS AND METHODS:*** 88,206 NB samples (between the years 2018-2023) from the maternity hospitals of the Autonomous City of Buenos Aires were included in the analysis. Perkin-Elmer/Chromsystem non-derivatized reagents were used in the ABSciex-API3200 instrument. The cut-off point for the primary markers was established at: Leucine=243 umol/l, Valine=195 umol/l. Since 2022, aminoacid ratios have been implemented, with the following cut-off points: Valine/Phenylalanine=3.06, Leucine/Alanine=1.53, Leucine/Phenylalanine=3.97. It was proven that during the period 2018-2021, all relationships from recalled patients who were under treatment with parenteral feeding, gave normal results. Starting in 2022, newborns who received parenteral nutrition were only recalled if the values of Leucine, Valine and ratios were greater than the cut-off values. ***RESULTS:*** The recall rate per year was as follows: 2018: 0.94%, 2019: 0.74%, 2020: 0.86%, 2021: 0.85%, 2022: 0.15% and 2023: 0.14% ***CONCLUSIONS:*** The implementation of secondary markers in the analysis of the results of the MSUD allowed the recall rate to be improved significantly, optimizing the recall process.

P-154 - ULTRAMICRO-FLUOROMETRIC TEST FOR THE MEASUREMENT OF BRANCHED-CHAIN AMINO ACIDS IN DRIED BLOOD SPOT ON FILTER PAPER.

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INTRODUCTION: Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by defects in the branched-chain α-ketoacid dehydrogenase complex. The classic presentation occurs in the neonatal period with developmental delay, failure to thrive, feeding difficulties,

and maple syrup odor in the cerumen and urine, and can lead to irreversible neurological complications, including stereotypical movements, metabolic decompensation, and death if left untreated. So timely diagnosis is important for successful treatment. ***OBJECTIVE:*** A simple fluorometric ultramicrotest for the measurement of branched-chain amino acids (BCAAs) that include leucine, isoleucine, and valine in dried blood samples spotted on filter paper is described. ***METHODS:*** The assay uses 3 mm discs of dried blood on Whatman 903 filter paper. Etanol (90 %) solution is used for deproteination, BCAAs were determined by measuring the change in fluorescence of Nicotinamide Adenine Dinucleotide (reduced form) at 450 nm, treated with L-Leucine dehydrogenase. Specially designed 96-well polystyrene opaque ultramicroplates, with a maximum capacity of 30 µL per well, are used for the reading. ***RESULTS:*** The fluorometric ultramicrotest is completed in 2 h, with measuring range of 115–6000 µmol/L. The intra and interassay coefficients of variation ranged between 7.6-9.4 % and 8.9-13.5 % respectively, depending on the BCAAs concentrations evaluated. Percentage recovery was 98 ± 4 %. Limit of detection (LOD) and limit of quantitation (LOQ) were 114.8 and 167.5 µmol/L, respectively. The mean BCAAs concentration, in 1000 dried blood samples from the National Neonatal Screening Program was 265,9 ±113,4 µmol/L. Cut-off value calculated was 550 µmol/L that represented the 99th percentile of the distribution. Our assay showed high Pearson and concordance correlation coefficients regarding LC-MS/MS. ***CONCLUSIONS:*** The analytical performance characteristics of this method suggest that it can be used for the neonatal screening of MSUD, as part, of ultramicroanalytic system (SUMA).

P-155 - DEVELOPMENT AND IMPLEMENTATION OF A TAILOR-MADE INFORMATION SYSTEM FOR NEWBORN SCREENING PROGRAM

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INTRODUCTION: We developed and implemented a comprehensive information system for our Newborn Screening Program, encompassing 12 maternity hospitals, 3 laboratories, and 2 medical services to address and follow up on suspected conditions. ***OBJECTIVE:*** To desribe the development of a new informatic system to be used in the newborn screening program. ***MATERIALS, METHODS AND RESULTS:*** The implementation was divided into several phases: Initial Phase: We started with the most complex laboratory, uploading information locally to ensure that maternity hospitals could access the newborn screening results through a web portal. Training Phase: All maternity hospitals were trained to directly enter newborn and screening sampling information into the system via the web portal. Laboratory Integration: The other two laboratories were integrated into the system, enabling an unified newborn screening report. System Development: We developed a system for resampling due to pre-analytical issues and elevated values and developed rules used in the analytical validation. Medical Follow-Up: Notification messages from Laboratories were developed for physicians who follow up on suspected conditions and the system also includes a system to record all the medical information related to diagnose and treatment of the newborns detected by our program. This endeavor required over 50 meetings for training and phase assessments, more than 100 development hours to adapt our system to the new program requirements, and the creation of a web portal for data entry and medical tracking. With this new information system we eliminated the use of excel files, paper forms for recall proess and established logical rules for accepting-rejecting newborn samples. ***CONCLUSIONS:*** We achieved traceability from sample collection to patient reporting including disease follow-up in one information system that is used for different users in the network. This home-made development ensures that all the data is centralyzed in one system improving the monitoring of the processes involved in the our program.

P-156 - EMOTIONAL ASPECTS AND IMPACT ON THE QUALITY OF LIFE OF CAREGIVERS OF PATIENTS WITH PHENYLKETONURIA

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INTRODUCTION: Phenylketonuria (PKU) is an autosomal recessive genetic condition, an inborn error of amino acid metabolism, caused by different types of mutations in the PAH gene, responsible for encoding the enzyme phenylalanine-hydroxylase that metabolizes the amino acid phenylalanine, preventing its conversion into tyrosine. The treatment is essentially dietary with the use of a food formula free of phenylalanine and a diet restricted in proteins of animal origin and proteins of high biological

value. Adherence to treatment is a challenge for the patient and their family, both from sociocultural and economic-financial aspects. The diet must be followed for the rest of one's life, and patients and family members may have their social and emotional lives affected by strict dietary treatment. The aim is to describe responses obtained in a questionnaire from the National Rare Diseases Network survey. ***METHODOLOGY:*** describe 8 aspects of responses obtained in the Jornada Assistencial de Valor (JAV-RARAS) questionnaire: Have you felt like a very nervous person? / Have you been feeling calm or peaceful? / Have you been feeling a lot of energy? / Have you been feeling too down? Have you been feeling full of vigor, full of will, full of strength? / Have you been feeling so depressed that nothing can cheer you up? / Have you been feeling exhausted? / Have you felt like a happy person? ***CONCLUSION:*** Most participants are not nervous or worried, but they also do not feel energetic. This suggests that caregivers understand and know how to deal with the condition of phenylketonuria, although they still face stressors from treatment and everyday life. Most participants are not nervous or worried, but they also do not feel energetic. This suggests that caregivers understand and know how to deal with the condition of phenylketonuria, although they still face stressors from treatment and everyday life. At SRTN-AM, the team includes a psychologist who assists the family from the first consultation and is available for support, being considered essential in the multidisciplinary care of phenylketonuria.

P-157 - EXPANSION OF THE NATIONAL NEONATAL SCREENING PROGRAM (PNTN) BASED ON CLINICAL AND ECONOMIC EVIDENCE: WHERE WE ARE AND WHERE WE WOULD LIKE TO BE

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INTRODUCTION: Neonatal screening (NS) is essential for detecting congenital diseases before symptoms appear, allowing interventions that save lives and improve the quality of life of thousands of people. Law N°14,154/2021 (PNTN) increased the number of diseases screened to 50. However, it determines that the list of diseases included will be reviewed periodically, based on scientific evidence, prioritizing the diseases with the highest prevalence and those with an approved treatment protocol and treatment incorporated into the Unified Health System (SUS). ***OBJECTIVES:*** to identify and describe the recommendations of the National Commission for the Incorporation of Technologies in SUS (Conitec) on the expansion of PNTN, as well as the challenges for evaluating the incorporation of these diseases. ***METHODS:*** this is a qualitative observational study, in which manual searches were carried out by report based on Conitec recommendations, from the date of publication of the law mentioned. ***RESULTS:*** Two Conitec recommendation reports were identified that evaluated NS for diseases included in the expansion of PNTN: medium chain acyl-CoA dehydrogenase deficiency (report n°792) and classic homocystinuria (report nº816) by MS/MS. For both conditions, Conitec unanimously decided to recommend incorporation into SUS. Limitations described in the reports included very low certainty of evidence, due in large part to heterogeneity among study samples. Another challenge identified was the independent assessment of the marker used in screening for classic homocystinuria, as some have a false negative rate of up to 50%. The reports highlight that including other genetic diseases in the MS/MS screening process, allowing simultaneous testing for multiple conditions, would significantly reduce the estimated budget impact for each technology. ***CONCLUSIONS:*** Of the 50 diseases, only two were evaluated by Conitec. The limitations described in the recommendation reports suggest that the format currently adopted may not fully capture the true clinical benefits and increase the budgetary impact of this expansion. To ensure full compliance with law n°14,154/2021 it is necessary to adopt other strategies, including investing in research based on pilot studies of the expansion of PNTN and in economic assessments that consider the simultaneous disease screening.

P-158 - IMPLEMENTATION OF A COMPREHENSIVE INFORMATION SYSTEM FOR THE MANAGEMENT OF THE NEWBORN SCREENING PROGRAM, MENDOZA-ARGENTINA

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INTRODUCTION: Quality management in all processes of the "Newborn Screening Program" (NSP) is critical and faces great challenges. The implementation of a comprehensive information system (IS) is a fundamental tool to meet the objectives and quality standards of the Program. ***OBJECTIVES:*** Describe the implementation and benefits of an IS for the comprehensive quality management of the NSP. Present quality indicators for critical processes, obtained through the IS. ***MATERIALS AND METHODS:*** An IS, software specifically designed for the NSP, was developed and implemented with modules for patient data management, automation of sending results, recitation registration and monitoring of patients in treatment. Using the IS, quality indicators of the NSP were analyzed in all its stages and processes. ***RESULTS:*** Period 2016-2023. Expansion of the IS with a greater number of data on newborns (NB): NB/samples received (140571/157430); reduction in validation time and sending of digitized individual-quantitative results (14 to 6 days); immediate establishment of percentiles-cutoff values for TSH, 17-OHP, Phe, GAL, BTD, BCAA and IRT, according to gestational age (GA), weight and methodologies; obtaining information for immediate recitation of NB, due to altered biochemical parameters or inadequate-rejected samples and effective communication of critical results in endocrinemetabolic emergencies; medical and social work registry for patient monitoring and adherence to treatments (342). Year 2023. Immediate obtaining of indicators and statistical-epidemiological information: coverage of the state/private management sector (99.5%/49.8%); NB evaluated/total samples received (15905/18393); Premature NB, differentiated according to GA, weight and number of samples (1513); collection time (2 days) and sample transit (3 days); inadequate-rejected samples (0.27%); determinations made (124761); recitation rate excluded premature NB (1.12%); NB cited and located (100%). The IS made it possible to streamline the obtaining of information in all stages and processes for continuous improvement and compliance with standards required for the "quality accreditation" of the NSP laboratory. ***CONCLUSIONS:*** It was possible to optimize times and indicators in all stages and processes, streamline communication for recitations and timely access to monitoring and adherence to treatments. In the context of patient-centered safety and comprehensive quality management, the implementation of an IS was cost-effective for the NSP.

P-159 - NEONATAL SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA AT A NEONATAL SCREENING REFERENCE SERVICE IN THE STATE OF SÃO PAULO / BRAZIL

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INTRODUCTION: Congenital Adrenal Hyperplasia (CAH) is the term used to characterize a set of diseases with autosomal recessive inheritance caused by the deficiency of one of the enzymes responsible for the synthesis of cortisol in the adrenal glands. ***OBJECTIVE:*** This work aimed to identify newborns (NB) who presented an initial result changed to 17OHP in the UNICAMP Neonatal Screening Reference Service, with an area covering 5 regional health areas in the state of São Paulo, comprising in averaged 7,0000 RN per month.***MATERIALS AND METHODS:*** In the period between 2018 and 2023, the neonatal screening laboratory at the State University of Campinas/São Paulo/Brazil screened 499,328 newborns. As recommended by the Ministry of Health/Brazil, blood samples collected after 48 hours of the newborn's life were accepted. 17OHP was quantified by the solid phase time-resolved fluoroimmunoassay method, with a competitive reaction between 17 OHP labeled with europium and 17 OHP from the sample (GSP Neonatal 17α-OH Progesterone Kit – Wallac Ou, Turku, Finland). Values of 17 OHP progesterone (17OHP) above 36 ng/mL in equivalent serum were considered altered. ***RESULTS:*** 94 newborns were identified who presented an initial result changed to 17OHP. All newborns were called to the outpatient clinic to collect serology for 17OHP, cortisol, androstenedione, testosterone, sodium and potassium. We identified 17 newborns confirmed with the classic form of CAH, with an incidence of 1: 29,372. High values of 17 OHP were found in 20 very premature newborns (between 28 and 31 weeks of gestational age) who died before confirmation by serology. Fifty-seven newborns were identified with altered values of 17 OHP in the screening that did not confirm the disease, but maintained outpatient follow-up with serology collection. ***CONCLUSIONS:*** This study made it possible to identify newborns who presented altered results of 17 OHP in neonatal screening, suggesting that this test is an effective method for neonatal CAH screening, capable of identifying children affected by the classic form of the disease.

P-160 - NEONATAL SCREENING PROGRAM IN ARGENTINA AT THE FUNDACION DE ENDOCRINOLOGIA INFANTIL (FEI): 39 YEARS OF EXPERIENCE

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INTRODUCTION: Since 8/1985 a neonatal screening program for Congenital Hypothyroidism(CH) and Phenylketonuria ((PKU) was conducted adding Cystic Fibrosis (CF), Galactosemia(GAL), Congenital adrenal hyperplasia(CAH) in 1997, Biotinidase deficiency(BD) in 2006 and Maple syrup disease(MSUD) in 2013. ***OBJECTIVE:*** To Communicate the results of detection in our program up to 04/2024. ***METHODS:*** Screening was performed (coverage 98%) in DBS obtained at 36hs to 7 days of life (median age: 3 days). Disease Markers, method of detection and cutoffs(CO) were for CH: TSH (RAI,IRMA till 1997, Delfia-IFMA thereafter) (CO: 15mU/l till 2003 and 10mU/l thereafter). PKU: Phenylalanine (fluorometry) (CO: 2.5 mg/dl), CF: Immunoreactive Trypsin(Delfia–IFMA),(IRT/IRT strategy)(CO: 70ng/dl), GAL: Total Galactose Enzymatic Colorimetric (CO: 12mg/dl) and since 2023 fluorometry (CO: 8mg/dl). CAH: 17OHprogesterone (Delfia-FIA)(CO: adapted to Gestational age and sampling age). BD: colorimetric qualitative. MSUD: Branched amino acids (enzymatic colorimetric) (CO: 4mg/dl). Detected newborn underwent confirmation studies and treatment was started according to results. Patients were followed up in our center or referred to specialized ones. Screened and detected newborns and the incidence are described for the whole period. Recall rate (RR) Diagnostic efficiency (DE), median age at diagnosis(MAD) and treatment(MAT) were calculated for the last 10 years. ***RESULTS:*** CH: 1.797.963 screened. 960 detected (1: 1872) RR: 0.78% and DE: 0.09. MAD: 12 days and MAT: 15 days. PKU: 1.807.757 screened. 135 detected (1: 13390). RR: 0.13% and DE: 0.03. MAD: 11 days and MAT: 16 days. CF: 887.250 screened. 140 detected (1: 6337) RR: 0.54% and DE: 0.025. MAD: 21 days and MAT: 59 days. CAH: 779.525 screened, 64 detected (1: 12180) RR: 0.38% and DE: 0.02. MAD: 11 days and MAT: 14 days.GAL: 784.043 screened. 26 detected (1: 30155) RR: 0.32% and DE: 0.006.MAD 15 days and MAT: 17 days. BD: 699277 screened 4 detected (1: 174.819). RR: 0.02% and DE: 0.01. MAD: 10 days and MAT 11 days MSUD: 226575 screened. 1detected (1: 226575) RR: 0.19% and DE: 0.003. MAD: 23 days and MAT 24: days. ***CONCLUSION:*** In the last 39 years we implemented a neonatal screening program with adequate analytical parameters and significant detection. CH,CF,CAH and PKU are prevalent conditions in our country while GAL, BD and MSUD are rarer.

P-161 - NEONATAL SCREENING QUALITY INDICATORS IN AMAZONAS

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INTRODUCTION: Amazonas is the largest Brazilian state, with a low population density, its river basin occupies 40% of its territory. It belongs to the Amazon basin and rain forest. The National Neonatal Screening Program in Brazil operates throughout the territory and aims for 100% national coverage. It uses as quality indicators: coverage; the percentage of newborns who undergo collection between 3 and 5 days of life; the median age at the first consultation for each disease; the number of collection points. ***OBJECTIVES:*** The service flowchart works with blood collections on filter paper in basic health units and maternity wards across the state. This collection is sent to a single laboratory in the state that operates at the Amazonas blood center. Children with samples with altered exams are called and referred to the Amazonas Neonatal Screening Reference Service for follow-up. The state currently screens for congenital hypothyroidism, phenylketonuria, cystic fibrosis, congenital adrenal hyperplasia and biotinidase deficiency, hemoglobinopathies and congenital toxoplasmosis. Quality indicators are evaluated annually. ***MATERIALS AND METHODS:*** Calculation of indicators. Coverage is calculated by the number of births sorted by the number of live births. Percentage of exams collected up to the 5th day of life. Calculation of the median age at the first consultation. Sum of locations registered for exam collection. ***CONCLUSION:*** In 2023, the neonatal screening indicators in Amazonas were as follows: Coverage 74.69%; Collection Percentage on Ideal Date 39%; Collection Points 113. The median age for each disease at the first consultation was: congenital hypothyroidism 46 days of age; phenylketonuria 11 months of age; cystic fibrosis 94 days of life; congenital adrenal hyperplasia 23 days of age; biotinidase deficiency 35 days of life. Hemoglopbinopathies and congenital toxoplasmosis are not monitored in the referral service and we do not have access to their indicators. We believe that our service is evolving more and more and efficiently serving the community.

P-162 - NEWBORN SCREENING IN CUBA USING THE ULTRAMICROANALYTICAL SYSTEM: 37 YEAR´S EXPERIENCE

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INTRODUCTION: Since 1986, SUMA technology has been used for the detection of inherited-metabolic diseases that occur in the neonatal period. ***OBJECTIVE:*** This work summarizes the results of 37 years of the Cuban neonatal screening program on inherited-metabolic diseases. ***METHODS:*** Information regarding neonates studied and detected for congenital hypothyroidism, phenylketonuria, congenital adrenal hyperplasia, galactosemia, biotinidase deficiency and cystic fibrosis was collected for the period 1986-2023. The Dried Blood Spot (DBS) samples are collected between the 5th and 7th days of life and sent to medical genetics reference centers, which are responsible for recording the data, and sent DBS samples to SUMA laboratories. Incidence of each disease and Positive Predictive Values (PPV), were calculated. Other indicators such as coverage, percentage of unsatisfactory samples, collection time, transfer, processing and issuance of results were also studied. ***RESULTS:*** More than 4.7 million Cuban newborns have been screened, and 1204 affected children have been detected. The overall incidence of inherited metabolic diseases identified by the program was 1: 3958 live births. The coverage exceeded 94% of the neonates studied. In general, the PPVs were low, this is related to the low incidence of these diseases. The percentage of unsatisfactory samples was less than 0.4%, more than 92% of the samples were collected between 5th-7th days of birth and more than 89% were sent and processed in the laboratory after 72 hours respectively. ***CONCLUSIONS:*** The expansion of the Cuban neonatal screening program to six inherited-metabolic diseases using SUMA technology, places Cuba among the most developed countries in the region in the field of newborn screening and demonstrates that the development of its own technologies allows the access to health programs on a massive scale.

P-163 - NEWBORN SCREENING IN GUATEMALA: 7-YEAR EXPERIENCE OF NEWBORN SCREENING PERFORMED AT ROOSEVELT HOSPITAL

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INTRODUCTION: Currently in Guatemala there are 410,000 births per year, of which only 5% undergo newborn screening (NBS). Every day in Guatemala three apparently healthy babies are born who have a latent Inborn Error of Metabolism. Roosevelt Hospital is a specialized hospital located in Guatemala City that routinely performs NBS since 2003. Guatemala is one of the Latin American countries that does not have a national NBS program or laws that promote it. ***OBJECTIVE:*** Estimate the incidence of congenital metabolic disorders in newborns at the Roosevelt Hospital in Guatemala, from 2017 to 2023, detected through NBS.***MATERIALS AND METHODS:*** Samples were obtained between 24 and 72 hours of life by dried blood spots. Neonatal TSH, 17-hydroxyprogesterone, immunoreactive trypsinogen, total galactose and phenylalanine tests were performed by fluoroimmunoassays developed by PerkinElmer®. Database was used during the period from 2017 to 2023, 61,267 newborns screened at Roosevelt Hospital. Confirmation of results was made based on diagnostic algorithms performed by the Ministry of Public Health and Social Assistance. ***RESULTS:*** Total incidence of diagnosed cases from 2017 to 2023 is 1: 1,056. Total number of diagnosed cases was established annually, 9 cases were diagnosed in 2017, 8 in 2018, 5 in 2019, 8 in 2020, 9 in 2021, 11 in 2022 and 8 in 2023. Reported incidence of disease was 1: 1,612 for Congenital Hypothyroidism, 1: 5,662 for Congenital Adrenal Hyperplasia, 1: 6,767 for Cystic Fibrosis, 1: 26,310 for Galactosemia. No cases were detected for Phenylketonuria. ***CONCLUSIONS:*** Guatemala is a country classified by the World Bank as having an uppermiddle income. However, although there is financial stability, it is a country with high rates of poverty and inequality, which is reflected in a deficient health system. Although NBS has been carried out for more than three decades, both the activities and the progress have been minimal, which results in low coverage at the national level, which means that the reported incidences do not correspond to a real estimate. Actively searching for and reporting these cases serves as justification and evidence of the need to create laws and programs that actively search for these diseases.

P-164 - PHENYLALANINE CONCENTRATION IN NEONATAL SCREENING OF CONFIRMED CASES - 20 YEARS OF EXPERIENCE. WHAT HAS CHANGED OVER TIME?

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INTRODUCTION: Phenylalanine concentration (CPHE) in initial newborn screening samples depends on exogenous protein intake and time of exposure to it, so the age of sample collection is a critical variable. The current decision algorithm defines an abnormal result when CPHE≥2.5 mg/dl, requiring the collection of second samples when CPHE<6.0 mg/dl and confirmatory testing when CPHE≥6.0 mg/dl. ***OBJECTIVE:*** To evaluate the CPHE in initial newborns samples in confirmed cases of Phenylketonuria (PKU) and Persistent Hyperphenylalaninaemia (HPA) in the period 2004-2023, to determine their behavioural patterns and propose possible changes in the decision algorithm. ***MATERIAL AND METHODS:*** The PKU and HPA newborns database was analyzed and the following parameters were calculated: a) number of cases, b) mean CPHE in initial samples [Phe units: mg/dl], c) number and percentage of PKU newborns with CPHE<6.0, d) number and percentage of HPA newborns with CPHE≥5.0. ***RESULTS:*** During the 20 years evaluated, 107 newborns were diagnosed with PKU and 130 with HPA. The mean CPHE was 9.8 and 3.8 for each group, while the mean for the first and second decade respectively was 11.2 and 7.6 in the PKU group, and 3.8 and 3.7 in the HPA group. 19/107 PKU newborns (17.8%) had CPHE<6.0, with no significant differences in the first and second decade (17.4 vs 18.4%). Nine of these 19 newborns had 5.0≤CPHE<6.0. 20/130 HPA newborns (15.3%) had CPHE≥5.0, with 8 of them having 5.0≤CPHE<6.0. ***CONCLUSIONS:*** The mean CPHE between PKU and HPA individuals showed significant differences. However, its behaviour between the first and second decades assessed showed no variation in HPA newborns, but a marked decrease was observed in PKU newborns. A reduction in the confirmatory cut-off value from 6.0 to 5.0 mg/dl could increase the screening system efficiency. A retrospective evaluation of this change would imply that 9 PKU and 8 HPA newborns would have reduced the age of diagnosis and start of treatment by requiring immediate confirmatory testing from the initial sample result. In addition, the number of unaffected newborns requiring confirmatory testing would increase by only 2/year, decreasing the risk of missed cases due to failure to collect second samples.

P-165 - SYSTEM FOR MANAGEMENT OF LABORATORY SPECIMENS DEVELOPED BY LABORATORIO HCPKU HOSPITAL SAN JUAN DE DIOS

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INTRODUCTION: Neonatal screening is a preventive health strategy that generates large amounts of data that require continuous monitoring. The regulations in Chile establish a computer system for birth data and sample processing (Norma General Técnica N°93/Res.Ex.N°206 del 20/04/2007.MINSAL). Until 2017, the available market solutions did not meet our needs, so we decided to test and perfect an open system for managing samples and results, resulting in a robust software for the management of laboratory specimens in the context of neonatal testing, the system offers an integrated approach to the entire laboratory process, spanning from sample reception to reporting and database management. ***OBJECTIVES:*** Present the benefits that the development of the computer system has provided in newborn screening of 70% population of our country. ***MATERIALS AND METHODS:*** Retrospective analysis of contract logs to identify improvements, development achievements, period 2018-2023. ***RESULTS:*** Timely and efficient management of processes related to sample reception, anomaly detection, newborn information management (from only abnormal samples to all), report generation (from days to immediate), traceability and monitoring of abnormal and unsatisfactory samples, loading of results, positive result management, cut-off points management, card management, and statistical reporting, contributing to enhanced efficiency (from few samples at day to all), accuracy, and traceability in laboratory workflows. Interconnectivity with MINSAL network of 80 maternity hospitals. Normal results reports can be achieve for maternity users immediately; abnormal reports improve from 24-48 hrs to same day of acceptance results analysis. ***CONCLUSIONS:*** Successful innovation product in newborn screening, property of Hospital San Juan de Dios, national registry traceable to 2018. Patent 20 2024 101 632 in Germany obtained in April 24 of 2024.

P-166 - OPTIMIZING NEONATAL SCREENING: PERFORMANCE ASSESSMENT OF THE NEOMAP® 5PLEX HT KIT FOR MULTIPLEX DETECTION OF T4, 17OHP, IRT, TSH AND IGM ANTIBODIES AGAINST TOXOPLASMOSIS.

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INTRODUCTION: Since the implementation of neonatal screening, numerous technological advances have facilitated the early detection of several congenital conditions. Among these innovations is the xMAP magnetic microsphere platform developed by Luminex Corporation, which enables the creation of multiplex assay methods for the simultaneous screening of multiple parameters. As newborn screening programs continue to expand, the use of these platforms is crucial to optimize testing time, sample volume, and material usage. ***OBJECTIVE:*** To evaluate the performance of the NeoMAP® 5plex HT kit for the simultaneous detection of T4, 17OHP, IRT, TSH, and IgM antibodies against toxoplasmosis (Tox), assisting in the screening of four diseases. ***MATERIALS AND METHODS:*** The accuracy of the method was evaluated by comparing the results obtained with other commercial kits, using samples with and without the presence of markers. 233 samples were used for the parameters of T4, 17OHP, IRT, and TSH, while for Tox, 723 samples were used, characterized as positive or negative for the presence of IgM antibodies against toxoplasmosis. The samples were analyzed on a multiplex magnetic microsphere platform, with results reported in Median Fluorescence Intensity (MFI) for Tox and in concentrations for the other parameters. Statistical analysis included the kappa coefficient for all markers and receiver operating characteristic (ROC) analysis for the Tox parameter, evaluating sensitivity, specificity, area under the curve (AUC), 95% confidence interval, and cutoff value. ***RESULTS:*** Agreement with other methodologies was 100% for T4, 17OHP, IRT, and TSH, using 233 samples. ROC analysis for the Tox parameter showed 100% sensitivity, 97% specificity, an accuracy of 97.6%, an AUC of 99.72%, and a 95% confidence interval of 99.36-100%, with a cutoff value of 359 MFI. ***CONCLUSION:*** The NeoMAP® 5plex HT kit demonstrated high accuracy and reliability for the simultaneous detection of T4, 17OHP, IRT, TSH, and IgM antibodies against toxoplasmosis. Its high concordance with existing methodologies and excellent performance in ROC analysis highlights its potential to improve newborn screening programs.

P-167 - A LINEAR REGRESSION MODEL TO ESTIMATE THE MEASURE OF NEONATAL TSH AT THE CUTOFF VALUE.

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INTRODUCTION: The Newborn Screening Laboratory of the J.M. Ramos Mejía Hospital is one of the three laboratories of the Newborn Screening Program of Buenos Aires City Government (NSP). Early detection of Congenital Hypothyroidism is performed by neonatal TSH (nTSH) measurement in dried blood samples (DBS), and the cutoff (CO) value is 8.0 uU/ml in whole blood. ***OBJECTIVE:*** To evaluate the analytical performance of the assay by making an estimation of the measure at the CO value with an 95% confidence using a linear regression model (LRM). ***MATERIALS AND METHODS:*** 16 DBS samples provided by the Fundación Bioquímica Argentina´s External Quality Control Program (PEEC), received between February 2022 and February 2024, were analyzed by using Time-Resolved Fluoroimmunoassay (DELFIA Perkin-Elmer). Those samples had peer group media values of nTSH between 1.0 and 20.0 uU/ml. LRM was performed in R Studio software version 4.4.0. The dependent variable (DV) was defined by the result obtained by our laboratory, and the independent variable (IV) was defined by the peer group value. The normality of the DV was inspected by Shapiro-Wilk Test. Regression coefficients such as slope, intercept, correlation (r) with a 95% confidence were calculated, as well as the coefficient of determination R Squared (R2) and the Adjusted R Square (A-R2). The evaluation of the regression assumptions (using the regression residuals) was performed running Ramsey's RESET test for linearity, Shapiro-Wilk Test for normality, Durbin-Watson Test for independence and BreushPagan Test for homoscedasticity. Null hypothesis for each assumption was accepted if $p>0.05$. No outliers were found by using Cook's Distance. ***RESULTS:*** DV normality was proven ($p>0.05$). Results obtained from the regression were: slope = 0.977 [0,838 - 1,117], ($p<0.05$); intercept = 0,004 [-1,211-1,219], ($p>0.05$); r = 0.970 [0.914-0.989], ($p<0.05$); R2 = 0.941; A-R2 = 0.937. Residuals' linearity ($p>0.05$), normality ($p>0.05$), independence ($p>0.05$) and homoscedasticity ($p>0.05$) were accepted. CO estimated value was 7.8 [7.2

- 8.4] uU/ml, and BIAS%=-2.25%. ***CONCLUSIONS:*** Through the linear regression model, we can verify that analytical performance of the assay at the cutoff value is acceptable, providing another useful tool to assure the quality of the test results reported by the NSP.

P-168 - ANALYSIS OF LABORATORY PERFORMANCE USING RESULTS FROM CDC'S NEWBORN SCREENING QUALITY ASSURANCE PROGRAM: OPPORTUNITIES FOR QUALITY IMPROVEMENT

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INTRODUCTION: The Centers for Disease Control and Prevention (CDC) Newborn Screening Quality Assurance Program (NSQAP) is an accredited proficiency testing (PT) provider (ISO/IEC 17043: 2023) that provides comprehensive quality assurance dried blood spot (DBS) materials to newborn screening (NBS) laboratories worldwide. ***OBJECTIVES:*** To evaluate the performance of the NBS laboratories participating in NSQAP through the analysis of PT summary data from 2016-2023. ***MATERIALS AND METHODS:*** NSQAP provided DBS materials for 16 PT programs used by NBS laboratories to demonstrate competency, verify the accuracy and reliability of test results and meet regulatory/accreditation requirements. DBS were prepared from whole blood of 50% hematocrit, enriched with biochemical markers, and packaged with desiccant for shipment. NSQAP collected and analyzed PT results from participants, and each was given an individual evaluation of their performance. Laboratories representing the six worldwide regions recognized by the International Society for Neonatal Screening reported PT results to NSQAP. ***RESULTS:*** In the period 2016-2023, 594 laboratories from 82 countries participated in PT programs. The European and Asia Pacific regions had the largest number of laboratories in PT programs (30%), followed by Latin America (17%), North America (16%), Middle East and North Africa (6%), and Sub-Saharan Africa (1%). PT programs with the most participation were Amino Acid PT (83%), Hormones and Total Galactose PT (74%), and Acyl Carnitine PT (66%). Over the period of study, 570 laboratories had unacceptable results, with 15% averaging more than five unacceptable results per year. On average, 60% of laboratories reported unacceptable results per year. The 12,157 unacceptable results represented 1.2% of all PT specimens tested and were classified as false positive (66%) or false negative (34%) errors. PT errors rates for regions ranged from 0.6-1.8% with the lowest in North America and the highest from the Latin American region. ***CONCLUSIONS:*** Our study showed many laboratories made PT errors each year and some repeatedly had errors. Each laboratory is responsible for investigating the source(s) of errors and taking steps to minimize the risk of recurrence. Laboratories should establish procedures for reviewing NSQAP evaluations as part of their quality management system and use the evaluations for quality improvement.

P-169 - USEFULNESS OF THE RECALL RATE DUE TO ABNORMAL RESULTS AS A RETROSPECTIVE INDICATOR OF ANALYTICAL PERFORMANCE IN NEWBORN SCREENING

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INTRODUCTION: When monitoring the analytical performance of the measurement methods, Newborn Screening (NBS) Laboratories have some additional statistical tools available that complement the Internal Quality Control and External Quality Assessment. These are the measures of central tendency of the results corresponding to each analytical run: mean, median and mode. Likewise, the Recall Rate due to abnormal results (RR) is also a useful indicator, albeit of retrospective application, provided that fixed cut-off values must be used and these must remain unchanged during the period under evaluation. ***OBJECTIVE:*** To present a practical experience demonstrating the RR usefulness as a retrospective analytical performance indicator in the measurement of neonatal TSH. ***MATERIAL AND METHODS:*** The behaviour of the monthly RR in NBS for Congenital Hypothyroidism was retrospectively evaluated between January/2021-December/2023. TSH was measured with the Chemiluminescence Microparticle Immunoassay from Abbott adapted to dried blood spots, using PerkinElmer calibrators, and controls provided by PerkinElmer and CDC. In the period evaluated, 18 lots of Abbott Reagents, 6 lots of PerkinElmer calibrators, 4 lots of PerkinElmer controls, and 8 lots of CDC controls were used, while the cut-off value remained unchanged (8.5 uU/ml). ***RESULTS:*** In the initial period (January/2021-May/2022) the RR remained at stable values (Mean±SD) of 0.31±0.08% (RRMAX=0.46%). In June/2022, the RR suddenly raised to 0.54% reaching until March/2023 an average of 0.56±0.12% (RRMAX=0.79%). From April/2023 until December/2023, the RR recovered values similar to those of the initial period, of 0.37±0.07% (RRMAX=0.51%). The traceability records review

showed that the period of highest RR values coincided with the use of a specific lot of TSH calibrators. ***CONCLUSIONS:*** The RR is a retrospective analytical performance indicator that can reflect changes in the accuracy of measurement methods. The observed change in the RR behaviour revealed a positive bias in the TSH measurement during the critical period, resulting in an 80.6% increase in newborns with abnormal results. A direct relationship with the use of a specific calibrators lot was observed, allowing to assume the existence of an error in the assignment of TSH values, thus leading to a TSH concentration overestimation and, consequently, to the observed increase in the RR.

P-170 - DATA SCIENCE FOR ANALYSIS OF DEMOGRAPHIC INFORMATION OF THE NEONATAL METABOLIC SCREENING SAMPLES WITH THE RSTUDIO TOOL

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INTRODUCTION: The pre-analytical phase of neonatal metabolic screening plays a crucial role in the quality of results. Factors such as the sample's transit time, age at the time of sample collection, and quality of samples can significantly affect the effectiveness of the screening and the timely detection of genetic and metabolic diseases in newborns. RStudio is an open-source, free programming language that allows data processing, statistical analysis, and data visualization. ***OBJECTIVE:*** To analyze data from the pre-analytical phase of neonatal metabolic screening using the RStudio tool to identify areas for improvement in sample collection, handling, and transport. ***MATERIALS AND METHODS:*** A dataset of demographic and pre-analytical phase from newborns' samples undergoing neonatal metabolic screening throughout 2023 was used. Descriptive and statistical analysis techniques were employed using RStudio. Sample transit time, age at the time of sample collection, and the incidence of unsatisfactory samples were analyzed. ***RESULTS:*** The analysis of the pre-analytical phase revealed that sample transit time varied significantly among collection centers (N=159), ranging from 1.0 to 6.2 days (average 2.8 days), potentially affecting sample integrity. Additionally, it was observed that the age at the member to collect the sample. Additionally, in November 2023 the recruitment of a second sample for preterm and low birth weight babies is included. Data from the periods July-October 2023 and November 2023-February 2024 are time of first sample collection varied from 3.0 to 9.5 days, (average 4.6 days). Finally, the incidence of unsatisfactory samples also exhibited variability from 0 to 22.7%, averaging 1.6%. ***CONCLUSIONS:*** The identification of variabilities in the pre-analytical phase of neonatal metabolic screening allows decision-makers to bring forward measures to improve sample quality and, ultimately, increase the effectiveness of screening in the early detection of genetic and metabolic diseases in newborns. Therefore, transforming data into useful information through statistical analysis is possible, this enables conclusive decision-making based on complex data and facilitates communication of results through highquality graphical representations.

P-171 - UNIVERSAL SCREENING IN URUGUAY: THE TRANSFORMATIVE IMPACT OF ACTIVE PATIENT RECRUITMENT STRATEGIES

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INTRODUCTION: Newborn Screening Programs aim to detect congenital diseases early, before clinical symptoms appear at birth, thereby preventing serious consequences for the patient and reducing infant morbidity and mortality. One of the biggest challenges is ensuring that every newborn receives appropriate coverage. Although Uruguay is a small country, with approximately 35,000 births per year, it faces communication issues that can be crucial in obtaining samples from all newborns, especially in rural areas. In Uruguay, the screening program involves collaboration among several organizations, the laboratory, as the receiving institution for all samples, has the capability to monitor and implement measures to improve universal coverage ***OBJECTIVE:*** To evaluate the impact on the coverage achieved by the Newborn Screening Program in Uruguay, based on the patient recruitment strategy implemented by the Laboratory. ***MATERIALS AND METHODS:*** A retrospective study covering the years 2021 to 2023 is conducted. Coverage is determined by comparing processed samples with births registered in the civil identification records of Uruguay during the study period. Starting in August 2022, the newborns are compared every 10 days with the samples received and communication is made with the health provider or family

analyzed. ***RESULTS:*** A growth in coverage was observed during the years 2021, 2022, and 2023, reaching 98%, 99.4%, and 99.9% respectively. This represents a total of 951 newborns not screened compared to 27 newborns before and after the implementations of the recruitment strategies. The receipt of a second sample in premature babies increased from 40-44% (July-October 2023) to 80-88% (November 2023-February 2024). ***CONCLUSIONS:*** and/or DISCUSSION: The implementation of active strategies in patient recruitment has had a highly positive impact, enabling the achievement of universal screening with nearly 100% coverage.

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