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Editor–in–Chief: Roberto Giugliani

Latin American Society of Inborn Errors of Metabolism and Neonatal Screening

SPECIAL SUPPLEMENT WITH THE ABSTRACTS

2019 BUENOS AIRES SLEIMPN XI

Congreso Latinoamericano de Errores Innatos del Metabolismo y Pesquisa Neonatal

BUENOS AIRES, ARGENTINA - MAY 12-15, 2019

FOREWORD FROM SLEIMPN

Eighteen months after the successful ICIEM in Brazil, our Society is gathering again, this time in Buenos Aires, Argentina, for the XI Congress of the SLEIMPN (May 12-15, 2019)

For those of us who have been part of the SLEIMPN for many years, it is a pleasure to whiteness its growth, not only in the number of members, but also in que quality of the scientific production in our Region.

The main theme of our Congress is ***"From NBS to treatment: a shared challenge".*** I strongly believe that SLEIMPN is uniquely positioned to address this challenge, by exchanging knowledge and ideas to improve care in all aspects of the continuum that exists from a Newborn Screening (NBS) test to the treatment of patients and families affected by Inborn Errors of Metabolism (IEM).

The scientific program includes plenary and parallel sessions covering relevant topics of IEM and NBS. Additionally, there will be three pre-congress courses on Nutrition, Genetics and Newborn Screening, as well as sponsored satellite symposiums. More than 30 faculty members, from around the world, will be generously sharing their knowledge.

We hope that the record of the 279 abstracts of the free communications presented at this congress in this Special JIEMS Supplement will contribute to the field of IEM and NBS.

Jose E. Abdenur
President of SLEIMPN
President of the XI Latin American Congress of Inborn Errors or 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 ***11th Congress of the Latin American Society of Inborn Errors of Metabolism and Neonatal Screening*** (Buenos Aires, Argentina, May 12-15, 2019).

In this special supplement you will find 279 abstracts submitted as free communications and accepted for presentation. In the index you will find first those abstracts accepted as oral communications and then those presented as posters, sub-divided in different categories.

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

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

Roberto Giugliani

JIEMS Editor-in-Chief

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TOPIC INDEX

Book of Abstracts

ABSTRACTS SELECTED FOR ORAL PRESENTATION

O-001 - INHIBITORS OF C-ABL KINASE FOR THE TREATMENT OF THE NEURODEGENERATIVE NIEMANN-PICK TYPE A DISEASE

Zanlungo S[1], Marín T[1], De la Fuente C[2], Acuña M[1], Castro J[1], Cortés C[3], Marugan J[4], Dulcey A[4], Gorshkov K[4], Zheng W[4] et al.

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INTRODUCTION: Niemann-Pick type A (NPA) disease is a fatal lysosomal neurodegenerative disorder characterized by the deficiency in acid sphingomyelinase (ASM) and accumulation of sphingomyelin and cholesterol in lysosomes and autophagy alterations.
We have described that c-Abl kinase is activated in other neurodegenerative diseases and recent studies show a role for c-Abl in autophagy and cellular clearance. Although there are several c-Abl inhibitors approved by the FDA, most of them are poorly selective and present low CNS penetration.
OBJECTIVE: Our aims were: i) to evaluate c-Abl participation in the autophagy alterations and neuronal pathology in Niemann-Pick type A (NPA) disease and ii) to test the effect of the in vivo treatment of a NPA model mice with the new c-Abl inhibitor ABLy-1, designed by our group, with high selectivity and greater CNS penetration than other inhibitors.
MATERIALS AND METHODS: In in-vitro NPA models we evaluated c-Abl activation, autophagy flux and cell viability. Then we evaluated the gene-expression profile in the human NPA fibroblasts treated with Imatinib, a c-Abl classic inhibitor. In the NPA mice we evaluated c-Abl pathway activation in cerebellum and the effect of c-Abl inhibition with Imatinib on locomotor function, Purkinje cell loss, inflammation, autophagy markers. Currently we are using a diet supplemented with Nilotinib and ABLy-1 a new c-Abl inhibitor, and evaluating their effect on disease progression.
RESULTS: We found autophagy flux alterations and autophagosome accumulation around nucleus in NPA cellular models. Moreover, we found progressive neurodegeneration, inflammation, an impairment locomotor function and increment in autophagy markers in NPA animal model. In-vitro as well as in-vivo NPA models showed activation of the c-Abl pathway. c-Abl inhibition improved the autophagy flux, revealed differentially expressed genes involved in the disease pathogenesis, decreased number and changed distribution of autophagosomes and reduced neuronal death and improved locomotor function in the NPA mouse model.
CONCLUSION: c-Abl is activated and relevant in NPA neurodegeneration and autophagy alterations, supporting the potential use of c-Abl inhibitors for clinical treatment of NPA patients.
FONDECYT: 1150186(SZ), 1161065(AA) CARE- UC Projecto Basal AFB170005, CONICYT-PCHA/Doctorado Nacional/2015-150038, MSCA-RISE-2016-Lysomod-734825, FONDEF D10E1077.

O-002 - IN VITRO REDUCTION OF LYSOSOMAL GANGLIOSIDE ACCUMULATION BY RECOMBINANT HUMAN BETA-HEXOSAMINIDASE PRODUCED IN PICHIA PASTORIS

Espejo-Mojica AJ[1], Vu M[2], Rodríguez-López A[1,3], Beltrán L[1], Díaz D[1], Mosquera A[1], Li R[2], ZhengAlméciga-Diaz CJ[1]

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INTRODUCTION: Enzyme Replacement Therapy (ERT) is based on the capacity of heterologous lysosomal enzymes to be taken up and targeted to the lysosome, where they can degrade the accumulated substrate. β-hexosaminidases are hydrolases involved in lysosomal degradation of GM2 gangliosides. Recombinant human beta-hexosaminidases (rhHex-A and rhHex-B) produced in Pichia pastoris have been proved to be taken up by different culture cells via cation independent manner.
OBJECTIVE: To evaluate the therapeutic effect of recombinant beta-hexosaminidases in lipid storage reduction using Tay Sachs (TSD) patient fibroblasts and TSD neural stem cells model (NSCs).
MATERIALS AND METHODS: Recombinant hexosaminidases were produced in Pichia pastoris GS115 without any further modification. TSD patient fibroblasts were obtained from Coriell Institute. TSD-iPSCs were differentiated to TSD-NSCs at NCTAS-NIH using PSC neural induction medium kit. Nile Red and Lysotracker staining assays were used to evaluate lipids storage and lysosomal mass, respectively. Twenty-four hours before treatment, TSD fibroblasts and NSCs were seeded in 96-well black clear

bottom plates. Purified rhHex-A and rhHex-B were added at 50 and 100 nM final concentration. Twenty-four, 48 and 72 h after treatment, the cells were treated with 50 nM LysoTracker Red DND-99 dye or 1 μM Nile Red in complete DMEM media at 37 °C for 1 h and 10 min respectively. The plates were fixed and stained simultaneously. The images were acquired using the INCell Analyzer 2200 imaging system.
RESULTS: NCS derived from TSD iPSCs were a useful cellular model to evaluate the effect of recombinant hexosaminidases in the degradation of lysosomal stored lipids. Results showed that TSD fibroblasts and NSC treated with rhHex-A had a significant reduction of stored gangliosides respect to wild type cells. Normal levels of lysosomal lipids storage were observed after treatment of TSD-NCS and fibroblasts with rhHex-A. On the other hand, rhHex-B did not show consistent results.
CONCLUSIONS: These results showed that rhHex-A produced in P. pastoris could be used for further preclinical and clinical assays towards the development of an ERT for TSD. In addition, these results confirm the potential of this host in the production of recombinant protein for other lysosomal storage diseases.

O-003 - EVALUATION OF THE FREQUENCY OF NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE IN ADULT PATIENTS WITH GAUCHER DISEASE TYPE 1

Wilke MVMB[1,2], Dornelles AD[2], Schuh AS[1,3], Vairo FP[2,4,5], Basgalupp SP[1,10], Siebert M[6,7,10], Nalin T[2], Piltcher OB[8], Schwartz IVD[1, 2, 9, 10]

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INTRODUCTION: Gaucher disease (GD) is an inborn error of metabolism caused by deficiency of beta-glucocerebrosidase (GCase). More than 400 mutations of the GCase gene (GBA1) have been described. GD is conventionally classified into three clinical forms, on the basis of neurological involvement: type 1 is considered the non-neuropathic form, whereas types 2 and 3 affect the nervous system. Parkinson's disease (PD) is the second most common neurodegenerative condition. The classic motor symptoms of PD may be preceded by many non-motor symptoms (NMS), which include hyposmia, REM sleep behavior disorder, constipation, cognitive impairment, and depression. Population studies have identified mutations in GBA1 as the main risk factor for idiopathic PD. The present study sought to evaluate the prevalence of NMS in a cohort of patients with GD type 1 from Southern Brazil.
METHODOLOGY: This is an observational, cross-sectional study, with a convenience sampling strategy. Cognition was evaluated by the Montreal Cognitive assessment (MoCa), daytime sleepiness by the Epworth Scale, depression by the Beck Inventory, constipation by the Unified Multiple System Atrophy Rating Scale, and REM sleep behavior disorder by the Single-Question Screen; hyposmia by the Sniffin' Sticks. Motor symptoms were assessed with part III of the Unified Parkinson's Disease Rating Scale. Patients were also genotypes for a GBA1 3?-UTR SNP (rs708606).
RESULTS: Twenty-three patients (female=13; on enzyme replacement therapy=21, substrate reduction therapy=2) with a mean age of 41.45±15.3 years (range, 22-67) were included. Eight patients were heterozygous for the 3?-UTR SNP (rs708606). Fourteen patients (8 over age 40 years) presented at least one NMS; daytime sleepiness was the most frequent (n=10). Two patients (aged 63 and 64, respectively) also presented motor symptoms, probably drug-related.
CONCLUSIONS: NMS were prevalent in this cohort. We highlight the importance of a multidisciplinary follow-up focusing on earlier diagnosis of PD, especially for patients with GD type 1 over the age of 40.

O-004 - CELL-DELIVERED AND LYSOSOMAL-ACCUMULATION REDUCTION BY GLYCOENGINEERED N-ACETYLGALACTOSAMINE-6-SULFATE SULFATASE (GALNS) FOR MORQUIO A DISEASE TREATMENT

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INTRODUCTION: Mucopolysaccharidosis IV A (MPS IVA, Morquio A disease) is a lysosomal storage disease produced by mutations in GALNS enzyme. We had reported the production of recombinant GALNS in Pichia pastoris yeast as an alternative for Morquio A ERT. The modification in the N-glycosylation pathway in P. pastoris NRRL Y-11430 strain, allows to obtain a more humanized and homogeneous glycan profile. Glycoengineered recombinant GALNS produced in P. pastoris have been proved to be taken up by different culture cells.
OBJECTIVE: To evaluate the effect of recombinant glycoengineered GALNS in lysosomal mass reduction using MPS IVA fibroblasts and iPSC-derived cardiomyocytes and chondrocytes.
MATERIALS AND METHODS: Recombinant glycoengineered GALNS was produced in the yeast Pichia pastoris NRRL Y-11430. Fibroblasts from MPS IVA patients were obtained from Coriell Institute. MPS IVA iPSC were generated by using the non-integrating CytoTune-Sendai viral vector kit. Cardiomyocite differentiation was performed using STEMdiffTM Cardiomyocyte Differentiation Kit; while chondrocyte differentiation was performed following the protocol reported by Suchorska W et al. 2017. The MPS IVA fibroblasts and iPSC-derived cardiomyocytes and chondrocytes were treated with 50 and 100 nM of recombinant GALNS. Control cells were treated with PBS 1x. After treatment, the cells were treated with 50 nM LysoTracker Red DND-99 dye. The images were acquired using the IN Cell Analyzer 2200 imaging system.
RESULTS: iPSC-derived cardiomyocytes and chondrocytes were successfully obtained and expressed the expected protein markers. MPS IVA fibroblasts and iPSC-derived cardiomyocytes and chondrocytes showed significant increase in lysosomal mass. Results showed a significant reduction ($p<0.05$) in the lysosomal accumulation in MPS IVA fibroblasts, which ranged between 25 and 40% of WT levels. Reduction between 11 to 16% of the lysosomal accumulation was observed after treatment of MPS IVA cardiomyocytes and chondrocytes.
CONCLUSIONS: The results showed that developed cells models can be used in the evaluation of new therapies for MPS IVA. It was observed that recombinant GALNS produced in a glycoengineered yeast showed significant reduction of the lysosomal mass in all treated cells. These results pave the way in the development of a new ERT for MPS IVA patients.

O-005 - NATURAL HISTORY OF TYPE IX GLYCOGEN STORAGE DISEASE: A BRAZILIAN MULTICENTRIC STUDY

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INTRODUCTION: Type IX glycogen storage diseases (GSD-IX) are caused by mutations in genes encoding for phosphorylase kinase subunits, resulting in subtypes IX-a, b, and c. Its diagnosis has been challenging due to wide variability of phenotypes and inheritance patterns. They can cause ketotic hypoglycemia, short stature, hepatomegaly, cirrhosis and hepatocellular carcinoma or even present as oligosymptomatic phenotypes. GSD-IX natural history is not fully known. Treatment involves avoiding hypoglycemia through use of cornstarch, frequent feeding and high protein intake.
OBJECTIVE: To describe the natural history of a cohort of Brazilian patients with GSD-IX.
METHODS: Retrospective observational multicentric study. Informed consent was obtained from all participants. To be included, patients needed to have a genetic diagnosis of GSD-IX.
RESULTS: Seventeen individuals (GSD-IXa: 12; GSD-IXb: 2; GSD-IXc: 3), from eleven families, were included (male: 14; 82.3%). The mean age at inclusion was 13.8 years (range: 3-55 years). Hepatomegaly triggered the initial investigation in 10 cases (58.8%). First manifestations were observed during neonatal (n=3); infant (n=10); and children (n=4) ages. The specific GSD subtype was diagnosed on average at 11.3 years; and 76.4% of subjects had received a clinical diagnosis of another type of GSD before genetic confirmation. Hepatic biopsy was performed in seven individuals (41.1%), showing fibrosis in three cases. Other findings included alteration of transaminases (14/17); increase of muscular enzymes (14/17); hypoglycemia (13/17); hypertriglyceridemia (13/17); hypercholesterolemia (10/17); and hyperlactacidemia (8/17). Muscular signs and symptoms were identified only in subtypes IXa and IXb. Three individuals required use of gastrostomy to maintain adequate intake and prevent decompensation. Regarding genetic analysis, four pathogenic known variants were identified in the X-linked form. In autosomal recessive forms, five variants were identified, including four novel mutations (PHKB: c.1972-2A>G, c.2181delT, c.572_576delAGATT; PHKG2: c.454C>T).
DISCUSSION AND CONCLUSION: This is the largest GSD-IX case series already described worldwide and extends the current limited knowledge about clinical variability in patients with type IX GSD. Wide clinical heterogeneity was identified. Laboratory data demonstrate high prevalence of hepatomuscular manifestations. It is observed that many individuals went through investigational invasive procedures, however these were minimally informative in diagnostic process. Long-term studies involving follow-up of these patients until adulthood are necessary.

O-006 - DESCRIPTION OF THE PRESENTATION, NEUROLOGICAL OUTCOME AND MORTALITY OF THE UREA CYCLE DISORDER IN 41 PATIENTS DIAGNOSED AT GARRAHAN HOSPITAL.

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INTRODUCTION: We describe a cohort of patients with urea cycle disorder (UCD) who have been diagnosed or are being followed up at the Pediatric Garrahan Hospital.
OBJECTIVES: To correlate the biochemical data, at the time of diagnosis with the specific enzymatic deficiency and the type of presentation. To analyze the family history, the delay in diagnosis and the neurological outcome at the last control.
METHODS: A retrospective study of the patients diagnosed with UCD between 2000 and 2017. The medical records of the hospital were reviewed. The biochemical data including the amino acids profile were those obtained at the time of diagnosis.
RESULTS: We assessed 41patients (33 families, 22 females, 19 males). A molecular study was performed on 20 patients. 17/41 patients had had a neonatal presentation, the remaining 24 a late-onset presentation; the majority of these patients had delay at diagnosis, (average 7,7 months (1–57)), only 3/24 with late-onset UCD presentation were diagnosed during the first month as soon as the symptoms began. 20 patients had a family history. 19/41 showed some grade of developmental delay; in 10patients this delay was severe. 25/41 had ornithine transcarbamylase deficiency (OTCD); 7 had arginine succinic synthetase deficiency (ASSD); 5 had arginine succinate lyase deficiency(ASLD) and one had carbamoylphosphate synthetase deficiency. The remaining 3 patients were not categorized.
14/34 had hepatitis. 10patients died and 6 of them had had a neonatal presentation.
CONCLUSIONS: UCD is still a severe disease with high mortality and morbidity and high developmental delay. The delay in diagnosis is significantly associated with intellectual disability (p: 0.016). Patients who had ammonia values higher than 250mmol/l have higher intellectual disability (p: 0.001). Glutamine values at debut were not associated with greater neurological compromise or mortality. Comparatively, the patients with ASLD were those that showed higher values of ammonia, all of them had a neonatal presentation. The patients with ASSD were those who showed higher values of transaminases. OTCD had shown the highest incidence and mortality, coinciding with the global incidence.
To diagnose a severe disease early, in the immediate neonatal period due to the family history, improves the neurological result and death can be prevented.

O-007 - GROWTH PATTERNS OF PKU PATIENTS IN THE FIRST YEARS OF LIFE

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INTRODUCTION: The first years of life are characterized by the highest growth rate of human life, and nutritional deficits could have a permanent impact on development. The aim of this study was to investigate growth patterns in the first 3 years of life of patients with phenylketonuria (PKU) and its association with metabolic control.
METHODS: A retrospective cohort study was conducted in Hospital de Clínicas de Porto Alegre, Brazil. Patients with PKU diagnosed through NBS that started dietary treatment <6 months of age were included. PKU type was classified as classical PKU, mild or not determined. WHO Z-scores of weight-for-age (W/A), height-for-age (H/A), BMI-for-age (BMI/A) and head circumference-for-age (HC/A) were assessed at birth, before treatment, and at 6, 12, 18, 24 and 36 months of age. Mean and SD of phenylalanine (Phe) and tyrosine plasma levels were collected in year 1, 2 and 3.
RESULTS: Forty-seven PKU patients were included (55% male), being 43% classical PKU, 48% mild, and 9% not determined. Pre-treatment measurements were similar among PKU types. Median age of the beginning of treatment was 45 days (range: 11-156). Mean Phe plasma levels were: 5.9±2.4 mg/dL in year 1; 6.4±2.8 mg/dL in year 2; and 7.5±3.8 mg/dL in year 3. In classical PKU patients, mean Phe plasma levels and Phe variability (measured by SD) were higher ($p<0.05$). Anthropometric indices W/A, H/A and BMI/A were within reference ranges for most patients, with no differences according PKU types. At 36 months, 1 patient presented short stature and 7 (15%) were overweight. An increase in overweight rate was observed in the second year of life and then remained stable. HC/A was within reference range for all but one patient (Z-score -2.3). However, classical PKU patients presented lower HC/A Z-scores at 6, 12 and 36 months (median at 36 months: -1.06). Phe variability, but not mean Phe, was inversely correlated with HC/A Z-scores at all points ($P<0.05$).
CONCLUSIONS: Growth parameters were adequate for most patients, but the increase in overweight prevalence warrants attention. Our data suggest that avoid high Phe variability is important, since it was consistently associated with lower head circumference.

O-008 - TARGETED METABOLOMICS ANALYSIS FOR PROPIONATE METABOLISM DISORDERS

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BACKGROUND: Disorders of propionyl-CoA metabolism result mostly from a defect in propionyl-CoA carboxylase or methylmalonyl-CoA mutase in propionic acidemia (PA) or methylmalonic aciduria (MMA) respectively. These disorders are the most frequent forms of branched-chain organic acidurias. Global metabolomic profiling offers novel opportunities for the study of these diseases.
OBJECTIVE: this study aims to evaluate the targeted metabolomics profiles of patients with disorders of propionate metabolism.
METHODS: We analyzed 98 dry blood samples for 9 PA and 20 AMM patients using targeted metabolomics approach. Data were processed using multivariate analysis with the MetaboAnalyst 4.0 software.
RESULTS: Hierarchical clustering analysis (HCA) clearly distinguished between the metabolomic profile of AMM and PA patients. The first tree principal components account the 61.3% of variance explained, Orthogonal partial least squares-discriminant analysis (orthoPLS-DA) classification modeling analysis have satisfactory results (Q2: 0.675 R2Y: 0.803). Our metabolomics studies revealed alterations of specific metabolites and glycine was the main important metabolite responsible of the differentiation with a VIP value of 1.7 in almost all principal components, and has a 6.13 fold change rate. C3/C2, the classical biomarker used in newborn screening was higher in AP patients with a fold change rate of 0.5.
CONCLUSIONS: Besides classical biomarkers of propionate metabolic defects, metabolomics analysis could discover others that could facilitate differential diagnosis and might be important for a better understanding of pathogenesis, treatment optimization and clinical follow-up.

O-009 - PEDIATRIC LIVER TRANSPLANTATION FOR INBORN ERRORS OF METABOLISM

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The aims of this article were to report a single-center experience of pediatric liver transplantation for Inborn Errors of Metabolism (IEM)
MATERIALS AND METHODS: The medical records of 40 patients younger than 18 years undergoing liver transplantation (LT) from March 1993 to December 2018 at Juan P. Garrahan Pediatric Hospital of Buenos Aires where 811 (LT) were performed, there were reviewed. The variables measures were: Patient demographics, indications, cirrhotics or non cirrhotics, graft type, survival, postoperative complications, growth and schooling.
RESULTS: 40 patients LT were performed (22 female, 18 male) at a median age of 57 months (range, 1- 217 months). IEM was 5% of the LT in 25 years. The median time follow-up was 3.1 years (range, 0.01- 22.7 yr). LT indication were: cirrhosis complications in 21, quality of life in 10 and 9 acute liver failure.15 were prioritized to access LT. IEM were 25 cirrhotic and 15 non cirrhotic in the explants.
The cumulative 1, 5, and 10-year patient and graft survival rates were 74.4%, 74.4% and 68.6% and 74.4%, 74.4% and 68.6% respectively. For non cirrhotic vs cirrhotic disorders cumulative 1, 5, and 10-year patient survival rates were 80% vs 70.6%, 80% vs 70.6% and 80% vs 64.1%. There were 16 whole grafts and 24 reduced. 1 combined liver–kidney transplantation was performed in methylmalonic acidemia. Biliary and vascular complications were 22% and 20% respectively and one retransplants were done. Five had a liver tumor: 2 adenomas and 3 hepatocellular carcinoma. 55% had acute cellular rejections and 9% developed chronic rejection. Four Post-transplant lymphoproliferative diseases were developed. 52% had growth failure and improved by 37% after LT and 43% had education according to their age.
CONCLUSION: Liver transplantation is an alternative therapy that improves the survival, growth and quality of life of a group of IEM with different clinical manifestations. The risk assessment and the LT benefit should be comprehensively addressed by an interdisciplinary team before the LT indication and careful monitoring and specific management of the disease is necessary even after LT.

O-010 - GENETIC DIAGNOSIS AND GENOTYPE-PHENOTYPE ASSOCIATION IN 113 BRAZILIAN INDIVIDUALS WITH REDUCED BIOTINIDASE ACTIVITY

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INTRODUCTION: Neonatal screening for biotinidase deficiency (BD) is mandatory in Brazil since 2012. Our group has been studying the mutational profile of BTD gene in Brazilian individuals detected by neonatal screening since then, and has already published the results for 72 patients (Borsatto et al. 2014 and 2017).
OBJECTIVES: To provide an update of the genetic diagnosis of BD in Brazil, including the results by Borsatto et al. 2014 and 2017.
METHODS: One hundred and thirteen individuals were included (male=57; parental consanguinity=5), from different regions of Brazil (southeast=17, northeast=28 and south=68). Enzyme activity was available in plasma for 98/113 individuals (current normal=7, heterozygous=52, partial BD=23, borderline heterozygous/partial BD=9, profound BD=4, and borderline heterozygous/normal=3.) Genomic DNA was extracted from blood samples in EDTA or buccal epithelial cells using commercial kits followed by PCR, purification and sequencing of exons 2, 3 and 4 of the BTD gene. The reference sequence NG 00819.1 was employed to identify the variants. The software Polyphen2, SIFT and Mutation Taster were used to predict their pathogenicity.
RESULTS: Considering the whole sample, 27 pathogenic variants were identified. The most frequent were c.1330G>C (p.Asp444His), c.755A>G (p.Asp252Gly) and c.1368A>C (p.Gln456His), with allele frequency of 42%, 4% and 3%, respectively. In addition to the five novel variants published in our previous study, three novel variants were found: c.1321G>A (p.Gly441Arg), c.855G>T (p.Gln285His) and c.269T>A (p.Leu90His); all predicted to be pathogenic in silico. The BD classification according to the genotype was: heterozygous=41; partial BD=26; normal=23; profound BD=4; and undetermined=19. The classification based on genotype matched the biochemical phenotype in 69% cases.
CONCLUSION: Currently, neonatal screening for BD in Brazil mainly detects heterozygous individuals. Profound BD is rare. Although the association between genotype and phenotype is not always consistent, genetic analysis helps in the classification of borderline cases and consecutive discordant enzymatic results.

O-011 - PHASE 2/3 TRIAL TO ASSESS THE SAFETY AND EFFICACY OF LENTI-D HEMATOPOIETIC STEM CELL GENE THERAPY FOR CEREBRAL ADRENOLEUKODYSTROPHY

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OBJECTIVE: Cerebral adrenoleukodystrophy (CALD) is characterized by inflammatory demyelination leading to progressive loss of neurologic function and death. Early diagnosis and treatment are key in ensuring optimal long-term outcomes.
METHODS: Lenti-D Drug Product (DP) is an investigational gene therapy for the treatment of CALD. Boys with CALD (≤17 years) enrolled in an open-label phase 2/3 study of the safety and efficacy of Lenti-D DP underwent full myeloablation with busulfan and cyclophosphamide followed by infusion of autologous CD34+ cells transduced with elivaldogene tavalentivec (Lenti-D) lentiviral vector. The primary efficacy endpoint is the proportion of patients who are alive and free of major functional disabilities (MFD) at Month 24. The primary safety endpoint is the proportion of patients who experience either acute (≥Grade 2) or chronic graft-versus-host disease (GVHD) by Month 24. Additional assessments include engraftment failure, and changes in neurologic function score and Loes score.
RESULTS: As of April 2018, 29 patients received Lenti-D DP (median follow-up 34 months, min-max, 0.4-54.0). Of the 17 patients who reached 24 months of follow-up, 15 (88%) remain alive and MFD-free with evidence of disease stabilization. One patient succumbed to disease progression; another was withdrawn from the trial due to neuroimaging changes with no changes in neurological functioning noted. None of the other 12 patients have 24 months of follow-up (median follow-up 4.2 months, min-max, 0.4-11.7). One was withdrawn due to neuroimaging changes with no changes in neurological functioning noted and 11 remain in the study with no evidence of MFDs at last follow-up. No graft failure, GVHD, or transplant-related mortality were reported. There was no evidence of replication competent lentivirus or insertional oncogenesis. Most adverse events were consistent with myeloablative conditioning.

CONCLUSION: These data suggest that Lenti-D DP stabilizes neurologic disease progression and appears to be a promising gene therapy for CALD.

O-012 - OUR EXPERIENCE WITH GLYCOSYLATION DISORDERS AFTER STARTING WITH SCREENING AND MOLECULAR STUDIES AT THE NATIONAL NEWBORN SCREENING LABORATORY

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INTRODUCTION: Congenital disorders of glycosylation (CDG) are a group of genetic diseases caused by hypoglycosylation of proteins and lipids. Nearly 70 inborn errors of metabolism have been described due to congenital defects of glycosylation, present as clinical syndromes, affecting multiple systems and impacting nearly every organ. Symptoms of CDG are widely variable, but some are common for several CDG types, such as psychomotor retardation, failure to thrive, coagulopathies, dysmorphic features, seizures and stroke-like episodes. Isoelectrofocusing of transferrin (TIEF) is the screening test for N-glycosylation defects. Based on the TIEF pattern, protein N-glycosylation disorders have been subdivided into two groups: CDG-I caused by defects in the assembly of glycans and their attachment to proteins; and CDG-II caused by defect in the processing of the glycans. The most frequent CDG type, over 85% of cases, is PMM2-CDG. Confirmation of clinical and biochemical diagnosis of CDG-I relies on enzymatic studies followed by molecular analysis to detect underlying gene defects. We think that in our country, CDGs remain under or misdiagnosed.
OBJECTIVE: Present our experience with CDG diagnosis after we started with TIEF at the NBS laboratory.
MATERIALS AND METHODS: On November 2017, TIEF assay was started in our NBS laboratory and the neuropediatric and pediatric community was informed. Our laboratory has molecular area, so, sequencing of PMM2 gene of patients with CDG type I pattern was performed.
RESULTS: Since November 2017 to December 2018 there have been performed 49 TIEF studies, 4 CDG type I patterns has been identified and 2 CDG Type II. PMM2-CDG were confirm in 3 of the 4 patients with CDG type I pattern with known pathogenic variant in both alleles.
CONCLUSIONS: Congenital disorders of glycosylation are part of a wide group of inborn errors of metabolism. It is a challenge to confirm the diagnosis but it is very important due to it frequency and the possibility to give genetic counseling to the family. In Uruguay, the awareness of pediatric and neuropediatric community and the introduction of TIEF and molecular study of PMM2 gene, have allowed to identify and confirm the diagnosis 3 patients in a short time.

O-013 - NEONATAL HYPERTHYROTROPINAEMIA: LOOKING AT THE END OF THE CONGENITAL HYPOTHYROIDISM SPECTRUM

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INTRODUCTION: TSH based neonatal screening (NS) for congenital hypothyroidism (CH) was initially designed to detect severe forms preventing their mental impairment. Nevertheless, when TSH cutoff level is lowered a wider spectrum of disorders may be identified. In them serum determinations may show hyperthyrotropinemia (HTT) defined as a slightly elevated TSH with normal thyroxine (T4) and Free thyroxine (FT4) for the reference age values, suggesting mild and compensated CH.
It is not clear if this picture is harmful for neurocognition and no consensus is found in the literature about its management.
OBJECTIVE: To prospectively evaluate and follow up NS detected patients with HTT describing their clinical features, perinatal history, thyroid profile and images.
PATIENTS AND METHODS: We included NS detected patients referred to our center for confirmation who showed HTT (serum TSH between 9 y 20 uU/ml and normal FT4). Patients were clinically evaluated and followed by a pediatric endocrinologist. Initial thyroid serum profile was assessed in mothers and children and biochemical controls and a Tc99 thyroid scintigraphy were performed according to individual characteristics.
RESULTS: From 12-2016 to 11-2018, 34 patients were enrolled (median age (range): 14.5 days (7-30)). 62% had been exposed to iodide. All were asymptomatic. 1 presented goiter. Median (range) of initial TSH was 13.3 uUI/ml (9-20), T4 11.95 ug/dl (7.6-17.8), T4l 1.6 ng/dl (1.06-2.13), 41% had high TG levels. In 23 evaluated patients 22 eutopic glands and 1 goiter were evidenced on scintigraphy. During follow up 2 groups could be observed: a) Those with transient HTT (n: 20) that achieved normality at a median age of 1 month (0.5-11), b) Those still on follow up (N: 14): 6 with stable HTT that did not received treatment and 8 treated with LT4 on individual bases as: increasing TSH levels , goiter or decreasing thyroid hormones.
Neurologic development was always normal.

CONCLUSIONS: Neonatal HTT detected through NS represents the tail of a milder spectrum of disorders with still unknown consequences. In our cohort more than half of them were transient.Nevertheless studies have to be extended to characterize this population.

O-014 - CYSTIC FIBROSIS: A 6-YEARS EXPERIENCE OF NEWBORN SCREENING IN THE PUBLIC HEALTH SYSTEM OF SOUTHERN BRAZIL

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INTRODUCTION: Cystic fibrosis (CF) is a genetic disease of a great clinical variability. The morbidity and mortality is mostly caused by progressive respiratory impairment and gastrointestinal disorders. In Southern Brazil, the Newborn Screening (NBS) is based on immunoreactive trypsinogen (IRT) and sweat tests, medical appointment and molecular screening for the most frequent mutations in our state.
OBJECTIVE: to describe the most frequent clinical, laboratory characteristics and mutations/polymorphisms found in babies with a confirmed diagnosis of CF during the first medical evaluation.
MATERIALS AND METHODS: it was a cross-sectional and descriptive study of the newborns diagnosed with CF, screened from 2012 to 2018 by the Reference Service in NBS from Rio Grande do Sul state/ Brazil. Laboratory, clinical and genetic data were collected.
RESULTS: In total, 61 patients were included, of whom 20% had low birth weight and only 9.8% were asymptomatic at the time of the first clinical evaluation. Steatorrhea (31.1%), cough (29.5%) and meconium ileus (24.6%) were the most observed clinical manifestations and the median age at the first visit was 35 days. IRT had significantly lower values in neonates with a history of meconium ileus, and significantly higher values in patients who had the p.Phe508del mutation. The allelic frequency of the mutations found were: F508del (65.6%), G542X (4.1%), 3120+1G>A (3.3%), N1303K (2.5%), R1162X (1.6%) and others mutations (2789+5G>A, G85E, 1717-1G>A, R334W, 711+1G>A, 3191delC, R1066C, 3272-26G>A, 1812-1G>A and D1152H) with a frequency of 0.82% were also found. The genotypic frequency of the IVS8TGmTn polymorphism variants found were: TG10T7 (68.4%), TG11T7 (18.4%), TG10T9 (13.2%) and TG12T7 (1.3%). The T5 allele was not observed in these patients.
CONCLUSIONS: this work shows the importance of a NBS for CF because provides the opportunity to undertake preventive and treatment before the development of irreversible changes in the respiratory tract and other complications, contributing to quality of life and patient survival.

O-015 - AN EXPERIENCE IN MOLECULAR DIAGNOSIS IN ARGENTINEAN PATIENTS WITH CYSTIC FIBROSIS. CURRENT AND FUTURE CHALLENGES.

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INTRODUCTION: cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the transmembrane conductance regulator gene (CFTR). More than 2000 variants have been identified (www.genet.sickkids.on.ca/cftr). Since 2012 there are molecular pharmacological therapies for individuals affected of specific mutations.
AIMS: 1) Molecular diagnoses. 2) Confirm the diagnosis in children and/or young adults with clinical compatibility 3) Establish the mutation's spectrum and frequency in the CFTR gene.
PATIENTS: from Hospital de Niños/Córdoba (sections Neumonology and Gastroenterology); Assistance Program for CF; private Health institutions and centers of Córdoba and other provinces in Argentina.
METHODS: 1) PCR/heteroduplex, multiple PCR, single strand conformational analysis, gel electrophoresis with denaturing gradient. 2) Oligonucleotides/PCR conditions were designed to perform complete sequencing, 27 exons/flanking sequences/deep intronic zones. The most frequent mutations in the CFTR gene worldwide were investigated. The complete genotype was determined. If stated an incomplete or unknown genotype, the full gene analysis was performed.
RESULTS: Fifty mutations were identified, 10 with percentages greater than 1% (c.1521_1523delCTT, p.Phe508del: 51.63%; c.3909C>G, p.Asn1303Lys): 4.47%; c.1624G>T, p.Gly542*: 3.66%; c.3196 C>T, p.Arg1066Cys: 2.44%; c.2657+5G>A, 2789+5G>A: 2.03%; 2 mutations with 1.63% (c.3140-26A>G, 3272-26A>G and c.1657C>T, p.Arg553*) and 3 with 1.22% (c.1000C>T p.Arg334Trp; c.1766+1G>A, 1898+1G>A and c.3454G>C, p.Asp1152His). 142 patients with classic cystic fibrosis were defined through

2 positive sweat tests or by molecular analysis. In addition, 9 CFTR related disease by molecular diagnosis were detected. Total: 151 patients.
CONCLUSIONS: The recognition of 2 mutations in people with CFTR-related diseases (inconclusive or even normal sweat test values) confirmed the usefulness of genetic analyzes.
Molecular diagnosis was essential to investigate the genotype of the patient due to the availability of molecular therapies, thus we developed conditions to carry out the full exome sequencing by Sanger.
Challenges: -to establish the pathogenicity of a new genomic change (variants of uncertain significance), -to analyze and to understand results of next-generation massive technology (NGS), -to educate specialist physicians for young-adults, to evaluate the effectiveness of molecular treatments in patients.
Grants: Assistance Program for CF, SECYT, PICT 2010, SLEIMPN.

O-016 - NEWBORN SCREENING PROGRAM FOR HEMOGLOBINOPATHIES IN THE STATE OF YUCATAN, MEXICO.

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INTRODUCTION: Hemoglobinopathies are qualitative or quantitative alterations of globin derived from genetic mutations whose consequences can be a structural modification or reduction of the synthesis of a globin chain (thalassemias). Around 400 variants of hemoglobin are known around the world and any chain can be affected: alpha, beta, gamma or delta. In the state of Yucatan, Mexico since 2012 an expanded neonatal screening program including the identification of these genetic variants was implemented.
OBJECTIVE: To describe the frequency of hemoglobin variants found in the state of Yucatan, Mexico from 2012 to 2018.
MATERIALS AND METHODS: Descriptive and observational study of the newborn screening for hemoglobinopathies accomplished in the period from 2012 to 2018. High performance liquids chromatography and isoelectric focusing were used to analyze blood samples obtained by heel puncture and collected on filter paper.
RESULTS: 117,732 newborns (NBs) were screened and 697 were detected with a hemoglobin variant (686 carriers and 11 cases). Variants found were: 564 HbS (81%), 103 G-Philadelphia (15%), 18 HbC (2.6%), 4 β-variants (0.5%), 4 α-variants (0.5%) and 3 HbD (0.4%). The eleven affected NB cases correspond to: sickle cell disease (8), β-thalassemia (2) and HbC (1).
CONCLUSIONS: The frequency of abnormal variants found in the state of Yucatan is 0.6%, being sickle cell disease the most prevalent one (1: 11,773 NBs).

O-017 - EXPANDED NEWBORN SCREENING IN CHILE (26 CONDITIONS). RESULTS OF A PILOT PROGRAM.

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INTRODUCTION: Since 1992, Chile implemented a national program of Newborn Screening (NBS) for Phenylketonuria (PKU) and Congenital Hypothyroidism (CH), preventing intellectual disability in more than 2,500 people. In 2015, the Ministry of Health (MH) of Chile proposed to expand the number of pathologies and in September 2017 INTA started the Pilot Program (PP) to screen 26 pathologies. The first stage of the PP was initiated at Hospital San Juan de Dios (HSJD), which runs the regional laboratory of the national PKU-CH program.
OBJECTIVES: To present the implementation and results of the PP of NBS for 26 pathologies.
MATERIALS AND METHODS: INTA trained medical and laboratory team of HSJD in preanalytical, analytical and postanalytical processes of the expanded NBS and analyzed samples of dried blood spots (DBS) of all the newborn at HSJD maternity. The applied techniques were: Tandem Mass Spectrometry (MS/MS), Fluorometry (FL) and Immunofluorometry (IFL). For FL and IFL commercial kits were used and for MS/MS "in house" non-derivatized technique was used.
RESULTS: Of total 4.554 DBS analyzed, 3.752 (82.4%) corresponded to newborn of term. Recall rate was 1,6% (95% for MS/MS reanalysis). Samples were taken at mean of 1,7±0, 6 days of life. Results reports were available at mean of 8,4±2, 2 days of life. Of the total samples analyzed, 2/4.554 were positive. A case of a medium chain acyl-CoA dehydrogenase deficiency (MCAD) (diagnose at 29 days of age) and the second case a Glutaric Aciduria type-1 (diagnose at: 23 days of age) could be stablished.
CONCLUSIONS: the excellent results obtained with the training of the staff of the HSJD, allowed a low recall rate and early diagnosis of 2 positive cases, and allows us to assert that this applied system can be reproduced all over the country. However, there are some challenges that must be considered within its expansion: the acquisition of adequate equipment

capabilities, preparing human resources in these technologies and to modernize the registration system to implement the PP in a national scale.

O-018 - DEVELOPMENT OF A HOME-MADE FLUOROMETRIC METHOD FOR THE MEASUREMENT OF BIOTINIDASE ACTIVITY IN DRIED BLOOD SPOTS: PRELIMINARY RESULTS.

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INTRODUCTION: Newborn screening (NBS) for Biotinidase deficiency (BD) is conducted determining the Biotinidase activity in dried blood spots (DBS) using colorimetric assays (quali or quantitative) or fluorometric methods (FM). Colorimetric methods (CM) are the most widespread used. They measure the released p-Amidobenzoic Acid (PABA) from N-Biotinyl-PABA as a purple compound quantifiable at 540nm. FM measures the fluorescence of 6-Aminoquinoline produced by the cleavage of the susbtrate Biotinyl-6-Aminoquinoline, at 355nm/460nm. NBS for BD was implemented in the Fundación Bioquímica Argentina in 1997 using a quantitative colorimetric home-made method (Q-CM), and until Dec/2017, 1,810,521 newborns were screened.
OBJECTIVE: To present the preliminary results of the development of a home-made FM for the measurement of Biotinidase activity in DBS and the comparative results regarding to the in-house Q-CM used in routine.
MATERIALS AND METHODS: Biotinyl-6-Aminoquinoline (Hangzhou Sage-Chemical) 27.0 mM was prepared in absolute ethanol. DL-Dithiotreitol (Hangzhou Sage-Chemical) 13.0 mM was prepared in potassium phosphate buffer 0.15 M, pH=6.5. Biotinidase calibrators in DBS were prepared following an own protocol developed in 1999, and their activities expressed in nmol 6-Aminoquinoline/min.ml serum, were assigned against a 6-Aminoquinoline (Aldrich) calibration curve. Measurements were made in black 96-microwell plates (Greiner Bio-One) in a Victor2 Fluorometer (PerkinElmer). Control materials were prepared in the laboratory. Newborn samples were obtained from daily routine. Assay protocol: 1/8" discs impregnated with blood were eluted and incubated 4 hrs at 37°C with 50 µl of phosphate buffer 0.15 M, pH=6.5, containing Biotinyl-6-Aminoquinoline (0.675 mM) and Dithiotreitol (1.5 mM). The reaction was stopped adding 200 µl of absolute ethanol. After 30 minutes, plates were centrifuged and measured at 355nm/460nm.
RESULTS AND CONCLUSIONS: The FM developed resulted analytically and technically reliable and robust. It was linear (r=0.984) in the Biotinidase range evaluated (0.400-5.000) and precise (CV=8.8 y 5.8 % at 0.441 y 3.439 nmol/min.ml serum, respectively). It became slightly more expensive than the Q-CM developed in house, however, its technical simplicity (two reagent dispensing steps against five, without needing to transfer supernatants for measurements), and the higher sensitivity of the fluorometric measurements, support its implementation in routine. FM and Q-CM showed an acceptable newborns results correlation (r=0.805), but more data are needed for more significant results.

O-019 - HEMATOCRIT AN UNCONTROLLABLE VARIABLE IN NEWBORN SCREENING?

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Dried blood spots (DBS) are valuable samples for newborn screening laboratories. Although there are many advantages in using these materials, the hematocrit parameter remains an uncontrollable variable. Cutoff values for newborn screening determinations are based on an average hematocrit value (55%).
OBJECTIVE: to study the hematocrit variable influence on neonatal screening results and analyze the impact on outcomes.
We analyzed 1124 samples from 2 newborn screening laboratories (CEMIC-Hospital Garrahan), from preterm and term infants (gestational weeks 25-41), with or without hospitalization.
Using 3.2mm punch in a plate with Sodium Lauryl Sulfate (1.7 g/L) to calculate the hemoglobin value(spectrometry method) and applying a factor of 3.2 hematocrit was estimated. We design typical curve and 3 controls. 114 values of neonatal blood counts corresponding to the date of extraction of the DBS, the method was compared (R2: 0.9143).
TSH, Immunoreactive Trypsin (IRT) and 17OHProgesterone determinations were performed with MPBiomedicals and Perkin Elmer(DELFIA) reagents. Results were evaluated without and with hematocrit correction. Patients who exceed the cut-off value were recited for a new confirmatory sample.
183 samples (without correction) exceeded the cut-off value proposed by each laboratory: 49 for TSH; 44 for IRT; 90 for 17OHProgesterone. Three confirmed pathological patients were included.
Using the hematocrit estimation, only 18(36.7%) of 49 patients who exceeded TSH cut-off value without estimation had to be recalled; IRT 25(56.7%) of 44 patients and for 17OHProgesterone 39(43.3%) results from 90 patients were

higher than cut-off without estimation. Pathological samples continued to exceed the cut-off value.
If hematocrit correction had been used, only 82(44,8%) patients would have been recalled, due to a lower percentage of the DBS globular package. The average of hematocrits the 82 samples was 50.3% and median 51.5%, 101 samples that did not exceed the cut-off value, mean 39.9% and median 41.6%. The estimation of hematocrit would allow the correction of volume in the DBS sample, being this very simple to calculate.
We suggest the use of hematocrit estimation for samples that exceed the cutoff value. Lowering the percentage of recitations would avoid the anguish that causes to the family the recalling for confirmation for false positive results.

O-020 - RESIDUAL NEWBORN SCREENING SAMPLES: HOW LONG ARE THEY USEFUL FOR RETESTING WHEN STORED IN UNCONTROLLED CONDITIONS?

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INTRODUCTION: The main justification for retaining residual newborn screening (NBS) samples is to document that a specimen was collected, received, and properly analyzed; and to make available a suitable material for retesting when a previous NBS result must be validated. Reanalysis of the original dried blood spot (DBS) specimen may be the only way to ascertain and document if a specimen mix-up or others events have taken place. However, little or inconsistent information is available about how long residual DBS are useful for retesting, especially when storage is made in uncontrolled conditions (UCC) of temperature and humidity.
OBJECTIVE: To present the results of retesting DBS from newborns diagnosed with Phenylketonuria (PKU), Congenital Hypothyroidism (CH), Cystic Fibrosis (CF), Galactosemia and Congenital Adrenal Hyperplasia (CAH) in the period 1995-2017, stored in UCC, in order to demonstrate how long they are useful to reconfirm a previous abnormal NBS result.
MATERIALS AND METHODS: DBS from newborns with PKU (94), CH (71), Galactosemia (157), CF (68) and CAH (141) collected since 1995 until 2017, stored in cardboard boxes at room temperature in UCC of humidity were retested for Phe, TSH, IRT, Galactose and 17OH-Progesterone. Results were compared to those obtained at the NBS time.
RESULTS: 90 % of DBS with Phe in the range 6-20 mg/dl stored since 2005 onwards kept a concentration > cut-off (2.5 mg/dl). 96 % of specimens with TSH > 200.0 µUI/ml showed abnormal values (≥ 11.0 µUI/ml) after 12 yrs of storage. 86 % of samples with IRT in the range 150-250 ng/ml presented values above the cut-off (70.0 ng/ml) after 3 yrs. On average, Galactose decreased only just 15 % in samples stored during 20 yrs, but it showed a rise in samples from newborns diagnosed with UDP-Gal-4-Epimerase Deficiency, probably due to the UDP-Galactose hydrolysis. 17OH-Progesterone kept abnormal values after 10 yrs when their initial values were ≥ 34 nmol/l.
CONCLUSIONS: As a general rule, DBS stored in UCC showed a decrease in the analytical recovery proportional to the storage time, being the magnitude of this effect highly dependent on the analyte stability. Analytes like Phe, TSH, Galactose and 17OHP-progestrone can keep abnormal values for more than 10 yrs.

O-021 - SCREENING FOR CONGENITAL IMMUNODEFICIENCIES - SCID, AGAMAGLOBULINEMIA AND OTHER T AND B CELL LYMPHOPENIAS IN BRAZIL

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INTRODUCTION: Congenital immunodeficiencies are a group of diseases very often considered pediatric emergencies because of their ability to compromise severely newborn's health. Those are usually associated with a high mortality rate when undiagnosed and receive early treatment. In general, they are caused by genetic changes with an autosomal recessive or X-linked pattern.
OBJECTIVE: Implementation of a screening exam for early identification and/or monitoring of patients with congenital immunodeficiencies, SCID, agammaglobulinemia and other T-cell and B-cell lymphopenias - also known as primary immunodeficiencies.
METHOD: DNA isolation in 3.2 mm dried blood spot samples (DBS) followed by amplification using RT-qPCR Multiplex (Real Time Quantitative PCR) technique. Quantification of TREC (T Cell Receptor Excision Circles) and KREC (Kappa-Deleting Excision Circles) amplified fragments by RT-qPCR in DNA samples extracted from DBS.
RESULTS: Sample from 1200 geographically dispersed patients were selected, associated with two undetectable positive controls for the TREC and KREC targets - previously validated - and amplified by the RT-qPCR methodology. Through statistical analysis the minimum healthy cut-off value of 35 copies/µL of TREC and KREC in blood was established. None of the 1,200 patients was classified as undetectable or inferior to the internal cut off. The assay was validated and established routinely in the laboratory. During the period, a

patient with two independent collections with an interval of two weeks had KREC amplification profile classified as undetectable, indicating the need for cautious medical monitoring and follow up investigation by other techniques.
CONCLUSIONS: DNA extraction steps, amplification and analysis were successfully optimized for the absolute quantification of TREC and KREC copies in DBS samples using RT-qPCR. The result of the TREC and KREC assay has shown to be highly reproducible, robust and low cost, associated with satisfactory profiles of sensitivity and specificity. The test was also incorporated in the routines of different neonatal screening tests, since it is possible to be performed in the same sample harvested for these purposes.

O-022 - PHENYLALANINE HYDROXILASE (PAH) GENOTYPING IN PKU ARGENTINE PATIENTS

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INTRODUCTION: Phenylketonuria (PKU) is an inborn error of phenylalanine metabolism that leads to severe mental retardation and is predominantly caused by mutations in the PAH gene.
OBJECTIVE: To characterize genotypically a cohort of Argentinean patients
METHODS: Genotyping was carried out in 103 Argentine PKU patients from 90 unrelated families. The cohort included 12 pair of siblings that had an identical phenotype and genotype and 1 pair of discordant brothers that shared only one common allele.
RESULTS: 101 patients were completely characterized and in 2 only 1 mutation was found. 51 known pathogenic mutations and 3 new variants were found by sanger sequencing. 9,7% of individuals were homozygous. Mutations were distributed along the 13 exons and concentrated in exon 7 (30%), exon 11 (10%), exon 2 (8%), exon 12 (6%) and exon 10 (6%). 64% were missense, 8% nonsense, 14% frameshift and 12% abnormal splicing. 65% were placed in the enzyme catalytic domain, 15% in the regulatory and 8% in the oligomerization zone. Regarding allele frequency (AF) calculated excluding one of the coincident siblings, the 9 more frequent mutation that accounted for 57% of 179 alleles were: p.R261Q (AF=10.6%), c.1066-11G>A (AF=9,5%), p.R408W (AF=8,3%), p.Y414C (AF=5,5%), p.A403V (AF=5%), p.V388M (AF=5,0%), p.R158Q (AF=5,0%), p.L48S (AF=4,0%) and p.I65T (AF=4,0%).
Predicted phenotype was assigned by Guldberg activity value (AV) and compared with the phenotype based in tolerance to Phe intake assessed between 4 and 7 years of age under stable conditions. According to tolerance, 31% were hyperphenilalaninemias (HPA), 16.5% were mild-PKU, 29% moderate-PKU and 23.5 % severe-PKU. Overall concordance with predicted phenotype was 63% with coincidence between prediction and clinical assessment of 93% in HPA, 73% in mild PKU and 63% in severe patients. Nevertheless a weak concordance (21%) was found in the moderate PKU group where AV prediction was milder that the one assessed by tolerance. In this group 68% of patients harboured p.R261Q and p.V388M mutations.
CONCLUSION: PAH gene mutation spectrum in our cohort is highly heterogeneous, with predominant mediterranean influence (mainly Spanish), but with differences with other Latin-American countries.The finding of R261Q and V388M mutations influenced the phenotype prediction.

O-023 - MSUD GENOTYPE AND PHENOTYPE CHARACTERIZATION IN CHILE

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INTRODUCTION: Maple syrup urine disease (MSUD, OMIM 248600) is an autosomal recessive inherited metabolic disease caused by deficient activity of the branched-chain α-keto acid dehydrogenase (BCKD) enzymatic complex. BCKD is a mitochondrial complex encoded by four genes: BCKDHA, BCKDHB, DBT, and DLD. MSUD is predominantly caused by mutations in the BCKDHA, BCKDHB, and DBT genes encoding the E1α, E1β, and E2 subunits of the BCKD complex, respectively.

OBJECTIVE: To characterize the genetic basis of MSUD by identifying the point mutations in the BCKDHA, BCKDHB, and DBT genes in a cohort of Chilean MSUD patients and to describe their phenotypic heterogeneity.
METHODS: Descriptive cross-sectional study with 18 MSUD patients involving PCR and sequencing.
RESULTS: We identified eight mutations in these 18 patients analyzed, 75% encoded in BCKDHB gene. Four new pathogenic mutations: p.T338I (BCKDHA), p.G336S, p. P240T (BCKDHB) and p.G406D (DBT). Exon 6 included the majority of mutations (41.7%) and 88% of mutations were missense. Eleven cases were homozygous. The majority of subjects (94%) had the classic phenotype with diagnosis at 16.5±7.3 days. We found no genotype and phenotype correlations.
CONCLUSION: The most frequent mutations in our Chilean MSUD population were p.I241K and p.200*, both of Spanish origin. Most of the pathogenic variants were encoded in BCKDHB gene, as described in literature. It is not possible to predict phenotype by detecting the genotype. Four new pathogenic mutations were identified in our population.

O-024 - GENETIC HYPERPHENYLALANINEMIA AND MAPLE SYRUP URINE DISEASE IN BRAZILIAN PATIENTS: DEVELOPMENT OF DIAGNOSIS USING GENE PANELS AND NEXT-GENERATION SEQUENCING

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BACKGROUND: Genetic hyperphenylalaninemia is caused by defects in phenylalanine hydroxylase gene that leads to phenylketonuria (PKU) or in its co-factor, causing tetrahydrobiopterin (BH4) deficiency, or by DNAJC12-associated variants. Maple syrup urine disease (MSUD) is characterized by variants in the alpha-keto acid dehydrogenase complex.
AIMS: To develop a genetic diagnosis for PKU, BH4 deficiency and MSUD using a gene panel by next-generation sequencing.
METHODS: Thirty-four (female=18) non-related patients with biochemical diagnosis of PKU (n=19), BH4 deficiency (n=3) or MSUD (n=12) were included. Eleven PKU and one MSUD patient had previous Sanger sequencing (one allele found= 7 patients; two alleles found= 5 patients). DNA samples were sequenced in a panel containing genes related to PKU (PAH), BH4 def. (PTS, GCH1, GCHFR, QDPR, PCBD1 and SPR) and MSUD (BCKDHA, BCKDHB and DBT) in Ion Torrent platform. The analysis was blinded. Variants were filtered and classified by Enlis Genome Research software.
RESULTS: This approach was able to identify both variants in 28 of 34 patients. In only one PKU patient with genotype p.[(Arg408Trp)];[(Arg241His)] by NGS and p.[(Arg408Trp)];[(Arg408Trp)] by Sanger there was disagreement. Seventeen variants were found: four in PAH gene (one novel, p.Pro175Arg); five in PTS gene variants (two novel: p.Asn45Ile and p.Thr135Ala). In MSUD related genes, eight variants were found in BCKDHB gene (5 novel, p.Gly131Val, c.79_80insCTGGCGCGGGG, p.Ile160Phe, p.Asn176Lys and p.Leu326Pro), one in BCKDHA gene (novel, p.Tyr413His) and 3 in DBT gene.
DISCUSSION: In patients with one or none allele found or discordant genotype, it is possible that the polymorphisms in primers sites or limitations of the technique are the explanation for the discrepancies. All the results will be validated by Sanger sequencing. Further analysis will be performed in patients without the two alleles identified.
CONCLUSION: Next-Generation Sequencing is a fast and effective method to elucidate diseases with common clinical and biochemical symptoms.

ABSTRACTS SELECTED FOR POSTER PRESENTATION (IEM)

P-001 - TRANSITION FROM CHILD TO ADULT IN PATIENTS WITH INBORN ERRORS OF METABOLISM (IEM): OUR EXPERIENCE WITH PATIENTS DERIVED FROM PEDIATRIC HOSPITAL

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INTRODUCTION: Advances in diagnosis and treatment of IEMs have improved their prognosis and there are more patients who reach adulthood and need to be transferred to an appropriate center for their age.
OBJECTIVE: To describe our experience in the care of adolescents and adults with IEM derived from a pediatric hospital: population characteristics, strengths and difficulties encountered in monitoring, challenges to be addressed.
MATERIALS AND METHODS: Review of medical records (MR). We describe filial and anthropometric data, statistics of consultations and interventions carried out.
RESULTS: Our team consists of a specialist doctor and a nutritionist.
From 2011 to 2018, 20 patients have been referred: 65% women, 35% men.
Age first consultation: 18.9 ± 2.55 years
BMI: 24.7 ± 4.86 kg/m2
Pathologies: - 20%: alteration of urea cycle
- 15%: glycogenosis III and phenylketonuria

- 10%: propionic acidemia, fructose intolerance/fructosemia, glycogenosis IA
- 5%: deficit of HMGCoALiasa, deficit of betaketothiolase, isovaleric acidemia and homocysteinuria
Progression of referrals 2011-2018: from 1 to 20 patients. 20% did not attend to consultation during 2018.
Consultations/patient/year: between 1 and 2.93.
Interventions: calcium supplementation in 40% for not meeting requirements.
Strengths: - 100% understand their illness and know treatment guidelines.
- 100% brought copy of pediatric MR
- 10% had hospitalization due to metabolic decompensation of infectious origin.
- Fluid contact with derivative pediatricians.
Difficulties: - 20% bring dietary records
- 20% discontinuously comply dietary guidelines (according to availability of formulas and aproteic foods).
- We don´t have a specialized laboratory. Patients do analysis in pediatric center.
- Up to 2017 there was a neurologist specialized in IEM. Today patients must be referred.
- Difficult compliance with emergency letter on guard with metabolically decompensated patients.
Challenges to address: - Chronic complex disease in the context of adolescence.
- Physiological or pathological situations that appear concomitantly: pregnancy, overweight (30%), obesity (10%), dyslipidemias
- Contraception and incorporation of family planning (Genetic Counsel).
CONCLUSIONS: The experience in the transition has been positive and opens the expectation of interaction between pediatric and adult hospitals, serving as experience for other transitions of other chronic diseases.

P-002 - METABOLIC CHARACTERIZATION OF THE POPULATION WHO ASSIST SOME DISABILITY ATTENTION CENTERS OF THE CITY OF CALI AND AREAS OF INFLUENCE

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INTRODUCTION: Inborn errors of metabolism (IMD) are biochemical alterations of genetic origin due to errors in the structure or function of protein molecules. The majority of these EIM give rise to diseases that produce alterations in the physical, mental and other structural anomalies that affect the good functioning of the individual. I In Colombia, to date there is not an expanded screening program for Congenital Metabolism Diseases that allows an early diagnosis of these diseases, for this reason those affected are not identified in a timely manner, suffering the serious consequences of the disease.
OBJECTIVE: Metabolically characterize the population that attends disability care centers of the City of Cali and areas of influence
METHODOLOGY: descriptive, observational, non-experimental, prevalence study, in 1000 patients of all ages, attending different disability care centers of the municipality. The presence of EIM was determined through biochemical tests (amino acids, carbohydrates and mucopolysaccharides) and data analysis and statistical tests were performed.
RESULTS: 22.6% of the patients were positive for any of the tests carried out in the screening; of these patients, 88 were female and 138 male, with ages between 0 months and 66 years. In the amino acid analysis, 165 patients had positive results for this test (16.5%): 34% were positive for the Dinitrofenilhidracin + Ferric chloride test, 19% positive for Dinitrofenilhidracina test and 15% positive for Ferric Chloride. Also 11% of the 1000 patients analyzed were positive for the analysis of carbohydrates by the Benedict test and 1.8% of the patients had a positive result in the analysis of mucopolysaccharides: 15 patients tested positive for cetyl pyridium chloride, 1 for acid albumin and 2 for both tests.
CONCLUSION: A positive result in one or several diagnostic tests indicates that there is a probability that the patient has a metabolic disease. Early diagnosis and appropriate and timely treatment of these diseases in the city could allow patients to lead a better quality of life, reducing the consequences and damage to organs and systems, which impacts the morbidity and mortality attributed to this cause.

P-003 - SCREENING FOR 9 COMMON JEWISH GENETIC DISEASES IN 441 ASHKENAZI JEWS IN ARGENTINA

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INTRODUCTION: One in five individuals of Ashkenazi Jewish descent carry a mutation for a recessive disease.
There is little information available about the frequency and prevalence of inherited disorders in this population in

Argentina, despite being the sixth largest Jewish community in the world and the largest in Latin America.
OBJECTIVES: Screening for 9 common Jewish genetic diseases in Argentinian Jews who have at least one Ashkenazi grandparent.
The project aims at raising awareness about the high prevalence of Ashkenazi Jewish genetic mutations and diseases.
MATERIALS AND METHODS: During 2018, Ierusha Foundation offered several educational lectures in Jewish organizations throughout Buenos Aires, where attendants could get a free non invasive genetic testing through buccal epithelial cells.
The results were returned by a geneticist, who provides genetic counseling.
A total of 441 samples were screened for the following 9 monogenic disorders: Fanconi Anemia (FANCC), Cystic Fibrosis (CFRT), Glycogen storage disease type 1 (G6PC), Maple Syrup Urine Disease (BCKDHB), Tay Sachs (HEXA), Canavan (ASPA), Gaucher (GBA), Hyperinsulinism (ABCC8), Niemann Pick (SMPD1).
The samples were analyzed at Genia Molecular Genetics Laboratory, using the DNeasy® Blood & Tissue Kit from Qiagen® for extraction and purification of genomic DNA. The amplification was carried out through a pool of primers designed with AmpliSeq ™ technology and the sequencing of the amplified regions through Post-LightTM Ion Semicondutor Sequencing (Next Generation Sequencing).
RESULTS: Among the 441 samples screened, 138 mutations were found (31,29 %): CFTR: 69 cases (50 %), GBA: 40 (28,98 %), ASPA: 11 (7,97 %), G6PC: 10 (7,24 %), HEXA: 12 (8,69 %), ABCC8: 6 (4,34 %), BCKDHB: 5 (3,62 %), SMPD1: 3 (2,17 %), FANCC: 1 (0,72%).
21 cases were double heterozygous and 5 cases homozygous: 4 CFTR, 1 GBA
CONCLUSIONS: The high rate of mutations detected (31,29 %) represents an incidence of 1 in 3, higher than expected in this population.
This new data about the Argentinean Jewish Ashkenazi community will contribute to the prevention of genetic diseases and provide new epidemiological information.

P-004 - NIEMANN-PICK TYPE C DISEASE IN ADULTS: UNRAVELING DIFFERENT CLINICAL PHENOTYPES

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BACKGROUND: Niemann-Pick type C disease (NP-C) is an inborn error of metabolism caused by defective intracellular transport of cholesterol. Although, early childhood and late infantile presentations are the classical presentation of the disease, more adult patients with NP-C have been described, expanding the neurologic spectrum of the disease.
Objectives To report the adult clinical phenotype of NPC among a cohort of patients with movement disorders
MATERIALS AND METHODS: Retrospective study and review of neuroimaging, neurophysiological, biochemical and molecular studies carried out in the course of 30 adult patients with NPC suspicion.
RESULTS: 14 patients were referred because of generalized dystonia with progressive cognitive decline/dementia; 11 had cerebellar ataxia with vertical ophtalmoparesis; 3 patients had dystonia without an apparent cognitive decline, but with eye ophtalmoparesis; 2 patients had a complex neurological picture with cerebellar syndrome, generalized dystonia, ophtalmoplegia, cognitive decline and pyramidal syndrome. Three out of 30 patients were confirmed to have NPC by filipin staining (1 patient required molecular analysis). Regarding clinical presentation, all positive NPC cases had VSGP with typically downward gaze palsy. None of the patients had previous history of prolonged jaundice.
CONCLUSIONS: Neurological manifestations in NPC patients are extremely variable. Better understanging of the natural history of the disease is crucial for evaluation of potential therapeutic approaches in such devastating disorder.

P-005 - CLINICAL PRESENTATION OF GLYCOGEN STORAGE DISEASE IN A REFERENCE CENTER IN SÃO PAULO, BRAZIL.

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INTRODUCTION: Glycogen Storage Diseases (GSD) are inherited metabolic disorders related to the inadequate functioning of enzymes or transporters involved in glycogen synthesis and degradation. The overall incidence is estimated at 1: 20,000 – 43,000 live births. GSDs can be divided into those with hepatic impairment, which manifests as hypoglycemia and fasting intolerance, and those with neuromuscular involvement. Some types may exhibit both manifestations. The severity of the disease ranges from mild disorders with normal lifespan to fatal cases if untreated. The treatment is based on specific diet aimed at euglycemia and prevention of metabolic disorders and complications of the disease.
OBJECTIVES: To describe the first clinical and laboratory features of patients with GSD who are followed at the Reference Center in Inborn Errors of Metabolism.

MATERIALS AND METHODS: Retrospective evaluation of physical medical records.
RESULTS: Among the 28 patients diagnosed with GSD, 12 (43%) were classified as type I and 11 (39%) as type III. Eighteen (64%) were male and 11 (39%) were children of consanguineous marriage. The median age at onset of symptoms, diagnosis, first consultation and initiation of treatment was 3 months, 19 months, 28 months and 32 months, respectively. Clinical features that led to the diagnosis were hepatomegaly (n=27), failure to thrive (n=16), neuropsychomotor development delay (n=10) and seizures (n=9). The first laboratory tests showed hypoglycaemia (n=20; mean = 41 mg/dL), hypercholesterolemia (n=22; mean = 245 mg/dL), hypertriglyceridemia (n=26; mean = 537 mg/dL), increased aspartate aminotransferase (n=24; mean = 221 U/L), increased alanine aminotransferase (n=22; mean = 129 U/L), hyperlactatemia (n=18; mean = 61 mg/dL) and metabolic acidosis (n=14). Hepatic biopsy was performed in 46% of patients and 11% underwent molecular testing. Nowadays, the median age of the patients is 19 years old and only one of them has died.
CONCLUSIONS: GSD type I is the most prevalent in our service, just as hepatomegaly is the most common manifestation. The knowledge of the clinical and laboratory characteristics of GSD's patients is fundamental for the pediatrician. Early diagnosis, estabilishment of specific diet and periodic monitoring are essential to prevent complications of the disease.

P-006 - HEREDITARY FRUCTOSE INTOLERANCE: NGS APPROACH TO IMPROVE AND CONFIRM THE GENETIC DIAGNOSIS OF BRAZILIAN PATIENTS

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INTRODUCTION: The ALDOB gene comprises 9 exons and encodes the aldolase B (E.C.4.1.2.13), a key enzyme in energetic pathways as glycolysis, glycogenesis, and gluconeogenesis. Individuals with aldolase B deficiency (hereditary fructose intolerance – HFI), an inborn error of fructose metabolism, present hypoglycemia after fructose intake, liver dysfunction and mild hepatomegaly. The analysis of the ALDOB sequence has been used to perform the diagnosis of this disorder.
AIMS: To analyze the ALDOB gene in Brazilian patients with clinical suspicion of HFI.
MATERIALS AND METHODS: Fifteen unrelated patients were analyzed by NGS in IonTorrent PGM platform (Life Technologies) with a customized panel including the exonic regions and the intron-exon boundaries of ALDOB gene. The minimal coverage was 200X. The variants found were confirmed by automated Sanger sequencing. Patients with no mutations detected by NGS were also analyzed by Sanger. The haplotype analysis was performed with LDlink suite and data of populations from 1000 Genomes project.
RESULTS: Six patients had the diagnosis of HFI confirmed (from South region: 5; from Minas Gerais-MG: 1). Three different mutations were identified: c.448G>C in exon 5 (n=6 alleles, all from the South), 360_363delCAAA in exon 4 (n=4; South=3, MG=1) and 178C>T in exon 3 (n=2; South=1, MG=1). The analyses demonstrated that c.178C>T and c.360_363delCAAA mutations present two different haplotypes each: one haplotype was present in patients from MG and other in patients from the South. In nine patients, no mutations were detected after NGS and Sanger sequencing.
CONCLUSION/DISCUSSION: The genetic profile of the patients in this study is similar to the one observed in a study including patients from other American countries (USA, Canada, Argentina). However, the frequency of mutations is different from that found in a previous study with Brazilian patients from MG in which the mutation c.448G>C was the less frequent allele found. We suggest a targeted analysis in ALDOB to detect the c.178C>T, 360_363delCAAA and c.448G>C mutations as an approach to perform the diagnosis of HIF in Brazil.

P-007 - REPORT OF TWO CASES OF MUTATION IN THE PHOSPHORYLASE KINASE (PHKA2) GENE IN CARTAGENA DE INDIAS, COLOMBIA

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INTRODUCTION: The glycogen storage disease (GSD) type IX is a rare disease of variable clinical severity that mainly affects the liver tissue. Individuals with hepatic phosphorylase b-kinase (PHK) deficiency due to mutation in the PHKA2 gene (GSD IXa) may present hepatomegaly with elevated serum transaminases, ketotic hypoglycemia, hyperlipidemia, and poor growth with considerable variation in clinical severity.
OBJECTIVE: to identify and describe the different clinical manifestations of two brothers with the same type of mutation

in the PHKA2 gene (GSD IXa), which represent the first two cases described in Colombia.
MATERIALS AND METHODS: Two children were studied, from the city of Cartagena, who according to the symptoms, findings to the physical, clinical and biochemical examinations performed in the Biochemistry Laboratory of the University of Cartagena, had high suspicion that they had some glycogenosis In addition, genetic studies were carried out at the Center for the Diagnosis of Molecular Diseases (CEDEM) in Madrid-Spain, through massive sequencing analysis, bioinformatic analysis, bioinformatic analysis of mutations and confirmation by sequencing of Sanger.
RESULTS: we present the cases of two siblings, who according to the symptomatology, clinical, biochemical and genetic tests carried out, get to diagnose and confirm that they suffer from GDSIXa with mutation c.919-2A> G in hemicigosis of the PHKA2 gene, the which represents a new variant of this gene.
CONCLUSIONS: the development of the so-called next generation sequencing technologies (NGS), such as those used in this study, is currently the method of choice to confirm the diagnosis of GSD, avoiding the use of a test invasive as the liver biopsy.

P-008 - LONG TERM FOLLOW UP OF LIVER TRANSPLANTATION IN PATIENTS WITH GLYCOGEN STORAGE DISEASE TYPE I IN A TERTIARY HOSPITAL IN BUENOS AIRES, ARGENTINA

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INTRODUCTION: Glycogen storage disease type I(GSDI) is an inborn error of carbohydrate metabolism. GSDI affects liver and kidney. Additionally, GSDIb have impaired neutrophil function and inflammatory bowel disease. Treatment is based on avoiding hypoglycemia and its complications.
OBJECTIVES: Descriptive analysis of GSDI 4 patients who underwent liver transplantation (LT) indications and outcome.
PATIENTS AND METHODS: Retrospective cases were obtained from Garrahan records. From a total of 32 GSD, we analyzed 4 GSDI patients who underwent LT between 2006 and 2016.
RESULTS: We described 4 GSD patients: 3 Ib and 1 Ia. GSD Ib have symptoms at an earlier age than Ia (7 months vs 16). All GSDIb had prior to LT neutropenia and inflammatory bowel disease. None had renal involvement.
Median age at LT was 9.5 years (7-12 years). All received cadaveric liver transplant. Immunosuppressive regime consisted of steroids, tacrolimus,sirolimus,mycophenolate and cyclosporine. The anatomical pathology of liver explant revealed adenomas, steatosis, fibrosis and hepatocellular carcinoma (1).
The indication for LT included hepatic adenomas (3) and poor metabolic control (3). Time follow-up was 5.5years (2-12). Global survival was 100%. Metabolic control normalized in all patients and in those with growth-retardation, catch-up was achieved post transplant (3/3).
Short-term complications (<1 year) were: hypertension (1), CMV infection (2) tacrolimus encephalopathy(1), acute liver rejection(2), acute renal insufficiency (1), vena cava thrombosis (1) and lymphoproliferative disorders(1). Long-term complications in GSDIa was obesity and microalbuminuria.In GSD Ib were proteinuria, nefrocalcinosis, microalbuminuria, thyroid carcinoma, neutropenia. Renal dysfunction developed after LT: microalbuminuria(2) and proteinuria (1).Persistent neutropenia was the most important complication(3/3).Two persisted with splenomegaly and thrombocytopenia.
CONCLUSIONS: LT allows to correct intolerance to fasting, release the diet improving the quality of life and reduce the risk of malignancy.However LT is not an innocuous procedure, it can bring with it complications related to the procedure, use of immunosuppressive medication adding comorbidity.
The benefit of LT depends on the extent of extrahepatic manifestations.Renal involvement is a documented complication in LT.The use of nephrotoxic medications has been proposed as one contributing factor added to the disease progression.It remains unclear why neutropenia improves after LT in some patients and persists in others.

P-009 - HEPATIC GLYCOGEN STORAGE DISEASES ARE ASSOCIATED TO MICROBIAL DYSBIOSIS

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INTRODUCTION: Glycogenosis (GSD) are diseases with a defective glycogen pathway. Manifestations like obesity, liver and inflammatory bowel diseases (IBD) are present in GSD and associated with dysbiosis. GSD treatment relies in large amounts of uncooked cornstarch (UCCS) and restriction of simple sugars. Host genetics and diet are the two main drivers of the gut microbiome.
OBJECTIVES: To characterize the faecal microbiome of GSD patients compared to healthy controls (HC), and its association with food intake and faecal pH.

METHODS: Cross-sectional, observational, controlled study with convenience sampling approved by local Research Ethics Committee. GSD patients (n=24; Ia=14, Ib=05, III=01, IX=03) on treatment with UCCS were recruited from the HCPA, Rio Grande do Sul (RS), Brazil, and compared with 16 unrelated HC, recruited among the RS population. Patients and HC were paired by sex and age (±1y). All participants must be ≥3 years of age and not on antibiotics. Patients and controls had their faecal microbiota evaluated through V4-16S rRNA gene sequencing. Microbiome diversity and structure were evaluated trough alpha and β diversity/PERMANOVA and LefSe/LDA analysis. Faecal pH, mean daily nutrient intake and relevant clinical data (IBD, obesity and current medications) were correlated with the gut microbiome.
RESULTS: Patients had higher intake of UCCS, prevalence of IBD (n=04/24) and obesity/overweight (n=18/24) compared to controls (n=0 and 06/16, respectively). To patients, the main calorie source was UCSS, and fat, calcium, sodium, and vitamin intake was lower. There were differences (p=0.001) among usage of ACE inhibitors (patients=11, controls=0), multivitamins (patients=22, controls=01), and mean faecal pH (patients=6.23; controls=7.41). Patients had lower diversity (average Shannon index, patients=2.48, controls=3.49) and distinct microbial community structure, which differed by the presence/absence of taxa (r^2=0.182; p=0.003) and their relative abundances (r^2=0.166; p=0.001). Several genera differed between the groups. The operational taxonomic unit abundance was influenced by faecal pH (r=0.77; p=6.8e-09), total carbohydrate (r=-0.6; p=4.8e-05) and simple sugars (r=0.057; p=0.00013).
CONCLUSION: GSD patients presented intestinal dysbiosis, showing low faecal microbial diversity. Several taxa previously associated with inflammatory bowel disease and obesity were present in cases and may contribute for phenotypic variation in patients. The main driver of these differences is unknown.

P-010 - A CLINICAL TRIAL EVALUATING THE USE OF UNCOOKED BRAZILIAN SWEET POLVILHO VERSUS UNCOOKED CORNSTARCH IN GSD IA: PRELIMINARY RESULTS

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INTRODUCTION: Hepatic Glycogen Storage Diseases (GSD) are a group of genetic diseases characterized by fasting intolerance associated hypoglycemia. The most commonly used treatment strategy is the frequent administration of uncooked cornstarch (UCCS). Although this treatment is successful, the adherence rate is not optimal and the use of large amounts of UCCS can lead to overweight and to a decrease in patients and caregivers quality of life, due to the need of taking the starch during the night. In-vitro studies by our group suggested a longer glucose release from uncooked sweet polvilho (SP), a product extracted from cassava, than from UCCS.
OBJECTIVE: To evaluate the short-term efficacy and safety of the use of SP in adult GSD Ia patients.
METHODS: A randomized, double-blinded, phase I/II crossover study is being conducted, comparing the use of UCCS and SP (100 grams of starch in 200 ml of water). The inclusion criteria are: age ≥16 years, being treated with UCCS and having a genetic diagnosis of GSD Ia. Ten patients were assigned to participate in two sequential overnight sessions. Each individual stays two nights hospitalized: one night using UCCS and one night using SP. After ingestion of each randomized starch, subjects are followed during the night and procedures are stopped after 10 hours of fasting or anytime if patient presents hypoglycemia (plasma concentrations <70 mg/dL). From an intravenous catheter, blood samples are taken every hour for glucose, lactate and insulin concentrations.
RESULTS: To date, four individuals [three male (21 to 26 years old) and one female (21 years old)] had finished two starch load procedures. Mean body mass index of participants was 29.53 (25.2 to 37.88). The SP kept the normoglycemia for a period at least equal to the UCCS. No distinction was made between the two randomized products regarding palatability. One subject presented severe hyperlactatemia (≥5,0mmol/l) during SP load procedure. No patient presented serious adverse events.
DISCUSSION AND CONCLUSION: Preliminary clinical data showed herein suggest this product may be a good alternative for treatment of GSD. Other six individuals will be evaluated until the completion of this protocol and accomplishment of statistical analysis.

P-011 - GLYCOGEN STORAGE DISEASE TYPE XI WITH AN UNREPORTED VARIANT IN SLC2A2: CASE REPORT

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INTRODUCTION: Glycogen storage disease type XI or Fanconi-Bickel Syndrome, is a rare disease whose incidence is unknown; due to a pathogenic variant in SLC2A2 (3q26.2-q27) with an autosomal recessive inheritance pattern, finding a deficiency in GLUT2 transporters. A wide spectrum of pathogenic variants in SLC2A2 has been reported, however, they have not been associated with any specific population.It is characterized by hepatorrenal glycogen accumulation, proximal renal tubular dysfunction and impaired glucose and galactose usage.Clinical manifestations appear from the first months of life, including growth retardation, polyuria, rickets, and subsequently hepatosplenomegaly.
We present a case of Glycogen storage type XI with a compound heterozygous variant of SLC2A2.
CASE REPORT: Male patient, known by the Genetics Department since 2 years old; product of the second pregnancy of non-consanguineous parents. Important family history: paternal aunt with breast cancer, two uncles and paternal grandfather with Diabetes Mellitus. Full-term pregnancy ended via normal vaginal delivery; weight and height suitable for gestational age. In the first year of life, growth retardation and development delay were identified, as chronic gastroenteritis, prominent abdomen due to hepatomegaly, hypoglycemia and recurrent infections. At physical examination the patient was found hypotonic, dolichocephalic, with prominent forehead, oval face, prominent cheeks, "doll face", long eyelashes and hepatomegaly. Neonatal screening results, sweat electrolyte tests, and brain TC Scan, within normal parameters. Sequencing analysis of G6PC, does not report pathogenic variants.
At 3 years old, hypokalemia and hypocalcemia was present, as well as metabolic acidosis. With the suspicion of Fanconi syndrome, sequencing of the SLC2A2 gene in peripheral blood sample was requested.
RESULTS: Two heterozygous variants were identified: c.609_612delTCAG (p.S203Rfs*47) in exon 5, probably a pathogenic variant not reported previously. The second identified variant is c.1250C> T (p.P417L) in exon 10, described in 1999 as a missense variant in homozygous state.
CONCLUSIONS: This work presents a case of Glycogen storage type XI, in heterozygous compound state, whose probably pathogenic unreported variant (p.S203Rfs * 47) is known to generate a reading frame shift and a stop codon, translating a truncated SLC2A2 protein.

P-012 - PARENTAL PERCEPTION OF THE USEFULLNESS OF EDUCATIONAL ACTIVITIES TO ENCOURAGE ADHERENCE TO PROTEIN/AMINOACID- RESTRICTED DIETS FOR PATIENTS WITH INBORN METABOLIC DISEASE AND THEIR FAMILIES

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INTRODUCTION: Inborn Metabolic Disease(IMD) patient's relatives require a high level of understanding and special training for the preparation and comply of these strict diets. Since2011 educational and culinary workshops were planned to anticipate difficulties to encourage adherence. After 7years of performing these activities an evaluation was made to verify the usefulness.
OBJECTIVES: To describe parental perception of the utility of educational workshops for IMD patients and their families.
METHODS: Metabolic dietitians designed a questioner orientated to relatives of children treated with protein/amino-acids restricted diets followed at our hospital from 2011-2018. Inclusion criteria: relatives attending +3workshops and at least one during 2017-2018.
The survey consisted of 15 questions based on possible changes and knowledge acquired about: cooking skills, nutritional habits (variety of menus /planning of daily menus and for special occasions, etc.), difficulties in attending and useful overview of these activities.
RESULTS: 71 families participated at least at one of the 54 workshops performed during these 7 years.
During 2017-2018, 9 workshops were realized and 28 families attended 1 or more. 20 families met with the inclusion criteria, and answer the survey 85% (17).
All participants made learned recipes more than once, referring satisfaction with the final product (94%).The explanation and demonstration of the step-by-step of the recipes and the elaboration with their own hands during the workshops made it easy to replicate them at home.
More than 80% of the participants reported having learned new concepts about the low protein / amino-acid diet during the workshops and that had facilitated compliance, helping them to elaborate a greater variety of menus and handling special occasions.
The most frequent difficulty to attend workshops is distance to the hospital (40%) being 50% the families that have been invited and didn`t concur.
Meeting other parents and children with similar diets(100%), considering their experience useful for others(35%) and being enthusiastic with new recipes(35%) make them feel encourage.
CONCLUSIONS: The answers on the questionnaires showed positive relatives perception of the usefulness of the program. Involvement of parents in the treatment is crucial to improve adherence. Metabolic team should be able to empower parents in participating actively on their children treatment.

P-013 - LIVER TRANSPLANT IN PEDIATRIC PATIENTS WITH INBORN ERRORS OF METABOLISM: IMPACT ON NUTRITIONAL TREATMENT

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INTRODUCTION: Liver transplant (LT) is a therapeutic alternative for different inborn errors of intermediate metabolism (IEM), whose treatment is based on specific dietary restrictions and supplementation with medical foods. This therapy can significantly improve the quality of life of those patients who suffer severe manifestations of the disease or metabolic decompensations that threaten life despite adequate medical and nutritional treatment.
OBJECTIVES: To describe the nutritional treatment, feeding route and growth of pediatric patients with IEM pre and post liver transplantation.
METHODS: A retrospective review of 9 pediatric IEM patients with specific nutritional therapy who underwent liver transplant in Garrahan Hospital. They were divided into 2 groups according to the type of pathology. 5 patients had IEM of protein/amino acid metabolism (UCD, TYR type 1, MSUD, MMA) and 4 with Glycogen Storage Disease type 1 (GSD1). Anthropometry (z score W/Y, H/Y and BMI/Y), dietary intake, type of diet and feeding route were analyzed.
RESULTS: 9 children (2 male/7 female) were transplanted at median age 7.6 (1.8-13.6).
Group 1: 60% (n=3) of pre-transplant patients had normal BMI and 40% were overweight (n=1) and obese (n=1). Post-transplant, last two patients improved their nutritional status. Pre-transplant, all of them were treated with medical food and protein restricted diet according to each disease. 40% needed enteral nutrition support complement to the oral intake, 20% required same and 40% fed only orally. Post-transplant, 4/5 gradually released the protein-restricted diet. Only 1 case who received a combined liver kidney transplant should continue with slight protein restriction.
Group 2: 75% (n=3) of patients presented normal BMI/Y and 25% obesity (n=1), after BMI was normalized. All of them were treated with uncooked cornstarch therapy tolerating up 3 hours of fasting. All patients required feeding tube and fructose and lactose free diet. Post-trasplant, all the children were released from their diet and tolerated prolonged fasting. Only 1 patient required protein control due to renal failure.
CONCLUSIONS: LT has been a successful therapeutic approach for our population that prevents metabolic decompensation, dietary restrictions and the improvement of quality of life, achieving adequate growth.

P-014 - EDUCATIONAL PARTICIPATORY AND CULINARY ACTIVITY PROGRAM AIMED AT PATIENTS WITH INBORN METABOLIC DISEASES AND THEIR FAMILIES: 7 YEARS OF IMPLEMENTATION

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INTRODUCTION: Inborn metabolic diseases (IMD) described as disorders of intoxication in most cases require a strict and demanding lifelong dietary treatment. Seven years ago, based on difficulties and barriers detected in a survey and previous experience, we designed a program to anticipate everyday situations and encourage diet compliance.
OBJECTIVES: To enhance adherence to nutritional therapy through the implementation of workshops for IMD patients and their families to improve culinary skills and nutritional education.
METHODS: Participatory educational and culinary activities have been designed by metabolic dietitians (2011-2018) aimed at IMD patients (6months-18years) treated with protein/amino-acid restricted diets and their families followed at Garrahan Hospital.
Workshops were organized considering age groups and divided into modules developing different topics such as: variety of daily menus; increase of fruit/vegetable intakes; consumption of medical food; calculation of protein intake; management on holidays/social occasions (eating out, parties, camps).
RESULTS: 54 workshops were organized from 2011-2018. 76 patients and 71 families participated (Phenylketonuria: 33%; Urea Cycle Disorders: 22%; Organic acidurias: 12%; Maple syrup urine disease: 9%; Tyrosinemia1: 10%; Homocystinuria: 6%; others: 6%).
Over 50% of patients began attending the program during the first year of implementation, increasing participation every year. Media: 6,8 patients/year.
50% was the attendance rate, varying from one workshop to another: distance and time (+3hours) to hospital being the first cause of no attendance (37%). The media of patients/workshop was: 5.8(1-23). 30% attended at least 1 workshop and 22% more than 6.
Recipes were adapted, trying to match classic/traditional Argentinean foods, using homemade low-protein flour and adding variety of fruits/vegetables to make them healthier, and most of our patients could reproduce them at home frequently. Everyone participated enthusiastically showing interest in both educational and culinary activities. We encouraged teenagers to take a lead role in their diet, promoting self-care and involving them in preparing and calculating their own menus.
CONCLUSIONS: Participation in these workshops presents the opportunity to share ideas, dietary experiences and recipes together with peers to improve conventional instructions for low protein recipes. Further evaluation and more clinical evidence are needed to assess the effectiveness of the program aiming to improve adherence and long-term metabolic control.

P-015 - NUTRITIONAL TREATMENT AND FOLLOW UP OF 2 NEONATAL CASES WITH 3-HYDROXY-3-METHYLGLUTARYL-COA LYASE DEFICIENCY

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INTRODUCTION: 3-hydroxy-3-methylglutaryl-coa lyase (HMG-CoA lyase) deficiency is an autosomal recessive disorder involved in ketogenesis and in the last step of leucine catabolism. It usually appears in the neonatal period with vomiting, metabolic acidosis and hypoketotic hypoglycemia. The main treatment includes emergency therapy; diet restricted in protein and fat, and avoids fasting. Given the few cases described, there is no consensus on optimal dietary management.
OBJECTIVES: To describe nutritional management and outcome upon diagnosis and during the first year of 2 neonatal cases with HMG-CoA lyase deficiency.
METHODS: We reviewed medical records of 2 patients diagnosed and followed at Garrahan Hospital from 2015-2018.Anthropometric, biochemical parameters and dietary analysis were recorded upon diagnosis and until 1 year old. Feeding regimens and fasting time were described.
RESULTS: Two female babies presented with vomiting, lethargy and hypoketotic hypoglycemia with metabolic acidosis. After sepsis was ruled out, diagnosis of HMG-CoA lyase deficiency was achieved (at 11 and 12 days) through acyl-carnitines profile (increasing of 3-hydroxy-isovaleryl/ 3-methylglutaryl carnitines) and urinary organic acids (elevation of 3-hydroxy-3-methylglutaric/3-methylglutaconic acids).
After achieving metabolic stability (emergency protocol) both patients were treated with dietary restriction of natural protein and carnitine supplementation (100 mg/kg/day). Leucine-free formula plus glucose polymers were prescribed, covering their requirements.
Case 1 started treatment at 26 days old. She was breastfeeding on demand, extending until first trimester. She did not develop any metabolic decompensation.Mean dietary intake was: 116±18 cal/kg;0,8±0,1g/kg natural protein;1,3g/kg leucine-free formula;96,5±10,5mg leucine/kg;34,8±0,7% of energy from fat.
Case 2 was fed with infant standard formula (at 12 days old) and required one admission for 48hs at 5months (gastroenteritis). Mean dietary intake was: 109±23 cal/kg;0,85±0,1g/kg natural protein;1,3±0,4g/kg leucine-free formula;79±3 mg leucine/kg;33,5% of energy from fat.
During the follow up, both were fed every 3hours and extended fasting to 3.5-4h without biochemical or clinical alterations and with good growth. No amino acid deficiencies were detected.
CONCLUSIONS: We report the initial dietary management of two cases, achieving adequate metabolic control, growth and outcome with normal development; breastfeeding being feasible in this condition. Low leucine, high carbohydrates diets and slight fat restriction, with frequent feeding, could be implemented safely during the first year with close monitoring by a metabolic team.

P-016 - CURRENT STATUS OF KETOGENIC DIET THERAPY IN PATIENTS WITH GLUCOSE TRANSPORTER 1 DEFICIENCY SYNDROME (GLUT1DS) IN ARGENTINA

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INTRODUCTION: Glut-1 deficiency is a metabolic disease, and the KD (ketogenic diet) is considered the first-line therapy in this syndrome, since ketones use another transporter to enter to the CNS that can provide the brain with an alternative source of fuel, correcting the impared brain energy metabolism.
AIM: We conducted a survey on the ketogenic diet therapy in 14 patients diagnosed with glucose transporter protein-1 deficiency syndrome (GLUT-1 DS) to evaluate the efficacy of the treatment with the classic ketogenic or modified Atkins diet from the viewpoint of patient' s families.
METHOD: A 3-page survey was distributed to all attendees of a family-centered meeting for GLUT1DS in November 2017, held at Hospital Pediatria Garrahan. The surveys were completed by parents, collected anonymously, and information analyzed in a database.
RESULTS: Surveys were received from 14 families of patients diagnosed with GLUT-1 DS, 4 patients were females and 10, males with a median age 7,8 years (3 to 18). The mean diet duration was 8 years (range: 5 month–16.5 years). The types of KD therapies used were the Classic KD (10) and the Modified atkins diet (4).
The ratio more frequently used was 4: 1, and most patients (13 of 14) used to measure urine ketones twice a week. The time between the diagnosis and the initiation of the KD was 6 month on average. The outcome in those with early diagnosis and intervention was surprisingly good. All but one patient with the classic phenotype became seizure free after treatment with the classic ketogenic or modified Atkins diet. Acetazolamide was effective in one patient with paroxysmal exercise-induced dyskinesia.
CONCLUSIONS: the families complain about the late diagnosis but they showed a high level of satisfaction with the efficacy of the KD therapy. Although the long-term prognosis in patients with GLUT-1 DS partly depends on the underlying genetics, our study supports the assumption that early

initiation of treatment with a ketogenic diet may positively affect the outcome.

P-017 - EVALUATION BY ANTHROPOMETRY OF THE NUTRITIONAL STATE OF PATIENTS WITH INBORN ERRORS OF METABOLISM IN PROTEIN-CONTROLLED DIETS

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INTRODUCTION: The nutritional treatment of the inborn errors of metabolism (IEM) of amino acids consists of limiting the supply of natural proteins and complementing it with specific formulas that exclude the toxic amino acid/s. It is known that through a protein-controlled diet (PCD), favorable results are obtained in the medical treatment, but there is little information about their impact on growth.
OBJECTIVES: To evaluate the nutritional state of patients with IEM that carry out protein restricted diets, through routine anthropometric measurements. To know the impact of said diets on the nutritional state.
MATERIALS AND METHODS: Cross sectional study from patients followed by the pediatric metabolic service at the Hospital Italiano of Buenos Aires, between November-December 2018.
Patients of both sexes are included who carry out a protein-controlled diet from early diagnosis during the first year of life, until the moment of evaluation. Patients should have clinical evaluations with the team, through biochemical analysis and dietary records while taking the formula. The indexes and measurements taken were weight, size, size/age and weight/age or BMI index. They were categorized by sex and age.
RESULTS: A group of 18 patients was included (56% female), within a range of 11 months - 24 years (with a median of 11,0 years). The diagnosis were 7 (39%) ornithine transcarbamylase deficiency, 6 (33%) phenylketonuria, 2 (13%) methylmalonic acidemia, 1 (6%) propionic acidemia, 1 (6%) citrullinemia type 1, and 1 (6%) maple syrup urine disease.
In the evaluation of the weight/age or BMI/age n=1 (6%) presented underweight, n=12 (67%) normal weight, n=4 (22%) overweight and n=1 obesity. In the evaluation of size/age n=3 (17%) presented short stature, 66% of this patients had a diagnosis of organic acidemia.
CONCLUSION AND DISCUSSION: The nutritional state was generally normal in the evaluated patients. The cases of short stature were associated to poor adherence to treatment, primarily by a failure to take the formula and/or wrong application of the protein-controlled diet. Hence, protein-controlled diet in these pathologies would have no negative impact on the nutritional state of the patients.

P-018 - COLOMBIAN PATIENTS WITH NEUROMETABOLIC/NEUROGENETIC DISEASES TREATED WITH KETOGENIC THERAPIES

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INTRODUCTION: Neurometabolic/neurogenetic diseases are a complex area in pediatric neurology with heterogeneous manifestations like ataxia, mental retardation and refractory epilepsy, because of these symptoms the use of ketogenic therapies (KT) is useful and is supported by the knowledge of its mechanisms of action and neuroprotective properties.
OBJECTIVE: Evaluate the efficacy of KT in patients with neurometabolic/neurogenetic diseases attended by Metabolic Therapies (MT) in Colombia.
METHODS: Multicentric retrospective observational descriptive study was carried out; We reviewed the data of patients with neurometabolic/neurogenetic diseases with RE, who received treatment with a KT with a formula based on medium chain triglycerides "KetoVOLVE®" as the sole source of food or combined with diet; during March 2014 to June 2018, throughout Colombia. Software SPSS v.22 was used.
RESULTS: n= 19 patients, 53% male, median of age 4,8y (0,8y to 23,2y). Diagnoses: non ketotic hyperglycinemia (13; 68%), 2 hydroxy glutaric aciduria L (2; 10,5%), neuronal ceroid lipofuscinosis (2; 10,5%), glut-1 deficit (1; 5,5%) and deficit of 5-phosphate ribose isomerase (1; 5,5%). All patients receive KT but in different modalities determined by the ketogenic ratio (KR) like this: KR 1: 1 (32%), KR 2: 1 (21%), 2.5: 1 (5%), 3: 1 (21%), 4: 1 (21%) by enteral route feeding for 68% of patients. Median of time in treatment is 25,7 months (1 to 50 months). Mean of seizures/day before treatment 18, at six months of treatment, 1 seizure/day (decrease 95%) and after treatment, median 0 crisis/day. Secondary effects of KT reports: Constipation (5%), diarrhea (5%), improvement of constipation with the KT (37%). There was no change in the number of anticonvulsant drugs used. About nutritional status according with BMI there is no changes (-0,7 to -0,8 before and after KT).
CONCLUSIONS: Significant improvement was found in the number of epileptic seizures and the clinical condition of patients with the management of the KT with formula based on medium chain triglycerides in patient with neurometabolic /neurogenetic diseases with RE in Colombia.

P-019 - KETOGENIC DIET IN MITOCHONDRIALDISEASE: EFFICACY AND TOLERABILITY IN TWO PATIENTS

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BACKGROUND: Mitochondrial diseases (MD) are a clinically heterogeneous group of disorders caused by defects in the respiratory chain, the pathway of the ATP production system. The ketogenic diet (KD) is the gold standard therapy for pyruvate dehydrogenase (PDH)deficiency because it targets the metabolic defect directly, however, its use is extended to other MD since it may improve clinical symptoms, specially epilepsy and nutritional status.The aim is to describe the clinical efficacy and tolerability of the KD in two patients with MD.
Case 1: A 2-year-old boy presented at 3 months with swallowing and respiratory difficulties, central hypotonia, and seizures with persistent lactic-acidosis. The EEG revealed bilateral occipital spike wave and brain MRI showed increased white matter intensity and cerebellar atrophy. Molecular study confirmed PDH deficiency showing a heterozygous pathogenic variant in PDHA1(c.905G>A p.Arg302His). At 8 months of age the KD was started with formula.He was overweight with a weight-for-height of 140%. After 3 months on KD he improved significantly, became more alert, regaining the ability to swallow,seizures were completely controlled, and his EEG normalized. Antiepileptic treatment was discontinued and plasmatic lactate decreased. After 2 years weight-for-height was 117%.
Case 2: A 9-year-old boy presented with failure to thrive since birth. At the age of 6 he was admitted because of myoclonic epilepsy, cerebellar ataxia, and developmental regression. He had increased lactic acid. Brain MRI disclosed bilateral subthalamic nucleus involvement and EEG showed generalized spike-and-wave complexes. Muscle biopsy revealed ragged red fibers and MERRF disease was confirmed with a heteroplasmic variant in MT-TK (m. 8344A>G). Antiepileptic drugs failed to control epilepsy. Therefore, at the age of 7, he was put on a classical KD at a ratio of 2: 1 with semisolids and ketogenic formula via nasogastric tube. After 20 months on the KD his weight-for-height improved from 75% to 81% with control of generalized seizures of more than 75%.
CONCLUSION: In both cases the KD was safe and effective. Early treatment with the KD may be considered in mitochondrial patients, not only for those with PDH deficiency but also for other clinical phenotypes, especially those with refractory epilepsy.

P-020 - CLINICAL, TREATMENT AND OUTCOME FEATURES IN 7 ARGENTINEAN PATIENTS WITH VERY LONG CHAIN ACYL COA DEHYDROGENASE DEFICIENCY.

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INTRODUCTION: Very long chain acyl CoA dehydrogenase (VLCAD) deficiency (OMIM) is an autosomal recessive disorder of fatty acid oxidation, and the second most common disorder of fatty acid oxidation all over the world. Despite VLCAD deficiency is included in many newborn screening (NBS) programs worldwide; Argentina does not include it in its NBS and therefore does not have a true incidence of this disorder.
OBJECTIVE: The aim of this study is to analyze the clinical, biochemical, treatment and outcome features of 7 patients in Argentina, which is the first and largest existing description of Argentinean patients so far.
METHODS: We conducted a retrospective review of all health records of patients with VLCAD deficiency diagnosed and treated at our center, since the beginning of our metabolic service in 2008.
RESULTS: Severe early onset is the most frequent phenotype in our cohort, 71% of patients had a variable degree of hypertrophic cardiomyopathy which recovered after treatment, 71% presented hypotonia and 57% hepatomegaly at diagnosis. Family history of sudden death was positive in 28% of patients and only one of our patients died before diagnosis. In accordance with the WHO´s body mass index, 4 of 6 remaining children present obesity as a complication of diet and low physical activity and 1 has overweight. Based on a suggested score of severity proposed by Dr Diekman we could not find a correlation between the highest scores and the severity of the disease (understanding "severity" as the number of admissions even if the patient was following a treatment). One particular patient has a severe disease evolution with 22 hospitalizations of which 17 were without a trigger. All, except one patient, were under a high MCT dietary treatment plus cornstarch.
CONCLUSION: This study reports the clinical, treatment and outcome features of patients with VLCAD deficiency over the last 10 years. The paucity of the current published data about Argentinian patients makes it very difficult to estimate the incidence of VLCAD in the country. This is further aggravated by the lack of NBS and by the lack of knowledge of this disease by medical community in general.

P-021 - A CASE SERIES OF FATTY ACID OXIDATION DISORDERS FROM A TERTIARY TEACHING HOSPITAL IN SOUTHERN BRAZIL

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INTRODUCTION: Mitochondrial fatty acid β-oxidation disorders (FAOD) are a heterogeneous group of defects in fatty acid transport and mitochondrial β-oxidation, affecting energy homeostasis with multi-system involvement, including life-threatening manifestations. FAOD are inherited as autosomal recessive disorders and have a variable presentation, with either neonatal or later onset.
OBJECTIVE: To characterize phenotypically a series of patients with FAOD managed at an outpatient clinic in a tertiary teaching Hospital of Southern Brazil.
METHODS: Retrospective observational case series study including eight patients with clinical, biochemical and/or molecular diagnosis of FAOD.
RESULTS: Five female and three male individuals were evaluated, with mean age 11.07 years (three months to 39 years) and mean age of clinical presentation 22.12 months (18 hours to 14 years). The diagnosis were Long chain acyl-coA dehydrogenase deficiency (n=2); Multiple acyl-coA dehydrogenase deficiency (n=2); Carnitine palmitoyltransferase II deficiency (n=2); Carnitine palmitoyltransferase I deficiency (n=1); and Very long chain acyl-coA dehydrogenase deficiency (n=1). Mean age at diagnosis was 8 months (20 days to 36 years). Diagnosis was molecularly confirmed in five patients. Hypoglycemia was the initial symptom for 87.5% (n=7) patients. Other observed signs and symptoms included hypotonia (6/8); hepatomegaly (3/8); seizures (3/8); developmental delay (2/8); feeding problems (1/8); dehydration (1/8); intellectual disability (1/8); unspecific dysmorphisms (1/8); cardiomyopathy and arrhythmia (1/8). One patient diagnosed at age 36 presented lower limbs weakness and pain, rhabdomyolysis, hypoglycemia and deep vein thrombosis. Three patients had a sibling with previous history of unexplained death and one had consanguineous parents.
CONCLUSION AND DISCUSSION: This descriptive study emphasizes the multisystemic, severe and life-threatening character of FAOD, requiring integrated and multidisciplinary management. Although this is the most prevalent disorder in other series, no case of Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency was observed. Newborn screening for such diseases is not widely available, leading to late access to reference centers. Greater awareness of this disorder among assistants should aid their search for FAOD in cases of hypoglycemia, hypotonia, hepatic and cardiac manifestations that might otherwise be improperly managed. Larger studies should be done to better understand those symptoms in Brazilian patients, as well as unified ones on a national basis.

P-022 - REYE-LIKE SYNDROME TRIGGERED BY SYNCYTIAL VIRUS INFECTION IN TWO PATIENTS WITH FATTY ACID OXIDATION DISORDERS

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Reye syndrome is a rare but dangerous emergency that children suffer. The etiology and pathogenesis of the Reye syndrome is not clear. Today, special attention is paid to the development of so-called Reye-like syndromes in the context of metabolic defects. Defects of the fatty acid oxidation (FAO) often present in infancy as the metabolic demands of the developing brain are higher in the young brain, mainly due to its vulnerability to hypoxia, hypoglycemia and hypoketonemia. These disorders are often clinically and biochemical silent, but become manifest under specific stressors such as prolonged fasting, fever with infection, mild to moderate exercise and cold exposure. Recurrent hypoglycemia, hypoketonemia, hepatic encephalopathy and microvesicular steatosis of liver are by definition the classical signs of Reye-like syndrome and the pathological signature of FAO disorders.
Here, we report on two patients with Reye-like syndrome due to FAO disorders triggered by Syncytial Virus Respiratory infection (SVR).
Patient 1, is the first child of non-consanguineous parents, who at 8 months of age began with hypoglycemia, hyperammonemia, hepatomegaly with hepatocellular dysfunction, steatohepatitis and hypertrophic cardiomyopathy secundary to a SVR infection. Basic biochemical tests as well as plasma acylcarnitines analysis by gas chromatography-mass spectrometry (GC- MS) were performed.
Patient 2, is the first child of non-consanguineous parents, who in the first month of life began with hypoglycemia. Afterwards hyperammonemia, hepatomegaly with hepatocellular dysfunction, steatohepatitis and hypertrophic cardiomyopathy and myopathy were detected secundary to a SVR infection. Basic biochemical tests as well as acylcarnitines analysis by GC-MS were performed.
Both initial biochemical tests showed increase in AST and ALT with hyperammonemia and hypoketotic hypoglycemia. Liver ultrasound demostrated steteatohepatitis and the echocardiography, hypertrophic cardiomyopathy. Plasma acylcarnitine analysis demostrated a significant elevation of C6-C10 acylcarnitines in patient 1 typical of Medium-Chain Acyl-Coenzyme A Dehydrogenase deficiency; in patient 2, a rise in C14: 1, C14: 2, C14, and C12: 1 was seen, suggestive

of Very Long-Chain Acyl-Coenzyme A Dehydrogenase deficiency.
The description of these two cases confirmed the presence of Reye-like syndrome secundary to SRV infection in patients with FAO disorders in Latin America, highlightening SRV as a new trigger of this disorder.

P-023 - INFANT MORTALITY ATTRIBUTABLE TO INBORN ERRORS OF METABOLISM ASSOCIATED WITH SUDDEN DEATH IN INFANCY: A BRAZILIAN EPIDEMIOLOGICAL STUDY

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INTRODUCTION: Sudden unexpected death in infancy (SUDI) is one of the most frequent causes of death during the first year of life. From 0.9% to 6% of children with SUDI may have some inborn error of metabolism (IEM), and SUDI may be the main manifestation of these diseases. To date, there is no data on the frequency of IEM associated with SUDI associated in Brazil.
OBJECTIVES: To estimate and characterize, by region of Brazil, deaths related to IEM associated with SUDI in neonates and infants <1yo from 2002 to 2014.
METHODOLOGY: a descriptive, cross-sectional, population-based study of data obtained from the Brazilian Ministry of Health Mortality Information System (SIM). Death records were obtained for all infants (age<1yo) who died in Brazil in 2002–2014 in whom the underlying cause of death was listed as ICD-10 codes E70 (Disorders of aromatic amino-acid metabolism), E71 (Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism), E72 (Other disorders of amino-acid metabolism), or E74 (Other disorders of carbohydrate metabolism), which are known to be associated with SUDI.
RESULTS: 199 deaths of children <1year old in Brazil were recorded from 2002 to 2014 due to IEM associated with SUDI, with a estimated mortality rate of deaths of 0.67: 10,000 live births (CI95% 0.58-0.77). Of these 199 deaths, 18 (9.0%) occurred in the North, 43 (21.6%) in the Northeast, 80 (40.2%) in the Southeast, 46 (23.1% and 12 (6.0%) in the Central-West region of Brazil. In all regions, ICD10-E74 was the most frequent.
CONCLUSIONS: This 13-year time-series study provides the first analysis of the number of infant deaths in Brazil attributable to IEMs known to be associated with sudden death. According to our data, fatty acid metabolism disorders are not the most prevalent group of IEM associated to SUDI, probably due to the underdiagnosis.

P-024 - NEUROVISCERAL PAIN IN ERYTHROPOIETIC PROTOPORPHYRIA-RELATED HEPATOPATHY: REPORT OF A BRAZILIAN CASE

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INTRODUCTION: Erythropoietic Protoporphyria (EPP), an autosomal recessive disorder, is the most common porphyria in childhood. About 90% of the cases are caused by a loss-of-function variant and a low-expression variant in the FECH gene, reducing ferrochelatase activity to 10-30%. Protoporphyrin IX, a lipid-soluble molecule, is the main toxic substrate in EPP, causing immediate photosensitivity. Mainly produced in bone marrow, it progressively accumulates in liver, leading to liver failure in 5% of the cases. Whereas the photosensitivity is the major concern, primarily hepatic presentation has been reported.
OBJECTIVES: to report one case of protoporphyrin hepatopathy.
MATERIALS AND METHODS: case report.
RESULTS: a 14 year-old Brazilian girl was evaluated during a second consecutive episode of opioid-dependent abdominal pain, elevated transaminases, mild jaundice, autonomic signs and red urine. She had no medical issues but mild photosensitivity since childhood. Infectious and structural causes were excluded. Semi-quantitative porphobilinogen (PBG) test was positive and the findings were interpreted as an acute porphyria. The patient slowly progressed to discharge after standard acute attack management, but was hospitalized three more times in a 6-month interval. Meanwhile, hepatic biopsy showed ductular reaction with brown pigment deposits in biliary canaliculi and PBG and aminolevulinc acid (ALA) quantitative tests had normal results, leading to a revised approach. Plasmatic porphyrins demonstrated an extremely high protoporphyrin level (207 mg/dl; reference range: 0-1). Next-generation sequencing detected a previously undescribed likely pathogenic variant (p.Gln122Argfs*23) and the known intronic polymorphism c.315-48T>C, in heterozygosis in FECH. Segregation analysis wasn't performed. Light exposure

avoidance and beta-carotene were prescribed. Subsequent extensive approach to exclude differential diagnosis of abdominal pain, including magnetic ressonance, digestive endoscopy, colonoscopy and electroencephalogram, showed no abnormalities. A 7-month later comparative hepatic biopsy is ongoing.
CONCLUSIONS: neurovisceral pain, the remarkable finding in acute porphyrias due to ALA (and possibly PBG) accumulation, was described in a few reports of advanced protoporphyrin hepatopathy. There's no demonstration of those substrates' excess in the benign course of EPP. Since sequential liver and bone marrow transplantations are expected to achieve better outcomes in protoporphyrin hepatopathy, in the present case, the recurrent abdominal pain requires careful evaluation to management decision.

P-025 - CLINICAL MANIFESTATIONS OF COBALAMIN DEFICIENCY (CD) IN CHILDREN

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Cobalamin is cofactor of methionine and nucleic acids synthesis. Human is dependent on dietary sources. Its deficiency causes central/peripheral nervous system compromise and megaloblastic anemia. The most frequent etiology of CD in children is nutritional. We report 5 children with CD, 4 infants (8-18 months), 1 newborn. Clinical picture in infants: 3 patients were suspected due to moderate to severe anemia. One patient presented with acute tremor of the extremities. Patients rejected solid food and were mainly breast feeding; they presented failure to thrive, mild to moderate psychomotor developmental delay (PMDD), axial hypotonia in two. Relevant tests: Hemoglobin 6.5-9.2 gr/dl, 2 patients with aregenerative hemolytic anemia, 2 patients with macrocytic anemia. Very low cobalamin levels. The newborn was diagnosed at age of 12 days due to mild increment of propionylcarnitine in neonatal screening. CD causes: Four cases due to maternal CD. Two mothers presented subclinical pernicious anemia. Two mothers with CD of unknown cause. A patient was explained by a vegan diet due to parental option. Patients were treated with intramuscular hydroxycobalamin and have been followed for 6-20 months. Two present normal psychomotor development (including the newborn), 1 presents moderate PMDD, 2 present language delay.
CONCLUSIONS: CD should be suspected in all infants with PMDD and/or hypotonia of non-evident cause. It can present with hemolytic anemia. The cause of maternal CD can be unknown. Despite the treatment, CD in infants can leave long-term neurological compromise. Neonatal diagnosis and early treatment of CD can avoid neurological and systemic symptoms.

P-026 - HOMOCYSTEINE AS AN ACCESSIBLE DIAGNOSTIC TOOL FOR TREATABLE DISORDERS OF COBALAMIN METABOLISM

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INTRODUCTION: Homocysteinemia is defined as elevation of the homocysteine level in blood. Homocysteine is metabolized by transsulfuration and remethylation, cofactors are necessary in its metabolism. The transsulfuration to cysteine is catalyzed by cystathionine-beta-synthase and requires pyridoxal phosphate (B6) as a cofactor. Remethylation of homocysteine to methionine is catalyzed by methionine synthase or by betaine-homocysteine methyltransferase and vitamin B12 is the precursor of methylcobalamin, the cofactor for methionine synthase. In many of these conditions early treatment can prevent severe clinical compromise.
OBJECTIVES: To present a case series of 15 patients diagnosed with homocysteinemia between January 2015 and December 2018 in a tertiary hospital in Argentina and to describe the clinical biochemical and molecular findings.
MATERIALS AND METHODS: We performed a retrospective review of Medical records of all patients referred to the metabolic service at the Hospital Italiano of Buenos Aires, between 2015 and 2018. Patients were included who presented with elevated HCY.
RESULTS: A group of 15 patients was included (46% female), within a range at diagnosis of 1 months - 38 years (with a median of 6 months). The diagnosis were 2 (13,3.5%) CBS deficiency, 2 (13.3%) congenital malabsorption of B12, 4 (26,6%) Cobalamin metabolism defect (MTR, MTRR, and MMADHC), 1 (6.6 %) pernicious anemia and 4 (26,6%) had B12 deficiency but no further studies were done. In 2 (13.3%) the condition was secondary to maternal disease.
Most common clinical presentation was failure to thrive, anemia, hypotonia, seizures and encephalopathy. Treatment was initiated and changed the outcome in 15/15 patients. 10/15 had complete recovery.
DISCUSSION: Cobalamin metabolism disorders should be evaluated early in the diagnostic algorithm in any patient with suggestive clinical findings. Biochemical and molecular tools are available to determine the specific metabolic defect, and early treatment should be started as reversion of symptoms is frequent. We want to emphasize that total plasma homocysteine is a non expensive and usually available test that may change patients prognosis if used.

P-027 - ISOELETRIC FOCUSIN OF SERUN TRANSFERRIN FOR INVESTIGATION OF CONGENITAL DISEASE OF GLYCOSILATION: ANALYSIS OF THE EXPERIENCE OF TEN YEARS OF A BRAZILIAN REFERENCE CENTER

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INTRODUCTION: Congenital disorders of glycosylation (CDG) are genetic diseases of the glycoprotein, glycan and glycolipid metabolism, most of which are autosomal recessive. Most CDGs occur by defects in N-glycosylation or O-glycosylation pathways. Currently, there are over 100 CDGs reported. The clinical aspects range from prenatal symptoms (hydrops or ascites) to congenital malformations and neuropsychomotor developmental delay. The screening of CDGs involving N-glycosylation is most commonly isoelectric focusing (IEF) of serum transferring. In most cases, confirmation of diagnosis of CDGs involves genetic tests that are still difficult to access through the Unified Health System in Brazil.
OBJECTIVES: To characterize the cases screened for CDG by IEF in the Inborn Errors of Metabolism Laboratory (IEML) of the Medical Genetics Service at Hospital de Clínicas de Porto Alegre, Brazil.
METHODOLOGY: Observational, cross-sectional, retrospective study based on the review of laboratory records of patients investigated by the IEML from 2008-2017.
RESULTS: From 2008 to 2017, 1546 patients were screened by IEF; of these, 51 (3%; mean age = 24 months, IQ 25-75 = 11-57; male = 27) presented an altered pattern of IEF (median = 5 ± 2.8 cases / year). It was possible to obtain data on the diagnosis conclusion for 14 patients. Ten of them were false-positives (classical galactosemia = 4; hereditary fructose intolerance = 4; peroxisomal diseases = 2). The others were diagnosed with PMM2-CDG (n = 2), MPDU1-CDG (n = 1), and SLC35A2-CDG (n = 1). When cases with altered pattern were compared to those with normal patterns, we observed a higher prevalence of altered cases occurred when the investigation was performed in the age group of 11mo-3y. The occurrence of inverted nipples and hepatopathy increases the probability of occurring alterations in IEF by 11x, 4.6x, respectively.
CONCLUSIONS: Our data suggest that investigation of cases with suspicion of CDG is complex, and it is exacerbated by the occurrence of false positives in IEF and lack of access to diagnostic tests. The presence of inverted nipples and hepatopathy should suggest the need for investigation using IEF.

P-028 - GENETIC VARIANTS IDENTIFIED BY EXOMIC ANALYSIS IN CONGENITAL DISORDERS OF GLYCOSYLATION

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INTRODUCTION: Congenital Disorders of Glycosylation (CDG) are human genetic diseases due to 130 different defects in the pathway of glycoconjugates. These pathologies encompass defects of nucleotide-sugar biosynthesis or transporters, glycosyltransferases, vesicular transport, as well as in lipid and glycosyl-phosphatidylinositol anchor glycosylation. The clinical features range from a severe multisystem to mild phenotype and often associated with neurological impairments (hypotonia, psychomotor disability, strabismus, ie). Serum transferrin isofocusing (Tf-IEF) is the main standard method for screening of N-glycosylation disorders lacking terminal sialic acids. Nevertheless, biochemical analysis combined with Next-Generation Sequencing (NGS) technology plays a significant role in CDG diagnostic.
OBJECTIVE: Report improvements in CDG diagnosis in Argentinean patients using NGS technology
METHODOLOGY: This study included patients referred by pediatricians from Children's Hospital in Cordoba and other Argentinean medical centers. Ethical permissions and informed consents were obtained from the institutional review boards of CIEIS- Ethics Committee. Transferrin analysis (Tf-IEF) and Tf neuraminidase digestion were performed according to standard METHODS: Genomic DNA from

patients with altered Tf-IEF patterns was analyzed. We captured the exome of genes associated with human genetic diseases OMIM database (clinical exome sequencing, CES).
RESULTS: A neurological multisystem phenotype was observed in four patients with abnormal transferrin CDG-type I (di- and asialo-Tf increased. We identified an homozygous unreported missense variant in three of them (c.G753T; p.Arg251Leu in exon 2 of ALG-2 gene OMIM #607906). In silico analysis showed a moderately pathogenic variant (DANN score 0.9955; Mutation Taster 0.999; FATHMM-MKL 0.8844; Provean -3.33). Functional tests are underway. The fourth patient had non CDG gene variants, but an abnormal transferrin pattern as a coincidence or part of the syndrome, deserves further study.
CONCLUSION: It must to keep in mind a CDG in any unexplained syndrome, in particular when there is neurological involvement. Our results highlight the usefulness of NGS to CDG diagnosis. Together it provides insights to guide research towards new therapies (precision medicine).
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P-029 - WEST SYNDROME BY VARIANT IN ALG13 GENE ASSOCIATED WITH CDGIS WITH NORMAL PATTERN OF GLYCOSYLATED SERUM TRANSFERRIN ISOFORMS.

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INTRODUCTION: Congenital Disorders of Glycosylation (CDG) are new and rapidly expanding neurometabolic disorders with multisystem involment, broad phenotypic manifestations, and variable severity. The majority results from a defect of one of the steps involved with protein or lipid N-glycosylation pathway. Mutations in the ALG13 gene, which is located on the X-chromosome, are associated with CDG type Is and have been reported in 10 patients approximately until now.
OBJECTIVE: we report a female patient with a rare metabolic disease: CDG type Is. We discuss clinical, biochemical and molecular findings.
METHODS: retrospective medical record review of a patient diagnosed with CDG Is.
RESULTS: this case is about a female patient, 5yo, second child of non-consanguineous parents. She had poor visual contact, developmental delay, and spasms in flexion from the first months of life. Epilepsy was refractory to multiple drugs including ACTH. Seizures frequency decreased with ketogenic diet. Cerebral MRI showed hypoplasia of the corpus callosum and increased subarachnoid spaces. Metabolic screening including glycosylation studies by transferrin isoelectric focusing resulted normal. The ratio of the CSF glucose/plasma glucose was 0.35 (normal 0.65±0.1) so molecular analysis was performed for SLC2A1 gene resulting normal. She underwent exome sequencing and was diagnosed with a heterozygous pathogenic variant in ALG13 gene related to patient´s clinical phenotype.
DISCUSSION: The history and clinical findings identified are typical of CDGIs. The majority of patients with CDG type Is have epileptic encephalopathy, especially West syndrome. The CSF glucose/plasma glucose ratio has not previously been systematically studied and favorable response to the ketogenic diet has not been described in epileptic encephalopathy due to mutation in the ALG13 gene.
Since glycosylation studies are normal in patients with this mutation, the diagnosis of CDGIs can be missed if genetic studies are not performed.

P-030 - CLINICAL UTILITY OF CONGENITAL DISORDER OF GLYCOSYLATION GENE PANEL IN PATIENT WITH REFRACTORY EPILEPSY

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INTRODUCTION: Congenital Disorders of Glycosylation (CDG) are a growing group of multisystemic diseases caused by defects in the formation or processing of glycoproteins and/or glycolipids.
Most types of CDGs present in early infancy and the clinical manifestations may include failure to thrive, hepatopathy, hypoglycemia, protein-losing enteropathy, developmental delay, hipotonia, neurologic abnormalities, eye abnormalities, immunologic, skin and skeletal findings.
Type I CDG includes a group of disorders where there are defects in the biosynthesis of dolichol-linked oligosaccharides in the cytosol or endoplasmic reticulum (ER), as well as defects involving the transfer of oligosaccharides onto nascent glycoproteins.
CDG1K is a type I CDG caused by homozygous or compound heterozygous mutation in ALG1 gene, encoding beta-1,4-mannosyltransferase on chromosome 16p13. This type of CGD is characterized by predominant neurologic involvement.

CASE PRESENTATION: We present a patient referred to our hospital at one year for refractory seizures, lack of eye contact, failure to thrive, developmental delay and acquired microcephaly. She had mild hyperammonemia, abnormal coagulation studies, her LFTs were elevated and cholesterol was low. Her brain MRI showed cortical and central atrophy, visual evoked potentials showed axonal neuropathy and electroretinography has a normal response.
Transferrin isoelectrofocusing revealed a typical CDG type I pattern. No other pathological biochemical result was found.
A sequence analysis and deletion/duplication test of 102 genes of Congenital Disorders of Glycosylation was made. Two heterozygous likely pathogenic variants in trans configuration were identified in ALG1, c.826C>T(p.Arg276Trp) and c.863-2A>G.
Because her refractory epilepsy and repetitive status epilepticus family was counselled and ketogenic diet was started being free of seizures.
CONCLUSION: CDGs should be suspect in patients with microcephaly, neurologic involvement and liver compromise. Molecular panels are a rapid and accurate tool for diagnosis and should be consider early in the diagnostic workup.

P-031 - THREE CASES OF PMM2-CDG: CLINICAL, BIOCHEMICAL, NEURORADIOLOGICAL AND MUTATIONS, DESCRIPTION.

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INTRODUCTION: PMM2-CDG (MIM) or CDG-Ia is the most common type of congenital disorders of glycosylation (CDG), caused by mutations in PMM2 gene. It is an autosomal recessive condition. Estimated incidence of up to 1/20,000. Major clinical features of disease include neurologic involvement, including cerebellar hypotrophy, hypotonia, strabismus, epilepsy, failure to thrive, feeding difficulties and developmental delay. Physical exam can be notable for abnormal fat distribution with suprapubic or buttock fat pads and nipple inversion. Infections and fevers may trigger stroke-like episodes. Isoelectric focusing (IEF) of serum transferrin is the standard test for diagnosing CDG due to N-glycosylation. PMM2-CDG shows type I CDG pattern. The confirmatory diagnosis requires molecular study
OBJECTIVE: To present 3 cases of PMM2-CDG.
Cases:
Female, product of the first normal pregnancy and delivery. Healthy non consanguineous parents. 3 years of age at the moment of the diagnosis. Psychomotor developmental delay, failure to thrive, feeding difficulties. She suffered stroke-like episode during fever episode. Physical exam: severe hypotonia, strabismus, suprapubic and buttock fat pads, pectum excavatum, inverted nipples. Brain MRI: progressive cerebellum hypoplasia.
Male patient , product of forth pregnancy of healthy consanguineous couple. Congenital hypothyroidism. 4 years of age at the moment of the diagnosis. Development delay, hypotonia. Physical exam: strabismus, finger pads, ataxia. Brain MRI: cerebellum hypoplasia.
Male, healthy non consanguineous parents. Normal pregnancy and delivery. Psychomotor developmental delay. 3 years of age at the moment of the diagnosis. Physical exam: hypotonia, nystagmus horizontal, buttock fat pads, ataxia. Brain MRI: cerebellar atrophy.
All three cases have plasma CDG type I pattern on IEF and pathogenic known variant of PMM2 gene.
CONCLUSIONS: The clinical phenotype of PMM2-CDG is very suggestive. It is important to be aware when a patient with development delay is been studied. At present there is no specific treatment but the diagnosis is important because the genetic counseling of the family.

P-032 - NOVEL EXT2 PATHOGENIC MUTATION IN ARGENTINIAN FAMILY WITH HEREDITARY MULTIPLE OSTEOCHONDROMATOSIS

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Hereditary Multiple Osteochondromatosis (HMO) is characterized by the growth of benign cartilaginous tumors in the form of exostosis, mainly in the metaphysis of long bones. The prevalence is 1/50,000 individuals, and follows an autosomal dominant inheritance. There are at least three exostos in genes associated with HMO: EXT1, EXT2 and EXT3, with a higher frequency in EXT1.These are ubiquitously expressed tumor suppressor genes of the EXT gene family,encoding glycosyltransferases involved in the adhesion and/or polymerization of heparan sulfate chains (HS) in heparan sulfate proteoglycans (HSPG). They interact with numerous proteins, including growth factors, morphogens and extracellular matrix proteins. Each HSbinds to a serine unit of a proteoglycan core protein via O-linked-glycosylation binding. The truncated HSPGdisturb specific growth-factor–binding in chondrocytes, resulting in abnormal signaling and altered endochondral ossification, thus leading to HMO.

We present the clinical characteristics of an argentinian family with HMO, with a novel EXT2 frameshift mutation: c.211delC (p.Leu71Cisfs*20).
We evaluated three affected patients (the father, his son and daughter) with HMO. Both children presented with more extensive disease, while less obvious lesions were found in the father. In the male, tumors were detected at the level of the ribcage at 2 years of age, reaching the diagnosis of HMO at that time both in him and in his younger sister of 1 year old. Besides this, both have grown in tall percentiles of height. The father at that time was almost asymptomatic, with a few clinical protuberant lesions in proximal arm regions, and in close proximity to the knees, confirmed by radiological exams. Although no other family history was detected by the interrogation, there could be more family members in paternal branch with mild forms of the disease, which should be studied.
Although many aspects remain to be defined in genotype-phenotype correlation, in our patients it seems that the suggestion that mutations in EXT2 are associated with a milder phenotype than mutations in EXT1 could be true.

P-033 - ANALYSIS OF GLYCOSAMINOGLYCANS BY TANDEM MASS SPECTROMETRY: REPORT FROM THE MPS BRAZIL NETWORK

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INTRODUCTION: Mucopolysaccharidoses (MPS) are lysosomal storage disorders characterized by progressive accumulation of glycosaminoglycans (GAGs). Several methods, mostly colorimetric, are used for the measurement of urinary GAGs. Thin-layer chromatography and electrophoresis are also used to identify the different species of GAGs. However, the use of these methods is limited by several factors, being false positives and false negatives not rare. Tandem mass spectrometry (MS/MS) is a powerful tool to identify and quantify GAGs, and can be used in a variety of samples, at any age, and at any disease stage.
OBJECTIVE: To evaluate the potential use of MS/MS for analysis of GAGs in a variety of samples.
MATERIALS AND METHODS: Serum, plasma, dried blood spots, urine, cells and other biological samples are incubated with chondroitinase B, heparitinase and keratanase II for disaccharide digestion. Different classes of GAGs are separated by liquid chromatography tandem mass spectrometry. Normal ranges are defined by analysis of age-matched controls.
RESULTS: The use of this new method allowed analyses of samples from patients with clinical suspicion of MPS, and from patients in therapy for treatment monitoring.
CONCLUSIONS: The implementation of the LC/MS/MS method allows the measurement of GAGs in several types of samples, with higher sensitivity and specificity in comparison to the colorimetric methodologies. This novel assay will improve the diagnostic work-up in suspected patients and the follow-up of treatment, and will overcome difficulties in analyses from samples which need to travel long distances and/or cross country borders. Furthermore, the measurement of GAGS in dried blood spots could be explored as an alternative for newborn screening of MPS.

P-034 - QUALITY OF LIFE IN CAREGIVERS OF CHILDREN WITH MUCOPOLYSACCHARIDOSIS

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INTRODUCTION: Mucopolysaccharidoses (MPS) are a group of rare genetic disease, characterized by deficiency of glycosaminoglycan degradations that causes progressive and generalized symptoms. Caregivers of individuals with disabilities may have reduction in Quality of Life (QoL) due dedication to the patient.
OBJECTIVE: The present study aims to assess QoL in mother caregivers of children with MPS type I, IV and VI.
METHOD: Cross-sectional study using a convenience sampling strategy. The World Health Organization Quality of Life Assessment (WHOQOL-BREF) was used to assess QoL. This study was approved by the Ethical committee of Pequeno Príncipe Hospital (CAAE 71602817.7.0000.0097).
RESULTS: Seven caregivers of 7 patients with MPS (MPS I=1; MPS IV=3; MPS VI=3) were included. The average WHOQOL-BREF score was 72.7, with highest score in Social Relationships score (83.3) and lowest score in environment domain (55.0). No difference was identified between caregivers of patients with MPS I (60.0), IV (76.5) and VI (55.8).
DISCUSSION: Caregivers median score of physical, psychological and social relationships domains was almost identified in healthy population but score of environment domain was lower. Assessment of the socioeconomic status revealed that most mothers were living in low-income or middle-income setting, fact that could impact in perception in environment domain. Although previous study of caregivers of patients with MPS presents with poorest quality of life, in this study caregivers had better perception of their own quality of life, with better results in all studied domains.

P-035 - NUTRITIONAL STATUS IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS TYPE I AND II.

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INTRODUCTION: There is scarce information on body composition in Mucopolyssacharidosis (MPS), and how the accumulation of glycosaminoglycans (GAG) affects it. The aim of this study was to investigate the nutritional and metabolic aspects of adult male patients with MPS types I and II assisted at Reference Center for Inborn Errors of Metabolism at Universidade Federal de São Paulo.
METHODS: The body composition analysis was made by plethysmography, assessment of dietary intake by food recording 24h (three nonconsecutive days), resting metabolic rate by measuring oxygen consumption and energy requirements estimated by prediction equations. Anthropometric results (weight, height, body mass index) were compared with WHO references.
RESULTS: Five patients (3 MPS I / 2 MPS II) who were under enzyme replacement therapy (ERT) were included. The mean age at diagnosis and at the time of the study was 18.6 years (14y – 27y) and 24.1years (23y – 30y, respectively. The mean time under ERT was 3.5 years (1.1y - 5.8y). The mean value of resting metabolic rate was 1386 kcal/day (967 kcal/day - 1.803 kcal/day): one low, two normal and two high. The estimated mean energy requirement was 2240 kcal/day (1642 kcal/day - 2447 kcal/day). Blood glucose and total cholesterol levels of all patients were within the normal reference range. Serum high-density lipoprotein levels (HDL) were below the recommended in all patients. The evaluation of body composition by plethysmography showed that 3 out of 5 patients had about 9% fat (lean), one about 14.3% (moderately lean) and one 20.5% (overweight). Patients consumed macronutrients within the normal range distribution rate. There was no difference in body mass index between the patients with the mean 22.6 kg/m2(20.4-24.0kg/m2), which does not corroborate with the Brazilian population with more than 48.8% overweight according to the Brazilian Institute of Geography and Statistics (IBGE).
CONCLUSION: In this study, patients with MPS did not present significant alterations in the analyzed parameters, however, these results should be interpreted with caution since the influence of GAGs in the result of the body composition method used is not totally understood.

P-036 - OTORHINOLARYNGOLOGICAL FINDINGS OF PATIENTS OF THE COLOMBIAN SOUTHWEST WITH CLINICAL, ENZYMATIC AND MOLECULAR DIAGNOSIS OF MUCOPOLISACARIDOSIS II, IV-A AND VI.

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INTRODUCTION: Mucopolysaccharidosis (MPS) is characterized by excessive accumulation of glycosaminoglycan sulfate (GAGs) in organs and tissues. The accumulation of GAGs in the upper respiratory tract generates damage to the mucosa, produces respiratory infections and conditions such as hypertrophy of the tonsils and adenoids, macroglossia, apnea and otitis media; secondarily, it has been related to hearing loss.
OBJECTIVE: To characterize the otorhinolaryngological manifestations of patients with MPS
METHODS: Thirty-five patients (18 male and 17 female) with a diagnosis of MPS type II, IV-A and VI of the Colombian southwestern region aged between 2 and 60 years were evaluated. The otorhinolaryngological results of the patients were analyzed taking into account the type of MPS, sex, age during the study, audiological tests, audiometry test according to their age, and hearing treatments.
RESULTS: 6 cases of MPS II, 24 of MPS IV-A and 5 of MPS IV were reviewed. 65.64% of the patients evaluated according to the types of MPS (II, IV-A and VI), presented mild conductive hearing loss (17.14%) and bilateral sensorineural hearing loss (47.5%). 11.3% presented hypertrophy of the tonsils, 17.10% diagnosed a short neck and 5.7% presented apnea-hypopnea syndrome and macroglossia. 47.8% of the patients presented otitis media (OM). OM was reported in patients with MPS II in 33%, and in patients with MPS IV-A and VI occurred in 12.5% and 20% respectively. 20% of patients received treatment with hearing aids. No patient reported otosclerosis or tinittus. A direct relationship of hearing loss was found as age progressed.
CONCLUSIONS: In patients with different types of MPS, there is a high prevalence and progressive tendency to suffer audiological losses and recurrent infections, which is why a periodic follow-up is required, given the important repercussion of this pathology in the quality of life and in the development of these patients The early diagnosis of patients with MPS as well as the development of audiological studies allows us to approach a personalized medicine based on the

initiation of an adequate enzyme replacement therapy or other complementary therapies at an early age.

P-037 - OPHTHALMOLOGICAL MANIFESTATIONS OF PATIENTS OF THE COLOMBIAN SOUTHWESTERN WITH CLINICAL, ENZYMATIC AND MOLECULAR DIAGNOSIS OF MUCOPOLYSACCHARIDOSIS II, IV-A AND VI.

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INTRODUCTION: Mucopolysaccharidoses (MPS) are a group of hereditary metabolic diseases caused by the deficiency of lysosomal enzymes necessary to degrade glycosaminoglycans (GAG). The GAGs without degrading accumulate causing dysfunctions in cells, tissues and organs. The cornea is an organ that can be affected by the blockages of the metabolic pathways, which compromises the transparency, the optical function and its structural integrity. These accumulations of GAGs
have also been optically related to papiledemas, retinitis pigmentosa, optic neuropathy, glaucoma
and even blindness.
OBJECTIVE: To characterize the ophthalmological manifestations of patients with MPS
METHODS: A retrospective study of the clinical, ophthalmological findings of 35 patients diagnosed with MPS type II, IV-A and VI of the Colombian southwestern region. The ocular results were analyzed, taking into account the type of MPS, sex, age during the study, ophthalmological tests and diagnoses.
RESULTS: Thirty-five patients diagnosed with MPS, 18 male and 17 female aged between 2 and 60 years, were evaluated.The ophthalmological results showed that for the three types of MPS studied (II, IV-A and VI) the most frequent diagnoses were the light opacity in the cornea (42%), the transparent lens (14%) and hyperopia and astigmatism (14 %). Some 8.5% had refraction disorders such as anisometropia or presbyopia. 5% of the patients presented acute atopic conjunctivitis and 31.4% had a normal vision diagnosis. In the case of those affected by MPS II, the incidence of mild opacity in the cornea was reported in 66% of the cases, 25% for MPS IV-A and
60% in patients with LV. No patient presented with pigmentary retinitis or blindness. The typical ocular features derived from the MPS were more easily recognized in patients older than 6 years.
CONCLUSION: Ophthalmological complications that cause a significant reduction in vision are common in MPS. A large number of patients with MPS from the Colombian southwestern present corneal opacification, which can lead to difficulties in their diagnosis and follow-up.Therefore, it is necessary to promote timely diagnosis, monitoring and treatment of the disease, to recognize and evaluate the typical ocular features that appear early in patients with MPS thus ensuring a better
quality of life.

P-038 - EVALUATION OF EZETIMIBE AND PRANLUKAST AS PHARMACOLOGICAL CHAPERONES FOR MORQUIO A

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INTRODUCTION: Morquio A syndrome (MPS IVA) is caused by mutations in gene encoding for the lysosomal enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS). Although the enzyme replacement therapy (ERT) has shown some clinical improvements, it has limited effects on skeletal, corneal, and heart valvular complications, along with issues of immunogenicity, short half-life, and high cost. In this sense, it is necessary to explore alternatives that improve ERT or design new therapeutic approaches. Pharmacological chaperone therapy has been experimentally tested for several lysosomal storage diseases including MPS II, IIIC, and IVB, but not for MPS IVA.
OBJECTIVE: In this study, we describe the in-vitro characterization of two pharmacological chaperones for human GALNS.
MATERIALS AND METHODS: Compounds were identified in-silico against a set of drugs approved for human use. Interaction with the active cavity of the enzyme was evaluated using a recombinant GALNS. Efficacy was evaluated using Morquio A skin fibroblasts with different mutations. In addition, the selected drugs were tested in chondrocytes and cardiomyocytes differentiated from induced pluripotent stem cells (iPSC) from Morquio A patients.
RESULTS: Through a molecular docking-based virtual screening, we identified ezetimibe and pranlukast as potential pharmacological chaperones for GALNS. These compounds

bound to the GALNS active cavity and increased thermal stability of the enzyme in experiments. Both compounds increased the enzyme activity of recombinant GALNS produced in bacteria, yeast, and HEK293 cells. MPS IVA fibroblasts treated with these molecules exhibited increases in GALNS proteins and enzyme activity, and reduction in lysosomal mass. The abnormalities of autophagy pathway found in the patient cells were also ameliorated after treatments with these two compounds. Noteworthy, combination treatment of recombinant GALNS with ezetimibe or pranlukast exhibited an additive effect on reduction of the enlarged lysosomal mass. Reduction in lysosomal mass was also observed in MPS IVA chondrocytes and cardiomyocytes differentiated iPSC.
CONCLUSIONS: The results demonstrate that ezetimibe and pranlukast can be used in the production process of recombinant GALNS. Ezetimibe showed the potential to be used as a monotherapy for Morquio A treatment. Noteworthy, ezetimibe and pranlukast may be used in combination with ERT to improve the therapeutic efficacy for MPS IVA patients.

P-039 - IN VITRO EVALUATION OF BROMOCRIPTINE AS A POTENTIAL PHARMACOLOGICAL CHAPERONE FOR MORQUIO A DISEASE

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INTRODUCTION: Morquio A syndrome (mucopolysaccharidosis IVA, MPS IVA), is a lysosomal storage disorder caused by deficiency of the enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS). This enzyme hydrolyzes the sulfo-ester bonds of the glycosaminoglycans chondroitin-6-sulfate and keratan sulfate. Currently, MPS IVA treatment is mainly based on enzyme replacement therapy (ERT), which has shown some clinical improvements. Nevertheless, it has limited effects on skeletal, corneal and heart valvular complications along with issues of immunogenicity, short half-life, and high cost. In this sense, it is necessary to develop new therapies that improve the therapeutic efficacy for MPS IVA patients.
OBJECTIVE: In this study, we describe the characterization of a GALNS pharmacological chaperone identified by virtual screening.
MATERIALS AND METHODS: Bromocriptine was identified using the crystal structure of human GALNS and molecular docking-based virtual screening against a subset of ZINC. Bromocriptine was evaluated using a recombinant GALNS and Morquio A skin fibroblasts.
RESULTS: Computational analysis suggested that Bromocriptine binds to the active cavity of GALNS in a similar position of natural GALNS substrates. In-vitro evaluation using recombinant GALNS produced in Pichia pastoris showed that bromocriptine inhibits enzyme activity to 24.4% at 10 μM. These results suggest a competition with the fluorogenic substrate for the active cavity of the enzyme, which confirmed the computational models. We observed a 54% increase in GALNS activity during production of recombinant GALNS in HEK293 compared to control cells. Finally, MPS IVA GM00593 fibroblasts (p.R386C/p.F285del) treated with 10 μM bromocriptine allowed an increase of 60% in GALNS activity, while MPS IVA GM01361 fibroblasts (p.R61W/p.W405_T406del) treated with 0.1 μM bromocriptine, generated a 14.2% increase in GALNS activity. Finally, GALNS activity in GM00958 fibroblasts (p.A393S), was not improved in any treatment with bromocriptine.
CONCLUSIONS: Overall, the results suggest that bromocriptine is a competitive inhibitor of GALNS and might has a positive impact in the production of recombinant GALNS. In addition, this drug increase activity of mutated GALNS in a mutation-based manner. These novel GALNS pharmacological chaperone should has potential to be further developed to improve the treatment for MPS IVA.

P-040 - MUCOPOLYSACCHARIDOSES TYPE IIID: REPORT OF THE FIRST PATIENT IDENTIFIED BY THE MPS BRAZIL NETWORK

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INTRODUCTION: Mucopolysaccharidosis type IIID (MPS IIID) or Sanfilippo syndrome type D is caused by deficiency of the lysosomal enzyme N-acetylglucosamine-6-sulfatase. Among the four subtypes of Sanfilippo syndrome, this is the least frequent.
OBJECTIVE: To investigate a patient with clinical suspicion of mucopolysaccharidosis type III, in whom the more common types IIIA, IIIB and IIIC were previously excluded.
MATERIALS AND METHODS: Blood and urine were collected for biochemical tests (enzyme assays, glycosaminoglycans – GAGs - measurement by dimethylmethylene blue – DMB - colorimetric method,

identification of GAGs species by electrophoresis, and analysis of GAGs by liquid chromatography/tandem mass spectrometry–LC/MS/MS) and molecular analysis (gene sequencing by next-generation sequencing – NGS - using a customized panel which includes the GNS gene). A few other sulfatases were assayed to exclude multiple sulfatase deficiency. Age-matched controls were used for the quantitative measurements of GAGs.
RESULTS: The patient had deficient activity of N-acetylglucosamine-6-sulfatase (0,55 nmol/24h/mg of protein; normal range: 7-22) in leukocytes. Increased levels of urinary GAGs (374 µg/mg of creatinine; normal age-range: 67-124) were detected by DMB assay, and presence of heparan sulfate in urine was observed in the electrophoresis. LC/MS/MS of urinary GAGs revealed high levels of heparan sulfate (HS-0S: 85 ng/mg of creatinine [average age-matched controls: 2 ng/mg of creatinine], HS-NS: 35 ng/mg of creatinine [average age-matched controls: 0.5 ng/mg of creatinine]). NGS identified the variant c.624+1G>T in homozygosis in the GNS gene.
CONCLUSIONS: To the best of our knowledge, we are reporting the first Brazilian patient with MPS IIID.

P-041 - NOVEL MUTATION IN NAGLU GENE CAUSES SANFILIPPO SYNDROME TYPE B IN A CUBAN PATIENT.

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INTRODUCTION: Mucopolysaccharidosis IIIB (MPS IIIB) is an autosomal recessive disorder caused by an enzyme deficiency of alpha-N-acetyl-glucosaminidase, resulting in excess intralysosomal accumulation of heparan sulfate. The clinical spectrum varies, but is usually characterized by developmental delay, behavioral abnormalities and sleep disturbance in early childhood. Homozygous or compound heterozygous conditions in the NAGLU gene (NM_000263.3) are the cause of this syndrome. More than 100 mutations in this gene have been reported. Purpose: The aim of this presentation is to describe the clinical, biochemical and molecular findings of a Cuban patient with MPS IIIB, which have a novel pathogenic variant in NAGLU gene and unusual clinical signs.
METHODOLOGY: The diagnosis was performed by clinical findings suggestive of MPS, qualitative chemical tests and Thin Layer Chromatography (TLC) for urinary glycosaminoglycans, enzyme assay for N-α-acetylglucosaminidase and Sequence analysis of IDUA gene. The silico functional prediction was performed using Mutation Taster and mutalyzer 2.0.28.
RESULTS: The male patient was born after 38.5 weeks of gestation by normal vaginal delivery. He had a healthy birth weight of 3.28 kg and a length of 50cm. The early clinical characteristics observed by the parents were recurrent infections and diarrhea. During the first years the patient presents frequent respiratory infections, autistic and hyperactive behavior and neurological deterioration. He also experiences an occasional sleep disorder. Currently the patient has a slightly coarse facie, sinofris, progressive neurological deterioration, conduct disorder, language delay, regression and loss of acquired skills. Ulcerative colitis and intestinal polyps has being diagnosed. The biochemical assays showed an elevated heparan sulfate urinary excretion, and very low intralysosomal enzymatic activity. In the molecular study of NAGLU gene we detected the novel mutation c.640dupC; p.L214Pfs*59. The patient was a homo-zygote for the mutation and it was also seen in the Sanger sequence chromatogram of his parents. This variant was classified as disease causing during “in silico” evaluation.
CONCLUSION: The suggestive clinical findings and the enzymatic activity levels allowed the patient diagnosis as Sanfilippo B syndrome. The molecular study confirmed the presence of a novel mutation associated with this disorder.

P-042 - SCREENING OF MUTATION C.1360 C> T IN THE HGSNAT GENE IN TUNJA, BOYACÁ - COLOMBIA.

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INTRODUCTION: Mucopolysaccharidoses (MPS) are an heterogeneous group of genetic diseases that belong to lysosomal storage disorders. These diseases are characterized for multisystemic affectation associated with progressive motor disability, variable cognitive deficit and decrease in life expectancy. In Colombia, a population cluster was found in Boyacá (Villa de Runta) for MPS IIIC, located whith in 5 minutes from the department capital (Tunja) and has an estimated incidence of 1: 200 live births, where the main variant found was g.1360C > T in HGSNAT gene.
Given the high incidence of this subtype of MPS in Boyacá, it is considered essential to study the population frequency of the mutation c.1360C> T in HGSNAT gene in Tunja city.
OBJECTIVES: To analyze the pathogenic variant c.1360 C> T in HGSNAT gene in 400 individuals of Tunja population, from neonatal TSH dried blood spots, to calculate the frequency of heterozygotes in Tunja.

MATERIALS AND METHODS: Cross-sectional study in neonatal screening samples, after signing informed consent. The detection of the different genotypes in HGSNAT gene is carried out by High Resolution Melting - PCR (HRM-PCR); confirming carriers and affected by sequencing.
RESULTS: 108 samples analyzed allowed the detection of 2 patients with melting curves similar to that observed in the genotype of the heterozygous control, and 3 patients with melting curves similar to that observed in the genotype of the homozygous mutant control. 103 samples have a melting curve pattern similar to the wild genotype.
DISCUSSION: This cost-effective technique has allowed the rapid detection of non-wild type genotypes in a population at high risk for autosomal recessive diseases. These studies are valuable tools to evaluate the need to create specific programs for the study of carriers in inbreeding regions like Boyacá.

P-043 - UNRAVELING CLINICAL PHENOTYPES IN SANFILIPPO SYNDROME TYPES A AND B: CLINICAL, BIOCHEMICAL AND NEUROIMAGING FINDINGS IN A COHORT OF BRAZILIAN PATIENTS

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INTRODUCTION: Mucopolysaccharidosis type III (MPS III; also known as Sanfilippo syndrome) belongs to a group of rare, genetic lysosomal storage disorders and is characterized by a deficiency in 1 of 4 enzymes involved in the degradation of heparan sulfate. Four subtypes of MPS III (A–D) have been identified based on the enzyme deficiency, along with their underlying genotypes and biochemical pathways.
OBJECTIVES: To report 12 Brazilian MPS III patients (5 MPS IIIA and 7 MPS IIIB) and their "journey to diagnosis".
MATERIALS AND METHODS: Clinical, biochemical and radiological data retrospective analysis
RESULTS: Symptoms generally began between the ages of 2 and 6 years and include developmental and language delays, hyperactivity unresponsive to medication, aggressive behavior and sleep disorders. All patients – but one – showed the typical progression of the disease, divided into 3 phases: phase I with developmental and language delay, frequent ear and respiratory infections, and diarrhea (not present in 4 patients who showed no apparent gastrointestinal features); phase II with progressive cognitive deterioration, behavioral difficulties, and sleep disturbances was present in all 12 patients; phase III with dementia, motor function decline, swallowing difficulties, and spasticity was seen in 10 patients (all of them older than 10 years of age)
CONCLUSION: Patients with Sanfilippo can also present with symptoms that masquerade as a behavioral disorder. Several reports have shown patients to present with symptoms consistent with a variety of behavioral disorders, including autism, attention deficit disorder, and pervasive developmental disorder, which have resulted in misdiagnoses or delayed diagnosis of MPS III. All of our patients showed behavior problems in some point of the disease (attention deficit disorder and autism were the first diagnosis in 9 out of 12 patients). In our cohort, patients with MPS IIIA showed earlier onset of the disease, but no other clinical features that could differentiate it from MPS IIIB patients. Nevertheless, MPS IIIB patients showed wide range of clinical presentation with some early onset presentations (under 1 year of age) to the classical childhood presentation (2-4 years of age).

P-044 - MORPHOLOGICAL FINDINGS IN BLOOD SMEARS EXAMINATION OF PATIENTS WITH MUCOPOLYSACCHARIDOSIS TYPE VII (MPSVII)

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INTRODUCTION: Mucopolysaccharidosis VII (MPS VII) is an ultra-rare inborn error of metabolism caused by the deficiency of lysosomal enzyme Beta-glucuronidase (GUS). Phenotype may vary from severe form characterized with non-immune hydrops fetalis, skeletal dysplasia and mental retardation, to attenuated forms with skeletal abnormalities mainly. Biochemical diagnosis is made by the measurement of GUS activity in dried blood spots or leukocytes, and finding the causal mutations in GUSB gene. Cytomorphological alterations in leukocytes of patients with different lysosomal disorders, including mucopolysaccharidosis, have been reported.
OBJECTIVE: The aim of this study was to evaluate leukocyte cytomorphology in blood smears from patients with diagnosis of MPS VII
MATERIALS AND METHODS: Peripheral blood from 5 MPS VII patients (ages: 2, 4, 12, 13 and 22-year-old), were obtained by venipuncture and blood smears were stained with May Grunwald – Giemsa. Leukocyte cytomorphology was evaluated at 100X by optical microscopy.
RESULTS: Blood smears from 5 MPS VII patients were analyzed. All of them presented cytomorphological alterations in leukocytes from peripheral blood. Alder-Reilly inclusions were observed in neutrophils and eosinophils mainly, and occasionally were found in lymphocytes and monocytes. Also,

neutrophils showed thicker azurophilic granulations similar to the toxic granulations seen in patients with severe infections. Lymphocytes and monocytes observed presented cytoplasmic vacuoles and some of them showed granular inclusions.
CONCLUSIONS: Cytomorphological alterations were observed in peripheral blood smears from MPS VII patients. These alterations were found in different types of leukocytes, in a greater or lesser degree of complexity, regardless age of the patients. Blood smears examination could contribute with information to support diagnosis of MPS VII, as well as it could be an alert to suspect this disorder.

P-045 - OXIDATIVE STRESS IN CUBAN PATIENTS WITH MUCOPOLYSACCHARIDOSIS TYPES I, II, III AND IV WITHOUT ENZYME REPLACEMENT THERAPY.

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INTRODUCTION: Mucopolysaccharidoses (MPSs) are caused by deficiency of lisosomal enzyme activities needed to degrade glycosaminoglycans. These syndromes share many clinical features although to variable degrees. MPSs have a chronic and progressive disease course and involve multiple organs systems. Some of them have enzyme replacement therapy but Cuban patient have not this possibility. The unbranched polysaccharides accumulation in fluid and lysosome can explain some of the metabolic and clinical phenotypes. Besides inflammation, mitochondrial dysfunction, affections in autophagy and endoplasmic reticulum stress have been demonstrated in those disorders. Many researches reports oxidative stress presence in MPS patient. This condition has not been studied in Cuban patients diagnosed with different types of MPSs yet. Purpose: Considering these facts the aim of this study was evaluated oxidative stress parameters in Cuban Patients.
METHODOLOGY: A case and controls study was carried that included patients with MPS I, II, III and IV and matched controls in age and sex. Plasma levels of malonyldialdehyde (MDA), advanced products of protein oxidation (APOP), free thiol groups, uric acid, creatinine, iron, ferritin, trasferrin, ceruloplasmin and calcium were measured. Also, the intraerythrocytic activities of superoxide dismutase (SOD1), catalese (CAT) and glutathione peroxidase were quantified. All the techniques used were spectrophotometric.
RESULTS: Patients showed an increase in MDA, APOP and calcium levels compared to controls and the Cuban reference values. There was a decrease in the SDO1 activity and thiol groups concentrations in patients. No differences were found for the rest of the parameters measured.
CONCLUSIONS: The increase of the oxidative damage and the decrease in the antioxidant capacity suggest thatt the oxidative stress process is presence in those Cuban patients. These results suggest a beneficial effect if we use an antioxidative therapy while acceding an enzyme replacement therapy is beyond our budget.

P-046 - MUCOPOLYSACCHARIDOSIS: IS LESS DIAGNOSED THAN BELIEVED?

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INTRODUCTION: Mucopolysaccharidosis is a progressive, chronic and rare lisosomal storage disease due to accumulation of glicosaminoglicans (GAGS) caused by deficiency of any of the catabolic enzymes. It compromises several organs and systems such as CNS, bone, liver, cornea, hearing with variable severity. Because of this and low prevalence of the disease, early diagnose turns difficult.
OBJECTIVE: Assess the existence of patients with undiagnosed MPS disease at Genetic Unit in Complejo Médico Policia Fedral Argentina Hospital Churruca-Visca (CABA - Argentina).
MATERIALS AND METHODS: A retrospective analysis of 491 clinical histories of patients attended in 2016 were made. 52 of them were selected through stablished clinical criteria. Selected patients were analyzed through dried blood spots (DBS) for enzymatic activity for different MPS. All of the patients included in the study signed informed consent.
RESULTS: From 52 patients selected only 42 were contacted of whom 22 attended clinical consultation for clinical reevaluation. Only 16 were selected for enzymatic activity test in DBD. One positive test was detected for beta-D-glucuronidasa deficiency related to MPS VII diagnose in a 12 year old patient.
CONCLUSION: Through this analysis we can conclude there´s MPS subdiagnosis in the Churruca-Visca hospital population. As a consequence of 491 clinical histories revaluation a 12 year old patient was diagnosed for MPS VII. These results make us ask ourselves how many non diagnosed MPS patients exists and about the real world wide prevalence of MPS.

P-047 - COEXISTENCE OF MUCOPOLYSACCHARIDOSIS TYPE IVA AND NEUROFIBROMATOSIS TYPE 1 IN A CHILD WITH A SEVERE PHENOTYPE

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INTRODUCTION: Mucopolysaccharidosis IVA (MPS IVA) is a genetic disease with an autosomal recessive inheritance. Prevalence ranged from 1 case per 71.000 to 1 per 500.000 live births. Neurofibromatosis type 1 (NF1) is a disease with an autosomal dominant inheritance that affects multiple organ systems and has a wide range of variable clinical manifestations. Average global prevalence is ~1 case per 3.000 individuals.
OBJECTIVES: The aim of this report is to present the first case in the literature of the accidental coexistence of MPS IVA and NF1.
METHODOLOGY: Case report, it was approved by patient's family and the ethics committee.
RESULTS: The patient, now 4-year-old Colombian boy, is the third child of non-consanguineous healthy parents. He was vaginally delivered at 38 weeks of gestation. His birth weight was 3.4 kg (0.3 SD), length was 49 cm (-0.4 SD) and occipital frontal circumference was 42 cm (5.9 SD). He presented since his birth café-au-lait macules, skeletal bone dysplasia and swallowing disorder. He had a short stature (-3.6 SD) and low weight (-2.1 SD) at the age of 4 years. His medical history consisted of recurrent pneumonias (14 episodes), asthma and psychomotor retardation. Physical examination findings were macrocephaly, corneal clouding, tongue protusion dystonia, dental fractures, pectus carinatum, generalized dysostosis, thoracic hyperkyphosis, giant melanocytic nevus and genu valgus.
The patient have the pathogenic variant c.901G>T (GalNAc-6-sulfatase, GALNS, E.C.3.1.6.4) in homozygous state, which has a founding effect in our country, and the germline variant c.2326-1G>A (NF1 gene). A normal male karyotype (46, XY) was identified. Radiological findings showed bilateral hip dysplasia, platyspondyly and unfused posterior arch of C1. Enzyme replacement therapy was started at 2-years-old (elosulfase alfa, VIMIZIM®) with good clinical response and safety.
CONCLUSION: To our knowledge this is the first reported case of the coexistence of these two diseases, our hypothesis is that it was accidental, because they have different pathophysiologies. The patient has a severe phenotype that involves multiple organs and systems, taking into account that NF1 and MPS IV4 can affect the bone system. He had a good clinical response to enzymatic therapy however, his prognosis is poor.

P-048 - STANDARDIZATION OF A HORIZONTAL ELECTROPHORESIS METHOD FOR THE CHARACTERIZATION OF SERUM PROTEINS PRIOR TO DETERMINATION OF GAG'S IN MUCOPOLYSACCHARIDOSIS PATIENTS

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INTRODUCTION: In this work the standardization of the agarose gel electrophoresis (AGE) method was made for the determination of proteins with a "Horizontal System", between two separation reagents with SDS (sodium dodecyl sulfate) (causes denaturation of proteins) and without SDS; using different reagents such as diluent, buffer charge and developer, allowing to separate the molecules in weight and charge, under conditions of temperature, pH, and voltage.
In our university clinical laboratory there are no references for the standardization of electrophoresis METHODS: With our work it is possible to separate the proteins from the serum before being used for the separation of GAGs and the classification of the different types of Mucopolysaccharidosis. We propose a statistical analysis of the normal distribution between the two reagents.
OBJECTIVES: Standardize the electrophoresis method for the determination of serum proteins, prior to the determination of GAGs for the classification of Mucopolysaccharidosis.
Compare two separation reagents with SDS and without SDS.
MATERIALS AND METHODS: Materials; Agarose Gel (2%); (0.5X) pH 8 Buffer (TBE) tris base, boric acid, (0.5M) EDTA; buffer charge, (0.25%) bromophenol blue, (40%) sucrose; (2%) SDS; Samples: blood serum; METHOD: Horizontal electrophoresis in agarose gel, the equipment was programmed under conditions of 120 V, 1.0 mA, 1h at 20-25oC, according to the User`s Manual. 10µL of samples previously treated with and without (2%) SDS, heated at 95oC for 3 minutes and (40%) sucrose, (0.25%) bromophenol blue, in proportions 1: 1, 2: 1, 1: 2 , 1: 3. In the bands: dye solution (0.25%), coomassie blue, (40%) methanol, (10%) acetic acid, was used for 1 hour and was developed with distilled water.
RESULTS: The statistical analysis of normal distribution assumes equal variances with 0.958 (IC ± 1.299) and probability (p ? 1.00) using Anderson-Darling, Ryan-Joiner and Kolmogórov-Smirnov, there are no significant differences in the use or not of SDS.
CONCLUSIONS: It is recommended to use for the determination of GAGs and classification of Mucopolysaccharidosis.
The statistical analysis creates a support tool that allows determining the optimal conditions of temperature, pH and voltage, the use or not of SDS.

P-049 - BETA-GLUCORONIDASE QUANTIFICATION IN DBS

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INTRODUCTION: Beta-glucuronidase (GUSB), is a lysosomal enzyme in charge of hydrolyzing the glycosidic bond, releasing glucuronic acid present in the structure of complex carbohydrates. Specifically the enzyme participates in the glycosaminoglycans degradation. GUSB deficiency results in the presentation of a skeletal dysplasia known as Mucopolysaccharidosis type VII (MPS VII) or Sly syndrome
AIM: This study shows the implementation of a fluorometric method of quantification of GUSB in DBS and the construction of reference values for our population.
MATERIALS AND METHODS: DBS samples were obtained from healthy subjects of different ages and both sexes, prior signed informed consent. For the quantification of GUSB a modification of Civallero 2006 was used. We establish reproducibility, stability and sensibility of the technique using normal and affected individuals.
RESULTS: Once the enzyme test was standardized by modifying the Civarello method, an intraassay and interoperative variation coefficient of 5% was achieved, the samples stability was tested for up to 210 days at 4 °c or room temperature; the reference values range for our population were established using of 79 normal samples (50.8-173.7 nmol/h/ml)
CONCLUSIONS: The study allowed verifying that the enzyme beta-glucuronidase is highly stable in dry blood samples over filter paper. The samples can be stored at 4 °C or at room temperature for up to 8 months. In addition, the reference values for our population were established providing the medical community with an additional tool for preliminary evaluation in the diagnostic process of patients with suspected mucopolysaccharidosis type VII.

P-050 - REPORT OF A MPS TYPE VII PATIENT INVESTIGATED WITH TANDEM MASS SPECTROMETRY AND TARGETED NEXT GENERATION SEQUENCING

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INTRODUCTION: Mucopolysaccharidosis type VII (MPS VII), or Sly syndrome, is an ultra-rare autosomal recessive condition caused by storage of glycosaminoglycans (GAGs) which results from the deficient activity of the enzyme β–glucuronidase, encoded by the GUSB gene.
OBJECTIVE: To report a MPS VII patient investigated with newer biochemical and molecular METHODS:
MATERIALS AND METHODS: An eight years old patient from Bahia state was investigated, due to the presence of growth retardation, infiltrated face, corneal opacity, joint stiffness, gibbus deformity, neurological regression with cognitive impairment, respiratory distress and multiple dysostosis. Urine, blood, and dried blood spots (DBS) were collected for biochemical (enzyme assays by fluorimetry; evaluation of GAGs by colorimetry, electrophoresis, and liquid chromatography/tandem mass spectrometry - LC/TMS), and molecular analysis (targeted next-generation sequencing-TGNS, using a gene panel including the genes associated to MPS I, II, VI and VII).
RESULTS: Low activity of β-glucuronidase was detected in DBS, plasma and leucocytes; increased concentration of urinary GAGs was observed in the colorimetric assay, with presence of dermatan-sulfate (DS) and heparan-sulfate (HS) detected in the electrophoresis. LC/TMS revealed high levels of DS (20,18 ng/mg creat, with average age-matched controls = 6,15), HS-0S (22 ng/mg of creat, with average age-matched controls = 1,02 ng/mg) and HS-NS (6,41 ng/mg of creat, with average age-matched controls = 0,43). TGNS identified the pathogenic variant c.526C>T/p.Leu176Phe (HGMD CM950598) in homozygosis in the GUSB gene.
CONCLUSIONS: Although our MPS Brazil Network already diagnosed 23 MPS VII Brazilian patients since 1982, this is the first report of a MPS VII patient in whom the GAGs analysis was performed with LC/TMS and the abnormal result was confirmed by TGNS.

P-051 - EVALUATION OF PATIENTS WITH MUCOPOLISSACARIDOSE TYPE 1 WHO CARRIED OUT TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS IN BRAZIL

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INTRODUCTION: Type I mucopolysaccharidosis is a lysosomal disease, classified into severe and attenuated forms. Although for the severe form hematopoietic stem cell transplantation (HSCT) is recommended whenever the diagnosis is made before 36 months, in practice few patients perform HSCT.
OBJECTIVES: To review and describe the steps involved in the indication, performance and follow-up of patients with severe MPS I undergoing HSCT in Brazil, and to evaluate their results.
MATERIALS AND METHODS: A cross-sectional review study was carried out at the Medical Genetics Service of the Hospital de Clínicas of Porto Alegre, with the participation of the collaborating centers of the MPS Brazil Network, from March 2015 to January 2018. 9 patients were included. The variables evaluated were: transplantation center, age at diagnosis, mutations, type of donor, use of enzyme replacement therapy, age at transplantation, outcome after HSCT. The data were compared with those available in the international literature.
RESULTS: the mean age at transplantation was 3.7 years; however, mean age was reduced to 1.8 years when we considered the 8 patients who were transplanted after 2010. Considering these 8 patients, the age at diagnosis was 9 months, and the time between diagnosis and the first transplant ranged from 5 to 18 months. Conclusion and discussion: Neutrophilic time was comparable to those reported in the literature, which may demonstrate that the technique of HSCT is in agreement with the overall experience. Although diagnoses were made early, there was a large gap between diagnosis and HSCT procedure. The delay between diagnosis and the first HSCT may have contributed to the high mortality rate (4/9 patients died due to procedure complications) and low efficiency (6/9 had an unfavorable treatment outcome). In Brazil, 301 patients were diagnosed with MPS I so far and, to the best of our knowledge, only 9 performed HSCT. These data reiterate the need to take measures that may contribute to improve the efficiency of HSCT in MPS I in Brazil, in order to obtain favorable results closer to those observed in North America and Europe (above 80-90% of survival and favorable outcome).

P-052 - LEUCOCYTE ALPHA-N-ACETYL-GLUCOSAMINIDASE ANALYSIS IN COLOMBIAN CONTROL POPULATION AND AFFECTED PATIENTS WITH TYPE B SAN FILIPPO SYNDROME

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San Filippo syndrome is part of a group of glycosaminoglycan metabolic disorders commonly named Muchopolysaccharidoses. It is an autosomal reccesive inherited disorder affecting heparan sulfate metabolism via lysosomal enzymatic deficiency. Four different phenotypes have been described (A,B,C,D). This sub-classification can be done only by measurement of enzymatic catalytic activity on leucocytes or fibroblasts instead of clinically due to the variability in disease symptoms and affectations on osteoarticular and neurologic system among others. Here we present an approach to Type B San Filippo syndrome diagnosis through leucocyte enzymatic screening in a high-risk population.
MATERIALS AND METHODS: Analysis of leucocyte alpha-N-acetyl-glucosaminidase (NAGLU) was done by fluorometric method to asses cleavage of 4Methylumbelliferyl 2Acetamide 2Deoxy Alpha Dglucopyranoside used as a substrate in a buffer solution of citrate-phosphate 0.2M pH4.3. Screened population included 256 (0-20 years age) patients with MPS clinical suspicion and 450 normal controls were used to establish a normal range value. RESULTS AND **CONCLUSIONS**: Registered range of activity for controls was 0.6-4.26 nmol/mgprotein/hour. From 256 patients screened, seven cases (2.7%) were detected (ages between 3-16years). Activity range 0.0–0.24 nmol/mg protein/hour. More studies are needed to establish Colombian prevalence for this and the other 3 subtypes of the disease.

P-053 - HEALTH-RELATED QUALITY OF LIFE: A FOLLOW-UP TO ENZYMATIC REPLACEMENT THERAPY IN ADULT PATIENTS WITH MUCOPOLYSACCHARIDOSIS

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INTRODUCTION: The impact of enzyme replacement therapy (ERT) evaluated in phase I and II clinical trials has clinical results measured on physical tests, which assess aspects such as exercise tolerance, lung capacity, among others. It is necessary that this clinical impact of ERT in patients with Mucopolysaccharidosis be evaluated under a view of quality of life related to health in its social, psychological and emotional dimensions.
OBJECTIVE: To evaluate the impact of ERT on the quality of life related to health in patients with Mucopolysaccharidosis type IV A in a third level institution Pereira-Colombia
MATERIALS AND METHODS: A follow-up was carried out on a series of cases of patients with Mucopolysaccharidosis (MPS) type IV A (children and adults) confirmed by molecular

tests. An evaluation of the quality of life related to health was carried out before the start of enzyme therapy, and after a year of treatment a second evaluation was performed. Descriptive statistics and nonparametric inference tests were applied.
RESULTS: Four adult patients were followed up, with an average age of 32 years. At the beginning of the therapy the domains of quality of life show a moderate affectation (score 40 to 60), significant clinical changes are detected in all the domains with an improvement in the quality of life, Health domain (difference 4 points p = 0.875) psychological (difference 30 points p = 0.065) social (difference 32 0.0625) environment (difference 11 p = 0.31), however statistically this is probably not detected in the few patients in the sample.
CONCLUSIONS: Enzymatic therapy for adults patients with mucopolysaccharidosis type IV A brings improvement in aspects of mobility, pain reduction, resulting in changes in the health, social and psychological domains.

P-054 - EYE PATHOLOGY IN MUCOPOLYSACCHARIDOSIS TYPE I AND EFFECTS OF ENZYME REPLACEMENT THERAPY

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INTRODUCTION: Mucopolisaccharidoses type I (MPS-I) is an lysosomal storage disorder caused by deficiency in alpha-L-iduronidase (IDUA), which is involved in the degradation of glycosaminoglycans (GAG). Accumulation of GAG in ocular tissues can cause corneal opacity or neurosensory complications. Nevertheless, the time course and effect of intravenous enzyme replacement (ERT) in MPS-I are undetermined.
OBJECTIVE: To investigate the ocular alterations overtime as well as the effect of ERT on eye disease in MPS-I mice. To describe the histological findings in the cornea from a MPS-I patient treated for over a decade with ERT.
MATERIALS AND METHODS: Eyes were obtained from 2, 6 and 8 months-old normal and MPS-I mice. A group of MPS-I mice received ERT (1.2mg/kg of laronidase®) every 2 weeks from 6 to 8 months. Paraffin sections were stained with Hematoxylin-eosin/Alcian-blue, for GAG visualization, or picrosirius-red, for collagen structure. Corneal lesion was evaluated according to a scale grade of alteration. Thickness of cornea and retinal nuclear layer were measured overtime and compared with age-matched controls. Biochemical and histological evaluation was performed in the cornea from a MPS-I patient after 13 years of ERT.
RESULTS: Cornea from MPS-I mice showed GAG accumulation and structural alteration from two months ($p<0.05$), with a lesions score greater than normal mice. Collagen structure seemed altered at 8 months, but only a trend towards reduction in the MPS I mice was observed. A progressive loss of photoreceptors was found in the outer nuclear layer, starting at 6 months (24% reduction;$p<0.01$). Mice treated with ERT did not show improvements in eye pathology. A similar finding was observed in the cornea from a MPS-I patient. Her cornea still presented vacuoles with GAG accumulation within distended stromal cell and undetectable IDUA activity, despite ERT.
CONCLUSION: We provide data on the time course of ocular alteration in MPS I mice. Corneal alterations occur early, while retinal pathology shows up later in life, both of which probably affect the visual function. Our data suggest that ERT is ineffective to correct the ocular alterations in MPS-I mice and patients, indicating that the enzyme does not access the tissue at appreciable levels.

P-055 - SELECTIVE RETROSPECTIVE SCREENING DETECTS FIVE NEW CASES OF MUCOPOLYSACCHARIDOSIS TYPE VII

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INTRODUCTION: Mucopolysaccharidosis type VII (MPS VII; Sly syndrome) is a highly heterogeneous, ultra-rare lysosomal storage disorder, caused by the deficiency of β-Glucuronidase (βGUS). Patients' phenotypes vary from severe forms with non-immune hydrops fetalis (NIHF), skeletal dysplasia and mental retardation to milder forms with fewer manifestations. Epidemiological data of this disorder is really scarce and underdiagnosis of this disorder is suspected. Enzyme replacement therapy for MPS VII is available since 2017.
OBJECTIVE: To present results from a retrospective screening of MPS VII in patients with clinical features compatible with MPS spectrum, in whom other MPS had been ruled out previously.
MATERIALS AND METHODS: For this purpose, we analyzed 584 dried blood spots samples from Argentinean patients with clinical suspicion of MPS, collected between 2017 and 2018, where MPS I, II, IVA, IVB and VI were ruled out previously. βGUS enzyme activity was measured by fluorometric method with deproteinization. β-Galactosidase activity was also measured as a control enzyme, to assess

quality of DBS samples. GUSB gene was analyzed by Next Generation Sequencing.
RESULTS: We detected 4 patients with βGUS deficiency in DBS, from 584 samples analyzed. Ages of positives cases were 4, 11, 12 and 12 years old. The fifth case was a 2 years old girl, sister of one of the MPS VII patients diagnosed in this study, found from familiar screening. All five patients has a clinical course similar to MPS I, including the same degree of clinical heterogeneity. None of the patients had NIHF.
CONCLUSIONS: We detected 4 patients with βGUS deficiency in cases where others MPS but no MPS VII were suspected. Also, we could detect an additional case by familiar screening. These results clearly remark the importance of ruling out MPS VII in patients with phenotype and clinical features compatible with MPS spectrum, since the different types of MPS may have similar manifestations and share some signs and symptoms.

P-056 - CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF MUCOPOLYSACCHARIDOSIS TYPE IV A (MORQUIO SYNDROME A) IN A CHILEAN REFERENCE CENTER.

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INTRODUCTION: Mucopolysaccharidosis IVA (MPS IVA; Morquio A) is an autosomal recessive lysosomal storage disease caused by deficiency of N-acetylgalactosamine-6-sulfate sulfatase (GALNS), leading to intracellular accumulation of keratan sulfate and chondroitin-6-sulfate. Clinical manifestations include short stature, hypermobile joints, and dysostosis multiplex, including atlantoaxial instability and cervical cord compression. They also present typical dysmorphisms, corneal opacities, hearing loss, miocardic insufficiency, valvular stenosis and obstruction of the respiratory tract. Cognitive function is minimally impaired. Clinical presentations reflect a spectrum of progression from classic (severe) to attenuated (mild) phenotype
OBJECTIVE: To describe phenotype, clinical features and laboratory findings of patients diagnosed with MPS-IV.
METHODS: Retrospective-prospective and descriptive study. Review of clinical records and laboratory findings of MPS-IV patients who have been evaluated at the Pediatric Neurology Ward of San Borja Arriarán Clinical Hospital. Patients consent/assent was obtained. The study was approved by the Institutional Ethics Committee.
RESULTS: 12 patients (7 female), median age 13.79 years. Median age at clinical suspicion 1.99 years. Median age at diagnosis 5.54 years. Phenotype: classic 11 patients, attenuated 1 patient. All the patients with the classic phenotype showed 0-2% of normal GALNS activity in dried blood spot (DBS), while the patient with attenuated phenotype had GALNS activity less than 44% of the lowest control value. Neurological features: 10/12 patients presented developmental delay of motor skills and 8/12 severe cervical rachistenosis (2 complicated with myelopathy). Multisistemic illness: 9/12 sensorioneural hearing loss, 8/12 alteration of cardiac and pulmonary function, 6/12 corneal opacities and 4/12 hepatomegaly. All patients have been treated with enzyme replacement therapy (median age at first dose 11.62 years, median total time on treatment 3.16 years), one discontinued due severe adverse effect.
CONCLUSIONS: almost all patients had a classic phenotype with only one patient with the attenuated form. This is consistent with the findings of the International Morquio Registry. A high phenotypic variability was observed, with the skeletal manifestations being the most consistent clinical feature with a wide range of non-skeletal features. This study provides an overview of the clinical manifestations and diagnosis of patients with MPS IVA in a chilean reference center.

P-057 - "GROWING PAINS": THE CHALLENGES OF GETTING OLDER WITH MUCOPOLYSACCHARIDOSES

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INTRODUCTION The mucopolysaccharidoses are caused by deficiencies in enzymes involved in the sequential degradation of glycosaminoglycans (GAGs), which are ubiquitous in connective tissues. The resulting impaired degradation of GAGs in cells and tissues leads to substrate accumulation causing progressive multi-organ dysfunction. Seven types of mucopolysaccharidosis (MPS) disorders have been described, with MPS III and MPS IV each having two or more biochemical subtypes
OBJECTIVES: To report a cohort of adult Brazilian MPS patients and their clinical aspects
MATERIAL AND METHODS: Clinical, biochemical and radiological features of 13 adult patients with MPS (6 males; 7 females)

DISCUSSION: MPS disorders are multi-organ diseases that require multi-disciplinary management involving clinical geneticists, metabolic physicians, orthopedists, general surgeons, neurosurgeons, pulmonologists, cardiologists, neurologists, anesthesiologists, otolaryngologists, ophthalmologists, dentists, transplant physicians, psychiatrists, and physiotherapists. Skeletal and joint abnormalities are observed in all patients but one (an adult with MPS III), most complaints were from hip pain, and difficulties to walk longer distances (mainly patients with MPS VIA). Most patients remain unemployed, living with their relatives and without going to college. Depression and anxiety were common features, in particular in two patients with MPS VI and MPS II, both with normal IQ. All patients referred that adult clinics were not aware of MPS disorders and multidisciplinary care was not possible.
CONCLUSION: The management of MPS in an adult clinical setting creates challenges due to the patients' short stature and medical complexity, the fact that most internists are unfamiliar with MPS disorders, and the limited availability of assistance for multi-disciplinary patient care (coordination of timely, patient-friendly, integrated care by different specialists) in adult clinics.

P-058 - HEARING LOSS IN MUCOPOLYSACCHARIDOSIS IVA IS GENOTYPE DEPENDENT

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As in all forms of MPS, reduction in hearing in patients with MPS IVA can be attributed to multiple causes. Firstly, conductive hearing loss can be present and is most likely secondary to recurrent upper respiratory tract infections and frequent serous otitis media. Conductive loss can also be caused by deformity of the ossicles. Secondly, sensorineural loss may occur as a result of GAG accumulation. Abnormal auditory brainstem response (ABR) results have been described and are thought to be a combination of middle ear, cochlear, eighth nerve, and lower brainstem pathology.
Reduced GALNS activity results in impaired catabolism of two glycosaminoglycans (GAGs), chondroitin-6-sulfate (C6S) and keratan sulfate (KS). Clinical presentations of MPS IVA reflect a spectrum of progression from a severe ”classical” phenotype to a mild “attenuated” phenotype. 180 mutations have been identified in the GALNS gene, which likely explains the phenotypic heterogeneity of the disorder.
MATERIALS AND METHODS: Fourteen patients were evaluated. All the patients underwent a tonal audiometry to determine their auditory thresholds, both aerial and osseous, likewise they evaluated low, medium and acute frequencies, thus being able to identify the type and degree of hearing loss

RESULTS: The following alterations were identified: mixed hearing loss 50% (7/14), sensorineural hearing loss 29% (4/14) and 21% (3/14) normal audiometry. All patients had the 901G> T (GLY301CYS) mutation (11 in homozygotes and 3 in heterozygosis). 100% of patients in heterozygosis did not have hearing impairment

CONCLUSIONS: The hearing losses generate in the patients difficulties in their school development and in the acquisition of language. It is important to perform hearing evaluations at an early age to obtain a diagnosis and timely treatment. Prophylactic antibiotics may be useful to manage recurrent infections due to abnormalities in the ears, nose, and throat. As the disease progresses, patients may experience mixed hearing loss and may require tympanostomy tube insertion and/or hearing aids. It is important to know the genotype to identify the hearing prognosis of patients

P-059 - DEMOGRAPHIC DISTRIBUTION OF MUCOPOLYSACCHARIDOSIS IN BAHIA, BRAZIL: A CROSS-SECTIONAL STUDY- 2019

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BACKGROUND: Mucopolysaccharidoses (MPS) with worldwide incidence of 1.9 to 4.5 per 100,000 live births and the most common incidence is about MPS I (1 to 100.000 live births). In Brazil, the MPS network reported the diagnosis of 250 cases diagnosed until 2008. In Bahia state, the most common MPS is type II and VI. In Monte Santo-BA, the incidence of MPS VI corresponds to 1 case per 5,000 live births and it is associated with a high rate of inbreeding marriages. This study makes it possible to recognize the distribution of MPS types in the state of Bahia, located in the northeastern region of Brazil, being useful for the development of programs to promote and optimize health care for these patients and their families. METHODS: Cross-sectional, observational, descriptive study, based on a review of the medical records of patients diagnosed with MPS, attended at the Medical Genetic Service of the University Hospital Professor Edgard Santos, Salvador, Bahia, Brazil.
RESULTS: There are 51 patients diagnosed with MPS: 15.6%, MPS I; 33.3%, MPS II; 9.8%, MPS III; 1.9%, MPS IV; 33.3%, MPS VI and 5.8%, MPS VII. The 7 regions of Bahia state in accordance with the division of the Brazilian Institute

of Geography and Statistics, 1990. In relation to the city of origin of the patients: 2.2% was from West region; 4.4%, São Francisco Valley; 17.7%, North Center; 13.3%, South Center; 37.7%, Northeast; 24.2% from the Metropolitan Region of Salvador and 13.3%, South Bahia. Monte Santo, a city in northeast Bahia, there is the largest number of patients with MPS VI (8 subjects). The distribution of MPS in Bahia is heterogeneous, with a higher concentration of cases in the Northeast of Bahia (NE), in the Metropolitan Region of Salvador (MS) and in the Center North (CN), on this order. In NE (16 subjects), MPS VI (10 subjects in NE) and MPS VII (3 subjects in NE) are the most prevalent.
DISCUSSION: This distribution may be related to the founding effect of Brazilian immigration, configuring important sites for epidemiological studies on the disease and to offer specialized care for these patients.

P-060 - SANFILIPO DISEASE IN A BOLIVIAN PATIENT, CARRIER OF UNCERTAIN SIGNIFICANCE VARIANTS FOR OTHER GENETIC PATHOLOGIES

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INTRODUCTION: The Sanfilippo´s disease or mucopolisacaridosis (MPS) 3A occurs in 1/70,000 newborns (NB), is a rare disease with an autosomal recessive pattern besides the enzyme replacement therapy is still in study. The Cornelia de Lange syndrome occurs in 1/45,000 NB and is autosomal dominant. The Ritscher Schinzel syndrome has few reported cases also with an autosomal dominant pattern. These three conditions share in common some facial dysmorphism and generalized developmental delay.
OBJECTIVE: To describe the case of a bolivian patient with Sanfilippo disease, carrier of others genetic variants.
MATERIAL AND METHODS. Male, 4 years old, product of 1st pregnancy of non-consanguineous parents, mother and father of 21 years. Without exposure to teratogens, he was born full-term, eutocic delivery, without significant family history. Pathological antecedents of psychomotor development delay and behavior disorders. Physical examination show normal head circumference, weight and height, coarse facies, facial hirsutism, low-set auricular implantation, horizontal palpebral fissures, thick lips. Neck and thorax short, dorsal kyphosis. Ataxic March, language absent. No cardiac or ophthalmological pathology.
RESULTS: Positive Berry test, Enzymatic dose arylsulfatase B, alpha iduronidase, Idurnate sulfatase normal. Exoma: Gen SGSH, exon 6 c.703G>A p.(Asp235Asn) corresponding to missense mutation, pathogenic variant, in silico deleterious, and Intron 6 c.745+1G>C corresponding to substitution, probably pathogenic variant, in silico without previous report. Gene SMC3, exon 11 c.874A>T p.(Ser292Cys) corresponding to missense mutation, variant of uncertain significance (VUS), tolerated in silico. Gen CCDC22, exon 4 c.421C>A p.(Pro141Thr) corresponding to missense mutation, variant of uncertain significance, in silico deleterious.
DISCUSSION: This is a compound heterozygote for Sanfilipo disease, with a pathogenic variant and another probably pathogenic. The coexistence of two other VUS in relation to the Cornelia de Lange syndrome and Ritscher Schinzel whose facial features are striking. This case could exemplify the epistatic action of the reported genes or the effects of modifier genes.

P-061 - PITFALLS IN THE RECOGNITION OF COGNITIVE PHENOTYPE IN PATIENTS WITH HUNTER SYNDROME (MPSII)

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Hunter syndrome (mucopolysaccharidosis II) is an X-linked disorder caused by the deficiency of iduronate-2-sulfatase. In this heterogeneous multisystemic chronic disorder, progressive and early cognitive decline occurs over time in 2/3 of the patients (severe or neuronopathic form of the disease) while cognition remains in the average range in the other third (attenuated or non neuronopathic form). The onset and the slowing of development is later and more variable than in MPSI and MPSIII starting at any age before 5 years old.
OBJECTIVE: To create awareness about problems identifying progressive neuronopathic forms of MPSII even using adecuate neurocognitive assessments.
METHODS: As part of a prospective, longitudinal, observational study to evaluate neurodevelopmental status in pediatric patients with MPSII (HIT 090) we have screened 11 patients and recruited 6 male patients with formal cognitive assessments every 3 months in a median period of 2 years. The inclusion criteria were age range 2-13, sufficient auditory capacity and Developmental Quotient (DQ) >55 at baseline. The tools used were Differential Ability Scale (DAS II) for IQ and Vineland Adaptive Behaviour Scale (VABS II).
RESULTS: In this small sample we have recognized 2 not related MPSII patients (ages 6 and 8 yo) previously categorized as having severe or neuronopathic form only by clinical impression but with borderline IQ and no cognitive decline during 2 years. Both had hyperactivity and language impairment probably secondary to early hypoacusia. One of them attended special school. By other hand, a 9 years old patient showed a stable low IQ (60-65) during the 18 months

period of study but previous assessments from age 3 to 6 had shown a significant decline from DQ above 100.
CONCLUSION: Identification of progressive neuronopathic phenotypes in MPSII is challenging. As new treatments are being developed for the neuronopathic form, to differentiate progressive from non progressive patients becomes crutial to evaluate efficacy of these treatments. A group of MPSII patients with mild behavioural-cognitive impairment but no declining over time ("pseudo-neuronopathic" form) should be identified as a minoritary phenotype.

P-062 - LABORATORY OF DISEASES LYSOSOMAL AS NATIONAL REFERENCE CENTER. THE CHALLENGE OF THE RELATIONSHIP WITH THE MINISTRY OF HEALTH

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INTRODUCTION: In 2015, Chile promulgated Law 20,850, which creates a financial protection system for high cost diagnoses and treatments with universal coverage. Among the pathologies included in the law are: Gaucher disease, Fabry disease, Mucopolysaccharidosis (MPS) Type I, II and VI. For the diagnosis of these pathologies, the Ministry of Health of Chile (MINSAL), has accredited INTA as the only Laboratory to carry out the diagnoses, which must be adjusted in accordance with the Law.
OBJECTIVES: To present the development of our laboratory to get to offer a total of 5 tests for enzymatic activities associated with pathologies included in the Law. To show the results obtained.
MATERIALS AND METHODS: Patients with clinical suspicion are included in the Oracle registry platform of MINSAL, by a physician in charge. Heparinized blood samples reach INTA. White blood cells are isolated, which are sonicated. The amount of proteins is determined by the extract obtained and simultaneously subjected to the specific tests. These tests correspond to an enzymatic reaction in a specific buffer, occupying a substrate that can generate a fluorescent or colored product. This product is quantified and its relation with the concentration of proteins allows assigning a final result. The results are loaded on the same platform.
RESULTS: 114 samples were analyzed from the start of the Law, confirming the diagnosis of 80 patients corresponding to: 25 cases with Fabry disease, 28 with Gaucher disease, 12 with MPS I, 11 with MPS II and 4 with MPS VI.
CONCLUSIONS: Since the implementation of Law 20,850, our laboratory has had to adapt pre and post analytical processes to comply with the guarantees granted by this law. The consolidation as a national reference laboratory for the confirmatory diagnosis of these pathologies, in the context of a law that guarantees access to treatment, requires us to maintain a constant quality control of all pre and post-analytical processes and to implement new diagnostic techniques.

P-063 - DIFFERENTIAL NATURAL HISTORY OF LATE INFANTILE CLN6 AND CLN2 DISEASES OF NEURONAL CEROID LIPOFUSCINOSES

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CLN6 and CLN2 diseases show onset ages at late infantile (LI) and adult (A) ages. CLN2 has also a juvenile or protracted form (1). The clinical course of LI-CLN6 and LI-CLN2 needs to be carefully differentiated to facilitate early diagnoses.
OBJECTIVES: To point out the differences among the natural history of LI-CLN6 and LI-CLN2 diseases. Three Argentine individuals suspected of a NCL were evaluated under clinical, biochemical, morphological and genetic criteria. Other 27 were formerly published as affected of CLN2 disease (1). The 3 CLN6 cases showed TPP1 values in the control´s range. Onset symptoms of LI-CLN2 cases were speech delay or failure at 2-4y, and short after that seizures, visual failure, movement disorder, early death. CLN6 cases showed symptoms onset at 2-3.3y with decreased motor function; frequent falls 2-4.5y; assisted march 4.4-6.11y; total prostration 5.11-9.6y; language delay 3.3-4y; speech difficulties 4.4-4.5y, speech loss 5.11-9.6y; visual loss 3-7y; blindness (only reported in 1/3 cases) 5y; refractory seizures with generalized atonic myoclonic movements and lateralization of the trunk 3-5.9y; early death: 1/3 15y, 1/3>18y 1/3 living at 10.3y. In the CLN6 disease the electron microscopy of skin biopsies showed dense fingerprint profiles and some curvilinear bodies (CV). The LI-CLN2 skin morphology was mostly CV. Genetic variants; CLN6: Case 1, E4c.486 + 8C> T / E7 c.755G> A; Case 2, E4c.307 C> T / E6 c.556dupC; Case 3, E4c.461_463delTCA/E3 c.250T>A. DNA variants in CLN2, as published (1). The natural history of LI-CLN6 disease was stated in 3 Argentine cases and crucial differences with the LI-CLN2 disease were found at clinical, morphological and biochemical levels. Clinically LI-CLN6 disease is an early movement disorder in contrast to CLN2 that initiates frequently with speech delay or failure, followed by seizures. The suspicion of CLN6 disease can be emitted on the base of the movement disorder at onset and lacking TPP1 deficiency. No A-CLN6 disease (Kufs) was recognized up to

date in Argentina, thus a study of the differences with adult and juvenile CLN2 disease is pending.
(1) Kohan R, Pesaola F, et al 2015. BBActa. 1852: 2301 -2311.

P-064 - BIOCHEMICAL DIAGNOSIS OF NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 IN DRIED BLOOD SPOTS: 28 CASES IN TWO YEAR OF EXPERIENCE

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INTRODUCTION: Neuronal Ceroid Lipofuscinosis type 2 (CLN2) is a rare, neurodegenerative lysosomal disorder caused by mutations in TPP1 gene, resulting in deficiency of the enzyme tripeptidyl peptidase 1 (TPP1). The classic phenotype is the most frequent with late-infantile onset, presenting with seizures starting between 2-4 years of age and a history of early language delay, followed by rapid psychomotor decline and early death. The atypical phenotypes are supposed to be rarer, characterized by later onset and longer life expectancy. CLN2 incidence ranges from 0.22 to 9.0 per 100000 live births, but is possible that it is underestimated. Diagnosis can be made measuring TPP1 activity in dried blood spots (DBS) or leukocytes, followed by genetic test. Enzyme replacement therapy is available since 2017.
OBJECTIVE: Present our two-year experience in the biochemical diagnosis of CLN2.
MATERIALS AND METHODS: Between October 2016 to January 2019, 397 DBS were screened for CLN2. Most of them were from Argentinean patients and few samples were sent from Chile, Uruguay and Paraguay. TPP1 enzyme activity in DBS and leukocytes was measured with fluorogenic substrate. Beta-Galactosidase activity was also analyzed in all DBS as a control enzyme, to assess sample quality. Although the TPP1 assay was not available at our center before 2016, we had not had any CLN2 request before that year.
RESULTS: From 397 DBS samples analyzed, 28 showed low TPP1 activity: 0 - 4.2 pmol/h/punch (Normal range: 40 – 279), and 10 were confirmed in leukocytes. Mean age at diagnosis was 10.8 years (range: 4 to 20 years). CLN2 patients were: 17 from Argentina (61%); 6 from Chile (21%), 4 from Paraguay (14%) and 1 from Uruguay (4%).
CONCLUSIONS: From 397 patients, 28 were positives for CLN2 giving a diagnosis rate of 7%. The availability of a therapy for CLN2 increased the clinical suspicion of this disease. DBS are easy to submit and have contributed to increase the recognition of this disease.

P-065 - INCIDENTAL DETECTION OF ARGENTINE FAMILY WITH GLA MUTATION FOR FABRY DISEASE THROUGH PRECONCEPTIONAL TEST BY NEXT GENERATION SEQUENCING MULTIGENE PANEL

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Fabry Disease is a X-linked lysosomal storage disorder caused by decreased or absent activity of the enzyme α-galactosidase A, due to mutations in GLA gene. The mayority are point mutations (missense, nonsense and splice sites mutations), although there are also 'short-length' and gross rearrangements. There is no obvious 'hot spot', and the mayority are non-recurrent private mutations.
In general, patients with Fabry disease are detected by clinical suspicion, the genetic study being part of the diagnostic confirmation.
We present a family in which a GLA pathogenic mutation was detected: c.1069C> T (p.Gln357 *) as an incidental finding in the index case (female), through a preconceptional multigenetic panel by Next Generation Sequencing (NGS),including GLA gene.
No family history of renal disease, neither stroke nor heart disease was detected.
Family mutation test was carried out on her relatives; her mother as well as one of her sisters and a niece were found heterozygous for the mutation; his father, the other sister, her maternal grandmother and her aunt do not carry the mutation.
Comprehensive evaluations were carried out in the heterozygous patients (ophthalmological, cerebral MRI, echocardiogram, echostress test, cardiac MRI, and renal function studies), detecting only cornea verticilata in the three adult heterozygous, and a mild cardiac hypertrophy with a symptomatic paroxysmal supraventricular tachycardia in the mother. The patients continue in clinical follow-up, maintaining expectant behavior in relation to specific treatments for Fabry Disease.
We conclude this is a fresh mutation occurred in the mother of the index case, transmitted to two of her daughters. This variant has not been reported yetin the literature.
With the increasing indiscriminate access to molecular studies by multigenetic panels by NGS, it is very likely that more incidental cases of patients with pathogenic mutations of unsuspected diseases will be detected. Genetic counseling by a specialist prior to each molecular study is essential, even in

these cases of prenuptial or preconceptional commercial genetic tests.

P-066 - GAUCHER DISEASE TYPE 1 AND CANCER: A STUDY OF A COHORT OF PATIENTS FROM ARGENTINA

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INTRODUCTION: Patients with Gaucher disease (GD) are considered to be at an increased risk of malignant disorders. Much of the observation reported to date is based primarily on European or North American studies, but no studies have addressed this issue in South America.
OBJECTIVES: Evaluate the incidence and characteristics of malignant diseases in a cohort of Argentine patients with GD type 1, and direct relatives (parents and siblings) during their follow up.
METHODS: Medical doctors in charge of Gaucher patients, from all around the country, mostly hematologist and pediatricians, were requested to report patients and direct relatives with malignancies confirmed by histopathological study.
A form was sent, without patient identification.
RESULTS: Out of a total of 124 patients, one event of cancer was reported in 15 of them, and 2 patients had 2 events.
All patients were receiving enzyme replacement therapy (ERT), none were splenectomized.
The mean age of the patients that developed CD was 51 years (range: 27-68) 8 females, 7 males.
CD reported were: colon (3), kidney (2),breast, lung, ovary, hepatocellular carcinoma, prostate, testicle, rectum, mieloma, Non Hodgkin Lymphoma (NHL) and retroperitoneal sarcoma (1 case each).
Progression of the CD was presented in 60 % and 40 % died as a consequence of the CD after 2.5+- 1.5 years of diagnosis.
Time between GD and CD diagnosis: 0-28 years, 2 cases simultaneous.
GD patients direct relatives with CD: 8 cases.
Mother 4 cases: uterus, ovary,breast, breast and colon.
Father 1 case: colon. Brothers 3 cases: pancreas, ovary, breast and thyroid.
2 families jew ashkenazi (370/84 GG) with multiple cancer.
Family 1: mother breast and colon, sister: breast and thyroid.
Family 2: mother, maternal aunt and grandmother: breast.
CONCLUSIONS: In a population of 124 patients with GD type 1 from Argentina the search of malignancies was performed.
A total of 15 patients with malignancies was found, 2 patients presented 2 neoplasms: kidney and colon and breast and ovary.
In direct relatives 8 cases were found and 2 families presented multiple cancers.
No pediatric case were reported.

P-067 - POMPE DISEASE IN CUBA. REPORT OF TWO CASES IN A FAMILY

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INTRODUCTION: In the Inborn Errors of Metabolism are the Lysosomal Storage Diseases and one of them is the Pompe Disease that causes a progressive metabolic neuromuscular disorder due to the deficiency of the acid α-glucosidase (GAA) enzyme. This disease in its onset in childhood is characterized by cardiomyopathy, muscle weakness, respiratory disorders and early death. In this report we show two non-twin sisters who were born in different years with signs and symptoms suggestive of a disease presenting themselves in the first year of life.
OBJECTIVE: Perform the biochemical diagnosis of the Specific Enzymatic Activity (AEE) acid α-glucosidase and the Activity Relative Enzymatic (AER) of the two sisters.
MATERIALS AND METHODS: A biochemical study was carried out on the two sisters to detect enzymatic deficiency of GAA. In both cases the two patients were studied, a healthy control and the mother, the father was not studied. The biological sample used was heparinized whole blood, to which the leukocytes were extracted to perform total protein determination and subsequently determination of EEE (nmol / mgprot / h) and AER (%), both enzymatic determinations were performed by a fluorometric method, using 4-methylumbelliferone as a fluorogen. Fluorescence was measured on a Shimadzu RF-5301PC spectrofluorimeter, at an excitation wavelength of 365nm and emission of 448nm. The criterion used for the positive diagnosis is patient / control AER $\leq$ 30%.
RESULTS: The results obtained in 2014 for the first daughter were 12.36 nmol / mgprot / h and 30% and the mother 23 nmol / mgprot / h and 46%. The second girl born and studied in the year 2019 showed an EEE and AER respectively of 0.52 nmol / mgprot / h and 3% and the mother 27 nmol / mgprot / h and 50%. It was shown that both sisters are descendants of

heterozygous parents because this is an autosomal recessive disease.
CONCLUSION: The diagnosis of Pompe disease was confirmed in both sisters.

P-068 - MUCOLIPIDOSIS II / III. ENZYMATIC DIAGNOSIS IN CUBA. PERIOD 2014-2018

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INTRODUCTION: Mucolipidosis II / III (ML) are lysosomal storage diseases with an autosomal recessive inheritance pattern, caused by the deficiency of the Manose-6-phosphate marker responsible for generating the recognition signal, causing defects in processing and localization of acid hydrolases. N-acetylglucosamine-1-phosphotransferase is the deficient enzyme in ML, whose function is the transport of enzymes involved in the degradation of substrates within the lysosome.
OBJECTIVES: To characterize the biochemical diagnosis of ML in Cuba in the last 5 years.
MATERIALS AND METHODS: Six patients with clinical suspicion of ML were analyzed, with their relatives and healthy controls, for a total of 20 samples. The biological sample studied was blood serum. The specific enzymatic activity (AEE) was determined by fluorimetric method in the Shimadzu RF-5301pc equipment at a wavelength (?) of emission 448 nm and of excitation 365 nm and spectrophotometric in the VS-850 equipment at 516 nm.
RESULTS: Two patients diagnosed with ML II / III were diagnosed. The first patient, male, of 2 years of age, from the province of Santiago de Cuba, with a family history of this disorder and the second patient, female sex, 5 years old, from the province of Havana, both showed clinical manifestations similar to what is reported in this type of pathology. There was a considerable increase in AEE in the serum of the first patient and a decrease in AEE inside the lysosome in the second patient, in relation to the controls used. The specific enzymatic activity of patient 1 was used as a diagnostic criterion with respect to healthy control, exceeding its value more than 5 times, while in the case of patient 2 the value of the relative enzymatic activity was obtained from the comparison on the healthy control, assuming positive results less than 30%.
CONCLUSIONS: In the last five years in Cuba of a total of 6 patients who were studied with clinical suspicion of Mucolipidosis II / III, only 2 were positive, which shows the low incidence of this disorder in our country.
Key Words: Lysosomal storage disease, Mucolipidosis II / III, Enzymatic diagnosis.

P-069 - NEURONAL CEROID-LIPOFUSCINOSES IN CHILDREN: IMPACT OF A NEXT-GENERATION SEQUENCING PANEL FOR DIAGNOSING

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INTRODUCTION: The neuronal ceroid lipofuscinoses (NCL) are a group of neurodegenerative disorders characterized by epilepsy, visual loss, myoclonus, and progressive mental and motor deterioration. In recent years, molecular genetics has emerged as a useful tool for enhancing NCL subtype classification (CLN1 to CLN14), recognizing more than 430 mutations in 13 genes.
OBJECTIVE: Molecular characterization of children with a presumptive diagnosis of NCL at an Argentinean public hospital.
PATIENTS AND METHODS: 4 late-infantile NCL (INCL) and 2 juvenile NCL (JNCL) pediatric patients were selected. Clinical data and complementary studies were analyzed. A next-generation sequencing panel including the seven most frequent NCL-related genes was designed. The 966 base deletion in the CLN3 gene was analyzed by allele-specific PCR in one case.
RESULTS: In the INCL group the mean age at onset was 3 years. The children presented with seizures (3) or cognitive decline (1). Two cases with classical INCL showed reduced activity of tripeptidyl-peptidase 1; both carried the same homozygous variant (p.Asp276Val) on the TPP1 gene (CLN2). A curvilinear pattern was identified on skin electron microscopy (EM) in one of them. Two cases with variant INCL disclosed compound heterozygous mutations in the MFSD8 gene (CLN7). Skin EM showed a curvilinear pattern in one, while it was normal in the other patient. Both patients with JNCL presented with visual impairment at a mean age of 6 years. They developed seizures and cognitive decline. Biallelic variants in the CLN3 gene were confirmed in one of them, who showed vacuolated lymphocytes and a mixed histopathological pattern on skin EM. Finally, in the second patient, biallelic variants were identified in the CLN5 gene.
CONCLUSION: This new methodological approach allowed to confirm the diagnosis in all cases. These results highlight the impact of an NGS panel as an efficient and non-invasive tool for accurate and early NCL diagnosis. Recognition of the molecular defects improves disease classification, therapeutic strategy, and genetic counseling, optimizing the comprehensive management of these patients.

P-070 - ATYPICAL PHENOTYPE OF NEURONAL CEROID LIPOFUSCINOSIS TYPE 2: CASE SERIES OF SIX PATIENTS FROM ARGENTINA

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INTRODUCTION: Neuronal Ceroid Lipofuscinosis type 2 (CLN2) is a rare, progressive disorder caused by mutations in the TPP1 gene resulting in deficiency of the enzyme tripeptidyl peptidase 1 (TPP1). The typical phenotype presents with seizures and/or ataxia in the late-infantile period (age 2-4), in combination with a history of language delay followed by progressive childhood dementia, motor and visual deterioration and early death. Atypical phenotypes are characterized by a later onset, and in some instances longer life expectancies. Typical and atypical forms of CLN2 have increasingly been recognized since enzyme replacement therapy became available.
AIM: to analyze the clinical, biochemical and molecular findings in six patients diagnosed with atypical CLN2.
MATERIALS AND METHODS: a retrospective medical record review was conducted at our centre for this case series of six CLN2 patients diagnosed between years 2016 and 2018. TPP1 enzyme activity was determined in dried blood spots (DBS) and confirmed in leukocytes. Genetic analysis was done in all 6 patients.
RESULTS: six patients were diagnosed of CLN2. The median age at first symptom was 7,2 years old (range 6-9) and the median age at diagnosis was 13,2 yo (range 9-17). Cerebellar atrophy and ataxia were present in all patients. The initial diagnostic method was exome sequencing in one patient and TPP1 enzyme activity in five patients. From the five patients that underwent DBS test, 4 showed absent activity. The mean activity in leukocytes of the 5 patients was 4,6 nmol/h/mg protein (range 1,7-8,8). Mutation analysis showed at least one of the following: c.887-10A>G and c.827A>T in each patient. Three patients are receiving enzyme replacement therapy and their symptoms remain stable.
CONCLUSIONS: this case series expands the clinical, biochemical and genetic characterization of atypical CLN2 patients. We didn´t find that residual enzyme activity underlines a late onset phenotype. As ataxia was the common symptom we suggest including TPP1 DBS enzyme activity in the workout of ataxia. It is very important to be aware of these atypical forms of the disease to ensure early diagnosis, optimal patient care, prompt treatment and family support.

P-071 - BIOCHEMICAL DIAGNOSIS OF NCL2 DIAGNOSIS. EXPERIENCE WITH THREE BIOLOGICAL SAMPLES

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INTRODUCTION: Neuronal ceroid lipofuccinoses (NCLs) are a group of 14 lysosomal storage disorders characterized by accumulation of autofluorescent lipopigments of heterogeneous chemical composition. Clinically NCLs mainly compromise central nervous system and are cause of progressive myoclonic epilepsy. NCL2 in one of the most common subtypes, caused by deficiency of the tripeptidyl transferase enzyme (TPP1). NCL2 presents in the toodler as a progressive epilepsy with fatal outcome in the first decade of life. Currently, an enzyme replacement therapy has been aproved for this entity, however in Colombia, diagnosis of NCL2 is difficult since no laboratories perform the enzyme activity determination.
OBJECTIVES: To implement TPP1 enzyme activity in Colombia population.
METHODS: DBS, blood and saliva samples were obtained from 100 healthy adult subjects and 3 NCL2 confirmed patients that signed informed consent. Leukocytes were isolated using dextran gradient. DBS samples were dried overnight at room temperature and stored at 4°C. Leukocytes and saliva were frozen until processing. TPP1 enzyme activity was performed according to the method reported by Kohan et al. Reproducibility, stability and specificity of the technique were experimentally assessed for the three samples. As a simple quality control, enzyme activity of glucuronidase and PPT1 enzymes were performed to the samples.
RESULTS: A good discrimination between healthy and NCL2 individuals was observed in saliva and leukocytes. In contrast, DBS samples displayed, low temperature stability, poor reproducibility and the presence of both false positive and false negative cases, a situation that was not observed in either leukocytes or saliva. In fact, this behavior contrasted with initial approximations for PPT1 enzyme activity, in the same samples, which displayed values comparable to those observed in other laboratories.
CONCLUSION: TPP1 enzyme activity determination in two samples (saliva and leukocytes) was implemented in our laboratory and is now available for NCL2 diagnosis in Colombia. The number of samples used in this study allows a characterization of the normal values dispersion. According to our results, saliva is proposed as a screening sample and leukocytes as confirmatory. The discrepancies observed, especially regarding DBS samples, reinforces the importance of standardizing technical conditions for enzyme activity determinations in each laboratory.

P-072 - TARGETED NEXT-GENERATION SEQUENCING: A POWERFUL TOOL FOR TYPE 2 NEURONAL CEROID LIPOFUSCINOSIS DIAGNOSIS CONFIRMATION

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INTRODUCTION: Neuronal ceroid lipofuscinoses (NCLs), a subset of lysosomal storage disorders, are rare inherited and severe neurodegenerative conditions. CLN2, the classical late infantile type, is caused by mutations in the TPP1 gene that lead to the deficiency of the TPP1 enzyme and seems to be the most prevalent CLN type in South America. It is characterized by a clinical picture initially dominated by speech delay, seizures and ataxia, followed by progressive dementia, motor and visual deterioration, and early death. The LSD Brazil Network, which was already providing enzyme diagnosis for CLN2, more recently implemented targeted next-generation sequencing (TNGS) for the CLNs.
OBJECTIVE: To evaluate TNGS as a tool to improve CLN2 diagnosis.
MATERIALS AND METHODS: In the period of one year (May 2017-April 2018), 656 Latin American cases (from Argentina, Brazil, Chile, Colombia, Ecuador and Mexico) were referred to the LSD Brazil Network for CLN2 investigation. Dried blood spots (DBS) were collected for biochemical (assay of TPP1 activity) and molecular (TNGS) analyses. Enzyme assay was performed using fluorimetry, and TNGS was performed using a previously validated panel including the TPP1 gene (with 100% of coverage).
RESULTS: From the 656 samples, 46 showed activity of the TPP1 enzyme below the lower reference level (4 nmol/h/mL). TGNS was performed in these samples, and in 37 of them pathogenic mutations in both alleles of the TPP1 gene were found, confirming the diagnosis.
CONCLUSION: Diagnosis of CLN2 can be conveniently performed in the same DBS sample, using enzyme activity for screening and TNGS for diagnosis confirmation.

P-073 - ALPHA-GLUCOSIDASE ENZYMATIC ASSAY USING NATURAL SUBSTRATE. OUR PATHWAY TO A MORE RELIABLE TEST FOR POMPE DISEASE DIAGNOSIS

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Acid alpha-glucosidase deficiency is the main cause of Pompe disease. This disorder caused by homozygous or compound heterozygous mutations in the GAA gene, generates a phenotypic expression characterized by proximal muscle weakness, respiratory failure and altered CK levels. Different approaches have been done to get an accurate diagnostic test. The preferred method for diagnosis of the disease is confirmation through biochemical assays showing absent or decreased enzyme activity in at least two samples. Here we show the results obtained in our laboratory in the search for a reliable enzymatic test to diagnose this disease. METHODS: Enzymatic assays were carried out using 4-methylumbelliferyl-Alpha-D-glucopyranoside (4-MUG) as substrate and acarbose as inhibitor. Abnormal values for inhibition percentage and iso-enzymes relation were considered probable cases. Five to 10 ml total blood was extracted from these patients to isolate leucocytes for confirmation. A similar technique using 4-MUG and acarbose was completed with these samples. Patients with consistent alterations in inhibition and isoenzymes relation where confirmed as positive cases. A method using glycogen as substrate was developed later to obtain specific enzyme activity levels.
RESULTS: A total of 13133 DBS samples referred from high-risk patients screened throughout the country were analyzed in a period of 14 years (2005-2018). Abnormal values in 930 samples were found. Isolated leucocytes were obtained and analyzed from these patients obtaining 69 altered values. Later, with the new glycogen assay available patients were called back and 50 samples could be recollected and analyzed with this technique. Low enzymatic levels (0.00 – 0.24 mmol/mgprotein/hour) were confirmed for all them. These results showed significant difference with reference controls. (Reference range values: 0.38 -2.93 mean 0.91).
CONCLUSION: Enzymatic assay using glycogen as substrate and inhibition with acarbose proved to be a trustworthy test for Pompe disease diagnosis.

P-074 - MILD LATE INFANTILE MULTIPLE SULFATASE DEFICIENCY: CLINICAL DESCRIPTION AND PRELIMINARY FUNCTIONAL ANALYSIS OF TWO BRAZILIAN CASES

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INTRODUCTION: Multiple Sulfatase Deficiency (MSD) is a rare lysosomal disease caused by biallelic loss-of-function mutations in the SUMF1 gene, which encodes the formylglycine-generating enzyme (FGE), involved in the post-translational activation of all sulfatases. The clinical presentation includes symptoms of the individual sulfatase deficiency disorders, with variable severity.
OBJECTIVES: to describe and perform functional analysis in two mild MSD cases.
MATERIALS AND METHODS: case reports and gene expression plasmid construction.
RESULTS: Patient 1 was referred to the medical geneticist at 17 months of age, presenting mild developmental delay and minimal dysmorphic features (flat face, bifid uvula, long fingers), with parental consanguinity and one male sibling prematurely deceased. Initial workup (neuroimaging and basic metabolic screening; not including tests for lysosomal diseases) had normal results. At subsequent evaluations, dry skin was observed. After a follow-up break, she returned when 8 years old, presenting neurological regression, aggressive behavior, ichthyosis and short stature. Neuroimaging showed dysgenesis of the corpus callosum, white matter hyperintensities and cerebral-cerebellar atrophy. Analysis of urinary glycosaminoglycans was requested and presented abnormal results, leading to enzyme assays, which confirmed MSD. Sanger sequencing detected a previously reported variant c.1A>G (p.Met1Val) in SUMF1, in homozygous state. Our biochemical studies indicated that, although p.Met1Val is as active as the wild type (WT), a reduced expression level (≤ 20% of WT) contributes to the loss-of-function that results in MSD. Patient 2 was referred to the medical geneticist at 10 years of age, presenting mild developmental delay, hepatomegaly and hypercholesterolemia since infancy. No conclusive diagnosis at the previous investigation. We found deficient activity of Arylsulfatase A and other sulfatases. A novel pathogenic variant p.Arg224Gln (c.671G>A) in SUMF1 was detected by next-generation sequencing, in heterozygosis. In-silico analysis and 3-D modelling indicate that this mutation is pathogenic. Our biochemical findings revealed that mutation-induced misfolding and reduced intracellular stability of FGE contribute to its loss-of-function. The second variant has not been detected yet.
CONCLUSIONS: Those two cases demonstrate how MSD diagnosis may be a real challenge, mainly when presentation is mild, and the importance of a comprehensive investigation. RNA studies from these cases are ongoing.

P-075 - NEURONAL CEROID-LIPOFUSCINOSIS TYPE 8 (CLN8), A CASE REPORT

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INTRODUCTION: Neuronal ceroid-lipofuscinosis (NCLs) type 8 is a rare neurodegenerative disease characterized by motors and cognitive deterioration, seizures, visual loss, retinopathy, cerebellar and cerebral atrophy. The symptoms started between the ages of 4 and 8 years. It is an autosomal recessive lysosomal disorder caused by the mutations in the CLN8 gene.
OBJECTIVE: We report a female patient with a rare metabolic disease: CLN8.We discuss clinicaland molecular findings.
METHODS: retrospective medical record review of a patient diagnosed with CLN8.
RESULTS: We report a 19 year old patient that initiated at the age of 6 with epilepsy and learning disability. At the age of 10 the epilepsy turned refractory to multiple antiepileptic drugs and developed progressive ataxia. At 17 years old, due to visual loss, she was diagnosed with bilateral macular degeneration. Brain MRI showed pronounced cerebellar atrophy. With this clinical phenotype, NCL was suspected. Using targeted next-generation sequencing, a variant in CLN8 was detected in this patient.
DISCUSSION: NCLs are the leading cause of dementia in children and adolescents. It presents with a varying age of onset, symptoms and disease course. Historically recognized by a debilitating set of symptoms: seizure/epilepsy, dementia and vision loss. CLN8 is one of them. We think it is very important to be aware of this disease to ensure early diagnosis, optimal patient care and family support.

P-076 - DIAGNOSTIC CHALLENGE OF DEPOSIT DISEASE IN CASE REPORT

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A 12-year-old female patient, a history of recurrent pain in lower limbs since 3 years of age. At 8 age, she presented pain in the left lower limb, afebrile, and absence of history of trauma or vaccination. Magnetic resonance imaging at the time evidenced acute osteomyelitis in the left distal femur and antibiotic treatment was initiated. Local bone biopsy report presented a discrete inflamatory fibrosing process in cortical bone tissue, with no malignancy or specific process. At 12, she presented recurrence of pain,at this time in the lower right limb, again without fever, traumas or vaccination. Laboratory tests revealed normocytic and normochromic anemia, not responsive to iron replacement, mild thrombocytopenia, without evidence of hemolysis. Magnetic resonance imaging of the right lower limb observed findings compatible with

hematological disorders and did not show lytic expansive lesions, blastic, sinus infarct or osteonecrosis. Forwarded to the tertiary service, performed myelogram showed numerous histiocytes with cytoplasm in "crumpled cellophane paper". The spleen and liver were discretely increased in abdominal resonance examination, there was alteration in second resonance in the right and left hip and thigh, with signs suggestive of avascular necrosis / right infarction. The bone densitometry of the total body column within the limits of normality. Before the myelogram, serum beta-glycoside dosage was below the normal range (0.53 with a reference value of 10-45), and quitotriosity was high (8.457 with reference value). Initiated enzyme replacement therapy 60 IU / kg biweekl

Recurrent limb pain is a common childhood symptom and is found in a variety of common pediatric diseases. Knowledge about rare diseases allows for clinical suspicion, and consequently, earlier diagnosis and treatment, with lower complications for the patient.

P-077 - GAUCHER'S DISEASE PATIENTS PROFILE IN A REFERENCE SERVICE OF THE STATE OF AMAZONAS – BRAZIL

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INTRODUCTION: Gaucher's disease is an inborn error of metabolism due to atypical lysosomal deposition (being the most common in this category), it is an autosomal recessive genetic disorder (chromosome 1p21) that compromises cellular functioning by accumulating glucocerebrosides, especially in macrophages. It is estimated to affect 1-9/100.000hab, manifesting itself under three clinical spectra, classified according to visceral (hepatosplenomegaly), hematologic (anemia and thrombocytopenia), bone (osteopenia and osteonecrosis), and nervous involvement and age of onset of symptoms, directly implicating in treatment and mortality rates. The diagnosis is guided by the clinical presentation, based on the activity levels of the malfunctioning enzyme – acid beta-glycosidase (ABG), and the detection of mutations, being the treatment done through enzyme replacement therapy (ERT) or inhibition of substrate synthesis.
OBJECTIVES: Describe epidemiological aspects of patients diagnosed with Gaucher's disease in Amazonas.
MATERIALS AND METHODS: This is a descriptive observational study carried out in the public health system of the state.
RESULTS: At the moment, 16 patients are being treated, 8 of which are female and 8 are male, with a mean age of 16 years (ranging from 1 to 35 years) diagnosed at 10 years old (ranging from 2 to 34 years). All patients are treated with ERT (imiglucerase and alpha-taliglycerase), classified into types I and III of the disease and are, for the most part, below the expected rate of development and body mass.
CONCLUSIONS: and discussion: The registration of data like these is important since Brazil is the third in world incidence, therefore, it is essential to have knowledge about the disease and recognize it before the patient, once the therapeutic approach and diagnosis are able to predict and even avoid possible complications and repercussions.

P-078 - SIMPLE TOOLS FOR FABRY DISEASE PHENOTYPE IDENTIFICATION

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INTRODUCTION: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations in the GLA gene. Two major phenotypes have been described: the type I "classic" and the type II "late-onset".
AIM: to describe simple tools for phenotype identification in clinical practice.
METHODS: Review of medical records of patients diagnosed with FD during 16 years of follow up and comprehensive literature review.
RESULTS: symptoms and signs description and age of onset is the first practical tool that clinicians may use for characterization. Late onset variants use to show cardiac or renal involvement after the third decade without the typical features described in children. Residual enzyme activity may correlates with the clinical phenotype, where less than 1% is related to classic phenotype. Mutation analysis using different databases and bioinformatic predictive tools also add other clue. Currently, plasmatic LysoGb3 measurement could be the second most important tool to define the phenotype and also may confirm the FD diagnosis. Lastly, endothelial involvement in tissue biopsy is only present in classic phenotype of FD. Description of intralysosomal inclusions in differentiated cells (podocytes, cardiomyocites, etc) does not allow phenotype characterization.
CONCLUSION: Phenotype identification in FD is mandatory because patient management, treatment prescription and clinical follow up are different in each case.

P-079 - BUILDING BRIDGES IN RARE METABOLIC DISEASES: THE INTERNATIONAL NIEMANN-PICK DISEASES REGISTRY (INPDR)

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BACKGROUND: Niemann-Pick diseases (NPD) are a group of rare inherited Lysosomal Storage Disorders (LSDs) that can affect both children and adults. Niemann-Pick type A/B is caused by acid sphyngomyelinase deficiency (ASMD) , presenting with both neurological and/or visceral finding with varying effects on other organs including the lungs. Niemann-Pick Type C disease (NP-C) is a trafficking lipid disorder caused by two diferente genes NPC1 and NPC2, leading to an accumulation of non-sterified cholesterol and sphingolipids in the liver, brain and spleen
OBJECTIVES: To describe the International Niemann-Pick Disease Registry (INPDR), a disease-specific registry collating the global data of patients diagnosed with Acid Sphingomyelinase Deficiency (ASMD) and Niemann-Pick Type C (NPC)
MATERIALS AND METHODS: Clinical, biochemical, neuroradiological data are collected, including the following items: demographic characteristics, genetic profile, clinical manifestations, quality of life assessment, among others.
RESULTS: Patient registries can fulfil a number of roles, including collecting data regarding disease natural history data, post-marketing surveillance tool and patient quality-of-life register. The International Niemann-Pick Disease Registry (INPDR) contains two linked, but separate, databases, one holding clinician entered data and the other containing patient recorded outcomes (PRO). Data from 236 patients, entered from 6 countries is presently held within the Registry. 74% of the patients entered in the Registry so far have NPC and 26% are diagnosed with ASMD. Most of the patients with NPC (71%) and ASMD (74%) were diagnosed below 12 years of age; in contrast, 15% of ASMD patients and 10% of NPC patients had their diagnosis after 30 years of age.
CONCLUSIONS: INPDR is a single, rare disease-specific registry collating Niemann-Pick data on a global basis. It was created by professionals and patients for worldwide use. It collects clinical data and patient reported data with separate datasets for ASMD and NP-C. It will replace the need for multiple registries and offer a single, effective data resource for NPD.

P-080 - IS LYSO-GL1 AN USEFUL BIOMARKER FOR GAUCHER DISEASE EVOLUTION AND SKELETAL INVOLVEMENT? EXPERIENCE OF A COHORT OF 197 ARGENTINIENAN PATIENTS

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INTRODUCTION: The Argentinean Gaucher Group is a collaborative group of treating physicians that monitors natural history and outcomes in 197 patients with Gaucher disease (GD). There is high prevalence of severe GBAmutation and as many as 87% of patients exhibit significant skeletal complications. Hence this cohort represents an informative cohort for evaluation of biomarkers that may reflect skeletal involvement, disease evolution and response to treatment.
OBJECTIVE: to determine which is the most specific biomarker for diagnosis and follow up in GD patients and taking into account the high prevalence of bone disease in Argentinean GD patients, evaluate if any biomarker is related to bone disease.
METHODS: In 197 patients with Gaucher disease, serum samples (total 417) were obtained during various therapies: 175 patients treated for up to 14 yrs on imiglucerase ERT and 22 patients treated with eliglustat SRT for up to 6 yrs. Samples were analyzed for 9 different biomarkers established and exploratory: Lyso GL-1; GPNMB; CHITO; MIP-1b; C5a; IL-1b; IL-6 and TNF-α..
RESULTS: We analyzed biomarkers based on presence and absence of bone disease (BD). By univariate analysis chitotriosidase and Lyso GL1 were significantly associated with BD: Chitotriosidase (without BD: 66.05 vs. with BD: 153.56 nmoles/h/ml (P=0.010)and Lyso GL-1: 57.70 vs. 125.4 ng/ml (P < 0,001). By multivariate analysis, Lyso GL1 significantly correlated with BD: multivariate statistical analysis using the bone lesion variable: elevated LYSO-GL-1 was associated with bone lesions severity (P= 0.003). Comparing biomarkers according type of treatment revealed patients on ERT had significantly elevated C5a compared to patients receiving SRT.
CONCLUSION: Our results support the use of Lyso GL1 for monitoring Gaucher disease and skeletal involvement. The increase of LYSO-GL1 values is directly related to the presence of bone disease (57.70 ng/ml without BL Vs. 125.4 ng/ml with BL) (P= 0.001) and with the severity of BL: no lesions: 57.70 ng/ml; bone marrow infiltration: 104,20 ng/ml; Erlenmeyer: 110,14 ng/ml; chronic osteonecrosis: 125,98

ng/ml; acute osteonecrosis: 152,81 ng/ml (P= 0,001). In this cohort of patients there is a higher prevalence of CHIT1 null homozygous and heterozygous(41%) making this biomarker less trustworthy.

P-081 - IS CHITORIOSIDASE AN USEFUL BIOMARKER FOR DIAGNOSIS AND TREATMENT MONITORING OF GAUCHER DISEASE? EXPERIENCE IN A COHORT OF 197 ARGENTINEAN PATIENTS

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INTRODUCTION: Chitotriosidase is an established biomarker for Gaucher Disease (GD) reflecting involvement of alternatively activated macrophages in disease pathophysiology. Several limitations have been highlighted including presence of common polymorphism in CHIT1 in heterozygous form in ~30% of patients and homozygous null allele in ~6% of patients that reduces circulating levels to 50% and lack of detectable chitotriosidase, respectively. The responsible polymorphism is a 24 bp duplication in exon 10 of CHIT1 that renders the gene inactive. The high prevalence of 24bp duplication impedes the abilty to compare biomarker levels among patient poplulations and in ~6% of individuals it is completely uninformative.
OBJECTIVES: to assess the prevalence of 24 bp duplication in an entire cohort of GD patients in Argentina and concurrently measure serum chitotriosidase to further assess its biomarker properties to correlate with GD manifestations.
METHODS: Serum samples (total 417) were obtained during different moments in timeline of treatment: 175 patients treated for up to 14 years with imiglucerase (ERT) and 22 patients treated with eliglustat (SRT) for up to 6 years (Table 1). Samples were analyzed for CHITO genotype and serum chitotriosidase was measured. We analyzed chitotriosidase based on presence and absence of bone disease (BD).
RESULTS: CHIT1 genotyping revealed a somewhat higher proportion of CHIT1 null homozygous patients compared to other populations: 28/193, 14.50 % (vs 6.0% in other populations). Hetero carriers were also slightly over-represented:: 86/194, 44.56 % (vs 35% in other populations), with concomitant decreased prevalence of wild type homozygous allele: 79/193, 40.94 % (vs 59% in other populations).
CONCLUSION: High prevalence of 24 bp polymorphism in Argentinian population therefore impedes broad application of chitotriosidase as biomarker of Gaucher disease and underscore the importance of concurrent CHIT1 genotyping to assess chitotriosidase in the clinic.

P-082 - N370S/RECNCIL GENOTYPE-PHENOTYPE CORRELATION IN A COHORT OF 197 ARGENTINEAN GAUCHER DISEASE PATIENTS

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INTRODUCTION: Gaucher disease (GD), the most common lysosomal storage disorder, is caused by homozygous or compound heterozygous mutations in GBA gene that results in defective lysosomal enzyme glucocerebrosidase (EC 3.2.1.45). The existence of pseudogenes in 1q21 GBA loci not only results in increased risk of generating complex alleles, but also hinders accurate GBAmutation analysis in the clinic and the genetic counseling of GD.
OBJECTIVES: To know argentinean GD patients genotype, to analyze the genotype-phenotype correlation and evaluate its correaltion with bone disease severity.
METHODS: We developed PacBio long read GBA deep sequencing to overcome the standard genotyping involving screen for common mutations or analysis of full coding regions, and furthermore, to maximize coverage depth and haplotype GD patients. We applied Sanger sequencing for validation of genotype ascertained by PacBio sequencing. These approaches are applied to genotype and haplotype a large cohort of Argentinean GD gDNA samples.
RESULTS: 144/184 (78.3%) of the evaluable samples were successfully genotyped and phased in identifying disease-causing mutations as allelic variants. The mutation N370S (79.8%) was the most frequent in our GD argentine patients. The genotype N370S / RecNcil (47.2%) was the most frequent followed by N370S/L444P (9.7%). Nine novel mutations were identified. Comparing our findings with the rest of the world we found that: In Argentina the genotype N370S/L444P (9.7%) is less frequent than in Europe (21.9%) and USA (14.3%) (Gaucher International data) and the Genotype

N370S/RecNcil is more frequent in Argentina 47.2% than the rest of Latin America (2.4%). The Genotypes N370S/N370S and L444P/L444P are also less frequent in Argentina than Europe and USA. The genotype N370S /RecNcil is associated with a more serious phenotype with early bone disease (p=0.005), such as the one found in the argentinean population.
CONCLUSIONS: Higher coverage depth and long-read whole GBA gene SMRT sequencing are essential to GD clinical diagnosis and genetic counseling. The most frequent genotype was N370S/ RecNcil in 47.2 % of the patients in contrast with other publications. The presence of the N370S/RecNcil mutation appeared to be correlated (p= 0.05) with the presence and severity of bone disease.

P-083 - ELIGLUSTAT FOR ADULT PATIENTS WITH GAUCHER DISEASE TYPE 1: EFFECTIVENESS AFTER 6 YEARS OF TREATMENT EVALUATED IN THREE ARGENTINEAN CENTERS

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INTRODUCTION: One option currently available for the treatment of type 1 Gaucher disease (GD) is substrate reduction therapy (SRT) with Eliglustat. This therapy has recently been approved and data on its effectiveness in Argentina is not available.
OBJECTIVES: to evaluate the effectiveness of Eliglustat used during 6 years in adult patients with GD in three centers of Argentina.
METHODS: Twenty-two patients ≥18 years with GD admitted to the phase III clinical trial ENCORE (GZGD012607) and followed for at least 6 years were included. For the analysis, patient follow-up was separated into three stages: 1) Stage 1 comprised the period of patient randomization and follow-up during 12 months. 2) stage 2, comprised the time between the 12 months and the 4 years of follow-up (extension of the ENCORE study); 3) Stage 3, "real life", included the follow-up of patients who continued for 2 years in treatment with Eliglustat and obtained data recorded by treating physicians during the follow-up outside the clinical trial. The main outcome evaluated consisted in the maintenance of therapeutic goals (TG).
RESULTS: Previous to the inclusion to the ENCORE study 95.5 % of the patients had different degree of bone lesion: bone marrow infiltration (95.5%), Erlenmeyer flask deformity (59%), chronic bone infarcts (59%) and chronic avascular necrosis (50%). At the end of stage 1 eliglustat was not inferior to imiglucerase regarding TG accomplishment. In Stage 2, all patients continued to fullfill al TG. There were no new bone lesions. Compliance to Eliglustat was 95 %. At the end of Stage 3, all patients still reached TG. There were no new bone lesions but a decreased in compliance to Eliglustat was found 65% (p= 0.001).
CONCLUSION: In our experience Eliglustat is a first line treatment of choice that can reach TG, but it requires a strict control of patients compliance to reach TG. With a follow-up time of 6.3 years (2 years out of the ENCORE study), all patients under treatment with Eliglustat maintained the TG. The bone lesions after 6 years of follow-up remained stable without new acute lesions or pain crises.

P-084 - DIAGNOSIS OF HEXOSAMINIDASE A DEFICIENCY THROUGH WHOLE EXOME SEQUENCING: REPORT OF TWO NORTHERN BRAZILIAN CASES

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INTRODUCTION: The diagnosis of Hexosaminidase A (HEX A) deficiency relies on the demonstration of absent to near-absent HEX A enzymatic activity in the serum, white blood cells, or other tissues from a symptomatic individual in the presence of normal or elevated activity of the beta-hexosaminidase isoenzyme. However, Whole Exome Sequencing (WES) has been an effective technology with remarkable impact in diagnosis of metabolic and neurologic diseases.
OBJECTIVE: To report two patients diagnosed with HEX A deficiency through WES.
METHODOLOGY: WES exams were performed before biochemical assays, searching for variants related to metabolic and neurologic diseases.
RESULTS: Patient 1: D.S.S, a 13-year-old male, third child of a non-consanguineous couple, started with neuropsychomotor regression at the age of 6. His older sister developed similar clinical presentation when she was 4 years old and died of uncontrollable seizures at the age of 12. He was referred to Medical Genetics evaluation because of worsening of ataxia/incoordination, speech, life skills, cognitive decline, spasticity and seizures. Ophthalmological evaluation was normal and CT scan showed reduced attenuation of the cerebral white matter. A homozygous pathogenic variant c.556G>A p.(Arg189His) was identified in exon 5 of HEXA gene. Then, complementary measurement of HEX A activity

showed extremely low result (>0,09µmol/l/h; Ref.: >= 2 µmol/l/h).
Patient 2: BSB, a 5-year-old male, second child of a non-consanguineous couple whose first son died at the age of 7 from a "demyelinating disease with progressive neurological deterioration". He had normal neuropsychomotor development until the age of 4 when he started with ataxia, speech/cognitive decline and seizures. MRI showed deep white matter demyelination and ophthalmological evaluation was normal. A homozygous pathogenic variant c.533G>A p.(Arg178His) was identified in exon 5 of HEXA gene. HEX A activity measurement (493,5 nmol/h/mL) was lower than normal reference range (550,0 to 1675,0 nmol/h/mL). He has been using levetiracetam with partial improvement of seizures. His parents decided to try acetyl-DL-Leucine as off-label use. They refer a slight improvement of ataxia.
CONCLUSIONS: WES can be used as a single test to diagnose metabolic disorders. Confirmation of the defect by a second measure (metabolites, enzyme assay etc) should also be performed.

P-085 - THE HFE1 P.HIS63ASP (RS1799945) MUTATION MAY ACT AS A MODIFIER IN GAUCHER DISEASE.

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INTRODUCTION: Gaucher disease (GD) is characterized by the accumulation of glucosylceramide in the lysosomes of reticuloendothelial system cells such as macrophages. The manifestations of GD consist mainly of hepatosplenomegaly, bone pain/deformations, osteonecrosis, anemia, and thrombocytopenia. Abnormalities in iron metabolism may play a central role in some of the clinical and biochemical features of GD. A candidate modifier gene is HFE1, the "causing" gene of hereditary hemochromatosis type I.
OBJECTIVES: To analyze the role of HFE1 variants in the phenotype of GD.
MATERIALS AND METHODS: Thirty-three GD patients (type I, n=30; type III, n=3) were enrolled. DNA samples were extracted from peripheral blood and the HFE1 gene was sequenced by next-generation sequencing using IonTorrent-PGM. Two outcomes were derived from clinical data: 1) "altered liver enzymes", comprising sustained alteration of ALT, AST or GGT while on treatment; and 2) "evidence of iron overload", comprising increased transferrin saturation, hemosiderosis on liver biopsy, or increased liver iron on MRI. Pearson's chi-square was used with a level of significance of $p<0.05$. Patients having and not having the each of the outcomes were compared regarding the frequencies of variants in HFE1.
RESULTS: Three known HFE1 variants were found: p.His63Asp (rs1799945; n= 6 patients; 18%), p.Cys282Tyr (rs1800562; n= 4; 12%), and c.340+4T>C (rs2071303; n=1; 3%). No patient was homozygote or compound heterozygote. Twenty-one patients (63.5%) were included in the "altered liver enzymes" group and 9 patients (27%) in the "evidence of iron overload" group. No significant differences of allelic frequency were found between the groups, although the allelic frequency for p.His63Asp, but not for the p.Cys282Tyr ($p=0.683$), was found to be borderline significant (altered enzymes: 6/42; normal enzymes: 0/24; $p=0.063$).
CONCLUSIONS: Although statistical significance was not achieved, the borderline p-value may be due to the low sample size. Therefore, our data suggest that the HFE1 p.His63Asp may be a phenotype modifier in GD.

P-086 - NIEMANN PICK DISEASE: CLINICAL, BIOCHEMICAL AND MOLECULAR CHARACTERIZATION OF ARGENTINEAN PATIENTS AND THE REPORT OF A NOVEL MUTATION

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INTRODUCTION: Niemann-Pick disease (NPD) is a group of rare autosomal recessive lysosomal storage disorders. NPD has been divided into two distinct entities: a) acid sphingomyelinase deficiencies (ASMD) (including NPD types A and B) activity coded by SMPD1 gene, and b) NPD type C (including C and D), produced by deficiency of either the NPC1 or the NPC2 transport proteins. Type A NPD is a fatal neurodegenerative disorder of infancy: type B NPD is a less severe form, the most patients have litle or no neurologic involvement and survive into adulthood. Type C NPD is a

complex lipid storage disorder caused by defects in cholesterol trafficking, resulting in a clinical presentation dominated by neurologic involvement. AIM: to report the clinical, biochemical and molecular studies for the characterization of patients, in the context of a systematic clinical research protocol of this phatology in Argentina.
METHODOLOGY: We present a diagnostic algorithm for NPD consists: I- compatible patient selection II- histological and biochemical studies III- enzymatic determinations (acid sphingomyelinase and chitotriosidase) IV- filipin test in fibroblast culture V- molecular analysis.
RESULTS: we studied three nosological defined patients with NPD: two type B NPD and one type C NPD. The type B NPD, patients of non-consanguineous parents with hepatosplenomegaly, however they did not present any neurological symptoms. Bone marrow biopsy show foam cells. The plasma chitotriosidase was slightly increased. ASM activity level was lower. The SMPD1 gene sequencing revealed that the patient 1 is homozygous for the mutation p.R608del, patient 2 is compound heterozygous, allele1 p.Ser147LeufsTer19 and allele 2 a novel mutation (p.Lys578Thr). The type C NPD, patient presented ataxia, mental and motor retardation and language impairment with seizures and hepatosplenomegaly. The plasma chitotriosidase was slightly increased. Functional studies in fibroblasts with Filipin were positive. The NPC1 gene sequencing indicated that the patient is homozygote for the missense mutation p.R1186H as regards the other.
CONCLUSION: Patients with NPD present with a large phenotype spectrum of nonspecific disease manifestations that can lead to considerable diagnostic delay and missed cases. Early diagnosis of NPD is priority for appropriate management.

P-087 - ENZYMATIC ALPHA-GALACTOSIDASE A (GLA) AND BETA-GLUCURONIDASE (GUSB) RELATION USED TO SUPPORT DIAGNOSTIC IDENTIFICATION IN WOMEN WITH FABRY DISEASE.

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Fabry disease is an sphingolipid metabolism disorder affecting enzymatic activity of GLA. The disorder causes a multisystemic affectation with X-linked chromosome (xq22.1) heredity. With an estimate range of 1: 40.000 to 1: 120.000 in men and 1: 117.000 in women both with Gaucher disease are considered the most prevalent sphingolipidoses worldwide. Classic male diagnostic approach has been done demonstrating low enzymatic activity levels of GLA on DBS screenings, followed by confirmation of the screened positive results in leucocytes. Carrier women diagnostic has been more challenging due to the random inactivation of X chromosome causing variable enzymatic activities that can be comparable to normal values until 40% of cases. In this work we present a preliminary approach for a possible identification of carrier women with Fabry disease by means of an analysis of the relation between GLA and beta-glucuronidase performed on DBS and leucocytes.
MATERIALS AND METHODS: We quantified the activity of GLA and GUSB by final point fluorometry. DBS and leucocyte samples were obtained from 25 male and 25 female normal controls (ages between 15 and 40 years) to establish normal range. Similar samples were obtained from 14 Fabry confirmed males, 2 obliged carrier females (mothers of affected patients) and 14 patients (both female and male) with clinical suspicion of Fabry disease.
RESULTS: Reference ranges obtained for GLA/GUSB relation on DBS: 0.04-0.21 and on leucocytes: 0.1-0.4. Affected males: 0.01-0.08 on DBS and 0.01-0.032 on leucocytes. Obliged carrier females (DBS): 0,034 y 0,038. Females with clinical suspicion presented values on DBS <0.038 and on leucocytes: 0.16. Obliged carrier values were under lower normal controls limit. Is possible that this relation could be a useful tool to better conduct the analysis for female carriers of Fabry disease. More studies are needed to establish this possibility.

P-088 - SEVERE LIVER AND LUNG INVOLVEMENT WITH NO EVIDENCE OF NEUROLOGICAL IMPAIRMENT IN AN INFANT WITH ACID SPHINGOMYELINASE DEFICIENCY AND NOVEL VARIANT IN SMPD1 GENE

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Acid sphingomyelinase deficiency (SD), also known under the acronym Niemann-Pick A/B disease, is a rare autosomal recessive genetic condition in which sphingomyelin accumulates in lysosomes of macrophages and other mononuclear phagocyte cells in different organs and tissues. These anomalous deposits are the cause of clinical symptoms presented by patients with SD.
We report the clinical findings of an infant presenting severe liver and lung involvement and novel variant in SMPD1 gene, which encodes acid sphingomyelinase enzyme. The 9-year-old female infant was referred for clinical investigation of recurrent severe respiratory infections, hepatosplenomegaly and signs of early liver failure. Laboratory workup showed 10-fold increase in chitotriosidase, a non-specific marker of

lysosomal deposits, and remarkably decreased levels of acid sphingomyelinase enzyme.
Liver biopsy depicted advanced fibrosis and enlarged macrophages (Kupffer cells) with profuse cytoplasmic deposits. Molecular analysis demonstrated the novel homozygous variant c.1148A>G, which predictively determines a missense at codon 383 (p.(Asn383Ser)).
Last clinical follow-up occurred at the age of 1y2mo. At that moment, no neurological involvement was noticed, while lung involvement has progressed to oxygen dependence and hepatic dysfunction to cirrhotic stage.
The vast clinical variability of symptoms and signs may be a challenge for early diagnosis of SD, especially in young children. Another clinical challenge is to determine neurological prognosis for patients with novel variants, for which, in the present case, remains to be determined.

P-089 - PERIPHERAL NERVOUS SYSTEM DISORDER IN NIEMANN PICK TYPE C DISEASE

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INTRODUCTION: Niemann Pick type C (NPC), a rare and progressive genetic disorder, is inherited in an autosomal recessive manner, with worldwide incidence estimated about 1/100.000 live births. In Brazil, until 2015, it were identified 75 new cases of NPC according to Rede NPC data. Pathogenic variants in the related genes must be found in individuals to confirm the diagnosis. The treatment is based on multiprofessional rehabilitation and the disease modifying therapy, Miglustat.
OBJECTIVE: to describe six patients with NPC molecular diagnosis and clinical or electrophysiological peripheral neuropathy findings. METHOD: A retrospective observational study of six individuals with infantile form of NPC based on biochemical criteria and/or molecular study, from 2002 until 2019, followed up in the Medical Genetics Service located in the Complexo Hospitalar Professor Edgard Santos – COM HUPES.
RESULTS: All the patients presented pathogenic variant at NPC1 gene, with diagnosis after at least 3 years of disease progression. Patient 1 presented juvenile form, and the others, early infantile form of NPC. All patients presented clinical signs of peripheral neuropathy; only 4 underwent electrophysiological study - ENMG. Two patients exhibited a demyelinating pattern and other two, axonal neuropathy.
DISCUSSION: Even-though peripheral nervous system commitment in NPC disease is still lacking of solid literature material, it has been published isolated case reports referring demyelinating peripheral neuropathy in infantile form patients. In this study, all patients presented evidence of peripheral neuropathy. The patient 1, juvenile form, exhibited axonal sensory-motor polyneuropathy, with polyphasic potential and reduced recruitment at ENMG. Patient 3, with five years of disease and two under specific treatment, presented axonal pattern, polyphasic potential and recruitment with severe rarefaction. The Patients 4 and 5, early infantile form, with 3 and 5 years of disease progression, respectively, prolonged latency and reduced velocity. They both showed a demyelinating pattern. Until 2003, 4 cases of NPC, infantile form, and peripheral neuropathy had been related in literature. In 2018, a patient with infantile form presenting pancytopenia and axonal peripheral neuropathy was published. Standard studies in individuals with NPC are needed in order to have adequate characterization of peripheral nervous system commitment in the disease.

P-090 - SLEEP DISORDERS CHARACTERIZATION IN KRABBE DISEASE PATIENTS' FROM THE REFERENCE CENTER OF BAHIA, BRAZIL

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INTRODUCTION: Krabbe disease (KD) is an autosomal recessive lysosomal disorder affecting the white matter of central and peripheral nervous systems. It comprises a spectrum ranging from infantile to later onset disease. Sleep disorders can increase morbidity and health care costs. In controlled studies, volunteers who were restricted to four to five hours of sleep for a few days experienced worsening neurocognitive, behavioral, metabolic, and autonomic parameters.
OBJECTIVE: To describe a serial cases of 2 individuals diagnosed with Krabbe disease followed in an reference center in Salvador, Bahia, Brazil and their sleep disorders.
METHOD: Observational, descriptive study, from data review of patients with Krabbe disease diagnosis followed in a reference center. Three types of questionnaires were applied to identify sleep disorders, such as the Sleep Disturbance Scale for Children (SDSC), range from 26 to 130 with a cut-off point of 39 that characterizes sleep disturbance; the Epworth Sleepiness Scale (ESS) to measure the daytime sleepiness, score >10 points indicates sleepiness; and the Conners' Scale short Form to suspect of hyperactivity disorders with a score ≤ 12 to girls and score ≤ 17 to boys as a positive finding.

RESULTS: Two twin girls with neuropsychomotor development regression onset one 1 year and 2 months old and the other 2 years and 6 months old, associated seizures, truncal hypotonia, spasticity of extremities an biochemical diagnosis of Krabbe's disease 2 years and 10 months old and both presents loss of milestones. They are 4 years and 3 months old and both cases are later onset type of KD. The SDSC questionnaire observed that the score of Patient 1 and Patient 2 were the following values 62. Both patients pointed above the cutoff point, characterizing the sleep disorder. The analysis of Conners scale and Epworth short form scale showed that Patient 1 e 2 presented the following values 3 and 1, indicated normality.
CONCLUSION: The sleep disorders should be performed in Krabbe disease, which are very frequent despite the lack of sufficient data in the literature. Sleep disturbances can interfere with the quality of life of the patients and caregivers.

P-091 - DEGLUTION AND LANGUAGE ALTERATIONS IN KRABBE'S DISEASE: A CASE REPORT OF TWO TWIN SISTERS

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INTRODUCTION: Krabbe disease (DK) is a rare condition characterized by a lysosomal deposit due to the deficiency of the galactocerebrosidase enzyme (GALC) and by a rapid neurodegeneration. This inborn error of metabolism results in demyelination of the central and peripheral nervous system. There isn't information about speech therapy in this disease.
OBJECTIVE: To describe the clinical deglutition and language evaluation in this area of three-years-old twin sisters, both with clinical diagnosis of DK.
MATERIALS AND METHODS: The case was described from three axes: clinical history, global clinical manifestations and speech-language pathology. The Clinical Evaluation Protocol for Childhood Dysphagia (PAD-PED, 2014) was used for the clinical evaluation of the oral and deglutition motor-sensory system. For the functional evaluation of the deglutition, was used food in the liquid and pasty homogeneous consistency. The Behavioral Observation Protocol (PROC, 2004) was used to evaluate the language.
RESULTS: The clinical history of the twins reveals neuropsychomotor development was adequate up to two years and two months old, when they began to loss of motor and cognitive abilities. From the clinical findings observed, it was established as a hypothesis diagnostic the Moderate to Severe Neurogenic Dysphagia for the consistencies assessed and language disorders in both children at three-years-old.
CONCLUSION: The global motor and orofacial and language manifestations interfere directly in the performance of feeding and communication, impacting on nutrition and the quality of individuals and their families. This disease presents rapid progression when the onset is early.

P-092 - TREATMENT OF LATE- INFANTILE NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 DISEASE (CLN2) WITH ENZYME - REPLACEMENT THERAPY WITH INTRAVENTRICULAR INFUSION OF CERLIPONASE ALFA: REPORT OF TWO CASES

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BACKGROUND: Late- infantile Neuronal Ceroid Lipofuscinosis type 2 disease (CLN2), is a progressive disease which typically has beginning during the stages of infant or preschool, with a progressive deterioration in mental, motor, vision, language skills and with epilepsy usually difficult to manage. The frequency depending on the ethnic origin, reaching frequencies of 1 / 385,000 inhabitants in Finland, up to 1 / 1,000,000 inhabitants in other Scandinavian countries. In Colombia there is no record that allows the estimation of the frequency of this disease. Typically the age of onset varies between 2 and 7 years. It is transmitted in an autosomal recessive way, by mutations of the TPP1.1-4 gene). Until April 2017, no treatment was available that potentially would change the natural course of disease.
GOALS: Describe two cases of late infantile Neuronal Ceroid Lipofuscinosis type 2 (CLN2), currently in treatment with enzyme-replacement therapy with intraventricular infusion of Cerliponase alfa.
RESULTS: We report two cases which are patients of 5 years of age, male and female, with myoclonic epilepsies, with a reflex component to sounds and low-frequency photostimulation, associated with progressive ataxia and regression of motor and language skills. Symptoms about 2 years of evolution, with neuroimaging that show cerebral and cerebellar atrophy; the diagnosis of Neuronal Ceroid Lipofuscinosis type 2 (CLN2) was confirmed by enzymatic and genetic method, with mutation confirmed in the TPP1 gene. The treatment of enzyme- replacement with Cerliponasa α was started, it was applied intraventricular every 2 weeks, through the Ommaya reservoir. When the treatment was started, the patients were in a phase of progressive skills

regression, and after the beginning the stabilization of the disease was found. We have not found new clinical deterioration until now. No significant gains in neurodevelopment have been documented, although subjectively parents have reported improvements in some skills

CONCLUSIONS: Treatment intraventricular with Cerliponase α every 2 weeks is effective in controlling and stabilizing the disease. In our patients we have not found deterioration from the basal point which they started the therapy.

P-093 - SUBSTRATE REDUCTION THERAPY IN FIBROBLASTS OF MUCOLIPIDOSIS II AND III PATIENTS

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BACKGROUND: Mucolipidosis II and III (ML II and III) are autosomal recessive diseases caused by mutations in GNPTAB and GNPTG genes, causing defects in GlcNAc-1-phosphotransferase. This enzyme adds manose-6-phosphate residues in lysosomal hydrolases, which allows to enzymes entry in lysosomes. These diseases have no treatment, and we hypothesize that the use of substrate reduction therapy and immunomodulation may be a therapeutic approach.

METHODS: Fibroblast of 2 MLII/III alpha β and 2 MLIII gamma patients and 1 control were treated with 10μM Miglustat, 20μM Genistein and 20μM Thalidomide. Total proteins were extracted. ELISA and immunofluorescence confocal microscopy were performed to evaluate the presence and impact of heparan sulfate substract. Enzymatic assay was carried out to evaluate the indirect impact of substrate reduction.

RESULTS: The substrate reduction results were observed in all patients for all treatments, with a mean reduction of 25.05%, 33.07% and 35.57% in heparan sulfate for Genistein, Miglustat and Thalidomide respectively. The same was observed in immunofluorescence assay. In 60-70% of treatments, there was an increase in enzymatic activity, with averages of 102% (1-414%) in β-glucuronidase, 60% (1,58-246,87%) in α-Mannosidase and 27,89% (17,21-38,18%) in β-galactosidase. Miglustat treatment was more efficient with increases in 80% of the cases ranging from 2 to 414% of activity in the different enzymes.

DISCUSSION: The data present encouraging results, since increases above 10% of the residual activity of the enzyme may bring benefits in the phenotype of patients with inborn errors of metabolism. However the low sample size should be considered. Now, inflammatory response tests will be performed to evaluate and understand the results of treatment with Thalidomide.

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P-094 - TPP1 ACTIVITY IN CEREBROSPINAL FLUID OF FOUR CLN2 AFFECTED CHILDREN UNDER INTRATHECAL CERLIPONASE ALPHA THERAPY

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INTRODUCTION: Neuronal Ceroid Lipofuscinosis disease CLN2 is a neurodegenerative disorder caused by Tripeptidyl Peptidase 1 (TPP1) deficiency. It is commonly diagnosed by enzyme activity measurement in leukocyte pellet. Cerliponase alpha is a recombinant enzyme approved for use as enzyme replacement therapy (ERT). This therapy is performed at the Children's Hospital Cordoba, Argentina, since 2017 as an intrathecal infusion into the ventricle cerebrospinal ?uid (CSF) ideally every 15 days. The range of TPP1 activity in cerebral CSF remains unknown.

OBJECTIVES: To develop a reference interval of TPP1 enzyme activity in CSF of controls, and to quantify the TPP1 activity in the CSF of infused subjects to follow-up the variations along the treatment.

MATERIALS AND METHODS: TPP1 activity was quantified in CSF from 29 controls (lumbar puncture samples provided by Central Laboratory of the Children's Hospital), and from 4 patients along intrathecal treatment (obtained before every infusion under informed consent of the parents).

RESULTS: Control´s TPP1 activity was 19.36 - 379.50 nmol TPP1/24h/mg protein (215.24 ± 96.37 [mean ± SD] nmol TPP1/24h/mg protein). Activity of subject #1 was 0 - 638.6 nmol TPP1/24h/mg protein. Activity of subject #2 was 6.26 - 5630.69 nmol TPP1/24h/mg protein. Activity of subject #3 was 1.52 - 802.84 nmol TTP1/24h/mg protein. Activity of subject #4 was 0 - 3239.10 nmol TPP1/24h/mg protein. All individuals showed marked decrease of activity along the successive infusions, and some of the values were in the deficiency range.

DISCUSSION: Spinal CSF was validated as control biological sample provider. Despite the subjects under ERT received the same doses of enzyme, activity of TPP1 in CSF showed a broad range. During the first phase of treatment, 3 out of 4 individuals showed activity near 10-fold the controls' range. Only subject #1 showed certain stability of values along

all the infusions. The remaining individuals showed a tendency to stabilization along infusions after an initial peak, with some unexpected deficient values. It remains as an open question if TPP1 activity assay could be used as a biomarker; further studies are needed for a better understanding of TPP1 activity variations along intrathecal Cerliponase therapy.

P-095 - A SYSTEMATIC LITERATURE REVIEW OF ENZYME REPLACEMENT THERAPY IN EARLY-ONSET POMPE DISEASE

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INTRODUCTION: Pompe disease (PD) is an inherited disorder characterized by the deficiency of acid alpha-glucosidase, leading to progressive glycogen accumulation in the tissues. The former untreatable perspective of the disease has changed since the approval of enzyme replacement therapy (ERT). Previous systematic review (SR) on early-onset PD (EOPD) haven't evaluated important endpoints such as quality of life (QOL) and safety, thus creating the need for new assessments of clinical outcomes.
OBJECTIVE: To evaluate evidence available on the efficacy and safety of ERT for EOPD. METHODS: We systematically searched Medline/PubMed and Embase for prospective clinical studies published evaluating ERT for EOPD. Exclusion criteria were retrospective and transversal studies, trials with less than 5 patients and preclinical studies. We defined a priori the following outcomes as of interest: safety, quality of life, survival, time to onset of ventilation (TOV), deglutition disorder, cardiomyopathy, myocardial function and neuropsychomotor development. Assessment of quality of evidence was performed according to the GRADE criteria.
RESULTS: A total of 1470 articles were identified, 42 studies were eligible for full text reading and subsequently, 13 articles were included in our analysis. Only three of the endpoints analyzed in this study had moderate or high GRADE scores favoring ERT. Survival was evaluated in 6/13 studies and increased in all of them (GRADE moderate). TOV was evaluated in 7/13 studies and 4/7 showed its increase by ERT (GRADE high). Cardiomyopathy was evaluated in 10/13 by left ventricular mass, reduced in 8/10 studies after ERT (GRADE moderate). Safety data were described in 6/13 studies (GRADE low) and all analyzed antibody formation, present in at least 85% of patients evaluated. Antibody titers were not correlated with severe adverse events (AEs) or infusion-associated reactions (IARs) nor were associated with treatment efficacy and clinical outcomes. Regarding IARs, most were mild to moderate in severity. DISCUSSION: Our results add information over previous published SR on ERT, as includes data from observational prospective studies, showing benefit for survival, TOV and cardiomiopathy. Findings suggest ERT is safe in EOPD, once most AEs were mild to moderate and antibody formation did not seem to interfere with any outcome evaluated.

P-096 - CRIM-NEGATIVE CLASSIC INFANTILE POMPE DISEASE PATIENT ON ERT SINCE 40 DAYS OF AGE

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INTRODUCTION: Pompe disease (PD) is a progressive and often fatal muscular disease caused by a deficiency of the lysosomal enzyme acid--glucosidase (GAA). It is a rare autosomal recessive disorder. The clinical spectrum of PD varies with respect to age at onset, rate of disease progression, and extent of organ involvement. The classic infantile form exhibit rapidly progressivity, prominent cardiomegaly, hepatomegaly, weakness and hypotonia. Death occurs due to cardiorespiratory failure in the first year. This form of PD represents the most severe end of the disease spectrum. The advent of specific enzyme replacement therapy (ERT) necessitate early diagnosis because this change the natural history of the disease Few patients have mutations that prevent to synthesize any enzyme and are label CRIM negative. This is a poor prognostic factor. CRIM negative patients required immunomodulation therapy prior starting ERT.
AIM: To present an infantile PD, CRIM negative patient that started ERT at 40 days of life.
Case
17 months of age male patient product of the second normal pregnancy of healthy non-consanguineous couple. Prenatal diagnosis for PD showed the same mutations as his older sister who have died when she was 1 year of age and she had deleterious mutations in the GAA gene that were known as severe: CRIM negative. Patient prenatal echocardiogram showed hypertrophic cardiomyopathy. The newborn echocardiogram confirmed the cardiomyopathy and plasma CPK was very high. The patient received immune tolerance induction with rituximab, methotrexate, and gamma globulins. ERT started at 40 days of life. He has not presented until now adverse effect. Antibodys have been negatives. The clinical picture of the patient is completely different from that of his sister. He sat down at 7 months, achieved walking at 13 months, he is able to stand up from ground alone, and he has several words and normal behavior.

CONCLUSIONS: ERT is beneficial for PD classical infantile. It is very important to think about this diagnosis because as early the confirmation the greater the benefits of this therapy. CRIM negative patients required immunomodulation therapy prior starting ERT.

P-097 - OUTCOMES OF A CLN2 PATIENT TREATED EARLY WITH CEREBROVENTRICULAR ENZYME REPLACEMENT THERAPY

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INTRODUCTION: Neuronal Ceroid Lipofuscinosis(CLN) is a rare progressive disorder caused by a deficiency of tripeptidyl peptidasa 1(TPP1). CLN2 most commonly presents with seizures and/or ataxia in the late-infantile period (age 2-4), often in combination whit a history of language delay, followed by progressive childhood dementia, motor and visual deterioration, and early death. Recombinant human tripeptidyl peptidase1has been developed to treat CLN2.AIM: to describe the outcomes of a CLN2 patient who received early treatment with cerebroventricular ERT.
MATERIALS AND METHODS: we analyzed the CLN2 Clinical Rating Scale electroencephalographic (EEG) characteristics and MRIof a patient with CLN2 after 20 months of treatment with cerebroventricular ERT.
RESULTS: a 4-year-old male was diagnosed after his affected16yo brother with classic phenotype. He started treatment at 2 years of age presenting at the time of diagnosis, language delay, behavioral disorders and normal examination.MRI and EEG with photic stimulation were normal. After 20 months of treatment his neurological exam, the MRI and EEG with photic stimulation were still normal.. Language delay remained stable. He didn´t present complication regarding therapy.
CONCLUSIONS: CLN2 natural history studies estimates a loss of 2 points per year in the Clinical Rating Scale. Our patient remained stable after 20 months of ERT so we conclude that ERT prevented the onset of CLN2 symptoms in him so far.

P-098 - ATYPICAL PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY (PDHC) DUE TO PDHA1 GENE DEFECT, PRESENTING AS CHARCOT-MARIE-TOOTH DISEASE (CMT).

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BACKGROUND: The pyruvate dehydrogenase enzyme complex is composed of 3 catalytic subunits (E1, E2, E3), 2 regulatory subunits, 3 cofactors and one binding protein. Mutations in the X-linked PDHA1 gene are the most common cause of PDHC. The disease typically presents in neonates with lactic acidosis, brain malformations and dysmorphic features, however milder/atypical presentations are known. CMT is the most common hereditary cause of peripheral neuropathy. Mutations in >80 genes are associated with the disease, with an AR, AD or X-linked inheritance. Recently, mutations in one of the PDHC genes, PDK3, were found to be responsible for X-linked CMT type 6, however mutations in the PDHA1 gene have not been associated with CMT.
AIMS: To present a previously unreported association of atypical PDHC deficiency presenting as CMT due to pathogenic variants in PDHA1.
Clinical Report: Patient presented at 3 y with toe walking and uncoordinated gait. Later, speech delay, sensory loss, temperature sensitivity, numbness and burning of hands and feet were noted. He was diagnosed with CMT at 5 y based on an abnormal nerve conduction velocity study. Over time he developed ADHD, anxiety, abnormal sleep, migraines, fatigue and leg pain. At 14 y after a CMT gene panel was normal, WES was performed revealing a de-novo pathogenic variant, c.214C>T (p.Arg72Cys) in PDHA1. Biochemical testing showed elevated lactic acid and alanine, and PDHC activity in fibroblasts was 9 % of the control mean, confirming PDHC deficiency. Physical exam was positive for signs of peripheral neuropathy (pes-cavus, absent patellar/achilles reflexes, abnormal gait, tremors) and hypermobility. Brain MRI was normal. He was started on a high-fat/low-carbohydrate diet (20 grams of carbohydrate/day), thiamine (1000mg/day) and gabapentin. Since initiation of treatment, fatigue, headaches, sleep and leg pain have improved. However, there have been no changes in biochemical parameters.
CONCLUSION: This case highlights CMT as an atypical presentation of PDHC deficiency and reports on a new association with PDHA1 gene defects. PDHC deficiency should be considered as part of the evaluation for CMT and PDHA1 gene testing should be added to existing CMT/hereditary neuropathy gene panels.

P-099 - ROLE OF SOCIAL WORK IN THE FOLLOW-UP AND INTERVENTION OF

PATIENTS WITH INBORN ERRORS OF METABOLISM, INTA, UNIVERSITY OF CHILE

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INTRODUCTION: Phenylketonuria (PKU) if diagnosed and treated early prevents intellectual disability, and its evolution will depend on adherence to treatment. To support adherence in 2016, the Social Work (SW) discipline was integrated into the multidisciplinary team of a reference center for PKU in Chile.
OBJECTIVE: to describe the contribution of SW in the follow-up of PKU patients.
METHODOLOGY: Descriptive study of 120 PKU attended by SW: 64 children and adolescents (CH&A) derived by social case and / or low level of adherence and 56 women between 14-35 years with partial or total abandonment of the treatment with risk of Maternal PKU Syndrome (MPKU). A psychosocial interview and socioeconomic qualification (SEQ) was conducted to detect risk factors or protective factors of adequate adherence. Different strategies were used to improve adherence.
RESULTS: 45/64 CH&A have low socioeconomic status and less adherence to treatment and are compared with 19 with low SEQ, but adequate adherence. They do not differ in economic income characteristics or in housing or employment, slightly in education. They differ in family functioning and the degree of adaptation of the family to treatment. Being the factors of > risk: "lack of recognition of the health problem" and "motivation to change". The strategies used to promote adherence were: family interview, home visits, weekly and monthly telephone contact, coordination with networks, weekly monitoring of phenylalanine (Phe) level and, in case of high complexity, request of protective measures before Family Courts. In 15/45 CH&A improved their attendance to controls, increased the number of analysis of Phe level and/or improved their metabolic control by lowering Phe level from 7,1 to 4,9 mg/dL and greater parental commitment was observed. Of the 56 women at risk of MPKU: 18/56 returned to the follow-up program or improved adherence.
CONCLUSIONS: The contribution of SW is significant but limited in number. It is suggested to observe adherence on a regular basis, maintain continuous communication with the family or patient and conduct a psychosocial interview at the time of diagnosis to the family of patients, in order to detect early factors that could affect adherence to follow-up.

P-100 - INBORN ERRORS OF METABOLISM (IEM) IN TELEMEDICINE: EXPERIENCE AT GARRAHAN HOSPITAL

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INTRODUCTION: Telemedicine provides health services to patients in which their access is limited by geography, lack of technological resources or specific doctors.
In the case of IEM, where the number of medical references specialists and laboratories focus on the diagnosis of these pathologies are not enough to meet the demand in Argentina, telemedicine ensures the equal access all over the country of the technology and experience available at Garrahan hospital, which guarantees that a broad coverage of the specialty is provided in all argentine´s territory1.
National Health Secretary supports Telemedicine implementation2.
OBJECTIVE: To describe the number of distant consultations received by the IEM services at Garrahan Hospital.
MATERIALS AND METHOD: Descriptive and retrospective study of distant consultations received by the IEM services since October 2016 to September 2017.
RESULTS: There were received 744 consultations and there were analyzed 363 cases, what differs from the consultations number, because each case originated new consultations. These were from Buenos Aires 12,8%, CABA 16,2%, Tucumán 9,30%, Salta 8,10%, Mendoza 7,80% y other provinces 45,8%.
The 30% comes from the argentine northwest (NOA). 42 diagnostics were made (12%). They are detailed below: Galactosemia, PhenylketonuRia, Biotinidase deficiency, Mucopolysaccharidosis, Mitochondrial Disorders, Gangliosidosis, Maple Syrup Urine Disease, Argininosuccinic Aciduria, Glutaric Aciduria, Melthylmalonic Acidemia, Cobalamin Deficiency, 3-Methylglutaconic Aciduria, 2-Hydroxyglutaric Aciduria, Disorders of Urea Cycle, and Fatty acid oxidation defects.
CONCLUSIONS: Having reached an accurate diagnosis in the 12% of the cases, it results similar as reported in the literature, when studying patients with risk criteria to IEM.
42 patients were able to access treatments and monitoring by this service due to this tool, during the analyzed period.
Observing an increase in the number of consultations along a year, it makes to infer that telemedicine should be incorporated in other centers.

P-101 - HIGH-COST DRUG LAW IN CHILE (20,850). IMPACT ON THE INBORN ERRORS OF METABOLISM

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INTRODUCTION: In 2015, Chile promulgated Law 20,850, which creates a universal coverage financial protection system for high cost diagnoses and treatments in our population. Among the pathologies included in the first decree, 6 of the 14 conditions were within the group of the Inborn Errors of Metabolism (IEM): Gaucher Disease (GD), Fabry Disease (FD), Mucopolysaccharidosis (MPS) Type I, II and VI, Tyrosinemia type I (Tyr I). The law establishes access and opportunity guarantees for diagnosis and treatment, either with enzyme replacement therapy for Lysosomal Diseases or with substrate inhibition for Tyr I. INTA fulfills the role of being the exclusive diagnostic confirmation center for these diseases, which requires analyzing positive cases and assigning the respective treatment according to previously designed protocols and deadlines guaranteed by law.
OBJECTIVES: To present data of patients with IEM incorporated into Law 20,850 and discuss its impact on this group of pathologies.
MATERIALS AND METHODS: Since the start date of the regime of Law 20,850, 224 applications have been received. 176 patients are in follow-up (34 GD, 90 FD, 10 MPSI, 18 MPSII, 8 MPS VI, 16 Tyr I), 17 applications were discarded, 14 applications were closed and only 17 requests are pending. Since the beginning of the Law, 4 new pathologies have been incorporated into the field of Nutrition, Oncology, Neurology and Endocrinology, totaling a list of 18 pathologies.
CONCLUSIONS: Law 20,850 allows guaranteeing access to diagnosis and treatment of some IEM that benefit from high-cost treatments. This permits the establishment of a predictable and traceable system for the incorporation of new treatments and new patients to high-cost therapies. The long-term challenges are multiple; however, this approach can serve as a precedent for other countries in Latin America.

P-102 - IEM WITH GENETIC CO EXISTENT CONDITION. OUR EXPERIENCE WITH PKU AND OTC

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INTRODUCTION: Genetic co-existent conditions with IEM are rare, but have been reported specially with PKU. The identification and reporting of co-existent conditions are essential because it may alter morbidity and mortality of the IEM. Neuropsychological symptoms of an undiagnosed co-existent condition may be mistakenly attributed to the basic IEM. The association enhances the complexity of treatment and management burden for patients and caregivers of these cases.
AIM: to present the experience of our center with three cases of IEM with co-existent genetic condition: OTC and hyperphenyalaninemia with Down syndrome and PKU male with microdeletion of X chromosome.
Cases
7 years old, male, PKU was diagnosed by NBS with good biochemical control with treatment started at 15 days of age. Behavior abnormalities were evident during the first year and BH4 deficiency was studied and discarded. An autism spectrum disorder and particular clinical dymorphism was evident at 2 years when CHG array was performed. A duplication of 1.7 bp in the Xp22.31 region was evident. This duplication is linked to pathological phenotype in a large number of cases associating intellectual disability.
8 years old, female, postnatal diagnosis of trisomy 21, with associated congenital heart disease surgically corrected at 7 months of age. At 4 years of age in the context of infectious respiratory disease, she presented encephalophatic episode with deterioration of consciousness, with plasma ammonium: 224 ug/dl, urinary organic acids showed elevated orotic acid and plasma aminoacids high glutamine. OTC gene sequencing showed known pathogenic variant.
6 years old, female, Down syndrome was evident at birth. Hyperphenylalaninemia was detected by NBS and remains stable during subsequent controls.
CONCLUSIONS: when a case of PKU detected by NBS has a good biochemical control but the neurodevelopment is not normal, it is mandatory to look for other associated disease that explains the complex situation. Down syndrome is a frequent genetic disease and could be associated with rare IEM. An encephalopatic episode requires always measure ammonia no matter the known patient´s disease. When genetic condition co exists with treatable IEM, the patient and caregivers may need medical and social special support.

P-103 - DYSTONIA TREATMENT IN PATIENTS WITH PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION (PKAN)

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BACKGROUND: Pantothenate kinase-associated neurodegeneration (PKAN) is a type of neurodegeneration with brain iron accumulation (NBIA). The phenotypic spectrum of PKAN includes classic PKAN and atypical PKAN. Classic PKAN is characterized by early childhood onset of progressive dystonia, dysarthria, rigidity, and choreoathetosis. Pigmentary retinal degeneration is common. Atypical PKAN is characterized by later onset (age >10 years) and more gradual progression of disease. Treatment for NBIA disorders remains symptomatic.
OBJECTIVE: To describe clinical response of dystonia in PKAN patients treated with pharmacological and surgical treatment. METHODS: Retrospective descriptive study, analysis of clinical records and revision of videos of pediatric patients with PKAN.
RESULTS: 11 genetically confirmed patients (8 males / 3 females). 6 presented typical presentation and 5 atypical PKAN. Average age of onset: 6 years. The initial symptoms were gait disorders associated with frequent falls (7/11) and focal dystonias (4/11). Dystonia with prominent cranial involvement and cognitive impairment were present in all patients. 7 patients showed spasticity. The eyes of the tiger sign T2-weighted MRI was seen in 10/11 patients. Symptomatic treatment for dystonia included oral treatment with trihexyphenidyl, benzodiazepines, baclofen, tetrabenazine and levodopa showed mild or no response. Botulinum Toxin-A Injection was used for focal dystonia with transient response. Two patients were treated with deep brain stimulation (DBS), both with good response, one patient recovered gait and one patient was treated as management of dystonic storm with significant reduce of dystonia. No adverse effects were reported.
CONCLUSIONS: In our serie of PKAN patients, poor response to pharmacological dystonia therapy was observed. Surgical treatment with DBS showed significant reduction of dystonic symptoms, improving quality of life in our patients.

P-104 - THE USE OF MOLECULAR ANALYSIS FOR THE CONFIRMATION AND THE THERAPEUTIC ORIENTATION OF METABOLIC FINDINGS IN INBORN ERRORS OF METABOLISM.

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INTRODUCTION: The clinical manifestations of Inborn Errors of Metabolism (IEM) in the neonatal period can mimic other more frequent pathologies leading to possible confusions and delay in diagnosis, including the initiation of therapies that may hinder the specific metabolic investigation.
METHODS: Describe the evolution of the patient in a Neonatal Intensive Care Unit, with a severe and complex condition, which despite altered metabolic examination, its diagnosis and therapeutics could only be safely confirmed after the molecular investigation of the newborn and your parents.
RESULTS: Term newborn, first of the young non-consanguineous couple, mother with activity Lupus during the gestation in use of several immunosupressors and pulmonary hypertension. On second day of life, the newborn presents a severe gastrointestinal bleeding with hypovolemic shock. He presented hepatomegaly, increased prothrombin time and aminotransferases. To control the clinical situation received transfusion of several blood products. On fourth day positive for Cytomegalovirus in the urine, started therapy with ganciclovir. After 2 days he maintained a clinical and had edema legs and ascites , in this moment a genetic evaluation was requested. On 8th day, the neonatal screening test (collected before blood transfusions), with an increase in galactose and a decrease in GALT activity, was received. Immediately introduced lactose-free diet and molecular analysis was performed on oral swab DNA sample, complete sequencing of the GALT gene was performed by Next Generation Sequencing (NGS). Two mutations were observed, pathogenic and probably pathogenic. Subsequently, the parents' research revealed trans variants, identifying the molecular profile of the patient as a composite heterozygote for two variants in GALT. Corroborating the clinical diagnosis and the maintenance of the therapy. The evolution was only favorable with disappearance of edema with 30 days of life.
CONCLUSION: In complex and rare diseases, the rapid recognition of the diagnostic possibility and parallel research of differentiation with common causes that can mimic it, are of the utmost importance. It is not uncommon for the affected patient to receive blood products, blocking out metabolic investigations. In this way, molecular research presents itself as a resolutive tool.

P-105 - PRESENTATION OF A HEREDOGRAM OF POSSIBLE MITOCHONDRIAL MYOPATHY ACCOMPANYING FOUR GENERATIONS IN A FAMILY IN AMAZONAS STATE, BRAZIL

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INTRODUCTION: Ernester et al. (1959) described the first mitochondrial disease on a euthyroid patient who had a long history of symptoms related to a permanent hypermetabolism state with morphological and biochemical alterations of the mitochondria (Luft's disease).
OBJECTIVE: To describe a case report of probable mitochondrial disease in 04 generations in a family from Amazonas State in Brazil. Materials e METHODS: Clinical case report and heredogram survey.
RESULTS: DLF, 41, was consulted in a medical genetics service reporting the following symptoms: Myopathy, muscle pain and exercise intolerance, Asthma, Mental Confusion, Deafness, food intolerance, Meniere's syndrome, myopathic facets and psychiatric illness. In her heredogram survey it is possible to identify several relatives in four generations on the maternal side affected by the same symptoms as hers in varying degrees. Patient reported that in the first generation there were 16 children that died before one year of age with sudden death after intense weeping and 2 surviving daughters with symptoms of myopathy; in the second generation patient reported 10 children deaths before one year old presenting the same clinical condition of the sixteen children of the first generation, one abortion ocurred and 4 survivors (3 female and one male) with symptoms of myopathy. In the third generation there were 3 daughters all showing symptoms of myopathy all of them are alive in the moment; and in the fourth generation (proband) has two children of one union and another one of a second union, all of them presenting myopathy and intolerance to exercises and with IQ test above the standard considered normal.
CONCLUSION: Based in the heredogram survey, it is possible to visualize a clear inheritance of mitochondrial disease, besides signs and symptoms compatible with mitochondrial diseases. Exoma was requested and results are being expected.

P-106 - DEVELOPMENTAL DELAY-HYPOTONIA-THROMBOCYTOPENIA: SUSPECTED FROM MITOCHONDRIAL DISEASE DUE TO HETEROPLASMIC VARIANT ON MTCYB GENE

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INTRODUCTION: Mitochondrial diseases has a wide clinical spectrum, it may involve an alteration on mitochondrial structure or function that implicate a pathogenic mutation on the inherited mitochondrial or nuclear DNA. Heteroplasmic mtDNA have tissue segregation patterns than vary widely, for example, muscle have higher levels of the mutant mtDNA, whilst levels in blood decrease over time.
OBJECTIVE: Describe clinical-molecular correlation of heteroplasmic variant in MTCYB gene
METHODS: Retrospective analysis of clinical history and molecular results of a pediatric case with developmental delay, hypotonia and thrombocytopenia.
RESULTS: A 2-year-old girl, during first trimester had a subchorial hematoma and caesarean delivery due to podalic position and umbilical artery restriction to 37 weeks of gestation. Parents non-consanguineous, healthy father and mother refers constant fatigue. During first year she shows mild hypotonia, retarded motor and language development. However, at 18-mo she presented small bruises on lower limbs secondary to thrombocytopenia with normal-sized platelets (92.000 plateles/uL), mild splenomegaly and unilateral hypoplasia renal. Acquired or medication induced platelet dysfunction were excluded. Bone marrow aspirate was normal. Whole exome sequencing (WES) identifies genetic "likely pathogenic" variant on MTCYB gene (m.15246G>A, p.Gly167Asp) in heteroplasmy (52% in blood). All known genes causing of congenital thrombocytopenia were normal. She continues clinical follow up, physical therapy, speech therapy and variable count of platelets; occasionally, low or normal levels.
CONCLUSIONS: We analyze the hypothesis if variant on MTCYB gene explain signs and symptoms like hypotonia and neurodevelopmental delay in this case. Because, the clinical spectrum of mitochondrial disease is broad and poorly understood, consequently, long-term prognosis are difficult to predict. MTCYB gene encoded subunit of respiratory complex III located within the mitochondrial inner membrane. Phenotypes describe by mutations in MTCYB are broad: hypotonia, retarded motor and language development, exercise intolerance, gait ataxia, cerebellar hypoplasia, seizures, hypertrophic cardiomyopathy and parkinsonism onset since childhood until adulthood. Usually, high mutation load is associated with more severity, however, variation in percentage heteroplasmy levels in tissues is common and change with age, for this reason is relevant genetic counseling and detailed clinical follow up.

P-107 - SLEEP DISORDER IN AN INDIVIDUAL WITH DEFICIENCY OF CYTOCHROME C OXIDASE 15: A CASE REPORT

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BACKGROUND: Deficiency of cytochrome C oxidase 15 (COX15) is a rare cause of autosomal recessive mitochondrial disease in infants. They are related to the identification of pathogenic variant in MTFMT gene. Its prevalence is estimated at 1/1.000.000 live births and the patients exhibit multi-systemic impairment, most commonly with a Leigh Syndrome phenotype. Sleep disorders are associated with increased morbidity, but only a few cases of primary mitochondrial syndromes associated to sleep disturbances had been published in the literature. METHODS: A case report of a patient with COX15 deficiency followed up at the Medical Genetics Service of the University Hospital Complex Professor Edgard Santos, Salvador, Bahia, Brazil. It was applied three different questionnaires to identify sleep disorders in children. They were: Sleep Disturbance Scale for Children (SDSC), ranging from 26 to 130 with a cut-off point of 39, which characterises a sleep disturbance; the Epworth Sleepiness Scale (ESS) to measure the daytime sleepiness: score >10 points indicates sleepiness; and the short form of Conners' Scale, used to suspect of hyperactivity disorders with a score ≤ 12 to girls and score ≤ 17 to boys as a positive finding.
RESULTS: A 3 years old male patient, non consanguineous parents, presenting at the service with previous recurrent infections and motor delay since 1 year of age. The parent refers no pregnancy or birth intercurrence. At neurological evaluation: bilateral palpebral ptosis, global muscle weakness, Gauss sign, global hipotonia and ataxia. Currently he does not climb stairs without support or ride the bike. He is also unable to raise the arms over the head. He underwent molecular analysis, which exhibited pathogenic variant in MTFMT gene (p.Arg332*/p.Ser209Leu), leading to Combined Oxidative Phosphorylation Deficiency 15 (COXPD15) diagnosis. The patient had positive finding at SDSC scale, with a 58 score. At Epworth and Conners' scales, 6 and 2 scores, respectively.
DISCUSSION: The result of this patient is compatible with sleep disorder. This condition can lead to increased morbidity and caregivers low quality of life. It is essential that geneticists identify the signs of sleep disturbances and try to manage critical findings regarding patients and caregivers quality of life.

P-108 - NOVEL ISCA2 MUTATION IN AN ARGENTINIAN PATIENT WITH SEVERE MULTIPLE MITOCHONDRIAL DYSFUNCTION SYNDROME-4

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INTRODUCTION: Multiple mitochondrial dysfunction syndrome-4 (MMDS4) is an autosomal recessive neurodegenerative disorder. Affected individuals typically attain normal development during the first months of life, presenting thereafter with progressive neurodevelopmental regression, nistagmus, optic nerve atrophy, leukoencephalopathy and biochemical abnormalities such as increased plasmatic glycine. Disease continues at a variable pace and seizures may develop. Loss of cognitive functioning and regression to a vegetative state occurs leading to death within the first years of life.
OBJECTIVE: We report a severe and rapidly progressive case of MMDS4 with a novel variant in ISCA2.
MATERIALS AND METHODS: Clinical assessment and detailed physical examination was realized. A complete exome sequencing (SureSelect Human All Exon V6, Agilent), mitochondrial genome sequencing (Illumina) and Sanger sequencing to confirm pathological findings, were performed using DNA isolated from a peripheral blood sample.
RESULTS: Clinical assessment revealed a three-month-old female patient with hypotonia, apnea and gastroenteritis. Biochemical findings included metabolic acidosis and hyponatremia. Encephalic MRI showed acute ischemia.
The patient was born from a healthy and non-consanguineous couple. Her parents had a previous child who died at the age of five months with similar symptomatology.
In complete exome sequencing a compound heterozygous mutation in the ISCA2 gene was detected. The first variant (c.334A>G, p.Ser112Gly) was classified as pathogenic (Variation ID: 514262), according to ClinVar, Centogene and the AMCG recommendations. The second variant (c.13dup, p.Trp5Leufs*96), a frameshift mutation in exon 5, has not yet been reported in the literature. It was classified as probably pathogenic according to Centogene and the AMCG recommendations. This variant was confirmed by Sanger sequencing.
Mitochondrial sequencing showed no relevant variants.
DISCUSSION: Molecular findings confirm the diagnosis of MMDS4, even though clinical assessment revealed a more severe phenotype than previously reported in the literature.
Thus, the presence of a novel frameshift mutation in ISCA2 broadens the spectrum of molecular variants associated with MMDS4.

P-109 - LEIGH SYNDROME AS A MILD PRESENTATION DUE TO A RARE COMPOUND HETEROZYGOUS VARIANTS IN NDUFAF6 GENE

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INTRODUCTION: Leigh syndrome (LS) it a disorder that affects directly the mitochondrial energy generation, this syndrome has a broad clinical and genetic spectrum, with wide and progressive neurodegenerative manifestations and early onset. Patients usually show global delay or developmental regression, hypotonia, ataxia, dystonia, and ophthalmologic abnormalities. All these clinical findings may be a manifestation of primary deficiency of the mitochondrial respiratory chain complexes.
OBJECTIVE: The primary objective was to analyze the clinical and molecular diagnosis in a patient with LS.
CASE DESCRIPTION: We present a 4 year colombian boy, first child of non consanguineous parents, delivery at 38 weeks by C-section owing to decelerations. During his first year he presented a normal neurodevelopment, after that he start to present expresion speech delay that became a progressive situation. He came at age of 4 to consultation with height and weight according to age, clinical exam present mild ptosis, clenched hands, and flat foot. MRI and lab test were performed, showing bilateral and symmetric hyperintensity in putamen and increase lactate pyruvate ratio. A multigene sequencing panel was performed guided to mitochondrial diseases; identifying a missense heterozygote uncertain significance variant c.371T>C;p.Ile124Thr and missense pathogenic heterozygous variant c.532G>C;p.Ala178Pro in NDUFAF6 gene (clinvar rs201732170; clinvar rs201088736).
CONCLUSIONS: LS has a enormous genetic heterogeneity, involving mutations in nuclear or mitochondrial DNA that affect the proper function of respiratory chain complexes. The biallelic mutations on the nuclear NDUFAF6 may generate a complex I deficiency, on literature research a single affected allele is not enough to cause disease, our hypothesis is that variant c.371T>C;p.Ile124Thr is pathogenic. Correlation clinical with genetic testing confirm the diagnosis of a mitochondrial disease by mutation in nuclear DNA with pattern of inheritance autosomal recessive and to guide optimal genetic counseling and management focused on nutritional interventions (diet rich in antioxidants) and rehabilitation for to preserve or even improve the patient's existing functioning.

P-110 - AADC DEFICIENCY IN BRAZIL: CLINICAL AND BIOCHEMICAL FINDINGS OF A RARE NEUROMETABOLIC DISORDER

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BACKGROUND: Disorders of monoamine neurotransmitter metabolism have been increasingly recognized. These compounds have numerous roles including modulation of psychomotor function; hormone secretion; cardiovascular, respiratory, and gastrointestinal control; sleep mechanisms; body temperature; and pain. Aromatic L-amino acid decarboxylase (AADC) is central in the synthesis of biogenic monoamine neurotransmitters. AADC deficiency is a severe neurometabolic disorder, usually underrecognized, presenting early in life with hypotonia, hypokinesia, oculogyric crises, autonomic dysfunction, dysphoric mood, and sleep disturbance.
OBJECTIVES: To describe a cohort of 5 Brazilian patients with AADC deficiency.
MATERIALS AND METHODS: Clinical, biochemical and radiological data retrospective analysis were reviewed, including the following items: demographic characteristics, genetic profile, and clinical manifestations.
RESULTS: All patients showed normal body weights in the first few months of life. Their growth, however, began to slow down at the end of the first year, and their weight gain was minimal between 1 and 4 years of age, although all of them were treated with a combination of pyridoxine, dopamine agonists, and monoamine oxidase inhibitors. Neurological symptoms became evident in all patients during the first 6 months of life. Intellectual disability, truncal hypotonia, hypokinesia and hypomimia , dystonic movements and typical oculogyric crises in all patients. None of our patients had full head control, defined by the ability to hold their head upright in the sitting position, at their termination point in the study.
CONCLUSIONS: AADC deficiency is a neurotransmitter disorder with features presenting as early as in the first month of life. Hypotonia, hypokinesia, oculogyric crises and autonomic are clinical hallmarks of the disease and may lead to clinical suspicion. Patients may show a number of movement disorders, most frequently dystonia. Diurnal fluctuation and improvement of symptoms after sleep is characteristic. The severity of the clinical phenotype is variable, but the majority of patients show minimal motor development in the absence of treatment.

P-111 - CASE SERIES OF PEDIATRIC PATIENTS WITH DEFICIT OF CEREBRAL CREATINE SECONDARY TO GUANIDINOACETATE METHYLTRANSFERASE (GAMT) DEFICIENCY IN ANTIOQUIA AND SANTANDER, COLOMBIA

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INTRODUCTION: Cerebral creatine deficiency is an inborn error of metabolism that may be secondary to L-arginine glycine amidinotransferase (AGAT) deficiency, guanidinoacetate methyltransferase (GAMT) deficiency, and the creatine transporter (CRTR) deficiency, the latter one being the most common of the three. There are few reported cases in literature around the world, by 2015 less than 20 cases of AGAT deficiency had been reported.
OBJECTIVE: Describe the phenotypic and genotypic findings in two patients with refractary epilepsy and autism spectrum disorder, in which creatine deficency was suspected and then confirmed.
MATERIALS AND METHODS: Describe two cases of confirmed cerebral creatine deficiency in Colombian population.
RESULTS: Two pediatric patients form different geographic regions of Colombia presented a history of refractory epilepsy and autism spectrum disorder. Innate errors of metabolism were suspected on both patients and finally the diagnosis of cerebral creatine deficiency was made by molecular demonstration of mutations on the guanidinoacetate methyltransferase (GAMT) gene. One of the patients had a brain nuclear magnetic resonance with spectroscopy that showed absence of creatine peak in the basal nuclei and semioval centers. Both patients are currently being treated with nutritional restriction of proteins of animal origin and nutritional supplement with monohydrate creatine and L-ornithine.
CONCLUSION: Cerebral creatine deficiency is a rare condition that should be suspected in children with developmental delay, hypotonia, drug resistant epilepsy and behavioral problems. Although the most common cause of this condition is the creatine transporter deficiency, all three causes should be studied when this entity is suspected. Brain magnetic resonance with spectroscopy is of great help when this diagnosis is suspected.

P-112 - GLUCOSE TRANSPORTER TYPE 1 (GLUT1) DEFICIENCY SYNDROME: DIAGNOSIS AND NUTRITIONAL TREATMENT WITH KETOGENIC DIET IN 8 CHILEAN CASES

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INTRODUCTION: Glucose Transporter type 1 (GLUT1) deficiency syndrome is an inborn error of glucose transport. Clinical manifestations are secondary to reduced glucose transport across the blood brain barrier, including: refractory seizures, developmental delay, microcephaly, persistent hypoglycorrhachia with normal glycemia. The diagnosis is suspected with glucose CSF/glycemia <40 (NV: > 60) and confirmed by molecular study in SLC2A1 gene (cr1p35-31.3). Treatment is based on a ketogenic diet (KD).
OBJECTIVE: To present the Chilean experience in diagnosis and follow-up of patients with GLUT1.
METHODOLOGY: 8 records of patients with GLUT1. Clinical picture, biochemical exams, molecular study, nutritional status and macro and micronutrient with KD were recorded.
RESULTS: 5/8 are men. Of the total 4/8 GLUT1 were diagnosed with mediana (Me) 9,0 years of age and 4/8 GLUT1 with (Me) 5,3 months. All had hypoglycorrhachia <40 mg/dl (range: 13-30) without hypoglycemia (80-90 mg/dl). The CSF/blood glucose ratio was (Me) 0,33. At the time of diagnosis, they presented myoclonic seizures, ataxia, and paroxysmal movements without response to drugs. They started DK and it has stayed between 18 years to 1 month. The seizures ceased after md 5 days of starting KD in children who were diagnosed at (Me) 5,3 months. The distribution of the caloric molecule was: Lipids: 87-85% (MCT oil, alpha linolenic acid and docosahexaenoic acid), Protein: 10-8% (0,8 to 2,0 g/wt/day), Carbohydrates: 3-6 %. Fasting levels of beta-hydroxybutyrate acid has been maintained over 2,0 mM/l and after meals lower 5 mM/l. The fasting blood sugar level was (Me) 80 mg/dL (NV: 60-90), Total cholesterol: (Me)141 mg/dL (NV: <200), LDL: (Me) 77 mg/dL (NV: <100), HDL: (Me) 62mg/dL (NV: >40), Triglycerides: (Me) 63.6 mg/dL (NV: <150), Vitamin D serum: (Me) 45,3 ng/ml (NV: >38), potassium: (Me) 4,4 mEq/L (NV: 3,4-4,7). All of them are supplemented with L-carnitine, vitamin C, sugar-free multivitamins, calcium. 7/8 GLUT1 have molecular study (C.177del.p; c.1088G>A; c.420delG; c57delA; 969del-C971T; c.143G>A; c.458G>C/p.R153P). According to nutritional status: 3/8 are eutrophic, 1/8 have malnutrition, 3/8 are overweight and 1/8 are at risk of malnutrition.
CONCLUSIONS: In patients with refractory epilepsy, GLUT1 deficiency screening and early diagnosis is important considering that KD is a safe and effective treatment for improving neurological manifestations

P-113 - IMPAIRED CHOLESTEROL BIOSYNTHESIS CAUSED BY BIALLELIC MUTATIONS IN CYP51A RESEMBLES GALACTOSEMIA

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INTRODUCTION: Congenital cataract (CC) is clinically and etiologically heterogeneous. Although mostly isolated, cataract can be part of many multisystem disorders of multiple congenital anomalies and inborn errors of metabolism, which further complicates the diagnostic process. Undoubtedly an opportune diagnosis is relevant to guide the management, justified by the metabolic causes with available treatment to rule out.
METHODOLOGY: Male patient born of consanguineous parents with a phenotype of bilateral CC, infantile liver cirrhosis with and hypogonadism. Carbohydrate gel electrophoresis normal, galactose level concentration below 30 nmol/ml and Enzyme activity measurement of galactose-1-phosphate uridyltransferase 2.03 (1.3-5.57) negatives. Clinical exome sequencing was performed to establish etiology.
RESULTS: clinical exome sequencing detected a homozygous mutation (c.1454 T>C) (p.Phe485Ser) in exon 10 of the cytochrome P450, family 51, subfamily a, polypeptide 1 (CYP51A1) gene, affecting phenylalanine, an amino acid highly conserved between species, it variant not has been previously reported in public database but with bioinformatics predictions (Mutation taster, Provean, SIFT, Polyphen) that classify it as pathogenic, established as the etiology of the patient.
DISCUSSION: The crystalline lens is an avascular tissue that receives nutrients from the aqueous humor, therefore it is exposed to the accumulation of different substances in lysosomal storage disorders, carbohydrate metabolism disorders or respiratory chain defects, despite the knowledge, biochemical tests are not available for most of these conditions, which highlights the importance of molecular studies on inborn errors of metabolism. In this case, a mutation was identified in the CYP51A1 gene that encodes lanosterol 14α-demethylase (CYP51), a regulatory enzyme involved in the late stage of the cholesterol synthesis pathway to eliminate the 14-alphamethyl group of lanosterol, causing an infantile liver failure with cataracts secondary to cholesterol accumulation, symptoms that resembles galactosemia.

P-114 - TWO GENETIC VARIANTS RELATED IN THE CLINICAL HETEROGENEITY OF A PEDIATRIC PATIENT

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INTRODUCTION: inborn errors of metabolism (IEM) are considered genetic disorders determined by blocking a metabolic step due to mutation of genes responsible for the operation of the same. The identification of genetic variants that affect gene expression and are related to pathological characteristics in diseases allow us to perform a personalized medicine and impact in the detection, treatment, prognosis, follow-up and Prevention through appropriate and assertive genetic counseling.
OBJECTIVE: To determine the etiology of the clinical heterogeneity of a pediatric patient through complete exome sequencing
METHODS: a 14-year-old male patient diagnosed with multiple congenital malformations, severe psychomotor retardation, intellectual disability, severe muscular atrophy, multiple osteoarticular malformations, globular abdomen, joint hypermobility and bone deformations. Initial biochemical and normal imaging studies were performed. Given the complexity of the clinical manifestations of the patient, complete exome sequencing was performed in search of gene alterations.
RESULTS: A pathogenic variant was identified in heterozygosis in the FGF23 gene, this result being compatible with the diagnosis of autosomal dominant hypophosphatemic rickets (ADHR). Likewise, a variant of uncertain significance was identified in homozygosis in the ABCD4 gene. This result is possibly compatible with the diagnosis of methylmalonic acidemia with homocystinuria type cbIJ, which is transmitted in an autosomal recessive manner. The diagnosis of ADHR is an IEM characterized by renal loss of phosphate, hypophosphatemia and inappropriate levels of 1,25-dihydroxyvitamin D3. Patients often suffer from bone pain, rickets and abscesses. Likewise, methylmalonic acidemia with homocystinuria type cbIJ is also an IEM, however, in this case there is a deficiency of vitamin B12 (cobalamin) which leads to conditions for megaloblastic anemia, lethargy, growth and development delay, intellectual deficit , and convulsions.
CONCLUSION: The performance of genetic tests supports and guides the making of medical decisions based on the patient's clinical history, through the identification of the causes of complexity, due to the presence of different genetic variants and the heterogeneity of their expression, which leads to the practice of a precision and predictive medicine, which allows an early diagnosis, directed and personalized treatment, monitoring and appropriate genetic counseling.

P-115 - VERIFICATION OF THE REFERENCE INTERVAL FOR THE DETERMINATION OF ESSENTIAL FATTY ACIDS IN BLOOD

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There are fatty acids that the body cannot synthesize, and therefore receive the name of essential fatty acids. These acids are omega-3 fatty acids and omega-6 fatty acids and must be contributed exclusively by the diet.
Alpha-linolenic acid (ALA) occupies the main role within the family of omega-3 fatty acids, as it is responsible for synthesizing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Linoleic acid (LA) is the most important within the family of omega-6 fatty acids and is responsible for synthesizing arachidonic acid (AA).
Currently it has seen its important application in intestinal anti-inflammatory activity, nutritional diets in athletes and in prenatal and neonatal period.
The objective of this work is to verify the reference interval of essential fatty acids in blood of three age groups.
We used 80 samples of centrifuged blood without anticoagulant (serum), 30 samples of patients older than or equal to 18 years (group1), 30 of between 1 and 17 years (group2) and 20 of children less than one year of age (group3). A non-commercial method of extraction and derivatization was used and analyzed by gas chromatography coupled to mass detection.
The following reference intervals were found for the different age groups in units umol / L; ALA (group1): 50 to 200, ALA (group2): 30 to 200, ALA (group3): 10 to 250; LA (group1): 450 to 1500, LA (group2): 600 to 1500, LA (group3): 600 to 1500; EPA (group1): 2 to 46, EPA (group2): 2 to 40, EPA (group3): 5 to 60; AA (group1): 180 to 900, AA (group2): 240 to 600, AA (group3): 100 to 900; DHA (group1): 50 to 250, DHA (group2): 35 to 150, DHA (group3): 10 to 250.
Reference intervals for essential fatty acids were found with the method developed in our Laboratory that responds to patients of the Argentine population and of different ages. We are able to quantify these essential fatty acids and their metabolic relationships in serum. This work also proposes to investigate the relationship between these analytes and the nutritional requirements of patients and their usefulness in anti-inflammatory treatments and prenatal and neonatal development.

P-116 - NITISINONE DETECTION BY LCMSMS IN DRIED BLOOD SPOT AND PLASMA SAMPLES IN CHILEAN TYROSINEMIA 1 PATIENTS IN FOLLOW UP. VALIDATION SAMPLE LEVELS WITH NITISINONE DEVELOPED METHOD IN WELLCHILD LABORATORY, EVELINA CHILDREN'S HOSPITAL, LONDON

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INTRODUCTION: Tyrosinemia type 1 (Tyr-1) is an inborn error of metabolism caused by defects in tyrosine metabolism and characterized by accumulation of tyrosine and toxic degradation products. Treatment of Tyr-1 patients is based on nitisinone (NTBC) administration. NTBC was developed as a herbicide and monitoring levels in dried blood spot (DBS) and plasma samples are necessary for optimal dosage. Sixteen patients are in active follow-up in our reference center and trimestral NTBC levels were analyzed at Evelina Children's Hospital in London during 2016-2018.
OBJECTIVE: To implement NTBC determination by LCMSMS in DBS and plasma samples and to compare NTBC levels obtained in our center with those reported by Dr. Charles Turner in London during the follow up of Tyr-1 patients between 2018-2019. METHODS: NTBC quantification by LCMSMS was implemented based on the construction of calibration curve by using mesotriene as internal standard. DBS samples were extracted using 100% methanol. ESI(+) was used as ionization method and analytes were detected by Multiple Transition Monitoring (transitions 330 > 218 for NTBC and 340 > 228 for mesotriene). Thirty DBS samples from Tyr-1 patients were analyzed in parallel with WellChild Laboratory and 26 plasma samples were analyzed for correlation with DBS levels.
RESULTS: We are able to detect NTBC by LCMSMS in DBS and plasma samples from Tyr-1 patients. Our method, shows good precision, accuracy and linearity with detection limit of 0,5 nmol/L. The concentration range determined in DBS samples from Tyr-1 patients was 12,0-43,3 µmol/L and 29,7-97,6 µmol/L for plasma samples. Parallel comparison of NTBC levels in DBS samples shows values 20% higher with those analyzed in WellChild Laboratory. NTBC levels in plasma and in DBS are well correlated being 2.4 times higher in plasma.
CONCLUSION: We validated in our laboratory the LCMSMS method used in the Laboratorio di Patologia Metabolica at Ospedale Bambino Gesu for the detection of NTBC in DBS and Plasma samples. NTBC determination of Chilean Tyr-1 patients in follow-up during 2018-2019 showed reproducible results, comparable with those obtained in Evelina Children's Hospital, London. Good correlation was observed in DBS and plasma samples.

P-117 - QUALITY ASSESSMENT IN INBORN INNATE OF METABOLISM IN CUBA

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INTRODUCTION: Inborn innate of metabolism are heterogeneous group of disorders, that may be inherited or may occur as the result of spontaneous mutation. The biochemical diagnosis of these diseases includes the detection of different metabolites in biological fluids. In Cuba, the National Center of Medical Genetics performs the biochemical diagnosis and follow up of patients with these diseases. The assurance of quality plays an important role in all genetic services, include the biochemical laboratories. In health, the implementation of quality management system helps to improve process development, to minimize mistake in assistance practice and to increase the safety and satisfaction of clients.
OBJECTIVE: The aim of this work is to present recommendations and strategies to insure quality result and increased patient satisfaction.
METHODS: We designed different strategies related with document control, external quality assessment, internal quality control, internal audit, management review and bioanalytical method validation in inborn innate of metabolism laboratories.
RESULTS: We implemented various documents such as standard operating procedures, log work, validation and training files. Besides, we established external and internal quality controls for the analytical process. The internal audits were considered as a review process to improve the system conducted by the laboratory. We defined quality indicators, turnaround times, and corrective actions for continual improvement.
CONCLUSION: Implementing of strategies for quality assessment will allow us to offer more reliable and robust services in the diagnosis of inborn innate of metabolism. Also, this system will increase the satisfaction for the patient and their family.

P-118 - METABOLOMICS THE NEW "OMICS" TECHNOLOGY IN THE CLINICAL PRACTICE

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INTRODUCTION: The metabolome is the collection of small molecules (metabolites) found within a biological sample and metabolomics is the comprehensive study and analysis of these small molecules. In human plasma, the metabolites that circulate in the body represent products of complex metabolic pathways and their measurement can have clinical relevance in diseased patients. The human metabolome is influenced by genetics, environmental factors, epigenetics and the microbiome. Metabolomics technology can be applied to diagnosis of inborn metabolic diseases, and to follow up treatments.
OBJECTIVE: To describe the usefulness of metabolomic analysis in cases of patients with suspected neurometabolic disease, but with nonspecific manifestations.
MATERIALS AND METHODS: Untargeted metabolomics analysis were performed on patients evaluated in the genetics and neurogenetics services, in whom the clinical manifestations suggested the possibility of a metabolic disease, but the results of other biochemical tests, and neuro-radiology, did not allow to propose a specific diagnosis. The test, MetaETA IMDTM (Metabolon Inc., Morrisville, NC, USA), has demonstrated utility in the identification of biochemical disease signatures associated with a long list of inborn metabolic diseases. To further characterize this test, we performed correlation studies between the clinical and biochemical phenotypes.
RESULTS: We identified diseases clinically validated on the Meta IMDTM test: SCAD, MCAD, MGA, ABAT, THB, BH4, MEDNIK Syndrome, GA type 1, HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) Lyase Deficiency, Trimethyllysine Hydroxylase Epsilon (TMLHE) Deficiency, and Citrullinemia.
As result of complementary analysis, we confirmed a case of GMAT Deficiency, a condition that is currently clinically validated. We also are also in the process of confirming other pathologies that are not clinically validated. In addition, we are monitoring the treatment of a patient diagnosed with mutant PDP1 gene.
CONCLUSION: Metabolomic analysis can be employed as a powerful tool to study undiagnosed patients, mainly those with complex manifestations and non-conclusive findings in the traditional tests. Additionally, for patients with known diagnosis and under treatment, this test is useful for follow-up monitoring of efficacy.

P-119 - DIAGNOSIS OF HMG-COA (3-HYDROXY-3-METHYLGLUTARYL-COA) LYASE DEFICIENCY BY UNTARGETED METABOLOMIC ANALYSIS IN PLASMA

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INTRODUCTION: HMG-CoA Lyase deficiency is a rare inborn error of leucine metabolism that causes severe episodes of hypoglycemia and metabolic acidosis. Misleading and delayed diagnoses are frequent.?
OBJECTIVE: The objective of this work is to describe the usefulness of metabolomic analysis in patients with hypoglycemic syndrome and suspected neurometabolic disease with nonspecific manifestations and non-conclusive biochemical findings.
MATERIALS AND METHODS: We present the case of a two-and-a-half-year-old Colombian patient, who presented

two episodes of severe hypoglycemia of difficult control with wide anion gap metabolic acidosis, which were preceded by frequent vomiting, stupor, and hypotonia. He was admitted twice to the intensive care unit, where hormone studies were normal. Plasma amino acids, ammonium and organic acids in urine were considered normal. The patient received symptomatic management, achieving full recovery on both occasions.
Given the possibility of metabolic disease, analysis by non-targeted metabolomics in plasma was performed (Metabolon Inc.) This test identifies molecules between 50-1,500 Daltons (Da). The identification is performed using four different types of high-performance Ultra Performance Liquid Chromatography (UPLC) instruments paired with Mass Spectrometry (UPLC/MS). The identification of each molecule is confirmed against a proprietary chemical library consisting of accurate molecular weight/mass plus information on any adductation, in source fragmentation, and/or polymerization, retention time/index on the chromatography columns, and mass spectral fragmentation patterns. Overall, process variability is assessed using stable isotope standards and duplicates.
RESULTS: Metabolomic analysis demonstrated elevated levels of 3-methylglutarylcarnitine, adipate, dodecanedioate, hexadecanedioate, and tetradecanedioate. 3-methylcrotonylglycine was not detected, and beta-hydroxyisovalerate was normal. HMG-CoA LYASE DEFICIENCY was considered, because more than 50% (5 of 7) of the biomarkers associated with the metabolomic biochemical signature of this disorder were outside the expected range. Treatment was started with dietary restriction of leucine as a precursor of the affected metabolic pathway and L-Carnitine supplementation.
CONCLUSION: Metabolomic analysis is useful for the diagnosis of HMG-CoA LYASE DEFICIENCY, and it is also a valuable tool for the study of patients with suspected metabolic disease.

P-120 - MAPLE SYRUP URINE DISEASE IN CHILE: CHARACTERISTICS OF DIAGNOSIS AND TREATMENT IN 45 CHILEAN PATIENTS IN FOLLOW-UP AT INTA, UNIVERSITY OF CHILE

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INTRODUCTION: Maple syrup urine disease (MSUD) is an autosomal recessive inherited metabolic disease caused by deficient activity of the branched-chain α-keto acid dehydrogenase (BCKD) enzymatic complex,
that catalyzes the last reaction in the catabolic route of branched chain amino acids (leucine, valine and isoleucine). The disorder varies in severity and the clinical spectrum is quite broad with five recognized clinical variants. The treatment consists in dietary restriction of BCAAs and close metabolic monitoring.
OBJECTIVE: Characterize MSUD Chilean patients in follow-up at INTA. METHODS: Retrospective study with 45 MSUD patients in follow-up.
RESULTS: 45 patients were included, 40/45 patients showed classic presentation, only 8/45 diagnosed before the onset of clinical manifestations. The average diagnosis age was 67 ± 231 days. Debut level average of offending amino acids was: Leucine 1118 ± 579 umol/L, Valine: 550 ± 598 umol/L and Isoleucine 454± 458 umol/L. The age of patients was between 9-18 years old (22/45) and the majority of patients in follow up were females (27/45). Regarding nutritional treatment, patients received Kcals: 1515 ± 458 kcal/day, Prot special formula: 2,0 ± g/kg/day, representing 97% of the daily protein intake. All patients received supplementation: L-Valine: 277±221mg/kg/day; L-Isoleucine 281±244mg/kg/day; Tiamine: 50 mg/day; L-Carnitine: 45±15 mg/wt/d. The nutritional assessment showed a majority of eutrophic patients 29/45, overweight and obesity 12/45 and only 4/45 under weight. Children under and over 5 years old showed good metabolic follow up: Leucine level: 254± 67 and 298± 136 umol/L, respectively. Most of our patients (35/45) have some psychomotor or neurodevelopmental delay. During the follow up there were 8/45 patients who died between 10 and 17 years old, due to causes non-related with uncompensated metabolic disease.
CONCLUSION: The existence of a newborn screening program is essential to allow the detection of patients in pre-clinical stage and decrease the severity of neuropsychological delay and lethality associated to MSUD. Our patients presented satisfactory adherence to nutritional treatment, laboratory and clinical follow up. Nevertheless adherence to treatment does not seem to be directly related to a good neurological outcome and multiple factors may intervene in the neurological delay that patients show.

P-121 - HYPERAMONEMIA AND PROPIONIC ACIDEMIA: CARGLUMIC ACID AND TIME OF AMMONIA REDUCTION DURING METABOLIC DECOMPENSATION

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INTRODUCTION: Propionic acidemia(PA),caused by propionyl-CoA carboxylase deficiency , is responsible for the

catabolism isoleucine, threonine, methionine and valine, odd-chain fatty acids and the three-carbon side chain of cholesterol. As a result PA patients have several disruptions in different metabolic pathways including TCA cycle, urea cycle, and glycine synthase complex resulting in lactic acidosis, hyperammonemia, and ketotic hyperglycinemia. Hyperammonemia in PA is explained by several complex mechanisms. Propionyl-CoA competitively inhibits N-acetyl glutamate synthase, the allosteric activator of carbamoyl phosphate synthase, the rate-limiting enzyme of urea cycle resulting in hyperammonemia.
High ammonium values can cause irreversible damage.
Carglumic acid is a synthetic analog of N acetyl glutamate, furthermore stimulates CPS 1.
MATERIALS: A descriptive retrospective study of metabolic decompensation with hyperammonemia in patients with a diagnosis of PA together with an analysis of the pharmacological treatment used between 2014-2018 were performed. The medical records of the hospital were reviewed including the biochemical data and time lapse of ammonia exposure.
OBJECTIVES: To evaluate the decrease in ammonia values; with respect to time and total value.
To analyse if the use of this treatment reduces the time of exposures to high ammonium values.
DESCRIPTION: This medication was used in 4 patients. During decompensation, the caloric was increased, the protein intake was decreased. The intravenous dose was given at 200mg/kg/d carnitine. A total of 15 decompensations were found, 12/14 used carglumic acid and in 2/14 only sodium benzoate was used. The average age was 37.4 months (range 19-65). The average ammonium on admission was 174 µmol/L (range 364-156µmol/L). During hospitalization, where sodium benzoate was used as an ammonium scavenger, the drop in time was 43-181 h (mean 91h). With the use of carglumic (100 mg/kg/day), the average drop in time was between 11-40 h with an average of 28.5 h.
CONCLUSION: Consistent with the literature, it is evident that carglumic acid has greater effectiveness in terms of ammonium reduction and the time in which this reduction occurs. It is emphasized that the treatment of decompensation with high caloric intake and low protein intake is essential, as well as treating the decompensation trigger.

P-122 - BIOCHEMICAL DIAGNOSIS OF METHYLMALONIC ACIDURIA IN CUBA DURING 2014 TO 2018

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INTRODUCTION: Methylmalonic aciduria (MA) is the most frequent organic aciduria (OA) in Cuba. It is a group of genetic diseases characterized by the excretion of high levels of methylmalonic acid (MMA) in the urine. The excretion of this metabolite may or may not be accompanied by elevated levels of homocysteine (Hcy) depending on the affected metabolic pathway.
OBJECTIVE: The aim of this work is to describe a laboratory methodology that combines the analysis of MMA and Hcy in the differential diagnosis and follow-up of the MA.
MATERIALS AND METHODS: Organic profile of 731 children with clinical suspicion of OA was analyzed by Gas Chromatography/Mass Spectrometry, in a period from 2014 to 2018. Hcy was quantified in plasma, in patients with high levels of MMA. The quantification of Hcy was performed by High Resolution Liquid Chromatography.
RESULTS: Seven patients with clinical features and high levels of MMA were diagnosed with MA. In them, we quantified plasmatic Hcy levels for realized the differential diagnosis. The concentration of Hcy in four patients was higher than the reference values, suggesting an MA combined with homocystinuria. From them, three patients once initiated the treatment with vitamin B12 and L-carnitine showed a decrease in the levels of both metabolites, corresponding to a satisfactory evolution. The remaining patients with high MMA levels had normal levels of Hcy, suggesting an isolated MA.
CONCLUSIONS: The determination of both markers permitted the differential diagnosis and biochemical monitoring of these diseases. The analysis of these two markers will allow us to infer the possible defect variant.

P-123 - METHYLMALONIC ACID COMPROMISES ENERGY METABOLISM AND GLUTAMATE UPTAKE IN C6 RAT ASTROGLIAL CELLS

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INTRODUCTION: Methylmalonic acidemia is an organic acidemia caused by deficient activity of L-methylmalonyl-CoA mutase or its cofactor cyanocobalamin and it is biochemically characterized by an accumulation of methylmalonic acid (MMA) in tissue and body fluids of patients. The main clinical manifestations of this disease are neurological and observable symptoms during metabolic decompensation are encephalopathy, cerebral atrophy, coma, and seizures, that commonly appear in newborns.

OBJECTIVES: The aim of this study was to investigate the toxic effects of MMA in an astroglial cell line presenting astrocytic features.
METHODOLOGY: Astroglial C6 cells were exposed to MMA (0.1-10mM) for 24 or 48 hours and cell toxicity, glucose consumption and mitochondrial metabolic function were analyzed. Cell viability and glucose uptake were determined by MTT reduction and glucose oxidase assays, respectively. Mitochondrial metabolic function was determined by measuring the oxygen consumption rate. Glutamate uptake was evaluated with L-[2,3-3H] glutamate.
RESULTS: MMA significantly reduced cell viability after 48-hour period and increased glucose consumption during the same period of incubation. Regarding the energy homeostasis, MMA (5-10 mM) significantly reduced basal respiration of cells after 48-hour exposition. Moreover, maximal respiration was reduced after exposition to MMA in all tested concentrations. Finally, MMA significantly reduced glutamate uptake in C6 rat astroglial cells after 48-hour exposition period.
DISCUSSION: MMA altered C6 rat astroglial cell viability and glucose consumption, suggesting that this organic acid compromises viability and stimulates anaerobic glycolysis. In addition, cell respiration was reduced after exposition to MMA, indicating that cell metabolism is compromised at resting and reserve capacity state, which might influence the cell capacity to meet energetic demands. Glutamate uptake was also compromised after exposition to MMA, which can be influenced by the impairment on cells energetic metabolism, affecting the functionality of the astroglial cells. Our findings suggests that these effects could be involved in the pathophysiology of neurological dysfunction of this disease.
Acknowledgments: This study was supported by grants from FAPESP (2015/25541-0), CAPES and UFABC.

P-124 - METHYLMALONIC ACIDEMIA'S CLINICAL EVOLUTION IN THE FIRST CHILDHOOD: DIFERENCES BETWEEN EARLY AND LATE DIAGNOSIS

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INTRODUCTION: Methylmalonic acidemia caused deficient cofactor of cyanocobalamin system or deficiency of methylmalonyl-CoA mutase enzyme, that can be unresponsive to vitamin B12 due to complete or partial deficiency. This disorder progress with crises of decompensation, precipitated by protein intake, with ketoacidosis, muscular hypotonia, irritability, and an important neuropsychomotor development delay, presented in neonatal period.
OBJECTIVE: Case report comparing clinical and neuropsychomotor development of two patients, one with late diagnosis and another with early diagnosis of Methylmalonic Acidemia.
MATERIALS AND METHODS: Review of medical records, interviews with patient's parents and children's physical examination, photographic record, and literary review with Medline / Pubmed and specialized literature.
RESULTS: CASE 1 - PFRS, female, DB: 06/11/2012, consanguineous parents, gestation and pregnancy without complications. neonatal deaths in the family.
2 days: ketoacidosis, respiratory discomfort; At 3, 7, 9, 12, 15 months: uncontrollable vomiting, ketoacidosis, pancytopenia.
1 year 6 months: diagnosed. Methylmalonic acid and child = 3479.9 mmol/mol creatinine. inception of adequate diet and supplementation.
Neurological clinic in diagnosis: microcephaly, malnutrition, mixed tetraplegia, axial hypotonia (without cervical support), absence of social contact, swallowing disorder, irritability, sleep disorder.
Evolution: periods of improvement and regression. Family did not follow proper dietary treatment. He presented several decompensations. Gastrostomy: 2 years 3 months.
3 years 3 months: weight / height adjusted for age. Social smile, adequate sleep, responding to stimuli, still with hypotonia and tetraplegia.
4 years 4 months: Death due to sepsis.
CASE 2: ALSQ, female, DB: 05/08/13
3 days: Acidosis, sepsis. Presented two altered samples in the neonatal screening test.
20 days: Methylmalonic acid (VR <36 mmol/mol creatinine) and child = 140 mmol/mol creatinine. Done protein restriction.
35 days: Started diet and complementation.
2 years 11 months: started school, took personal snack and knew what she could eat.
4 years 2 months: Adequate neuropsychomotor development.
CONCLUSIONS: the reported cases reassert the importance of early diagnosis by demonstrating an enormous difference between the evolution of pathology in a child diagnosed early and another with late diagnosis. It Reinforced the importance of investments in neonatal screening tests to avoid permanent damage in the neuropsychomotor development of children with metabolic errors.

P-125 - HEART MITOCHONDRIAL DYFUNCTION PROVOKED BY METABOLITES ACCUMULATING IN PROPIONIC ACIDEMIA

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INTRODUCTION: Propionic acidemia (PAcidemia) is an inherited disorder of organic acid metabolism caused by absence of propionyl-CoA carboxylase activity. It is biochemically characterized by predominant tissue accumulation of propionic acid (PA) in biological fluids and clinically by severe encephalopathy and cardiomyopathy. Maleic acid (MA) derived from PA is also highly excreted in urine of the affected patients
OBJECTIVES: Considering that the underlying mechanisms of cardiac disease in PAcidemia are practically unknown, we investigated the effects of PA and MA (0.1 - 5 mM) on important mitochondrial functions in the heart.
MATERIALS AND METHODS: Mitochondrial membrane potential (ΔΨm), NAD(P)H content, Ca2+ retention capacity and hydrogen peroxide (H2O2) production were evaluated using mitochondrial preparations from heart of developing rats supported by pyruvate/malate (PM) or α-ketoglutarate (α-KG) in the absence or presence of exogenous Ca2+ (30 micromolar). Data were analyzed by one-way analysis of variance followed by the post-hoc Duncan multiple range test. This study was performed with the approval of Ethics Committee for Animal Research of the Universidade Federal do Rio Grande do Sul.
RESULTS AND DISCUSSION: MA markedly decreased ΔΨm, NAD(P)H content and Ca2+ retention capacity in Ca2+-loaded mitochondria respiring with PM that were significantly reduced by cyclosporin A (CsA, inhibitor of mitochondrial permeability transition, mPT), indicating the involvement of mPT pore opening. These effects induced by MA were even higher using α-KG-supported mitochondria, but not prevented by CsA. Furthermore, PA provoked a moderate reduction of ΔΨm and NAD(P)H content in Ca2+-loaded mitochondria supported by α-KG, as compared to MA, and did not alter mitochondrial Ca2+ retention capactity. Finally, we verified that MA and PA did not induce H2O2 production regardless the respiratory substrate, rulling out the involvement of oxidative stress in the observed effects.
CONCLUSIONS: The data indicate that MA and PA to a lesser extent, disturb mitochondrial energy and calcium homeostasis in the heart. It is therefore proposed that mitochondrial dysfunction provoked by the accumulating metabolites may be involved in the cardiomyopathy occurring in patients affected by PAcidemia.
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P-126 - PROPIONIC ACIDEMIA (PA). CASE REPORT

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INTRODUCTION: The PA is produced by enzymatic defect in the catabolic path way of the methionine, valine, threonine and isoleucineamino acids (MTVI), and from the odd number fatty acids. The global prevalence is estimated in 1 out of 100.000 of newborns. The neonatal clinical manifestation is severe in the 70-80 % ofthe cases. Without diagnosis, the PA produces neurological deterioration slipping into a coma and finally the child's death. The PA management treatment includes a low-protein diet, with a specific formula free of implicated amino acids (MTVI).
OBJECTIVE: To describe the 1st clinical case of PA diagnosed in our institution.
MATERIALS AND METHODS: Observational, descriptive and retrospective study. Digitalized clinical record. Basal laboratory. Plasma AA, acylcarnitines and urinary organic acids.
RESULTS: A 5-day-old male patient was treated in our institution after screening, having family record with diagnosis of PA.
Date of birth: 04/01/16. Weight: 3000 Kg. Size: 48 cm. SG 37.(P / E: Pc 50; T / E: Pc 50).
Altered laboratory: hyperammonemia, increased lactic acid, hypoglycemia and ketonuria. At the time of the consultation, an expanded laboratory was requested – urinary organic acids, acylcarnitines and plasma AA - which were sent to the laboratory of J. P. Garrahan Hospital. After 18 days the diagnosis of PA was confirmed. Thus, breastfeeding was partially suspended and a special MTVI-free formula indicated.
After 6 months, the patient weighed 7,630 kg, P / E: Z = - 0.3; Size: 64 cm, Z = -1.28. He kept on being breastfeeding and receiving MTVI free formula and low protein meals.
1st year weighs 9,200 kg, P / E: Z = -0.42; Size: 73.5 cm, T / E: Z = -0.62.
2nd year weighs 10,900 kg, P / E: Z = -0.95; Size: 83.5 cm, T / E: Z = -1.19.
3rd year weighs 13,400 kg, P / E: Z = -0.56; Size: 90 cm, T / E: Z = -1,10.
At 18 months of age, he presented an internment for food transgression, with good recovery.
CONCLUSIONS: The child has good general condition, good growth and development; normal nutritional status, good adherence to dietary treatment.

P-127 - CLINICAL AND BIOCHEMICAL EVOLUTION OF THE FIRST PATIENT WITH MAPLE SYRUP URINE DISEASE WHO

RECEIVES A LIVER TRANSPLANT AT GARRAHAN HOSPITAL

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INTRODUCTION: Since 2005, elective liver transplantation(LT) has been implemented as a therapeutic alternative for maple syrup urine disease(MSUD). In 2017, the first transplant was carried out on a patient with MSUD.
MATERIALS AND METHODS: Review of clinical history and collection of biochemical data.
OBJECTIVES: To describe the clinical and biochemical outcome after LT of a patient with MSUD.
RESULTS: We describe patient with a neonatal diagnosis of MSUD with a severe form of the disease who has recurrent episodes of acute metabolic decompensations despite optimal medical management. For this reason, an elective LT was performed from an unrelated cadaveric donor at 3 years of age. The year prior to transplantation the values of leucine and isoleucine were of average 651.9µmol (range166-990µmol)(normal values 70-250µmol) and valine average 209µmol (range36-511µmol)(normal values 40-200µmol). The natural protein intake was of 0.21gr/kg/day. Prior to the transplant, she had been hospitalized 12 times, two of which required admission to the ICU due to sensory deterioration.
At 24 hours after LT, the branched chain amino acid were within normal parameters. Natural protein, was increased to 2gr/kg/day. After 33 days, she presented a mild acute rejection of the graft and required pulses of methylprednisolone with reduction of the natural protein intake at 1g/kg/day for 6 days without alteration in the amino acids. After transplantation, the values were stable: MS/MS: leucine+isoleucine average 215µmol (101-348µmol) and valine average 235µmol (92-375µmol) plasma amino acids were performed by Biochrom HPLC: Leucine average 300µmol/L (290-300µmol/d)(normal value 50-175µmol/L), isoleucine average 189µmol/L(180-190µmol/L)(normal values 6-110µmol/L) and valine average 380 µmol/L (330-420µmol/L)(normal values 64-294µmol/L). Currently she has a diet without protein restriction, the protein intake is estimated at 3gr/kg/day
CONCLUSION: According to what is described in the literature, the patient presents amino acids with values higher than normal. Currently, she is 4 years old, without decompensation and without the need for dietary treatment. The child attends kindergarten with improved integration and acquisition of new maturing milestones.

P-128 - MSDU EXPERIMENTAL PROTOCOL INCREASES THE SUSCEPTIBILITY TO LPS-INDUCED INFLAMMATION IN YOUNG WISTAR RATS

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INTRODUCTION: Maple Syrup Urine Disease (MSUD) is a metabolism inborn error caused by a deficiency of branched a-ketoacid dehydrogenase complex (BCKDC), with the accumulation of branched chain amino acids (BCAA) (leucine, isoleucine and valine). Patients with MSUD present a series of neurological dysfunction. Recent studies have been associated the brain damage in the MSUD with inflammation and activation of the immune system. Moreover, MSUD subjects are more susceptible to infections.
OBJECTIVE: In this regard, we investigated that the treatment with BCAA pool in young rats, MSUD experimental protocol, increases the cerebral cortex and hippocampus inflammation induced by lipopolysaccharide (LPS) exposition.
MATERIALS AND METHODS: The inflammation was analyzed through the determination of Cytokines levels and advanced glycation end products receptor (RAGE) immunocontent. Statistical evaluation was carried out using the two-way analysis of variance (ANOVA) with MSUD and LPS administration as independent variables.
RESULTS: We observed that high levels of BCAA in infant rats are related to increased brain inflammation induced by LPS administration, as well as, led to an increase in RAGE expression. The brain inflammation was characterized by high levels of IL1-β, IL-6, TNF-α and IFN-γ, and decreased content of IL-10.
CONCLUSION: Therefore, the results of this study show that MSUD is associated with a more intense neuroinflammation induced by LPS infection.

P-129 - GLUTARIC ACIDURIA TYPE I: NUTRITIONAL MANAGEMENT EXPERIENCE IN PEDIATRIC PATIENTS IN AN ARGENTINE POPULATION

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INTRODUCTION: Glutaric aciduria type 1(GA-1) is an inherited autosomal recessive metabolic error of lysine, hydroxylysine and tryptophan, due to deficiency of the enzyme glutaryl-CoA dehydrogenase. The clinical manifestations vary broadly, from classical forms (macrocephaly, dystonic encephalopathy and frontoparietal atrophy), to subacute, adult and/or asymptomatic forms. Nutritional management is the most important general therapy in these patients to avoid encephalopathic crises, neurological deterioration and inadequate nutrition.
GOALS: To show the casuistry and nutritional management in patients with GA-1. Children's Hospital. To provide family members and/or care givers with education in the nutritional management of patients with GA-1.
PATIENTS AND METHODS: Ten patients diagnosed with GA-1 with different phenotypes were followed nutritionally and clinically, all under a lysine, hydroxylysine and tryptophan restricted diet. Tables of specific amino acid and anthropometric requirements were used to evaluate nutritional status. General biochemical indices and determination of amino acids were measured. All families were trained with special diets and food selection.
RESULTS: The gastrostomy performed on 3/10 patients allowed for improved nutritional management, adherence to diet and growth; 2/10 patients died due to intercurrent infections; 2 other patients evolved very well neurologically, one thanks to neonatal diagnosis and early treatment and the other despite receiving a partial diet. The rest of the casuistry presents severe dystonic symptoms with nutritional compromise. Food education for family members helped to improve the nutritional management of children by exchanging knowledge and motivations.
CONCLUSIONS: Nutrition is the most useful tool in inborn errors of intermediate metabolism. GA-1 with a close interaction between nutrients and disease requires specific dietary management. Interdisciplinary management, education and the integration of family members as part of the team are the key elements for good nutritional management.

P-130 - LIPID, PROTEIN AND DNA DAMAGE IN GLUTARIC ACIDURIA TYPE I PATIENTS AND THE BENEFICIAL EFFECTS OF L-CARNITINE

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The deficiency of the enzyme glutaryl-CoA dehydrogenase is known as glutaric acidemia type I (GA1) and involves the metabolism of the amino acids lysine, hydroxylysine and tryptophan. This defect results in an accumulation of glutaric acid (GA) in the organism. The mechanisms of brain injury presented by GA1 patients is poorly understood. However, studies have demonstrated the involvement of oxidative stress. The prognosis of GA1 depends on the early diagnosis and the institution of the treatment with L-carnitine (L-car). This compound is recommended for the GA1 treatment, aiming to induce the excretion of toxic metabolites and restore the secondary deficiency. L-car has also demonstrated an important role as antioxidant in some neurometabolic diseases. In agreement with recent several studies in the literature, focusing the involvement of free radicals in neurodegenerative diseases, the aim of this work was to evaluate oxidative damage to lipids (isoprostanes), protein (di-tyrosine), and DNA (urinary oxidized guanine species) in urine from GA1 patients at diagnosis moment and after treatment. Besides that, we aim to verify if the present treatment with L-car is able to protect the organism against these processes. We studied twelve GA1 patients at diagnosis and twelve patients under treatment with L-car from the Hospital de Clínicas de Porto Alegre. The present work evaluated the urinary oxidative stress parameters di-tyrosine, isoprostanes, and urinary oxidized guanine species in GA1 patients, measured by commercial kits, before and after the L-car treatment (100mg/Kg per day). We also determined the free L-car levels in blood spots by LC/MS/MS. Ethics Committee from HCPA approved this study. Patients at diagnosis moment had L-car deficiency, which was correct by treatment. GA1 patients presented significantly increased levels of isoprostanes, di-tyrosine, and urinary oxidized guanine species. The L-car supplementation induced beneficial effects reducing these biomarkers levels. Free L-car was negatively correlated with isoprostanes levels in patients at diagnosis moment. GA1 patients have a pro-oxidant status and L-car has a very effective protective role. Treatment with L-car is useful in GA1 not only by promoting the excretion of the toxic metabolites and by restoring the secondary L-car deficiency, but also for the antioxidant benefits.

P-131 - LATE ONSET GLUTARIC ACIDURIA TYPE 1 PRESENTING AS LEUKODYSTROPHY

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INTRODUCTION: glutaric aciduria type 1 (GA1) is an autosomal recessive disorder caused by mutations in the

GCDH gene, resulting in deficiency of enzyme glutaryl-CoA dehydrogenase. This leads to accumulation of metabolites, mainly glutaric acid and 3-hydroxyglutaric acid, which result toxic for the CNS. GA1 patients present with an acute onset in 80–90% of cases , developing an acute onset type with striatal injury following catabolic stress during the first 6 years of life, and consequently a predominantly dystonic movement disorder. The term late-onset has been used for patients diagnosed after the age of six years, who presented with non-specific symptoms and predominantly white matter changes on MRI.
METHODS: Revision of clinical record of a patient diagnosed with GA1
AIM: To describe a late onset case of GA1
CASE: A 22-year-old female patient complained of headache. Her physical examination was normal. MRI of the brain revealed confluent bilateral symmetric white matter lesions on T2 and FLAIR, with widening of Sylvian fissures and frontotemporal hypoplasia. A molecular leukodystrophy panel showed negative results. Exome testing identified a pathogenic variant in homozygosis (p.ArgG409Trp) in the GCDH gene, mutation that has been associated with late onset GA1. Laboratory tests revealed a high level of urinary glutaric acid and 3-hydroxyglutaric acid, very low plasmatic carnitine and elevated glutaryl carnitine, confirming GA1 diagnosis. She started treatment with L-carnitine and restriction of natural protein.
DISCUSSION: Here we present clinical, biochemical, neuroradiological and genetic data of a late onset GA1 patient. The clinical presentation was non-specific, frontotemporal hypoplasia and white matter abnormalities were seen on MRI. Diagnosis was achieved through exome sequencing and subsequent biochemical analysis. Expanded NBS would have detected this case at birth, but it wasn´t requested because it is not mandatory. Many doctors are not educated about the importance of this test. Regarding molecular panels, as late onset GA1 can present with white matter abnormalities we recommend to include GCDH in the leukodystrophy genetic panels.
CONCLUSIONS: it is important to perform metabolic tests in adult patients with white matter lesions in MRI since some treatable metabolic diseases (such as GA1) can present images of leukodystrophy.

P-132 - IDENTIFICATION OF ERYTHRO 2,3-DIHYDROXY-2-METHYLBUTIRATE IN URINE

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INTRODUCTION: deficiencies of 3-hydroxyisobutyryl-CoA-hydrolase (HIBCH) and short-chain enoyl-CoA-hydratase (ECHS1) are characterized by the urinary excretion of 2,3-dihydroxy-2-methylbutyrate (23DH2MB). This metabolite can be identified by the routine method of GC-MS. It can be present in small amounts in normal samples and has been suggested as an identifier for these pathologies. However, the pure metabolite standard is not easy to obtain, therefore it is difficult to differentiate normal samples from pathological ones. 23DH2MB have two isomers, erythro and threo, both of which are present in the urine of normal patients. In some samples analyzed in our laboratory, the chromatograms show peaks of 23DH2MB with heights similar to those published and / or presented in congresses, but it is the ratio of areas between the erythro and threo metabolites that must be taken into account in order to associate it with any pathology. We do not have the metabolite standard.
OBJECTIVE: to present a practical and simple example for the identification of the peak of erythro-23DH2MB in samples of urinary organic acids, by comparing the retention time of the same with the one that appears in other pathologies such as propionic and methylmalonic acidurias where it is elevated with respect to the threo metabolite.
METHOD: gas chromatography with mass spectrometry detection, and derivatization of the urine with BSTFA + TMCS, previous extraction with two organic solvents.
RESULTS: chromatograms of overlapping suspected samples are presented with chromatograms of samples with methylmalonic aciduria. In this pathology, as in propionic acidemia, the erythro isomer is elevated in a ratio greater than 10: 1 with respect to the threo isomer (slightly displaced). Therefore both isomers can be differentiated and correlated with pathologies by comparison of the chromatograms.
CONCLUSIONS: in the absence of a 23DH2MB standard, the superposition of chromatograms of suspected samples with samples of methylmalonic or propionic aciduria as well as the isomer ratio allows us to rule out HIBCH and ECHS1 diseases.

P-133 - IN SILICO PREDICTION OF THE PATHOGENIC EFFECT OF HISPANIC R108C VARIANT OF MUT GENE

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INTRODUCTION: Methylmalonic aciduria (MMA) is an inborn error of propionate metabolism. Isolated MMA is mainly due to pathogenic variants in MUT gene, which cause null or deficient methylmalonyl CoA mutase activity (MCM). This mitochondrial enzyme catalyzes the isomerization of methylmalonyl-CoA to succinyl-CoA using adenosylcobalamin (AdoCbl) as cofactor. To date, approximately 250 pathogenic variants have been reported, being c.322C4T (p.R108C) one of the most commonly found

in Hispanic population. We previously found it in 40% of the alleles of a cohort of Mexican patients, two of them presented it in homozygous state and coursed with the severe Mut0 form according to phenotype. Until our knowledge there is no information about the structural effect that this variant could have over the enzyme.
OBJECTIVE: To perform an in silico prediction of the structural pathogenic effect of the Hispanic R108C variant of MUT gene.
METHODS: Structural analysis of arginine residue from MCM at position 108 was performed based on previously reported MCM crystallographic structure (PDB Code: 2XIJ), in silico mutagenesis was performed for this variant in order to hypothesize its possible deleterious effect using Pymol software.
RESULTS: In wild type MCM, arginine 108 residue is located at substrate binding domain; actually, it is in close contact with substrate (mean distance 3.7 Å), the interaction is polar type between amino groups of arginine and oxygen atoms from phosphate and hydroxyl groups from CoA molecule. When substituting arginine, which has a longer lateral chain, for a cysteine residue, all these polar contacts with CoA molecule are probably lost.
CONCLUSIONS: As the in silico modeling predicts, the substitution of an amino acid with different lateral chain length and polarity could probably decrease substrate interaction with amino acid residues from the active site during catalysis, which could explain the severe phenotype observed in our homozygous patients. Functional studies are needed in order to stablish the pathologenic effect of this pathogenic variant.

P-134 - TRANSIENT 5-OXOPROLINURIA (PYROGLUTAMIC ACIDURIA) INDUCED BY POLIMEDICATION COMBINED WITH ACETAMINOPHEN

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INTRODUCTION: pyroglutamic aciduria is an inborn error of metabolism due to the deficiency of glutathione syntetase or 5-oxoprolinase in the gamma-glutamyl cycle; it can also be detected secondary to the treatment with acetaminophen in conjunction with antibiotics or antiepileptic drugs. These drugs saturate the cycle and produce elevation of 5-oxoproline (pyroglutamic acid, PA) leading to metabolic acidosis.
CASE: A 12 month-old (mo) female patient was on treatment with antibiotics and antiepileptic drugs because of sepsis and refractory seizures respectively. Multiple metabolic tests had been done since 2 mo and PA was detected in urine organic acids (UOA) for the first time at 12 mo. In a second sample we also found acetaminophen metabolites. The PA elevation was consistent with a deficiency in the gamma-glutamyl cycle but other clinical and biochemical features didn´t support the diagnosis. We asked for another sample to repeat UOA but requested to stop acetaminophen intake and obtained a completely normal result. Finally, the patient underwent chromosomal microarray testing resulting in a gross deletion of 9.7 Mb (2q24.3-q31.1) associated to complex epileptic syndromes.
CONCLUSIONS: we assume the elevation of PA in our patient was secondary to the treatment with acetaminophen in combination with other drugs, because the discontinuations of acetaminophen normalized UOA. We emphasize the idea that clinical, pharmacological and nutritional information is essential for the interpretation of UAO.

P-135 - GLUTARIC ACIDURIA TYPE 1 IN CHILE: RESULTS OF 20 YEARS OF DIAGNOSIS AND FOLLOW-UP

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INTRODUCTION: Glutaric Aciduria type 1 (GA-1) is produced by the deficiency of the enzyme glutaryl-CoA dehydrogenase, accumulating glutaric acid and 3-hydroxyglutaric acid (GA, 3-OH-GA). The diagnosis is made by Tandem Mass Spectrometry (MS/MS) and confirmed by analysis of urine organic acids (UOA). Patients without early treatment have an acute encephalopathic crisis (AEC), followed by irreversible neurological symptoms. The treatment consists of a diet restricted in lysine, special formula (SF), L-carnitine and riboflavin supplementation.
OBJECTIVE: To present the Chilean experience in diagnosis and follow-up of patients with GA-1.
METHODOLOGY: 41 records of patients diagnosed with GA-1 were reviewed between 1998 and 2018. Pre and post diagnosis clinical picture, biochemical exams, neuroimaging, nutritional status and intake of lysine, proteins, calcium, iron and zinc were recorded.
RESULTS: 21 AG-1 are in active control (13 men/9 women), diagnostic age: 0,6-48 months of age; 9/21 cases debuted with AEC and 12/21 did not have AEC. Of the cases without AEC: 8/12 have neurological involvement (extrapyramidal symptoms) and 4/12 have a normal development. Prior to diagnosis, 20/21 cases had macrocephaly, delayed psychomotor development and/or abnormal movements. According to nutritional status: 8/21 are eutrophic, 9/21 have malnutrition, 2/21 are overweight and 2/21 are at risk of

malnutrition. Eleven have a gastrostomy. The diagnosis was made by MS/MS, confirming with presence of GA, 3OH-GA. Only 1 case was detected by an expanded newborn screening. 8/21 cases GA-1 are <6 years old and are on a lysine restricted diet with a contribution of 0.6±0.3 g intact prot/wt/day, 0.9±0.1 g prot of SF/wt/day and are supplements with: riboflavin, L-carnitine (x 76±39 mg/wt/day) and 12/21 are> 6 years old (6 are on diet and SF and 6 are without SF, but with low lysine diet.

CONCLUSIONS: GA-1 has a variable clinical presentation, and the neurological compromise can occur despite not having experienced AEC. The GA-1 in active control comply with the contribution of protein, energy, lysine and micronutrients according to the protocol for GA-1 and according to RDA. The GA-1> 6 years (5/12) receive doses of L-carnitine x 29±10mg/wt/day, and maintain free carnitine level above 70%.

P-136 - CLINICAL, BIOCHEMICAL AND MOLECULAR CHARACTERISTICS OF MALONYL-COA DECARBOXYLASE DEFICIENCY AND LONG TERM FOLLOW-UP OF NINE PATIENTS

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BACKGROUND: Malonyl-CoA decarboxylase deficiency (MLYCD) is a rare autosomal recessive disorder caused by defects in MLYCD gene. MS-MS newborn screening (NBS), has allowed pre-symptomatic diagnosis of more patients. Since its first description in 1984, >40 patients with MLYCD have been published, most as single case reports. Not much is known about the effect of early treatment on the natural history or long-term outcomes.

AIMS: To report clinical, biochemical, molecular characteristics and long term outcome of nine patients with MLYCD.

METHODS: This is a retrospective multi-site study of 9 patients, eight previously unreported. Diagnosis was based on biochemical, enzymatic and/or molecular data. Information was collected using a standardized data sheet. Brain MRI data were reviewed by the same neurologist and nutritional treatment was reviewed by the same metabolic dietitian.

RESULTS: All patients who had NBS test had elevated C3DC. Four patients had neonatal presentation, including hypoglycemia, acidosis, respiratory distress, hypotonia and seizures. Enzyme activity was extremely low (n=4). Most families were of Mexican descent and molecular testing revealed 8 novel mutations. One patient died of cardiac failure, the remaining 8 have a median age of 6.5 y (r1.3-14). Common disease manifestations included neurodevelopmental delay, hypotonia and microcephaly. Most patients had dilated cardiomyopathy, one had left ventricular non-compaction, all of them improved/resolved with treatment. MRI abnormalities were present in 4/6 patients, being the most prevalent cystic lesions in basal ganglia and periventricular white matter changes. Seven patients had a total of 23 admissions with an average of 28 hospital-days per admission. Long-term treatment included fasting precautions, carnitine supplementation and a fat restricted diet (20-37% of total calories) with medium chain triglyceride supplementation. No essential fatty acid deficiencies were reported.

CONCLUSION: Our findings significantly expand the number of reported cases and molecular spectrum of MLYCD. Additionally, we provide important information about long term manifestations and response to treatment. NBS can detect most MLYCD cases, however newborns can be symptomatic prior to the availability of NBS results. Early diagnosis and treatment appear to improve outcome and cardiac disease. However, current treatment modalities do not prevent neurodevelopmental manifestations.

P-137 - L-2 HYDROXYGLUTARIC ACIDURIA. A CASE CONFIRMED AT 43 YEARS OF AGE.

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INTRODUCTION: L-2-Hydroxyglutaric aciduria (L2HGA) is a rare neurometabolic disorder with an autosomal recessive mode of inheritance. It is characterized by elevated levels of L-2-hydroxyglutarate in biological fluids. It was first reported in 1980 in a Moroccan boy with psychomotor retardation. Patients have neurologic manifestations including mild-to-moderate psychomotor retardation, cerebellar ataxia, variable macrocephaly, and epilepsy. Has a slowly progressive disease course. Most patients reach adulthood. A consistent pattern of brain magnetic resonance (MR) with signal intensity abnormalities of the subcortical cerebral white matter (WM), putamen, and dentate nucleus had been described. We describe a case with symptoms and WM abnormalities since childhood that urine organic acid performed at 43 years of age, showed high 2-Hydroxyglutaric acid and molecular study confirmed pathogenic mutation in L2HGA gene. There is no specific treatment.

OBJECTIVE: to describe clinical course and MR findings of a case confirmed at adulthood.
CASE: female product of first pregnancy of consanguineous couple. Normal pregnancy and delivery. Development delay, mild mental retardation. She was evaluated for the first time when she was 27 years because she had cerebellar symptoms and gait ataxia since she was 4 years. Bilaterally symmetrical subcortical WM abnormalities were present since the first MR (29 years). 4 years latter involvement of both dentate nuclei was evident.There have been no clinical progression. Ammonia, lactic acid, amino acids were normal. At 43 years of age, qualitative urine organic acid profile showed high level of 2 hydroxyglutaric acid. At this age, epilepsy started. Because the clinical picture and MRI findings, sequencing of the L2HGA gene was performed. It was find a known pathogenic variant: homozygosis c.632G>T p.Gly211Val.
CONCLUSION: L2HGA is a rare slow progressive neurometabolic disease inherited as an autosomal recessive trait. Characteristic brain MR findings helps for the diagnosis. It is important to be aware about this disease in order to perform urine organic acids earlier during childhood to give adequate genetic counselling to the family.

P-138 - URINARY ORGANIC ACID ANALYSIS EXPERIENCE IN DETECTING ORGANIC ACIDURIAS AND OTHER INBORN ERRORS OF METABOLISM IN BRAZIL OVER A TEN-YEAR PERIOD

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INTRODUCTION: Gas chromatography/ mass spectrometry (GC/MS) of urine samples is the method of choice in the diagnosis and follow-up of Organic acidurias/ acidemias. However, due to the high costs of equipment purchase, operation and maintenance, there are few reports on the detection of these IEM in Brazil.
OBJECTIVE: To describe the organic acidurias/ acidemias, aminoacidopathies, Urea Cycle disorders, and fatty acid beta-oxidation defects detected by the analysis of urinary organic acids in a Brazilian private IEM reference laboratory.
METHODOLOGY: A cross-sectional study was performed. Urine samples were obtained over a ten-year period from patients with a clinical suspicion of IEM. Neurological dysfunctions, neuroimaging abnormalities, liver disorders, metabolic acidosis, hypoglycemia, hyperlacticemia, ketonuria, and hyperammonemia were the main causes for the request of this analysis. These samples were maintained at -20° C until analysis. The analytes of interest were extracted with ethyl acetate/ethyl ether following acidification of the urine and addition of internal standard. Sample extracts were thoroughly dried before derivatization with a 100: 1 MSTFA/TMS-Cl reagent mixture and identified as trimethylsilyl compounds on a gas chromatograph/ mass spectrometer.
RESULTS: Of the 8,873 urine specimens analyzed, 610 (7%) presented an IEM specific profile; other 929 samples (10%) presented nonspecific profiles. The majority of the analyzed samples, 6,838 (77%), were negative, while 496 (6%) presented undetermined results that would have to be characterized by other methodologies. Characteristic profiles of 33 different IEM were revealed from 262 patients. Organic acidemias/acidurias, aminoacidopathies and fatty acid beta-oxidation disorders were predominant. Methylmalonic acidemia, glutaric aciduria type 1, undefined Urea Cycle disorders, maple syrup urine disease and propionic acidemia were the most frequent IEM.
CONCLUSIONS: The analysis of urinary organic acids, especially when combined with the analysis of acylcarnitines in dried filter paper blood spots, is very useful in the diagnostic evaluation of patients with a clinical suspicion of an IEM. This analysis may be included in the diagnostic workup of neonates with severe symptoms due to acute and early forms of IEM, often confounded with sepsis, as well as of patients with insidious or late-onset forms, frequently with a predominance of neurological symptoms - “neurological organic acidosis”.

P-139 - GLUTATHIONE SYNTHETASE DEFICIENCY PRESENTING AS METABOLIC ACIDOSIS AND NEONATAL HEMOLYTIC ANEMIA

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INTRODUCTION: Glutathione synthetase deficiency is a rare autosomal recessive disorder resulting in low levels of glutathione and an increased susceptibility to oxidative stress. Patients manifest with a range of symptoms including metabolic acidosis, hemolytic anemia, neurological problems and massive excretion of pyroglutamic acid (5-oxoproline) in the urine. Wide clinical variation has been reported.
Treatment with antioxidants has been recommended in an attempt to prevent morbidity and mortality associated with the disorder.
CASE PRESENTATION: We present a 9 month old female patient referred to our hospital presenting metabolic acidosis and hemolytic anemia.
She was born at term, after an uneventful pregnancy and delivery, at 2 days of life she presented with tachypnea and

sleepiness. Blood gas analysis revealed a pH of 7.16, bicarbonate of 9 mmol/l and an anion gap of 31. Infectious causes were ruled out and she was transferred to our center.
With the suspicion of a neonatal metabolic disorder she was studied and Urinary organic acids chromatography revealed a large peak of 5-oxoproline, the aminoacids showed <8 umol/l glutamate (range 8-179), 139 umol/l glycine (range 154-338) and 3.5 umol/l cystine (range 6-43). This profile brought the suspicion of a glutathione cycle defect. With the biochemical profile and clinical presentation Glutathione synthetase deficiency was considered and treatment with bicarbonate, vitamins C and E was initiated immediately with good response.
Hemolysis was moderate, requiring some red blood cell transfusions. Non-conjugated bilirubin, lactate dehydrogenase and reticulocyte count were normal for age. Her red blood cell count remained stable only requiring transfusion on two viral respiratory tract infections and a gastrointestinal infection due to Salmonella and Adenovirus.
Her bicarbonate is also stable but low, despite intense antioxidant treatment.
Sequence analysis of GSS gene showed two Pathogenic variants, c.491G>A (p.Arg164Gln) and c.709C>T (p.Arg237*)
CONCLUSION: Glutathione synthetase deficiency and other erythrocyte metabolism defects should be considered in the initial assessment of neonates and infants with hemolytic anemia and/or metabolic acidosis. Early diagnosis and prompt treatment can improve long term outcomes.

P-140 - URINARY ORGANIC ACIDS PROFILE EXCRETION CHARACTERIZATION IN NEONATAL POPULATION

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INTRODUCTION: Organic acidurias are inborn errors of metabolism that can occur from the first days of life. Diagnosis is made through the analysis of urinary organic acids (OA) excretion profile by Gas Chromatography-Mass Spectrometry (GC-MS). Factors such as specific dietary habits and age can influence such profile, especially in infant population due to dietary changes and the normal maturation process that occur in the first year of life. Previous studies evaluated population from 20 to 150 days of age who were exclusively breastfed and another group that consumed infant formulas (Calvo A. et al. 2016). However, up to now there is little evidence regarding the urinary OA profile in the first days of life.
AIM: To describe and analyze the OA excretion profile of neonates between 5 to 72 hours of age.
METHODS: Collection of urine samples was carried out at an institution at Bogota city, from neonates born at term with adequate weight. A survey was applied to the mothers regarding the feeding history. Chemical examination was performed to each sample using standard urine stick. Creatinine concentration was determined using a commercial Jaffé METHOD: For OA extraction a liquid-liquid extraction process was done to finally establish the OA profile using GC-MS.
RESULTS: In OA profile observed we identify the presence of metabolites such as 2-hydroxybutyric, benzoic, acetoacetic, dehydrosuberic acids among others, which were not observed in a previous study with infant population (22 days-4 months). Likewise, we observe decreasing (lactic acid) or increasing tendency in different metabolites according to the age.
CONCLUSIONS: Our results evidence the importance of characterizing the evolution of the OA profile in the first month of life, since the OA excretion profile is characteristic for each population, depending on the age, diet and the general metabolism. In fact, we evidenced changes in the excretion pattern of specific metabolites that, wrongly, may lead to organic acidurias suspicion if compared to the patterns available in literature, which correspond mainly to older children and adults. Thus, our results contribute to a better interpretation of OA profiles in newborn population in the context of diagnosis of organic acidurias.

P-141 - DIAGNOSTIC DILEMMA OF INBORN METABOLIC DISEASE WITH HYPERAMMONEMIA IN A COLOMBIAN BOY WITH SUSPECTED DISEASE ON INTERMEDIARY METABOLISM

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INTRODUCTION: Hyperammonemia is a metabolic emergency, which can lead to acute and chronic complications like neurological damage and/or death. It can be caused by different pathologies but in the pediatric population inborn metabolic disease should always be suspected.
OBJECTIVE: Describe clinical follow-up and biochemical data collected in a boy with suspected disease on intermediary metabolism.
METHODS: Retrospective study of clinical history and biochemical analysis of a case from July 2009-October 2018 at the Hospital Pediátrico de la Misericordia Fundación HOMI (Bogotá, Colombia).

RESULTS: A 12-year-old boy, the third of three male children of unrelated parents with Colombian origin. Gestation and caesarean delivery without any complications (birth weight of 3225g). He had normal psychomotor development during the first six months of life until the administration of vaccines, when he presented fever, lethargy, irritability, hypotonia and vomiting. Subsequently, he presented developmental regression and progressive spastic tetraparesis. At 16-mo EEG showed generalized paroxysmal changes and biochemical analysis showed mild hyperammonemia, respiratory alkalosis and high orotic acid in urine, compatible with partial OTC deficiency. Whereby, he was treated with hypoproteic diet and sodium benzoate. At 5-yo, health care provider ceases sodium benzoate due to shortage, but surprisingly ammonium levels did not increase. Treating physicians re-evaluated the clinical evolution and the possible triggers and decided to perform biochemical analysis (plasma amino acids, urine organic acid, blood gases and others) several times, but the results were consistently normal. He continued treatment with hypoproteic diet and rehabilitation. Nowadays, the patient has severe motor and language delay, as well as, spastic tetraparesis. Recent analysis of serum metabolomic profile showed a type II glutaric aciduria.
CONCLUSIONS: We report the case of an adolescent boy with neurodevelopmental delay since the age of 6 months, as well as, vomiting, lethargy, seizures, spastic tetraparesis and episodic hyperammonemia. He received the treatment of an urea cycle disorder. However, a detailed clinical follow-up suggested an organic aciduria as a more compatible diagnosis, but urine organic acids were always negative. Complex and overlapping diseases require high- throughput technologies with better sensitivity to distinguish the type of metabolic disorders and provide a clear diagnosis.

P-142 - AN INFANTILE CASE OF METHYLMALONIC ACIDURIA WITH HYPEROHOMOCYSTEINEMIA (CBLC). A DIFFICULTO TO DIAGNOSIS DISEASE WITHOUT NEONATAL SCREENING AND WITH FEW EVIDENCES ABOUT THE BEST TREATMENT.

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The remethylation defects are rare diseases, with often significant delayed diagnosis and with few standardized treatment protocols.
The objective of the case presentation is to see the difficulties in the diagnosis and the follow up with hydroxocobalamin dose escalation.
The boy is the first son of non-consanguineous parents, with a normal pregnancy and delivery. He was hospitalized at 13 days of life, because feeding difficulties, 14% of weight loss, perianal lesions and bad general condition, with bone marrow aplasia. The diagnosis was sepsis until 35 days of life when a broad neonatal screening was done because the neurological symptoms persisted in spite of antibiotic treatment with negative bacterial and virus exams. With C3 elevation the assessment was expanded, finding low plasma methionine, methylmalonic acid in urine and high serum homocysteine, then a remethylation defect was suspected. It was confirmed with the finding of two pathogenic variant in MMACHC gene (c271duoAand c.331C>T).
With 3.4kg he began treatment with IM Hydroxocobalamin 1mg/d, betaine 800mg/d and L-carnitine 300mg/d with breast feeding. The serum methylmalonic acid (MMA) decreased from 6994 to 629 ug/ml (normal <104ug/ml) and the homocysteine from > 50 umol/l to 35. After five months with the same B12 dose and with 8 kg of weight (0.12 mg/kg/d) the MMA increased to 900 ug/ml and the homocysteine to 40 umol/l then the B12 dose was increased to 0,2 mg/kg and the betaine to 150mg/kg. Then the serum MMA decreased again to 345ug/ml, the homocysteine to 27 umol/l and the metionine was normal.
He has had normal growth and development without retinal lesions but with persistent nystagmus that was present since1 month old.
In conclusion it is difficult for pediatricians to think about the disease in spite of the severe clinical aspect. Patients like this could die in the first trimester of life no diagnostic. The increment of B12 doses seems again to be necessary. Longer follow up would tell us about neurological and ocular development.

P-143 - GLUTARIC ACIDEMIA TYPE 1. WIDE PHENOTYPIC EXPRESSION

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INTRODUCTION: Glutaric aciduria type-1 (GA1) is an autosomal recessive disorder caused by a glutaryl-CoA dehydrogenase deficiency due to GCDH gene mutations. This enzyme participates in the catabolism of lysine, hydroxylysine and tryptophan. Glutaric (in high excretory forms) and 3-hydroxyglutaric acid in urine and glutarylcarnitine in blood are increased, leading to a secondary carnitine deficiency.
Acute-onset forms present during the first years of life with acute encephalopathy with extrapyramidal signs. Further subtypes are insidious movement disorder and late-onset with non-specific symptoms. Macrocephaly is usually presented from early life.

OBJECTIVE: Describe clinical, biochemical and molecular aspects of GA1-patients assisted at present in our service. Emphasize the variable clinical presentations with at least two forms: acute and late-onset.
MATERIALS AND METHODS: 7 patients whose diagnosis was biochemically established through the measurement of urinary organic acid by GCMS, acylcarnitine profile, and serum carnitine (free and total) after clinical and neuroimaging (MRI) suspicion, are presented. Mutation analysis was confirmed by Sanger sequencing of gDNA. Treatment was started at diagnosis in all patients and continued until the age of 6 years. It consisted on a protein-restricted diet, supplemented with a special amino acid mixture and L-carnitine.
RESULTS: All patients were symptomatic during the first 2 years (4 to 22 months). 5 patients presented with severe early-onset encephalopathy during a febrile illness, and developed a dystonic dyskinetic tetraplegia. Two of them substantially improved on follow-up. MRI showed striatal changes, variable cortical atrophy and enlarged sylvian fissures.
The other 2 patients presented with non-specific symptoms (focal seizures) without neurological signs, and diagnosis was suspected after brain MRI showing enlarged sylvian fissures without striatal lesions, one of whom developed extensive white matter changes.
Only 2 patients presented with non-excretory biochemical phenotype.
Two patients were homozygous for the more frequent R402W mutation but presented with different phenotype.
DISCUSSION: Even though the small number of patients, they represent the wide clinical phenotype of GA1. The presence of macrocephaly and a correct MRI interpretation allowed the diagnosis in the oligosymptomatic forms.
Non-excretory patients need molecular diagnosis and demand an exhaustive acylcarnitines examination when low free-carnitine is present. No phenotype/genotype correlations were detected.

P-144 - ETHYLMALONIC ACID INDUCES BIOENERGETIC DYSFUNCTION IN RAT CEREBELLUM BY DISTURBING MITOCHONDRIAL SUCCINATE UPTAKE

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BACKGROUND: Ethylmalonic encephalopathy (EE) is a devastating neurometabolic disorder caused by mutations in the ETHE1 and biochemically characterized by ethylmalonic acid (EMA) accumulation. Individuals affected by EE present with chronic circulatory and gastrointestinal problems, and severe neurological symptoms, whose pathophysiology is not totally established. Therefore, we investigated the effects of EMA on mitochondrial bioenergetics and redox homeostasis in cerebellum of rats.
METHODS: Mitochondrial preparations or supernatants were prepared from cerebellum of 30-day-old Wistar rats and used for the evaluation of EMA effects (2.5-5 mM) on mitochondrial respiration (states 3, 4, respiratory control ratio and uncoupled state) and membrane potential, glutathione (GSH) concentrations, malondialdehyde (MDA) levels, and aconitase, citrate synthase and respiratory chain complex II activities.
RESULTS: Our results demonstrated that EMA decreased state 3, respiratory control ratio and uncoupled state in succinate-supported mitochondria. Inhibitory effects elicited by EMA on succinate-supported respiration were attenuated by nonselective permeabilization of the mitochondrial membrane, suggesting that succinate transport is impaired. We also verified that EMA dissipated mitochondrial membrane potential, which was prevented by cyclosporine A plus ADP and ruthenium red. EMA further decreased aconitase activity. However, MDA levels, GSH concentrations and citrate synthase activity were not altered by this organic acid.
DISCUSSION: Our findings indicate that EMA impairs mitochondrial succinate uptake and induces mitochondrial permeability transition in cerebellum. It is presumed that these pathomechanisms underlie the neurological dysfunction observed in EE.
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P-145 - INVESTIGATION OF THE ROLE OF C26: 0-LYSOPHOSPHATIDYLCHOLINE IN THE OXIDATIVE STRESS INDUCTION IN X-LINKED ADRENOLEUKODYSTROPHY

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INTRODUCTION: X-linked adrenoleukodystrophy (X-ALD) is caused by mutations in ABCD1 gene and is characterized by very long-chain fatty acids (VLCFA) accumulation. It is clinically heterogeneous, however male patients are at high-risk to develop adrenal insufficiency and/or cerebral demyelination. Since untreated adrenal insufficiency can be life-threatening and considering the possibility of cure when hematopoietic stem cell transplantation is performed in an early stage of the disease, prompt diagnosis is crucial for a good prognosis. Thus, an

increasing interest has arisen in the neonatal screening of X-ALD, which is possible through the analysis of C26: 0-lysophosphatidylcholine (C26: 0-LPC). Although a considerable number of studies has demonstrated the importance of this new biomarker for the diagnosis of X-ALD, its role in the pathophysiology of this disease has not been investigated.
OBJECTIVES: Considering that oxidative stress is a well described mechanism of damage in X-ALD, our objective was to investigate if this mechanism could be related with C26: 0-LPC accumulation in X-ALD patients.
MATERIALS AND METHODS: We measured blood C26: 0-LPC concentrations in five patients with X-ALD (2 children, one with CCER and the other with AMN; and 3 adult heterozygous women) by liquid cromatography tandem mass spectrometry. Oxidative stress was investigated in these patients through the measurement of the reactive species formation by the 2',7'-dichlorofluorescin oxidation assay (DCF) in plasma and by determination of plasma sulphydryl groups, whose reduction reflects protein oxidation.
RESULTS: Our results showed a significant increase of C26: 0-LPC in blood of X-ALD patients when compared with healthy controls of similar ages, being higher in the male X-ALD patients in relation to the X-ALD female carriers. We also verified a strong inverse correlation between plasma sulphydryl groups and C26: 0-LPC (r=-0,817, p=0,091) and a positive correlation between C26: 0-LPC and DCF (r=0,611, p=0,274).
CONCLUSIONS: The correlations verified in this study between oxidative stress parameters and C26: 0-LPC probably could be significant whether the number of analyzed patients was higher, which would make it possible to separate the patients according their phenotypes. Even so, preliminary data from this study suggest that C26: 0-LPC may be involved in the induction of oxidative imbalance in X-ALD, deserving further investigation.

P-146 - N-ACETYL-L-CYSTEINE, TROLOX, AND ROSUVASTATIN PROTECT GLIAL CELLS EXPOSED TO HEXACOSANOIC ACID AGAIST INFLAMMATION, LIPID PEROXIDATION AND NITRATIVE STRESS

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INTRODUCTION: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder caused by disfunction of the ABCD1 gene, which encodes a peroxisomal protein responsible for the transport of the very long-chain fatty acids from the cytosol into the peroxisome, to undergo β-oxidation.The major accumulated saturated fatty acids are hexacosanoic acid (C26: 0) and tetracosanoic acid (C24: 0) in tissues and body fluids. Recent evidence shows that oxidative and nitrative stress seems to be related with pathophysiology of X-ALD and many studies are associating antioxidants as an adjuvant theraphy, since there is no completely satisfactory treatment for this neurogenetic disorder.
OBJECTIVES: Considering that glial cells are widely used in studies of protective mechanisms against neuronal oxidative stress, we investigated whether C26: 0, incorporated in a lecithin vesicle, was capable to induce oxidative/nitrative damages and inflammation to glial cells and if the compounds N-acetyl-l-cysteine (NAC), trolox (TRO), and rosuvastatin (RSV) were able to protect cells against C26: 0-induced damages.
MATERIALS AND METHODS: C26: 0 was incorporated in lecithin vesicle by sonication. Glial cells were clultured in DMEM and at confluence, the vesicles containing lecithin and C26: 0 were added. A pre-treatment was performed for 2h at 37°C with NAC (100 μM), RSV (5 μM), and TRO (75 μM). Supernatants were collected for analysis. IL-1β was measured by an Invitrogen ELISA kit, NO equivalents and isoprostanes was detected by a Cayman kit.
RESULTS: It was observed that glial cells exposed to C26: 0 presented increased NO levels, high IL-1β levels, and increased isoprostane levels, compared to native glial cells without C26: 0 exposures. Furthermore, NAC, TRO, and RSV were capable to mitigate these damages caused by the C26: 0 in glial cells.
DISCUSSION AND CONCLUSION: Our data demonstrate, for the first time in literature, that C26: 0, by itself, induced in glial cells culture: lipid peroxidation, nitrative stress and inflammation. Furthermore, we verified that NAC, TRO, and RSV were capable to attenuate damages caused by C26: 0 in glial cells. The ability of these compounds to exert protective effects in glial cell culture might be of relevance as an adjuvant treatment for X-ALD, since there is still no completely satisfactory therapy for this disorder.

P-147 - SITOSTEROLEMIA IN COSTA RICA: REPORT OF THE FIRST CASE

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INTRODUCTION: Sitosterolemia is a rare autosomal recessive disorder of lipid metabolism characterized by increased intestinal absorption and a decrease in the biliary

excretion of cholesterol and plant sterols such as sitosterol. Increased plasma concentrations of plant sterols (especially sitosterol, campesterol, and stigmasterol) are observed once foods with plant sterols are included in the diet and have accumulated in the body. ABCG5 and ABCG8 are the only genes in which pathogenic variants are known to cause sitosterolemia. Because the proteins sterolin-1 (encode by ABCG5) and sterolin-2 (encoded by ABCG8) form a heterodimer transporter, affected individuals have biallelic pathogenic variants in either ABCG5 or ABCG8. Affected individuals can develop: a) Xanthomas (cholesterol deposits) in the tendons and around the pressure points, b) Hypercolesteronemia, atherosclerosis of early onset and c) Hematological abnormalities, including hemolytic anemia

OBJECTIVE: We present a 36-year-old female patient with a history of hypercholesterolemia, with painful masses in the Achilles tendon, knees and hands, and joint pain since childhood, with the family history of consanguineous parents and a younger brother with similar but milder symptoms. Description of the first biochemically and molecularly confirmed case of Sitosterolemia in Costa Rica.

MATERIALS AND METHODS: Biochemical analysis including: Serum lipoprotein electrophoresis, cholesterol, cholestanol and triglyceride measurements was performed. Hemoglobin analysis and Next Generation Sequencing (NGS) studies were performed. Imaging tests such as abdominal ultrasound and brain magnetic resonance imaging (MRI) were performed.

RESULTS: The proband had large xanthomas at the level of heels and Achilles tendon, elbows, knees and hands. Abdominal ultrasound and brain MRI do not report changes. Clinically there were no neurological symptoms. Biochemically she presented abnormal lipoprotein electrophoresis with elevated ultrasensitive CRP, hypercholesterolemia due to elevation of LDL. Molecular study reported a homozygous, pathogenic variant. c.647_657dupGTGAGCGAGG (p.Arg220Alfs*37) in the ABCG8 gene. Therapy with a restricted sterol diet and Ezetimibe was started.

Discussion and CONCLUSIONS: Sitosterolemia is a defect in the metabolism of cholesterol and plant sterols such as sitosterol, which can manifest from childhood and worsen with aging. The right diagnosis will allow a better approach and the correct management, as in this case.

P-148 - PRIMARY TYPE I HYPEROXALURIA IN A SCHOOL WAITING FOR HEPATORENAL TRANSPLANT IN BOGOTÁ, COLOMBIA

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INTRODUCTION: Primary hyperoxaluria type I is due to enzyme deficit of alanine-glyoxylate aminotransferase (PH type I) specific to hepatic peroxisome, causing excessive production of oxalate. Because oxalate is eliminated by the kidneys, the kidney is the first affected organ and manifests with the appearance of lithiasis, nephrocalcinosis and early renal failure.

CASE PRESENTATION: Son of consanguineous parents, with a maternal and paternal family history of renal lithiasis and renal failure and sister who died at 3 months of age due to "cystic kidney disease". At three months of age he presented urinary tract infection and at three years of age, was found nephrocalcinosis. Extrainstitutionally, he was misdiagnosed as renal tubular acidosis type I. At 4 years old, primary hyperoxaluria type 1 was diagnosed after levels of oxalate in urine of 24 hours were found in 216.2 mg of 1.73 m2 and confirmed by the finding of the homozigous mutation c.731T> C (p.Ile244Thr) in the AGXT gene. At the moment, the patient is treated with citrate solution, hydrochlorothiazide and pyridoxine. He does not present cardiac or ophthalmological alterations. He has had hearing loss and he has image diagnostic consistent with nephrocalcinosis associated with stage III chronic kidney disease.

CONCLUSION: Hyperoxaluria type I requires a high diagnostic suspicion, in order to initiate early the conservative treatment of the disease, slowing kidney damage and offer the only curative option than is the double hepatic-renal transplant. In Colombia, no cases have been published in children. The presence of lithiasis and / or nephrocalcinosis by oxalates requires discarding primary hyperoxaluria.

P-149 - DESCRIPTION OF PHENOTYPE, CLINICAL PRESENTATION, NEUROIMAGING AND FOLLOW UP OF A SERIES OF PATIENTS WITH X-LINKED ADRENOLEUKODYSTROPHY

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INTRODUCTION: X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder and is caused by mutations of ABCD1 (Xq28) gene. The dysfunction of the peroxisomal membrane protein codified leads to very-long-chain fatty acids (VLCFA) accumulation, which confirms diagnosis. The age of onset and morbidity are highly variable

and progression is unpredictable. This disorder has many different phenotypes and has a characteristic neuroimaging.
OBJECTIVE: To describe phenotype, initial symptoms, neuroimaging, laboratory, management and outcome of a series of patients with X-ADL. METHODS: Retrospective-prospective and descriptive study. Review of clinical records and Magnetic Resonance Imaging (MRI) of patients diagnosed with X-ADL who have been evaluated at the Neuropsychiatry Service of Hospital San Borja Arriaran since 1990.
RESULTS: 28 male patients with elevated VLCFA in plasma: 16 with childhood-cerebral form, 4 with Addison disease only, 5 asymptomatic and 3 with adolescent-cerebral form. The average age of symptoms onset was 7.8 years old (3 to 16 years old). Initial clinical presentation: behavioral disorders: 13/28, cognitive impairments: 10/28, adrenal insufficiency: 6/28, hearing loss: 6/28, visual loss: 6/28, seizures: 6/28 and gait disturbance: 3/28. MRI showed enhanced T2-signal in the parieto-occipital region in 17/28 (only one patient asymptomatic), frontal region in 3/28 and normal in 8/28 (4 Addison disease only and 4 asymptomatic). Management: 14 patients received corticosteroid replacement therapy (CRT), 6 received Lorenzo's oil, one patient had hematopoietic stem cell transplantation(HSCT) in an advanced disease stage with an unfavorable result and 5 patients received fludrocortisone. Third-teen patients are alive: 4 with Addison disease only, 4 with progressive deterioration and 5 persist asymptomatic, in regular control with MRI.
CONCLUSIONS: In our series of patients the most frequent form was the childhood-cerebral X-ADL and most of them initially presented with behavioral disorders and cognitive impairments, being the classic parieto-occipital pattern the most frequent neuroimaging alteration. Half of our patients needed CRT and the only patient who received HSCT died. Diagnostic suspicion must be high in patients that initiate cognitive impairment or behavioral disorders at school age associated with other subtle neurological symptoms, so to perform an early neuroimaging and study of VLCFA, and be able to offer specific treatment at an early stage.

P-150 - COGNITIVE ASSESSMENT OF EARLY DETECTED AND TREATED PKU CHILDREN

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INTRODUCTION: Early detected and treated PKU might present neurocognitive disfunction possibly related to the underlying disease.
OBJECTIVES: Characterize their cognitive profiles, assessing specific deficits and their relationship with variables of the disease and its treatment.
PATIENTS: 30 moderate to severe PKU children (9-10years), detected and adequately treated at median age of 18 days were selected and compared with a control group (CG) of 30 healthy children of the same age. All had absence of other concurrent diseases, parents with complete high school educational level and similar socioeconomic status.
METHODS: WISC IV, Rey-Osterrieth Complex Figure Test, Continuous Performance Test (CPT II), ITPA (Illinois test of psycholinguistic abilities), Verbal Fluency Test, Trail Making Test, Faces Test were administered.
Cognitive profile was related to age at start of treatment, initial phenylalanine (Phe) levels, Phe tolerance mg/day, first year median Phe levels (MPHEL),MPHEL 2-5years of age, MPHEL 6 years to evaluation, MPHEL year previous to evaluation, number of controls the year previous to evaluation. Student´s T test for independent samples was used for statistical analysis and Pearson´s for correlations. (Significance: $p<0.05$)
RESULTS: PKU showed normal average IQ (mean±SD) 92±6,3 vs. CG: 101,1±5,9 ($p<0.001$). Significant differences were found in PKU vs.CG with lower executive control associated to organization, regulation of impulsivity and divided and focalized attention.
No differences were found in memory, visuospatial skills, reaction times, processing speed or in language.
Higher MPHEL the first year of age were significantly and inversely correlated to executive control r: -.375 $p<0.05$. Having more controls the year previous to assessment was associated with less impulsivity r: -.456 $p<0.03$.
An inverse tendency was found between executive control with MPHEL (2 to 5 years) and(6 years to evaluation) r: -.362 p:.058 and r: -.357 p:.062 respectively. Executive control tended also to be associated with the frequency of previous controls r.343 p:.070
CONCLUSION: Our findings confirm the neurocognitive impact of PKU and reinforce the utility of early and adequate treatment to prevent mental impairment.
They also evidenced an specific vulnerability that has to be considered en the attention of these patients reinforcing the impact of tight control of Phe levels during early childhood.

P-151 - PARENTING STYLES AND COPING STRATEGIES IN PKU CHILDREN

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INTRODUCTION: Early detected and treated PKU does not lead to mental impairment but requires prolonged treatment, care, and control. As a chronic disease with intensive care of diet and habits it may influence the bonding between parents and child and the resources of the child to deal with conflictive situations.
OBJECTIVES: To describe the predominant perceived parenting styles in early detected and well controlled PKU

children from the perception of the child (son) and to identify their coping strategies.
PATIENTS AND METHODS: An intentional sample of 30 PKU children aged 9 to 10 years detected through neonatal screening and adequately treated since the first month of life with good adherence, was selected and compared with 30 healthy children of the same age (control group (CG)). Inclusion criteria were: absence of other concurrent diseases, parents with a complete high school educational level and a similar socioeconomic status.
The evaluation was performed with the Argentine coping questionnaire for children aged 9-12 years, Argentina Scale perception of the relationship with Parents and Test WISC III: comprehension subtest.
MANOVA´s were carried out as statistical analysis, with a significance level of $p < 0.05$.
Also relation between parenting styles and coping strategies was statistically assessed by Pearson´s.
RESULTS: Differently from the CG, PKU children perceived the relationship with their parents based on control. This control was considered strict to pathologic in the mother and perceived as acceptable in the father (both $p<0.05$)
Regarding to coping strategies PKU children showed a tendency to seek greater support and showed more lack of emotional control when facing conflictive situations
A positive correlation was found between the strict control and lack of emotional control r:.398 p<.03 and between the seek of support and the emotional dyscontrol r:.383 $p < 0.04$
CONCLUSION: The tendency to require more support and to have less emotional control when facing problems found in our PKU children cohort seems to be related to the strict maternal control. This profile may develop into a psychological and behavioral trait of greater dependency and impulsivity that has to be taken into account when monitoring PKU children evolution.

P-152 - PKU CLINC EXPERIENCE

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INTRODUCTION: PKU patients need individual follow up performed by a metabolic team.
OBJECTIVE: to describe the management strategy of PKU patients in our clinic.
PATIENTS AND METHODS: 133 patients (2 months to adulthood) from different Argentinian provinces and other Latin American countries. (Ecuador, Bolivia and Paraguay) are followed up a by a metabolic team (two doctors, one dietitian and one neuropsychologist) that works close to the laboratory where blood samples are processed.
RESULTS: After diagnosis, patients come to consultation monthly during the first year of age and then every four months. Phenylalanine (Phe) levels are tested fortnightly until age five and monthly thereafter. According to Phe tolerance current patients were classified as severe (n: 41) moderate (n: 39) ; mild (n: 9) and hyperphenylalaninemic (n: 44). Thirteen patients were late diagnosed (7 from Ecuador).
A neurocognitive evaluation is performed yearly or at least before starting kindergarten, elementary school, high school and college.
Treatment is instituted individually, considering clinical, social and emotional needs in every patient.
72 patients receive conventional treatment: diet + protein substitute which is indicated as amino acids mixture (n: 66), in two patients combined with glycomacropeptides (GMP) in 2 only as GMP.
Forty-two patients receive just diet counseling. Six patients (5 late diagnosed) are treated with neutral aminoacids combined with protein substitute and diet.
37 patients underwent a dihidrochloride of saprotpterine (BH4) test. 4 were tested as neonates while 33 were tested later with a 48 hours test (n: 28) or with a long term test (n: 5).
31 patients were responders (decrease from basal Phe blood level ≥30%). Thirteen of them began treatment with BH4. Four were able to withdraw protein substitute and nine continue with it: six as amino acid mixture and three combining also GMP.
5 women (1 moderate PKU, 1 mild PKU and 3 hyperphenylalaninemias) underwent successful pregnancies. Both PKU received conventional treatment and hyperphenilalaninemias diet counseling.
With acceptable adherence, our early detected PKU patients grow and develop normally. Late detected patients have improved their quality of life.
CONCLUSION: Our team works with international recommendations but individual assessment of affected children is provided and treatment designed accordingly.

P-153 - DEVELOPMENT OF A PKU RECIPE BOOK BASED ON TRADITIONAL MEXICAN CUISINE WITHOUT INDUSTRIALIZED LOW-PROTEIN PRODUCTS.

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INTRODUCTION: Diet for a lifetime can be difficult in Phenylketonuria (PKU), many factors could contribute to the lack of adherence. One important factor is creativity and variety of the daily diet and also the costs and availability of

different foods; in order to contribute to provide alternatives to this problem, many recipe books have been developed in different countries, most of them include industrialized low-protein products and are based in local habits and customs. Available, low cost options for each country might contribute to improve compliance.
OBJECTIVES: To elaborate a new recipe book for PKU patients, turning in to low protein some recipes of the daily Mexican cuisine, using ingredients that are locally available, without commercial low protein products.
METHODS: A search in different Mexican cookbooks was made in order to find the most common traditional recipes low in protein. For every recipe phenylalanine (PHE), tyrosine, protein and energy data were calculated using the USDA data. Metabolic dietitians and a mother of a PKU patient contribute to cook every recipe and took photographs of each dish.
RESULTS: Fifty-seven recipes were done; four basic recipes, twenty-three appetizers, sixteen main courses and fourteen desserts. The average protein per serving was 1.6 grams (minimum 0, maximum 4.4 g), the energy was 195 Kcal (0-987 Kcal) and the PHE was 52 mg (0-155 mg).
DISCUSSION/CONCLUSION: In Mexico it is difficult and expensive to find commercial low protein food products, so this new Mexican recipe book for PKU patients, which only use natural ingredients that are available at most local supermarkets in Mexico, contributes to make easier, attractive and cheaper their diet. This cookbook is a new option to provide variety in meal planning with fifty-seven recipes.

P-154 - PHENYLALANINE LEVELS DURING TREATMENT OF AN ADOLESCENT WITH PHENYLKETONURIA AND LEUKEMIA

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INTRODUCTION: The control of blood phenylalanine (PHE) levels is challenging in adolescence and it is especially difficult in those patients with serious comorbidities such as cancer. There are few cases on the literature that describe the metabolic control of patients with phenylketonuria (PKU) and leukemia. In Mexico pediatric cancer is a health problem, with more than 5,000 new cases annually, and a prevalence of 23,000 cases. Leukemia is the most frequent cancer in all ages and both genders.
OBJECTIVES: To describe the PHE levels during the treatment of a PKU patient with acute lymphoblastic leukemia treated with chemotherapy.
METHODS: A 10-month retrospective analysis of blood PHE levels of an early detected classical PKU male, who was diagnosed with acute lymphoblastic leukemia at the age of 17-year-old. Samples were obtained during hospitalizations, chemotherapy and in ambulatory surveillance performed at the National Institute of Pediatrics from Mexico.
RESULTS: Seventy-eight blood samples were collected, 31 (39.7%) determinations were above 360 μMol/L, 37 (47.4%) were below 120 μMol/L and only 10 (12.8%) were within the therapeutic range (120-360 μMol/L).
DISCUSSION/CONCLUSION: High blood PHE levels were observed at the leukemia diagnosis, as well as during infections, mucositis, g-tube surgery and concurrent complications such as acute appendicitis also high PHE levels were observed when non PHE-free-parenteral nutrition was used in an intermittent way, with a maximum amount of protein of 0.3 g/kg/d. Low PHE levels were related with fasting periods in which prescribed diet was not completed. Salvariova-Zivkovic et al. found that in a PKU patient with lymphoma; 28.9% samples were within the therapeutic range, higher than the 12.8% obtained by us. This difference could be explained because of long fasting periods and, the absence in our country of a specialized PHE free amino-acid parenteral solution. Notably, in both studies low PHE values were the most frequent ones. Metabolic control in leukemia-PKU patients is a real challenge, especially in underdeveloped countries in which therapeutic tools are not available and therefore, this case-report could be useful in Latin-American countries.

P-155 - PERCEIVED BARRIERS RELATED TO PKU TREATMENT IN BRAZIL

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INTRODUCTION: According to studies with phenylketonuria (PKU), Brazilian population metabolic control presented unsatisfactory indexes since childhood. Studies with similar chronic conditions had showed that individual decisions are influenced by perceived barriers, and it can impact in adherence to treatment.
OBJECTIVE: To inventory perceived barriers to PKU treatment and to evaluate if they are associated with adherence.
METHODS: Twenty three patients with PKU (M 18.0; SD 7.3; 6 – 34 y. o.) with Classical (n=10), Mild (n=12) and Undefined type (n=1) and 11 caregivers participated. 69% were early-treated. An inventory developed to this study was used to assess perceived barriers to treatment which was

answered by patients (13 years or older) and caregivers (of patients 6 to 17 years). This study was approved by the Research Ethics Review Committee of the University Hospital. Written consent was obtained from participants.
RESULTS: Considering blood Phenylalanine (Phe) collected in 12 months prior to the study, 54.5% of patients showed a median value above recommended one. An association was found between age and Phe level (rs = 0.47, p = 0.027). However when considering the perceived barriers as a control variable it is observed that the correlation becomes statistically non-significant (rs = 0.30, p = 0.187). Adult patients reported a higher number of perceived barriers compared to the other participants (i.e. adolescents and parent proxy-report of their children) (U = 20.500; p = 0.005). In contrast, the number of barriers did not differ according to patients' gender, caregiver's level of education, IQ < 80 / QI ≥ 80 classification of patients, PKU type, nor early or late treated PKU status. Phe level was also associated with the frequency of perceived barriers (rs = 0.50, p = 0.016).
CONCLUSION: These results suggest that adults are in higher risk to perceived barriers related to the dietary treatment of PKU. Perceived barriers are related to worst control of Phe levels, which corroborate with the hypothesis of association between barriers and nonadherence. These findings support the need for further research about barriers perceived by PKU patients.To tailor interventions to decrease these barriers may be beneficial to PKU patients.

P-156 - EDUCATIONAL ANIMATED FILM FOR CHILDREN AND ADOLESCENTS WITH PHENYLKETONURIA

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INTRODUCTION: Nutritional treatment is the mainstay of phenylketonuria (PKU) management and should be continued for life. Unfortunately, the adherence to diet is a difficult issue at all ages, especially in children older than 10 years old (1). The provision of educational materials such as books, pictures, brochures, among others, has been described as factors that can encourage diet adherence (2). In México the educational materials for support PKU treatment compliance, are scarce.
OBJECTIVE: To elaborate an animated short film addressed to PKU children and adolescents about the importance of maintaining the phenylalanine blood levels within therapeutic ranges and depicting fruits and vegetables as an important part of their treatment.
MATERIALS AND METHODS: Dietitians, chemist and medical personal trained in the PKU management, developed a simple script explaining some of the damages caused by the transgression of the phenylalanine restricted diet. The sketches of the drawings were made by a volunteer designer and the animation was done by a film student. Royalty free music was used for the animation film.
RESULTS: An original 3-minute animated short film was done and it has been shown to about 30 PKU patients and their parents, those who have expressed that it seems fun and useful, however a formal study has not been carried out to asses its impact in the Phe blood levels.
CONCLUSION: To the best to our knowledge, this is the first educative short animated film developed in Mexico devoted to PKU pediatric patients to encourage its compliance to the nutritional treatment.
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P-157 - PHENYLKETONURIA IN CHILE; ADHERENCE TO TREATMENT IN 130 PKU PATIENTS DIAGNOSED DURING THE NEWBORN PERIODPHENYLKETONURIA IN CHILE; ADHERENCE TO TREATMENT IN 130 PKU PATIENTS DIAGNOSED DURING THE NEWBORN PERIOD

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INTRODUCTION: Phenylketonuria (PKU) is caused by a deficiency in the enzyme phenylalanine hydroxylase (PAH). Treatment consists of a phenylalanine (Phe) restricted diet and an amino acid formula without Phe (AAF).
OBJECTIVE: To analyze the results of the clinical follow-up of 130 PKU of neonatal diagnosis in active control.
METHODOLOGY: A retrospective, cross-sectional study was performed in 130 PKU patients. Phe blood levels were analyzed according to treatment protocol from 1992 to 2007 where good metabolic control (GMC) was defined as: Phe<10 mg/dL; protocol of 2007 and 2014 which considered GMC: Phe<8 mg/dL, and the current protocol since 2014 that defines GMC: Phe< 6 mg/dl. In addition, dietary intake (Phe, calories,

proteins and minerals), intellectual quotient (IQ) and nutritional status were evaluated.
RESULTS: The age of diagnosis (dg) was 16.8 ± 8 days of life, Phe level at dg was mean 16.2 ± 7.9 mg/dL. Patients are currently between 4 months to 26 years old. 91/130 PKU maintain GMC according to protocol, 30/130 maintains regular metabolic control and 9/130 has poor metabolic control. PKU patients > 3 years of age (n = 68) with good metabolic control had a total IQ at mean 101.6 ± 15.3, unlike PKU >3 years (n = 9) with poor metabolic control, who registered an IQ of mean 72.4 ± 16.0. Phe intake was mean 400.15 ± 275.95 mg/day, protein intake mean 2.3 ± 0.41 g/kg/day, 89.4 % of which comes from AAF. The dietary analysis found a caloric, calcium, zinc and iron intake consistent with the RDI. The nutritional status according to WHO 2002 standards, found that 61.2 % were eutrophic, 18.5 % were overweight, 15.5 % were obese and 4.7 % were at risk of malnutrition.
CONCLUSIONS: Good metabolic control, long-term integral follow-up and the constant provision of the AAF are essential variables to achieve growth and development in normal ranges.

P-158 - EVOLUTION OF PKU ADULT PATIENTS DETECTED BY NEONATAL SCREENING

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INTRODUCTION: Dietary treatment is the mainstay of therapy for phenylketonuria (PKU), but adherence to low-phenylalanine diet decreases from adolescence. Newborn Screening (NBS) programs in Argentina started in the 90's and our hospital has been a reference center for PKU.
OBJECTIVES: Characterize a population of PKU patients older than 16yrs detected by NBS who were followed-up since then by the same professional's team. Understand their nutritional habits, difficulties to follow the treatment and knowledge about PKU through a survey. Describe their treatment adherence and socio-cultural level, through medical records.
MATERIALS AND METHODS: Over a 6 months period (Jul/2018-Jan/2019), 38 adult PKU patients were recruited to the survey. Patient's inclusion criteria were as follows: age ≥16yrs, confirmed diagnosis of PKU from NBS and being on follow-up.
A survey consisting in a set of multiple-choice questions and an open section for comments was designed and distributed by e-mail or during consultations.
RESULTS: 38 PKU patients aged 16-33yrs answered the survey and were included in the study. 76% of patients did not have knowledge about their phenylalanine intake. 87% required amino acid (AA) mixture, but only 9% correctly took the supplements and 68% consumed limited quantities of low-protein food. 80% reported difficulties with treatment, mainly with adherence to the diet outside home and phenylalanine monitoring compliance; however, 58% considered they did the diet correctly. Around half of patients showed poor treatment adherence. Socio-cultural, educational level and work opportunities were similar to the average population.
CONCLUSION: Despite the relatively small sample size, it reflects the outcomes of our PKU adult patients detected through NBS. Adherence to nutritional treatment was unsatisfactory, affecting all the social classes. Diet outside home and regular phenylalanine monitoring were their main difficulties. Patients did not consider the inappropriate frequency of AA mixture and low-protein food intake as a problem. A high number of patients seem to have a poor perception and knowledge about their disease.
Considering these results, we assume the need to implement a simplified diet, increase the multi-media material supply to patients, work in an early transition to health self-care, and create a local system of social working groups.

P-159 - GROWTH AND SIZE EVALUATION IN PATIENTS WITH PHENYLKETONURIA IN A PEDIATRIC HOSPITAL

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INTRODUCTION: To allow the physical growth phenylketonuric children requires phenylalanine-restricted diet, low in natural protein.
OBJECTIVE: The aim of this study was to evaluate growth and size of phenylketonuric patients with phenylalanine-restricted diet, low in natural protein, in a pediatric hospital at Mendoza, Argentina between January 1997 and December 2018.
MATERIALS AND METHODS: Descriptive and retrospective study.
It was included children with a diagnosis of phenylketonuria by newborn screening who began clinical-nutritional treatment in Division of GROWTH AND DEVELOPMENT: Data were taken from written medical records, with informed consent.
It were evaluated: 1) size: at birth and every 3 months in children under 1 year old and yearly afterwards; 2) growth: annual growth velocity (adequate: between P10 and 97); 3) types of Phenylketonuria: classic, moderate and mild according to the phenylalanine value in the diagnosis and the

phenylalanine daily intake; 4) metabolic control: adequate - phenylalanine values between 2-6 mg/dL in dried blood spot; 5) breastfeeding: at 6 months and 2 years. It was made descriptive statistics analysis.
RESULTS: N = 11 (7 female patients, 4 male patients). Mean age at the start of follow-up was 22 days of life. They presented Classic Phenylketonuria 6 patients (54.55%), moderate 1 patient (9.09%) and mild 4 patients (36.36%). The growth and size in all patients were according to the reference population. Metabolic control was adequate in 8 patients (72.73%). Breastfeeding at 6th months was in 9 patients (81.82%) and only in 1 at 2 years (14.29%).
CONCLUSION: The weight, height and head circumference were according to the reference population. In older than 2 years, the size was according to parents height ranges. In all patients with phenylketonuria growth in height was normal.

P-160 - EVALUATION OF THERAPEUTIC RESPONSE TO SAPROPTERINE DICHLORIDRATE FROM A GROUP OF FENILCETONURIC PATIENTS CARRIED OUT OF THE EXTENDED NEONATAL DISTRICT SERVICE IN THE FEDERAL DISTRICT

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INTRODUCTION: Phenylketonuria (FNC) is an inherited disorder of phenylalanine metabolism (Phe), characterized by a loss of hepatic phenylalanine hydroxylase (PAH) function, limiting the hydroxylation of Phe to tyrosine (Tyr), using tetrahydrobiopterin as a cofactor. Sapropterine dihydrochloride, the pharmaceutical version of 6R-tetrahydrobiopterin (6R-BH4), increases its residual activity in sapropterin-responsive phenylketonurons and, together with dietary control, helps to reduce Phe concentrations.
GOALS: To present the profile of the patients participating in the test and the percentage of responsiveness to sapropterin dihydrochloride.
MATERIALS AND METHODS: Ten samples were collected on filter paper from 12 patients on the drug for 28 days, two basal samples and two weekly samples. The Phe evaluation method was tandem mass spectrometry, using reference values between 2-6mg / dl and a cutoff value of 1.0 mg / dl to increase dietary Phe intake. Sapropterin was started after the second basal collection, at a dosage of 10mg / kg. After one week, the dose increased to 20mg / kg. Patients were evaluated weekly for drug tolerance, blood Phe and dietary Phe intake.
RESULTS: The mean age was 13 ± 4 years, being 58% female and 42% male. All patients are classical phenylketonuric by oral tolerance of Phe. The weight variation was 0.9 ± 1.4 kg. Of the participants, 58% responded to sapropterin, with a mean baseline Phe of 6.2 ± 3.5 mg/dl and a final of 4.4 ± 2.1 mg/dl. The mean Phe reduction in responders was 38.1% and that of the increase in TYR was 7%. Of the respondents, 03 presented reduction of TYR by 20%. There was no discontinuity in the use of medication due to adverse effects, showing good tolerance of the studied group.
DISCUSSION: The characteristics of the patients were considered in the interpretation of the results. There was good tolerance to the drug and an average response compatible with the international literature. Some genotypes are predictive of responsiveness and responsiveness is associated with specific alleles, so an unfolding of this study is needed to improve understanding of how FNC mutations influence PAH dynamics and increase understanding of the disease and its management.

P-161 - URINARY ORGANIC ACIDS CHROMATOGRAPHY ANALYSIS ON FILTER-PAPER IN PKU: AN ALTERNATIVE APPROACH IN THERAPEUTIC MONITORING OF SAPROPTERIN DIHYDROCHLORIDE RESPONSIVENESS?

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BACKGROUND: Sapropterin dihydrochloride is the synthetic form of tetrahydrobiopterin, the cofactor for the phenylalanine hydroxylase enzyme. Approximately 50% of patients with phenylalanine hydroxylase deficiency, also referred to as phenylketonuria (PKU), are responsive to sapropterin as evidenced by a clinically significant decrease in blood phenylalanine levels and/or an increase in dietary phenylalanine (PHE) tolerance
OBJECTIVE: To present a practical approach in therapeutic monitoring of a PKU patient being treated with sapropterin dihydrochloride
MATERIALS AND METHODS: Retrospective biochemical data review of phenylalanine levels measured in blood and urinary organic acids chromatography performed on filter-

paper and total urine (pre and post-trial of sapropterin dihydrochloride) in a Brazilian PKU patient (also affected by type 1 diabetes mellitus)
RESULTS: Markedly reduction of phenylpyruvic acid, phenylacetic acid and phenyllactate in urine were seen after 24-hours after sapropterin dihydrochloride introduction (20mg/kg/day) and remained reduced after one month of therapy. There was correlation between PHE levels decrease and better organic acids profile, however PHE blood levels showed greater variation in differents measurements in comparison to phenylpyruvic and phenylacetic acids levels that remained stable after reduction. Ketonuria was also observed after one month therapy, possibly reflecting poor diabetes mellitus control.
CONCLUSIONS: Although PHE levels and the phenylalanine/tyrosine ratio in blood have been the gold standard for diagnosis and follow-up of PKU patients, urinary organic acids gas chromatography/mass spectrometry (GC/MS)-based analysis may be a potential adjunctive tool to assess sapropterin dihydrochloride-responsiveness on a less invasive way, showing other biomarkers to further delineate biochemical findings in both treated and non-treated PKU patients.

P-162 - DISORDER OF TETRAHYDROBIOPTERIN CAUSED BY DEFICIENCY OF DIHIDROPTERIDINE REDUTASE (DHPR)

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INTRODUCTION: Hyperphenylalaninemias are manifestations of metabolic errors usually related to amino acid metabolism. Five defects that can lead to hyperphenylalaninemia are known: one in the enzyme phenylalanine hydroxylase, causing phenylketonuria, and in four enzymes involved in the synthesis or regeneration of tetrahydrobiopterin (BH4), an enzymatic cofactor involved in the synthesis of dopamine, serotonin, tyrosine, nitric oxide and glycerol.
BH4 deficiencies account for approximately 2% of cases of hyperphenylalaninemia with a worldwide prevalence of 1/1,000,000 live births and are designated according to underlying enzyme deficiency and may lead not only to hyperphenylalaninemia states but also to neurological symptoms and signs of neurotransmitter deficiency. These disorders promote a progressive deterioration of the neurological function, and cannot be avoided by phenylalanine restrictive diet alone.
OBJECTIVE: Case report of a patient with DHPR deficiency, presenting difficult diagnosis and therapeutic limitation with severe clinical and laboratory neurological alterations.
MATERIALS AND METHODS: This information was obtained by means of a medical record review, interview with the patient's parents, physical examination of the child, photographic record of neuroimaging, and literary review using Medline / Pubmed and specialized literature.
RESULTS: JPS, 7 years, consanguineous parents.
Prenatal and delivery without complications. Normal exams.
Onset symptoms at 2 months of age - seizures, start of anticonvulsant. Normal MRI.
1 year: significant delay in psychomotor development. Change RM
Definitive diagnosis: 1 year and 5 months. Brain CT showing absence of cerebral calcifications.
Specific treatment inception: 1 year and 5 months: L dopa / carbidopa and low doses of folinic acid due to adverse reactions, reaching ideal doses and association with 5 hydroxytryptophan with 1 year and 7 months. Sapropterin dihydrochloride (KUVAN) - important adverse reactions, therapeutic limitation. 6 years old MRI with typical signs of deposit leukoencephalopathy and severe DNPM changes even with specific treatment.
CONCLUSIONS: The reported case and other publications reveal the rarity of studies related to this pathology, the scarcity of methods of early diagnosis, besides evidencing the late institution treatment consequences and the current therapy limitation, with severe damage to the patient's psychomotor development.

P-163 - 48 HS BIOPTERIN TEST IN PKU. ADECUATE NUTRITIONAL PREPARATION

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INTRODUCTION: Dietary treatment with a phenylalanine (phe) restricted diet from newborn period and long life sustained is successfully in PKU. However, adherence to strict diet decreased over the years. Some PKU patients respond to pharmacological doses of tetrahydrobiopterin (BH4). Different tests have been developed to select the responsive patients. Our main experience is with short-term 48 hs test. A correct interpretation of these tests, need an increase of blood phe level between 6-8 mg/dl through diet. Patients and family concern and professional disregard of actual phe tolerance, allow misinterpreting test results.

OBJETIVES: Prove that an individual plan of feeding with fixed amounts of phe and menus which was previously agreed with family and patient allows more reliable test results; standardized diet maintained all the test long.
Recalculate phe tolerance of patients.
METHODS AND MATERIAL: An observational and retrospective study was performed. 29 patients were tested with BH4, using the 48-h test according Blau.
Tests were divided in 2 groups. Group A composed by 18 patients from 2011-2013 with no standardized diet previous test. Group B composed by 11 patients from 2014 to 2018 with standardized diet.
Phe tolerance is defined as the amount of phe (mg/day) that maintains blood phe concentrations within the target range. Tolerance was compared between the estimated previous test and after six months of BH4 tests.
Statistical analysis was performed with SPSS Statistics 18. From each patient, the coefficient of percentage variation was calculated to compare the variability of the Phe dosages performed on the initial day. The differences between groups were evaluated by a Mann-Whitney test.
RESULTS: Group B showed a minor variability, statistically significative (p-value=0.043) in relation to day 0 of the test (without BH4).
72% of patients were over restricted before test and showed a higher tolerance after the test, even in patients continuing with diet only.
CONCLUSIONS: Standardized diet allowed a minor variability of basal levels of phe, which is essential for assessing impact of BH4 on phe levels. Time and difficulties of reaching adequate phe values prior test was caused by over-restriction of diet.

P-164 - BIOCHEMICAL AND CLINICAL DIAGNOSE OF AMINOACIDOPATHIES AND ORGANIC ACIDURIA IN CUBA

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INTRODUCTION: The Inborn Errors of Metabolism (IEM) are biochemical disorders caused by gene mutations and several consequences in metabolic pathways. The aminoacidopathies and organic acidurias are two genetic diseases with severe clinical features and several affected systems. In Cuba, only hyperphenylalaninemias are include in the neonatal screening program. So, the biochemical diagnosis of other IEM is performed after the appearance of suggestive clinical manifestations.
OBJECTIVES: The aim of this work is to perform the biochemical diagnosis of amino acid and / or organic acidurias in patients with clinical suspicion and to determine the frequency of risk in the population studied.
MATERIALS AND METHODS: A selective investigation was realized in Cuban patients under 12 years of age with clinical manifestations suggestive of an IEM during the period 2014-2018. We analyzed samples of serum and urine from 107 patients and 23 cerebrospinal fluid (CSF). The urine samples were subjected to qualitative chemical tests, thin-layer chromatography for amino acids and the profile of organic acids by GC/MS. The samples of serum and CSF were evaluated by thin-layer chromatography for amino acids and the quantification of the amino acid profile by HPLC.
RESULTS: The suggestive biochemical diagnosis was made in 22 patients: 3 patients with maple syrup urine disease (MSUD), 7 patients with non-ketotic hyperglycinemia (NKH), 4 patients with hyperglycinemia secondary to an organic aciduria (1 isolated methylmalonic aciduria, 1 propionic aciduria, 1 pyruvate dehydrogenase deficiency and 1 dihydrolipoyl dehydrogenase deficiency), 3 patients with hyperglycinemia secondary to a fatty acid oxidation, 1 patient with ornithine aminotransferase deficiency (OAT), 1 patient with tyrosinemia type I, 2 patients with deficiency of methionine metabolism and 1 deficiency of methionine metabolism secondary to congenital disorders glycosylation (CDG). The risk frequency of these diseases was 20.6 % in Cuban studied population.
CONCLUSIONS: During the period evaluated, the biochemical diagnosis of aminoacidopathies and organic aciduria was performed in Cuban patients; and the frequency of risk was estimated.

P-165 - REFERENCE INTERVALS OF THE SERUM AMINO ACID PROFILE IN CUBAN CHILDREN.

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INTRODUCTION: Amino acids are organic compounds and biomarkers of error innate of metabolism and nutritional state. Reference values (RI) are an interval specified in the distribution of values obtained from healthy individuals of population. The establishment of RI is essential for clinical laboratory test interpretation. We validated an HPLC method for quantification of fourteen amino acids in serum in National Center of Medical Genetics. The amino acid values vary according to age, nutritional status and dietary habits in

population. In Cuba, the RI of amino acids are unknow in children.
OBJECTIVE: The aim of this work is to estimate the reference values of serum amino acids profile in Cuban children by HPLC.
MATERIALS AND METHODS: Serum samples from healthy children were analyzed (n = 154); two groups were distributed: Group 1: 1 day-4 months (n = 73) and Group 2: 2-7 years (n = 81). We analyzed the follow amino acid: Ser, Gly, His, Thr, Ala, Pro, Arg, Tyr, Val, Met, Ile, Leu, Phe and Lys. There were performed by a validated HPLC method, with pre-column derivatization, in reverse phase and detection at 254 nm. The Statistic 7.0 program was used for the statistical analysis. The RI were estimated from the calculation of the 2.5th and 97.5th percentiles.
RESULTS: We found differences between amino acid levels in both age group. Several factors such as age, diet, protein intake should be associated with these differences. Besides, each amino acid plays biological functions in the different stages of neurodevelopment and growth of the child.
CONCLUSION: The RI of the serum fourteen amino acids in Cuban children were established by HPLC METHOD: So, we will use these normal values for the diagnosis and biochemical follow up of congenital aminoacidopathies.

P-166 - PATIENTS WITH TYROSINEMIA TYPE I TREATED AT A HIGH COMPLEXITY PEDIATRIC HOSPITAL IN ARGENTINA: A RETROSPECTIVE STUDY

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INTRODUCTION: Hereditary tyrosinemia type 1 (HT1) is a rare inborn error of tyrosine metabolism which can be a fatal disorder without treatment. Early treatment may prevent acute liver failure, renal dysfunction, liver cirrhosis, hepatocellular carcinoma (HCC) and improves survival. Neurocognitive development can be impaired in some cases but the reason remains unclear.
OBJECTIVES: To characterize clinical and laboratory features present at diagnosis and follow up in a cohort of patients HT1. To describe the appearance of complications.
PATIENTS AND METHODS: We reviewed medical records (January 1990-June 2018) of 10 patients diagnosed and/or followed at Garrahan hospital.
RESULTS: From 10 patients, two were born before nitisinone became available and died from HCC. One received liver transplant.
Six patients had a family history of dead siblings. Median age at symptoms was 6 months (1-36), median age at diagnosis was 8.5 months (4 days-40m).
The clinical features at diagnosis included: liver (4), renal tubular dysfunction (4), acute liver failure (4), hepatic tumors(5), cardiomyopathy (2) and none (1). Median values of alpha-fetoprotein were 151309.5 ng/ml (range 23703-1499489) and normalized within the first year of therapy (except in 3 patients). Median follow up time were 10.5 years(5 months-16 years). Average delayed nitisinone treatment was 3 months (0-5m).
The other patient who underwent liver transplant for suspected HCC at 1 year has good outcome with renal involvement 6 years later.
The most common long term complication was impaired neurocognitive development. Evaluations of CI Wechsler Intelligence Scale for Children (WISC-IV) were administered to 5 NTBC treated children and one liver transplanted. IQ values ranged from mild-borderline and 3 patients without formal evaluation exhibited learning difficulties. We correlated with phenylalanine/tyrosine concentrations.
CONCLUSIONS: Treatment with nitisinone has improved survival rate of HT1. Treatment with nitisinone after two months of life is associated with cirrhosis and/or HCC. Three patients who received nitisinone before two months of life have not complications yet.
At long-term follow-up, most patients showed cognitive impairment. This highlights the importance of regular cognitive assessments at school entry and at later intervals. Prospective studies are required to characterize neurocognitive outcomes.

P-167 - LYSINURIC PROTEIN INTOLERANCE: INVESTIGATIVE PROCESS AND DESCRIPTION OF A NOVEL VARIANT IN SLC7A7 GENE

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INTRODUCTION: Lysinuric protein intolerance (LPI) or hyperdibasic aminoaciduria type 2 is an ultra rare inborn error of metabolism with autosomal recessive inheritance characterized by deficiency in the dibasic amino acid transporter (SLC7A7). The most prevalent symptoms are intestinal malabsorption, hyperammonemia, vomiting and hepatosplenomegaly. The diagnosis is made by detecting increased urinary excretion of lysine, arginine and ornithine, reduced plasma lysine, postprandial hyperammonemia, hyperferritinemia and dyslipidemia. Maintenance treatment involves protein restriction and citrulline administration.
OBJECTIVE: To describe clinical and molecularly the investigation steps of a complex clinical case that led to diagnosis of LPI. Informed consent was obtained.
CASE REPORT: A 11-year-old female patient born to consanguineous parents was referred for genetic evaluation

due to suspicion of glycogen storage disease (GSD). At 6 months, she started investigation due to progressive hepatosplenomegaly, growth restriction, chronic diarrhea, protein aversion, vomiting and recurrent otitis. At age 5, liver biopsy was compatible GSD and, even without hypoglycemia, GSD treatment had been instituted. She performed molecular and radiological investigation for hemochromatosis, with no evidence of iron deposition. At age 9, she presented muscular fatigability and reduced muscle trophism, and had a pathological tibial fracture secondary to osteoporosis. Laboratory tests revealed hyperferritinemia (levels greater than 1000ng/mL), dyslipidemia and mild hyperlactacidemia; investigation for lysosomal diseases was normal; amino acid dosage showed increase of alanine and glutamine and reduction of lysine. Urinary dosing was performed, with a significant increase of lysine, alanine and glutamine, associated with increased postprandial ammonia, confirming LPI. Complete sequencing of SLC7A7 gene identified the biallelic novel variant c.1109_1133del (p.Leu370Serfs*141).
DISCUSSION AND CONCLUSION: In the presence of complex clinical phenotypes that involve short stature, specific food aversion and somatic signs, it is important to establish the hypothesis of a hereditary metabolic disease, even considering its rarity. The definitive clinical and biochemical diagnosis is fundamental to terminate a prolonged diagnostic search and to allow adequate management and genetic counseling. LPI is an ultra rare inborn error of metabolism, but with possibilities of treatment and excellent clinical response, preventing consequences of the disease. Molecular investigation also led to description of a novel variant in SLC7A7 gene.

P-168 - DELAY IN THE DIAGNOSIS OF INTERMEDIATE FORM OF MAPLE SYRUP URINE DISEASE AND ITS GLOBAL REPERCUSSIONS: A CASE REPORT

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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 (BCKAD), which results in elevations of the branched-chain amino acids (BCAAs) in plasma, α-ketoacids in urine, and production of the pathognomonic disease marker, alloisoleucine. The disorder varies in severity and the clinical spectrum is quite broad with five recognized clinical variants that have no known association with genotype. The intermediate form of MSUD is characterized by up to 30% of BCKAD residual activity. These individuals may appear healthy during the neonatal period, although maple syrup odor in cerumen may be present. During the first years of life, they may experience feeding problems, poor growth, and intellectual disability, and are susceptible to similar neurologic features as individuals with the classic form.
OBJECTIVE: To report a case of intermediate form of MSUD diagnosed only after two years of progressing symptoms.
METHODOLOGY: A retrospective study was conducted. Clinical data were collected through the patient´s medical record.
RESULTS: A two-and-a-half-year-old male, born from a young, healthy and non-consanguineous couple started with progressive hypotonia, feeding problems and poor interaction at the age of 4 months. Developmental delay and stereotypical movements became even more evident during the second year of life. He still cannot walk and has severe language delay. After normal initial exams (Karyotype, Creatine Kinase-CK, skull CT scan, echocardiogram, etc) he was referred to Medical Genetics evaluation. Quantitative plasma amino acid analysis showed an increase of leucine, isoleucine and valine, confirming MSUD diagnosis. Genetic Counseling was then offered and dietary treatment was introduced with a mild positive response.
CONCLUSIONS: Unfortunately newborn screening for MSUD is not avaliable in Brazil´s public health system. Therefore, Brazilian pediatricians and neuropediatricians should be alert to MSUD possible diagnosis in young children with development delay.

P-169 - CHARACTERIZATION OF A COLOMBIAN POPULATION WITH AMINO ACID DISORDERS AND ORGANIC ACIDURIAS TREATED BETWEEN 2009 AND 2018.

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Neonatal screening is the tool used to identify serious metabolic diseases of newborn in which is known that early diagnostic and timely metabolic-nutritional management make the difference in the course of the disease preventing complications and even the dead. However, in Colombia, neonatal screening is not a public policy and patients affected are being detected so late, sometimes when complications appear.
Interdisciplinary work of Metabolic Therapies (MT) in last 8 years, besides the attention of these patients, has been aimed at educating and sensitizing health professionals to suspect metabolic diseases and prevent their complications (with metabolic-nutritional interventions) as soon as possible. This study is a first very simple approximation to knowledge the situation of Colombian metabolic patients.

Since 2009 MT has treated 194 patients, more common diseases: homocystinuria (HCYS), 48 patients, glutaric aciduria (GAC), 29 and organic acidemias (OA: MMA-PA), 24. 6y is median age of diagnostic [1,4y for maple syrup urine disease (MSUD) to 15y for HCYS]; methods of diagnostic more used are: quantification of amino acids in plasma, 35, blood and urine amino acids, 26 and HPLC, 12; 20 patients had genetic tests that confirmed their diagnosis and 14 that discarded it, 28 are pending of confirmation; 37 have died (19%). Median of age of onset of treatment is 5y (0.1y to 21.8y), 29% started treatment before 1y. Median of time in treatment is 124 months (21 to 288). The compliance is 80%, reasons to avoid the treatment are: disease is discarded, administrative procedures to achieve the formula and by rejection of the formula's flavor.
Now, 45 patients in treatment, 27% women, median age 9,3y (2,9 to 26,6) and diagnoses: GAC (27%), HCYS (18%), PKU (16%), MSUD (13%), OA (11%), DUC (7%), Isovaleric acidemia (4%), 3 β ketolase deficiency (2%) and 3 hydroxy 3 methyl glutaric aciduria (2%). Median of BMI (WHO) -1,14 to 0,18 before and after treatment.
CONCLUSION: While is approved the neonatal screening in Colombia, sensitization to medical teams is a fundamental task of those who are dedicated to the treatment of IEM in order to change positively the course of these diseases.

P-170 - NUTRITIONAL MANAGEMENT AND OUTCOMES OF TYROSINEMIA TYPE I PATIENTS IN A PEDIATRIC REFERENCE CENTER IN ARGENTINA

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INTRODUCTION: Hereditary tyrosinemia type I (HT1) is an autosomal recessive disorder caused by deficiency of fumarylacetoacetase (FAH), the last enzyme of tyrosine degradation. The treatment consists of inhibition of the formation of toxic metabolites by nitisinone and reduction of tyrosine levels through dietary treatment.
OBJECTIVE: To report the dietary treatment and experience of HT1 patients in follow up at Garrahan Hospital.
MATERIAL AND METHODS: A review of 6 patients (4 female and 2 male) with diagnosis of HT1 by classic biochemical and clinical characteristics in follow up. Plasmatic amino-acids(AA), alpha-fetoprotein, succinylacetone were monitored every 6 months as well as liver and kidney ultrasound and magnetic resonance imaging for the detection of nodules. Anthropometric measurements (weight, length, BMI) and dietary intake (3 days' food record) were analyzed at last control data. Detailed dietary intake of phenylalanine plus tyrosine (phe+tyr) and protein content from phe+tyr free amino acid formula (AA formula) were analyzed.
RESULTS: Median age at diagnosis: 3.5 months; 2 patients were diagnosed after sibling death. Normal growth was achieved (3 overweight/obese). Actual median age: 8.9 years (1.6-16)
All patients received AA formula, phe+tyr restricted diet and administration of nitisinone.
Dietary intake analysis: Phe+tyr: 655 ± 274 mg/day, protein from AA formula: 1.3 ±0.3 g/kg
16% (n=1) of the patients presented normal plasmatic tyrosine levels while 83% (n=5) still had high levels at last control. Alpha-fetoprotein levels remained stable in 5 patients, except 1 who started treatment last year
CONCLUSIONS: Most patients have acceptable metabolic control and up to present have not presented complications. It is difficult to maintain plasmatic tyrosine levels within normal range, proving especially challenging in adolescent period when compliance usually decreases. In order to ensure best care of these patients it is important to schedule regular appointments with them, their family and the multidisciplinary metabolic team.

P-171 - ALKAPTONURIA: NOT AN "ADULT DISEASE" ANYMORE – EARLY DIAGNOSIS FOR EARLY TREATMENT IS ESSENTIAL

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INTRODUCTION: Alkaptonuria is a rare metabolic disorder caused by mutations in the HGO gene leading to deficiency of homogentisate 1,2-dioxygenase enzyme. It results in an accumulation of homogentisic acid (HGA) which oxidizes spontaneously to benzoquinone acetate, a highly oxidant compound, in an process called ochronosis.
OBJECTIVES: To report two patients with alkaptonuria and their different outcomes
METHODS: Clinical, biochemical and imaging data retrospective analysis of two Brazilian patients with Alcakaptonuria diagnosed in different clinical settings
RESULTS: Patient 1, male, nine years old referred for evaluation of "congenital porphyria" due to abnormal urine staining observed in his dipers since 1 year and 6 months. At 3 years of age, the diagnostic was confirmed by detection of massive increase of homogentisic acid (HGA) in urine. Molecular examination was later performed, showing compound heterozygous mutations in HGO gene. Patiend did not show any findings of skin ochronosis. Further assessment of the patient with abdominal ultrasound, echocardiogram,

kidney function revealed early mitral valve thickening.Patient 2, male, 71 years old referred with 66 years for evaluation of peripheral neuropathy. Initial symptoms were pain and stiffening of the fingers with slow progression, associated with paresthesia (in median nerve territory) and Raynaud phenomena. In this period, were noted hyperchromic punctate lesions on the first and second fingers. His physical examination showed black hyperchromic spots on hands, face, ears, and sclera of both eyes. Patient was unable to walk anymore due to severe hip dysplasia (had bilateral prosthetic hip and knee replacement in the past). Eletroneuromiography was compatible with severe bilateral carpal tunnel syndrome and magnetic resonance imaging of wrists showed bilateral tendon ruptures. Diagnosis was confirmed with HGA elevation in urine.Further assessment showed aortic insufficiency of moderate degree and both colelithiasis and nephrolithiasis.
CONCLUSIONS: Alkaptonuria, also called endogenous ochronosis, is a rare metabolic autosomal recessive disease, which affects 1: 1,000,000 live births. A potential treatment with nitisinone has been proposed, because it inhibits the enzyme 4-hydroxyphenylpyruvate dioxygenase and decreases formation of HGA. Early disease recognition is necessary to better start patients follow-up and discuss therapeutic possibilities before irreversible organ damage.

P-172 - EXPERIENCE IN MANAGEMENT OF HEREDITARY TYROSINEMIA TYPE 1 IN A REFERENCE HOSPITAL OF PERU

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INTRODUCTION: Tyrosinemia type 1 (HT1) is an inborn error of tyrosine catabolism caused by the defective activity of fumarylacetoacetate hydrolase with progressive liver disease, renal tubular dysfunction and peripheral neuropathy. The estimated birth incidence is 1:100,000 worldwide. Treatment with oral nitisinone has notably improved prognosis and life expectancy.
OBJECTIVES: To describe 2 cases of tyrosinemia type 1 successfully treated in Peru.
MATERIALS AND METHODS:We present two cases of HT1 managed at Rebagliati Hospital of Lima, Peru.
RESULTS: Case 1: A 11-month infant, first child of healthy non-consanguineous parents. Born by cesarean section due to fetal macrosomia (4334g). Appropriate psychomotor development until sixth month. Since seventh month he had recurrent hypoglycemia, hypotonia and failure to thrive. It was noticed hepatomegaly, humeral fracture, rickets, and motor delay. It was found markedly high alpha-fetoproteins (AFP) (148, 912 ng/ml), altered liver profile, increased plasma tyrosine and methionine and high urine succinylacetone (423 ug/mg creatinin). At 13th month, it was started treatment with oral nitisinone at dose 1 mg/kg, protein-restricted diet and a medical formula. It was observed improvement of growth and psychomotor development and urinary succinylacetone got normal.AFP values decreased but did not reach normal ranges. It was performed liver transplantation due advanced cirrhosis and suboptimal response to treatment.
Case 2: A 10-month infant, fourth child from consanguineous parents, with positive family history of HT1 in two older sibs, one died from severe liver failure, and the other was underwent to a liver transplantation. He was born by normal delivery, weighted 3750g, had normal psychomotor development. He was referred because of hepatomegaly, AFP 185,000 ng / ml; high plasma tyrosine and elevated urine succinylacetone levels (39.7 mg/g UCr). Ultrasound reported chronic liver disease. At 11 months old, it was started oral nitisinone at dose 1mg/kg, protein-restricted diet and medical formula. Improvement of hepatomegaly and alpha-fetoprotein level was observed. Currently he continues on treatment with favorable evolution.
CONCLUSIONS: This is the first experience of management of HTI in Peru.
Following an adequate treatment, patients diagnosed with HT1 who were referred to the Rebagliati Hospital of Lima Peru have been successfully recovered.

P-173 - SLEEP DISORDERS CHARACTERIZATION OF CLASSICAL HOMOCYSTINURIA IN PEDIATRIC PATIENTS FROM THE REFERENCE CENTER OF BAHIA, BRAZIL

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INTRODUCTION: Classical Homocystinuria (HCU), an autosomal recessive inherited disorder, worldwide prevalence estimated in 1: 900.000 to 1: 1.800. Sleep disorders are common and affect sleep quality and quantity, leading to increased morbidity.
OBJECTIVE: To describe a serial of individuals diagnosed with HCU followed in a reference center in Salvador, Bahia, Brazil and their sleep disorders. METHOD: Observational, descriptive study, from data review of patients with HCU biochemical diagnosis followed in a reference center. Three types of questionnaires were applied to identify sleep disorders: the Sleep Disturbance Scale for Children (SDSC), range from 26 to 130 with a cut-off point of 39 that

characterizes sleep disturbance; the Epworth Sleepiness Scale (ESS) to measure the daytime sleepiness, score >10 points indicates sleepiness; and the Conners' Scale short Form to suspect of hyperactivity disorders with a score ≤ 12 to girls and score ≤ 17 to boys as a positive finding.
RESULTS: Three pediatrics patients with HCU. Patient 1, male, onset age 3y, diagnostic age 8y, current age 12y, presents EKG alterations, crystalline dislocation, spinal deformities, marphanoide appearance, cave foot, behavioural problems, and intellectual disability. Patient 2, male, onset age 4y, diagnostic age 4y, current age 8y, presents EKG alterations, severe myopia, spinal deformities, behavioural problems, intellectual disability. Patient 3, female, onset age 3y, diagnostic age 4y, current age 5y, presents severe myopia, crystalline dislocation. The molecular diagnosis indicated a mutation in homozygosis, the p.W323X/p.W323X, non-responsive to pyridoxine supplementation to all patients. The 3 pediatric patients have family positive cases of HCU, only the Patient 3 has parental consaguinity. The SDSC questionnaire observed that the score of Patient 2 and Patient 3 were the following values 34 and 33, respectively, while Patient 1 presented value = 54, above the cutoff point, characterizing the sleep disorder. Though Abridged Conners Scale, Patients 2 and 3 presented the values = 5 and 12, respectively. While Patient 1 presented value = 21, characterizing hyperactivity. In this study, no change was found on the Epworth scale.
CONCLUSION: The present study draws attention to the the medical geneticist over suspicion about the presence of sleep disorders which are pervasive in HCU.

P-174 - GENOTYPE-PHENOTYPE CORRELATION IN BRAZILIAN PATIENTS WITH CLINICAL DIAGNOSIS OF CLASSICAL HOMOCYSTINURIA

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Classical homocystinuria (HCU) is an autosomal recessive inborn error of metabolism, caused by a deficiency of the enzyme cystathionine β-synthase (CBS). This deficiency results in the elevated plasma levels of homocysteine and methionine and the most common clinical manifestations are dislocation of optic lens, mental retardation, skeletal deformities, and thromboembolism. The correlation between disease severity and genotype is still not well established. The aim of this study was to correlate genotype with phenotype in 22 Brazilian patients (19 families) with the clinical diagnosis of HCU.
RESULTS: The molecular analysis revealed eight known pathogenic mutations in the CBS gene described as causing HCU and two novel mutations non-pyridoxine responsive (G351R and L364V). All presented variations were classified according to ACMG guidelines and for the frequency of variants in the Brazilian population the Online Archive of Brazilian Mutations (ABraOM) was used. The most frequent mutation in our sample was G151R (seven patients). The phenotype was classified as severe (B6 non-responsive) and mild (B6-responsive). Patients who developed any new VTE and worsening of lens dislocations were classified in bad prognosis group (BPG), all the others were classified in good prognosis group (GPG). We used the software Prism 5.0, Graph Pad (San Diego, CA) and Mann-Whitney test to assess whether the difference in tHcys levels between two groups (GPG/BGP) was significant ($p < 0.05$). The patients on GPG presented the median tHcy level of 42±4 μmol/L (n=13) and patients on BPG, the median of 181±70 μmol/L (n=7) for years in treatment. The genotype-phenotype correlation for known mutations I278T, G151R, T353M, T191M, W323*, E302K, R379W, and R266K is in accordance with the literature. Gathering our data to all reports in the Brazilian population, G151R becomes the most frequent allele (n=20), followed by I278T (n=19), T191M (n=16) and W323* (n=14).
CONCLUSION: In summary, considering these findings, we characterized molecularly and clinically Brazilian patients with a late diagnosis of HCU and contributed to the disease genotype-phenotype classification with clinical outcome of years in classical HCU treatment.

P-175 - CAN THE TREATMENT OF CLASSICAL HOMOCYSTINURIA PATIENTS BE ASSOCIATED WITH THE DIVERSITY OF GUT MICROBIOTA?

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INTRODUCTION: Classical homocystinuria (HCU) is an inborn error of metabolism (IEM) with a combination of different treatments (formula, vitamins and diet) which varies

according to the needs of each patient. Diet and treatment are known to modulate the gut microbiota, which is currently associated with the host's health.
OBJECTIVES: To characterize the gut microbiota of a sample of HCU patients on treatment, by next-generation sequencing, and compare it with healthy individuals.
MATERIALS AND METHODS: Observational, cross-sectional, controlled study with convenience sampling. Stool samples were collected from 7 HCU patients on treatment from IEM Clinics of Hospital de Clínicas de Porto Alegre, Rio Grande do Sul (RS), Brazil and compared with 7 sex and age matched unrelated healthy controls, recruited among RS population. Clinical information was obtained from patients' medical records. Nutritional assessment was performed from 3-day food record and 24-hour food recall through the Nutribase™ Software. Bacterial DNA was extracted and evaluated through partial V4-16S rRNA gene sequencing (PGM Ion Torrent™ System) according to the recommendations of the Brazilian Microbiome Project. Microbiota structure was analyzed through MicrobiomeAnalyst online software. Statistical analysis between groups was performed through IBM SPSS Statistics software. The study was approved by the ethics committee of HCPA (n. 15-0218).
RESULTS: Among patients, there were different treatments: methionine-restricted diet (n=6/7); metabolic formula (n=4/7); pyridoxine (n=6/7); vitamin B12 (n=3/7); folic acid (n=6/7) and betaine (n=4/7). The daily intake of total fat (p=0.015), saturated fat (p=0.002), monounsaturated fat (p=0.008), cholesterol (p=0.004) and vitamin D (p=0.002) was lower in patients. HCU patients had higher Alpha-diversity, presenting increased richness of communities to Observed (p=0.017) and Chao1 (p=0.017) indexes. Shannon index displayed no difference (p>0.999). HCU patients and controls also differed in bacterial communities for Beta-diversity based on Principal Coordinates Analysis (PCoA) for PERMANOVA (r^2=0.202. p<0.026) and ANOSIM (r=0.464. p<0.026) measures.
DISCUSSION: HCU treatment is related to diet and vitamin supplementation, mainly B-complex, which plays an important role in bacterial and host metabolism. Despite the small sample size, the results revealed a potential relationship between treatment and bacterial diversity.
CONCLUSION: The HCU patients showed high diversity in bacterial communities than the healthy controls.

P-176 - DIAGNOSIS AND FOLLOW-UP OF PATIENTS WITH UREA CYCLE DEFECTS. REPORT OF LOCAL EXPERIENCE

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INTRODUCTION: Urea cycle disorders (UCD) are inborn errors of ammonia detoxification/arginine synthesis. The onset and severity of UCD, caused by hyperammonaemia, is highly variable; this depends on the specific mutation involved and correlates with the residual enzymatic function. The exact incidence of UCDs in Argentina is not known due to absence of newborn screening or a registry. Most of the patients are detected symptomatically, adding to high morbidity and mortality.
OBJECTIVE: To present a local experience in diagnosis, molecular findings and outcome of UCD patients from Argentina.
MATERIALS AND METHODS: Biochemical methods included determination of plasma and urinary amino acids and orotic acid through HPLC; quantification of plasma ammonia by spectrophotometry; genetic study consisted in PCR, restriction enzyme digestion assays or direct sequencing, SSCP or MLPA.
RESULTS: We present data from a single centre in Argentina, including 49 UCD cases. Most of them (26/49, 53%) presented in the neonatal period with classical presentation, and had a high mortality (25/26, 96%). Ornithine transcarbamylase (OTC) deficiency was the most common UCD, observed in 26/49 patients, with privative OTC gene mutations. Argininosuccinatesyntethase (ASS) deficiency was the next most common, seen in 19 cases, most of them from a populational cluster of CTLN1 with the same mutation. Argininosuccinate lyase (ASL) deficiency was diagnosed in 4 cases presenting worldwide recurrent missense changes. We observed a poor clinical outcome after an hyperammonemic crisis with an overall all time mortality of 57% (28/49 cases), and disability in 28% (6/21) among the survivors. The average detection rate calculated in our center is 4 new UCD patients per year, 30% of what is expected per year in Argentina.
CONCLUSIONS: The majority of patients in our serie showed neonatal severe onset, with a high mortality/morbidity. The presence of a geographic cluster of high prevalence of a point mutation in ASS is highlighted. This report shows our experience in the genetic characterization of UCD and notes that these disorders are not rare but need of awareness and diagnostic tools for accurate identification, which will lead to improve outcomes through early diagnosis and timely treatment.

P-177 - SINGLE CASE REPORT: ABNORMAL MOVEMENT DISORDER AND CEREBRAL MRI CORRELATION IN NEONATAL CITRULLINEMIA TYPE I

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INTRODUCTION: Citrullinemia type I is an autosomal recessive disorder caused by argininesuccinate sintetase deficiency (ASS1D). ASS1D is the second most common urea cycle disorder (UCD) and it has a variable clinical phenotype. Although movement disorders are described in UCD, with some exceptions (arginase deficiency), these are uncommon.
OBJECTIVES: We describe the clinical case of a patient with citrullinemia diagnosed at birth [compound heterozygote: c.970G>A(Missense)/c.601C>T(Nonsense)], with a history of a deceased brother in the neonatal period. There was a correlation between the clinical evolution and the cerebral MRI findings.
MATERIALS AND METHODS: Review of the clinical records, including laboratory results, amino acid profile and cerebral MRI findings, at diagnosis and during follow up, from birth to 6 years of age.
RESULTS: Since he was approximately 5-6 months of age, the patient evolved with a severe generalized dyskinetic-dystonic movement disorder of insidious onset. Nevertheless, he achieved an independent gait. Borderline cognitive profile with language skills mostly affected (IQ: 74).
Brain MRI performed at 6 years of age showed bilateral and symmetric hyperintense signals in T2 and FLAIR in the globus pallidus. No significant metabolite disturbance observed in spectroscopy. While diffuse posterior white matter involvement was observed in the first MRI (1month), there was no evidence of basal ganglia injury.
First ammonia control was 272 uMol/L (16h of life). Adequate response to initial management. During the first 50 days, ammonia did not exceed 150 uMol/l.
Prior to the second brain MRI, he had been hospitalized 25 times (4 per year). In 14/25(56%), ammonia was higher than 100 uMol/L(Max. 333 uMol/L). Only twice ammonia exceeded 250 uMol/L. Response to emergency treatment was optimal in all cases. Ambulatory controls: Mean ammonia 68.5 uMol/L; Mean glutamine: 731.2 uMol/L. Mean citrulline: 1767.8 uMol/L. Leucine slightly decreased during the first year.
CONCLUSION: Despite the early beginning of treatment and apparently unrelated to acute episodes of decompensation or chronic hyperammonemia, the patient developed a severe movement disorder of insidious onset with an evident image correlation. A second disease as well as epigenetic factors could determine the patient evolution. More case reports are needed in order to arrive general conclusions.

P-178 - MOLECULAR CHARACTERIZATION OF ORNITHINE TRANSCARBAMILASE (OTC) GENE IN ARGENTINEAN PATIENTS

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INTRODUCTION: Ornithine Transcarbamilase Deficiency (OTCD) is an X-linked inborn error of the urea cycle that causes hyperammonemia, due to mutations in the OTC gene. More than 500 variants have been described, including disease-causing mutations and polymorphisms, most of them being missense substitutions. The onset of OTCD symptoms is variable: hemizygous males with the neonatal-onset form resulting from null alleles present with a hyperammonemic comma in the first week of life, whereas heterozygous females and hemizygous males with partial defects in the OTC gene show various degrees of clinical symptoms later in life or even in adulthood. Besides, heterozygous women for an OTC mutation present a wide spectrum of clinical manifestations depending on the pattern of X inactivation in the liver, ranging from asymptomatic to almost as severe as in affected males.
OBJECTIVE: Describe molecular characterization of OTC gene in OTCD patients from Argentina. METHODS: DNA was extracted from peripheral blood from 33 individuals, corresponding to 12 unrelated families. Samples were sequenced by analysis of the 10 exons and the exon-intron boundaries of the OTC gene. Computational algorithms were applied to assess the severity of de novo missense mutations.
RESULTS: A total of 12 patients (5 males and 7 females) were diagnosed with OTCD based on biochemical findings and confirmed by molecular analysis. Maternal carrier status was confirmed for 2 males and 3 females patients, while in 3 female patients, mutations had occurred de novo. Carrier status was detected in 7 females who remain asymptomatic, and ruled out in 6. Ten different sequence variations were identified, including 5 novel substitutions. All of them, except for p.(Arg129His), found in two unrelated families, were private mutations. All the novel substitutions (p.(Ile85Ser), p.(His168Tyr), p.(Ser203Pro), p.(Pro305Leu) and p.(Asp297Thrfs26)), were predicted to be deleterious by in silico tools.
CONCLUSION: This study supports that OTCD is a heterogeneous disorder at the molecular level, such as described in other populations. Molecular analysis remains especially useful for detecting female relatives at risk of not only having another affected child but also presenting potentially fatal hyperammonemic crisis.

P-179 - DEFICIENCY OF ARGINASE: REPORT OF THE FIRST CASE CONFIRMED IN COSTA RICA

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INTRODUCTION: Argininemia is a Urea Cycle defect, caused by deficient activity or the total absence of the enzyme Arginase, coded by the ARG1 gene. Arginase deficiency causes elevation of serum Arginine levels and secondarily an increase in serum ammonium levels, milder than expected in the other disorders of the Urea cycle. This disease is inherited in an autosomal recessive manner. Clinical manifestations of this disease are: progressive spasticity, seizures and intellectual disability after the second year of life, when not treated early.
OBJECTIVE: This report presents the first biochemically and molecularly confirmed case of Arginase deficiency detected by the National Newborn Screening Program in Costa Rica.
MATERIALS AND METHODS: We describe the clinical and biochemical findings of a newborn who, despite being asymptomatic, presents increased serum Arginine levels, detected by Newborn Screening.
RESULTS: Mass tandem Spectrometry from dried blood spot detected a sustained increase level of Arginine in three consecutive samples. Subsequently plasma amino acid chromatography was requested showing an increase of serum arginine levels more than 6 times the cut-off for age. Serum Ornithine, Citrulline and Ammonia levels where within normal range. Urine organic acids analysis by GC-MS gas chromatography-Mass Spectrometry showed only a moderate peak of succinic acid. Next Generation Sequencing (NGS) for Urea Cycle disorders was performed reporting the variant NM_000045.32AEB_A: 101_128.c.382G> A-(p.Asp128Asn) in the ARG1 gene, in a homozygous state.
Discussion and CONCLUSIONS: The homozygous mutation NM_000045.32AEB_A: 101_128.c.382G>A-(p.Asp128Asn), in ARG1, has been reported as a variant of unknown significance. Biochemical findings such as serum elevation of Arginine levels, the absence of Argininosuccinic Acid or Orotic Acid in urine organic acid analysis and normal serum levels of other aminoacid within the Urea Cycle support the clinical effect of the mutation in the Urea Cycle. Prior to the development of a neurological deficit, a diet restricted in Arginine was initiated and close monitoring is maintained. A new disease-causing mutationin in the ARG1 gene is documented in the first patient with a confirmed diagnosis of Arginase Deficiency in Costa Rica through the National Newborn Screening Program.

P-180 - OTC DEFICIENCY. DESCRIPTION OF 7 PATIENTS OF ONE CENTER IN MONTEVIDEO.

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INTRODUCTION: Ornithine transcarbamylase (OTC) is the urea cycle enzyme that catalyzes the formation of citrulline. The OTC gene is located on the X chromosome. OTC deficiency is the most frequent hereditary defect of ureagenesis. The estimated incidence varies in different countries. Hemizygotes with complete OTC deficiency, presented acute hyperammonemia in the first week of life, while those with partial deficiency had a late presentation. The severity of OTC symptoms in women ranges from asymptomatic to almost as severe as in affected males. The clinical manifestations are caused by the toxic effects of hyperammonemia and glutamine in brain. Male and female may present lethargy, vomiting, behavioral abnormalities, cerebral edema, coma, and death. Biochemical abnormalities include increased plasma ammonia, glutamine and decrease citrulline, and increased urinary orotic acid. Carrier identification is important because genetic counseling. Chronic treatment includes ammonia scavengers in combination with limited protein diet and arginine or citrulline supplementation.
OBJECTIVE: To present our patients with OTC deficiency.
MATERIALS AND METHODS: We perform description of clinical, biochemical and molecular findings of patients with OTC deficiency followed in our center between January 2008 and December 2018.
RESULTS: The clinical phenotypes were: 1 hemizygotes with late-onset disease, 5 symptomatic and one asyntomatic heterozygous. The age of onset was below 6 years the heterozygous and at 18 months the male. All syntomatic patients had had more than one admission before the diagnosis. Clinical manifestations varied between cases, with one or more of the following signs and symptoms: drowsiness, lethargy, encephalopathy, seizures, vomiting, behavior alterations, and irritability. Biochemical findings: elevated plasma ammonia and glutamine, low citrulline and elevated urinary orotic acid. Genetic analysis, showed 7 different mutations. Regarding disease progression after start treatment, one adolescent female required admission because diet transgression several times, one was pregnant without symptoms during pregnancy or at or after delivery, the male had one symptomatic hyperammoniemic episode after start treatment but admission was not required.
CONCLUSIONS: Suspicion of OTC, early confirmatory diagnosis, and prompt initiation of treatment are essential to avoid new hyperammonemic episode that could cause irreversible neurological damage and or death and for the adequate family genetic counseling.

P-181 - INTERVENTION AND MEDICAL AND NUTRITIONAL TREATMENT OF A NEWBORN WITH HYPERAMMONEMIA. A CASE REPORT.

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INTRODUCTION: In Colombia, patients with Inborn Errors of Metabolism (IEM) are intervened after presenting clinical manifestations of the disease; most of them are detected at a later stage due to the absence of a neonatal screening program. The neonatal manifestation of the disease that leads to suspect an IEM is the non-improvement of its clinical status together with the limited diagnostic methods in health institutions, thus the quantification of ammonia could be a fundamental tool to direct the initial and subsequent intervention diagnosis of these pathologies.

26 years old mother infant, not consanguine parents, received exclusively breastfeeding, on the fourth day shows oral rejection, vomiting, drowsiness and jaundice. Emergencies is contacted, shows distal coldness, drowsiness and ventilatory failure; ventilatory support and antibiotic therapy is initiated. Presents altered state of consciousness, bilirubin encephalopathy is suspected. The child presented convulsive events, suspending phenobarbital and phototherapy.

Transfered without sedation, no response to tactile or pain stimuli. No respiratory effort and is supported on dopamine. On clinical examination: icteric, mild hepatomegaly, isochoric pupils, transaminase and elevated nitrogen compounds, leucocytosis, thrombocytosis, severe hyperammonemia with ammonium of 1261 mmol/L.

Due to the metabolic state and lack of dialysis in the institution, it was decided to perform exchange transfusion, dextrose fluids, fasting. Post-exchange ammonium of 158 and 315 after 24 hours. Sodium benzoate, sodium phenylbutyrate, lactulose and metronidazole decreased ammonium progressively in 72 hours (287-60). Nitrogen compounds in improvement and normalization of liver function.

Finding cerebral edema in NMR, dynamic management of Nutrition, Parenteral Nutrition (PN) with dextrose and lipids, full contributions and enteral contribution of initial protein 0.25 g/k/d.

Increments of 0.25-0.5 g/k/d. Improvement of neurological response Scheduled extubation is achieved. URCmed A, weaning of PN is started. Serum ammonium monitoring, achieving stability with protein intake 1.6 g/k/d and weight gain.

Metabolic studies report amino acid chromatography: Lysine elevation, normal pyruvate lactate ratio. Organic acids not conclusive.

CONCLUSION: Stabilization of the patient with exchange transfusion was achieved, although it is not recommended. In many of our regions where dialysis is not available, it could be an option for the treatment of metabolic emergencies.

ABSTRACTS SELECTED FOR POSTER PRESENTATION (NEWBORN SCREENING)

P-182 - COMPARISON OF TWO METHODS FOR MONITORING PHENYLALANINE LEVELS IN PHENYLKETONURIC PATIENTS: COLORIMETRIC VERSUS FLUOROMETRIC.

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BACKGROUND: In order to control Phenylketonuric (PKU) patients, blood phenylalanine (Phe) concentrations are frequently measured. Differences found in Phe levels depending on the method used for the analysis may hinder optimal management of patients. Guidelines suggest maintaining values between 2 to 6 mg/dl to control dietary adherence. We compared Fluorometric method in DBS with MS/MS and HPLC in a previous work and it is currently used by the physicians.

OBJECTIVES: To investigate differences in blood Phe concentrations analyzed by two different commercial methods (Fluorometric vs Colorimetric) used to monitor follow-up patients.

MATERIALS AND METHODS: 226 dried blood samples (Whatman 903) from 35 PKU patients under control were included in this retrospective analysis. All samples were tested by Neonatal Phe kit, PerkinElmer (fluorometric) and Quantase Neonatal Phe Screening kit, BioRad (colorimetric). For statistical analysis MedCalc V13.1.2.0 software was used.

To compare methodologies we performed: a) Linear regression between both analytical systems, b) Pearson correlation coefficient and c) Bland Altman (difference % plot). This analysis was repeated after correct the PerkinElmer calibrators concentrations with regard to the ISNS reference preparation (ISNS-RP).

RESULTS: Regression analysis: Phe_{Biorad} (mg/dl) = 0.03880 + 1.3920 $Phe_{PerkinElmer}$ (mg/dl); 95% CI: a= [-0.2641;0.3417] and b= [1.3482;1.4358] ($p<0.0001$). Pearson correlation Coefficient 0.9726, 95% CI: [0.9645;0.9789]. Concentration Range Phe_{Biorad}: 0 to 35mg/dl. Limits of agreement from Bland Altman plot (difference %): Mean (± 1.96 DS): -37.4 (-117.2;42.4).

Statistical analysis PerkinElmer ISNS-RP: Regression analysis: Phe_{Biorad} (mg/dl) = 0.03880 + 1.063 $Phe_{PerkinElmerISNS-RP}$ (mg/dl); 95% CI: a= [-0,2641;0,3417] and b= [1.0295;1.0964], ($p<0.0001$). Pearson correlation Coefficient 0.9726, 95% CI: [0.9645;0.9789]. Concentration Range Phe_{Biorad}: 0 to 35mg/dl. Limits of agreement from Bland Altman plot (difference %): Mean (± 1.96 DS): -5.0 (-65.9;56.0)

Agreement analysis: Phe values obtained by both methods were divided into three groups (mg/dl): A) < 2.6; B) 2.6-7.8 and C) > 7.8. Group A: 83.3 % (40/48); Group B: 80.4 % (82/102); Group C: 92.1 % (70/76). Total agreement: 85.0 %

CONCLUSIONS: The discrepancies observed between two commercial methods during the monitoring of patients with PKU are due to differences in the calibration of the assays. Phe levels obtained by the colorimetric method were higher than those obtained by the fluorometric method. When those values were corrected by ISNS-RP (factor=1.3095), they resulted equivalent. Clinical decision limits should be corrected according to the ISNS-RP when used by the neonatal screening method.

P-183 - COMPARISON OF MEASUREMENT PROCEDURES FOR THE NEWBORN SCREENING OF PHENYLKETONURIA AND PERSISTENT HYPERPHENYLALANINEMIAS

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INTRODUCTION: Our program performs the newborn screening (NS) through a two-stage analytical algorithm, with different methods, whose accuracy and linearity were verified for both according to CLSI EP15-A3 and EP6-A. We consider important the results comparison of the 1st stage, new method, with respect to those obtained in the 2nd stage, known method, to define the NS.
OBJECTIVES: Determine if the methods used in the two stages of NS of Phenylketonuria (PKU) and persistent Hyperphenylalaninemias (HPA) are statistically comparable.
MATERIALS AND METHODS: Protocol "Measurement procedure comparison" CLSI EP09-A3. Period September to December 2018. Concentration of Phenylalanine (Phe) in dried blood spots was determined by two METHODS: evaluated method, enzymatic-colorimetric / BioRad (BR) and comparison method, fluorometric / PerkinElmer (PE). We used 40 samples of patients with PKU and HPA in treatment with medical-nutritional and biochemical follow-up in our program. Samples concentrations were homogeneously distributed in the evaluated range and were processed in duplicate by both METHODS: For the statistical analysis we used EP Evaluator®12.0.
RESULTS: Concentrations range (mg/dL): 0.7 to 15.7 (PE) and 0.5 to 19.0 (BR). Mean mg/dL ± SD: 7.7 ± 4.2 (PE); 10.5 ± 5.8 (BR). Correlation coefficient = 0.9331. Deming regression analysis, 95% confidence interval: Intercept = -0.514 (-1.43 to 0.115); Slope = 1.442 (1.315 to 1.569); Standard error of the estimates (SEE) = 2.195; Medical decision point (MDP), Phe = 2.0 mg/dL (PE), was obtained 2.4 mg/dL (BR) limits from 1.9 mg/dL to 2.8 mg/dL.
CONCLUSIONS: Statistical comparison, BR method respect to PE: There was not evidence of constant systematic error between the measurement procedures: the Intercept confidence interval included zero. There was a significant proportional systematic error; the Slope confidence interval did not include 1. There was no significant difference in the MDP: 2.0 mg/dL was included in the confidence limits. We found an acceptable random error, taking into account the SEE. We conclude, although the proportional systematic error was significant especially for concentrations higher than 3.0 mg/dL, it was considered that the methods are statistically comparable for performing the NS of PKU and HPA, using the cutoff 2.0 mg/dL.

P-184 - OBTAINING A PHENYLALANINE CUT OFF FOR SAMPLES TAKEN BETWEEN 24 AND 36 HOURS OF LIFE

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INTRODUCTION: Determining a cut-off value is a crucial stage when starting the newborn screening, since the number of false positives must be reduced without compromising sensitivity. The cut offs are usually established at 36-72 hours of life, however is increasing the number of samples taken before that range, resulting in patient recall.
OBJECTIVE: To calculate a new cut-off value for Phenylalanine (Phe) and Phenylalanine/Tyrosine ratio (Phe/Tyr), in a cohort of patients whose samples were taken between 24 and 36 hours of life and to compare it with the current one established at 36 -72 hours of life.
MATERIALS AND METHODS: We analyzed 638 dried blood samples from full term newborns with breastmilk feeding, obtained between 24 and 36 hours after birth. The quantification of Phe was performed in an API3200 tandem mass spectrometer (ABSciex) using non-derivatized MassCheck reagent (Chromsystems).
The mean, the standard deviation and the 99.9 percentiles of the results (Phe and Phe/Tyr) were calculated. There were compared with those published in Region 4 Stork (R4S). The cut-off value was considered clinically validated if it was between the P99 of the normal population and the P5 of the true positive cases for Phe reported in the R4S and between the P25 and P75 of the distribution of cut-off values for Phe reported in the R4S.
RESULTS: Phe: Mean = 50.1 uM, SD = 9.46, P99.9 = 91 Phe/Tyr: Mean = 0.4, SD=0.19, P99.99= 2.15. Validation: Phe: Cut off = 91 uM, P99-P5=97-233, P25-75=113-150; Phe/Tyr: Cut off =2.08, P99-P5= n-3.4, P25-75=1.6-2.5; Current cut off values: Phe=115.30 uM; Phe/Tyr=1.77

CONCLUSION: The cut off values obtained are different from those calculated in the cohort whose sample was taken between 36 and 72 hours of life.
When analyzing the results, we observed that the clinical validation criteria are not met for Phenylalanine; reason could be differences in the hours of life of the samples from the database.
These new cut off values could be used for samples taken between 24 and 36 hours of life, avoiding recall these patients.

P-185 - PREVALENCE OF HYPERPHENYLALANINEMIAS DETECTED BY NEWBORN SCREENING IN A CENTRALIZED LABORATORY FROM MEXICO.

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INTRODUCTION: In developed countries, newborn screening for hyperphenylalaninemia (HPA) has been carried out for more than fifty years; however, in emerging countries the detection of this disease has been gradually implemented. In Mexico, newborn screening for this disease is recent and HPA types according with the severity and its birth prevalence are poorly known.
OBJECTIVE: To study the frequency of the different types of hyperphenylalaninemia according to the biochemical severity detected in a centralized laboratory from Mexico.
MATERIALS AND METHODS: Retrospective analysis of the results of 1,898,096 newborn samples screened for HPA in a centralized laboratory from Mexico. Phenylalanine (Phe) was quantified using dried blood on filter paper by an enzymatic fluorometric method (GSP Neonatal Phe kit, Perkin Elmer®); HPA cases were defined as all those second samples whose Phe blood levels were above 120 µmol/L and low tyrosine (Tyr) levels with a Phe/Tyr ratio >2, determined by MS/MS. HPA types were classified as follow: benign HPA 120-360 µmol/L, clinically significant HPA >360-600 µmol/L, moderate phenylketonuria (PKU) >600-1,000 µmol/L, classic PKU >1,000 µmol/L1. The geographic birth place of all HPA cases was also documented.
RESULTS: 1,898,096 newborns were screened; 57 cases of HPA were confirmed in 24 of 32 states of the country. Benign HPA was found in 25 cases (44%), clinically significant HPA in 7 cases (12%), moderate PKU in 9 cases (16%) and classic PKU in 16 cases (28%), these last 16 cases were found in the states of Jalisco, Zacatecas, Queretaro, Guanajuato, Oaxaca, Durango, Nuevo Leon, Veracruz, Colima and Baja California.
CONCLUSIONS: HPA were found in 1: 33,300 screened NB and the classic PKU cases were localized mainly in the center occident of Mexico.

P-186 - TETRAHYDROBIOPTERIN-DEFICIENT HYPERPHENYLALANINEMIA DIAGNOSIS FOLLOWING POSITIVE PHENYLKETONURIA NEWBORN SCREENING

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INTRODUCTION: Hyperphenylalaninemia (HPA) may be caused by either a deficiency in phenylalanine hydroxylase or in tetrahydrobiopterin (BH4), the essential cofactor required for the hydroxylation of aromatic amino acids. The most common forms of BH4 deficiency are 6-pyruvoyl-tetrahydropterin synthase deficiency and dihydropteridine reductase deficiency , which require a different treatment from classical HPA.
Tetrahydrobiopterin-deficient HPA is an autosomal recessive disorder characterized by mild transient hyperphenylalaninemia often detected by newborn screening. Patients also show increased excretion of 7-biopterin. Affected individuals are asymptomatic and show normal psychomotor development, although transient neurologic deficits in infancy have been reported. Patients may also develop hypomagnesemia and nonautoimmune diabetes mellitus during puberty.
CASE PRESENTATION: We present a one year old boy with diagnosis of hyperphenylalaninemia due to tetrahydrobiopterin (BH4) deficiency.
He presented positive newborn screening for Phenylketonuria. In successive controls Phenylalanine levels were within 1- 6 mg/dl (60-360 mmol/l) without protein restriction or phenylalanine restricted formula.
Biopterin and neopterin in dried blood spot were normal.
Hyperphenylalaninemia associated genes were sequenced finding an homozygous pathogenic variant in PCBD1 gene (c.292C>T, p.Gln98Ter,), compatible with tetrahydrobiopterin-deficient hyperphenylalaninemia.
Determination of urinary pterins was performed, resulting in neopterin 4398.0 nmol/mmol of creatinine (range 300 - 1600) biopterin 982.5 nmol/mmol creatinine (range 500 - 3500) Percentage of biopterin in urine 18.3% (range 50 - 75); ratifying the diagnosis.

Follow up with phenylalanine levels was performed monthly. At 7 months of age, after the introduction of meat in the diet his phenylalanine level climbed to 10.9 mg/dl
Treatment with sapropterin was started without protein restriction, normalizing phenylalanine levels.
At age 12 months all developmental milestones were attained. The patient presents to date no neurologic symptoms. Further follow-up monitoring development, neurologic symptoms and blood glucose will be assured.
CONCLUSION: Further evaluation of cases of hyperphenylalaninemia found in newborn screening, including molecular genetic analysis and/or urinary pterins, is useful in providing a definitive diagnosis for the patient and eventual specific treatment.

P-187 - GENOTYPE AND PHENOTYPE CORRELATION IN CHILEAN PKU PATIENTS

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INTRODUCTION: Phenylketonuria (PKU, OMIM 261600) is an autosomal recessive disease, caused by mutations in the Phenylalanine Hydroxylase (PAH) gene situated in chromosome 12q22-q24.2. The genotype is one of the main factors that determine the phenotype of this disease.
OBJECTIVE: Correlate genotype and phenotype in Chilean PKU patients.
METHODS: We classified the phenotype according to: phenylalanine (Phe) levels at diagnosis, phenylalanine tolerance at 1 and 5 years old in 57 PKU subjects. Then correlate the genotype (by Guldberg predicted value) with those phenotypes. Fisher exact test was used. Significance level was set at $p<0.05$. Statistical analysis was performed using STATA 13.
RESULTS: We identified 26 different mutations in 134 of the 142 alleles studied (94.4 %), 88.7 % of the subjects had biallelic pathogenic mutations. Compound heterozygous represented 85.9 % of the cases. Exon 7 included the majority of mutations (26.9 %) and 50 % of mutations were missense. The most frequent mutations were c.1066-11G>A, c.442-?_509+?del and p.Val388Met. The majority of subjects (52.3 %) had the classic phenotype. The sample with biallelic mutations (n=57) diagnosis Phe levels were 1092 ± 480 umol/L at 17.2 ± 10 days of age. Phe intake in the first year of life was 39.8 ± 8.5 mg/kg/d and 23.3 ± 14.2 mg/kg/d at age 5. There was a correlation between genotype and phenotype according to Phe levels at diagnosis and with Phe tolerance at 1 year of age ($p=0.02$ and $p=0.005$, respectively). According to genotype only 14 % could respond to BH4. Our most frequent mutation (p.Val388Met) has the highest discrepancy between genotype and phenotype.
CONCLUSIONS: Genotype characterization allowed us to predict the phenotype in our Chilean patients only during the first year of life (phe levels at diagnosis and tolerance). There is no concordance between genotype and phenotype in older patients. It is important to mention that cases with the p.Val388Met mutation have a more severe phenotype than described in literature.

P-188 - NEUROCOGNITION AND EARLY OVERTREATMENT IN CONGENITAL HYPOTHYROIDISM DETECTED BY NEONATAL SCREENING

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INTRODUCTION: Early diagnosis and treatment of congenital hypothyroidism (CH) prevents mental retardation. Although initial treatment with high doses of levothyroxine (LT4) is recommended, moderate hypertiroxinemia with suppressed TSH during the first months of some patients is difficult to avoid. If this is innocuous or constitutes a risk factor for neurocognitive impairment is controversial.
OBJECTIVE: To evaluate the cognitive outcome at age 9-10yrs of early detected and treated CH in whom suppressed TSH and moderate hyperthyroxinemia were present during the first six months of treatment.
PATIENTS AND METHODS: We retrospectively reviewed data on age, TSH and T4 levels at diagnosis, LT4 initial doses, etiology, symptoms of hyperthyroidism and T4 levels attained at 2 and 6 months of 35 CH patients early detected and regularly followed-up.
Patients were considered overtreated (OT) if TSH was persistently <0.5 uUI/ml along the first 6 months, or not-overtreated (NOT) when TSH was 0.5-6.5 uUI/ml in the same period.
No differences were found in (median): age (days) (OT=23, NOT=21), LT4 dose (ug/kg/day) (OT=12,9, NOT=12.1) initial severity of hypothyroidism reflected as TSH>40 uUI/ml (OT=89,5%, NOT=93,8%) and T4<2ug/dl (OT=42,1%, NOT=43,8%). Etiology was in OT: 12 ectopic, 4 eutopic and 3 athyreosis and in NOT: 5 ectopic, 5 eutopic, 5 athyreosis and 1 hypoplastic. Symptoms of hyperthyroidism were always

absent. T4 levels attained were moderately high in both groups at 2 months and within normal references at 6 months.
All children underwent evaluation with WISC-III (global, verbal and performance IQ, verbal comprehension, absence of distractibility, processing speed, perceptual organization, attentional amplitude, working memory), Faces Test (selective attention), CPT-II (omissions and commissions) and Trail Making Test (attention divided). School achievement was also registered. Student T-test with Bonferroni´s adjustment were used for analysis($p<0.05$).
RESULTS: Scholar level achieved was in all patients the expected for age. Developmental scores were always normal without differences between groups in the neurocognitive evaluation.
CONCLUSIONS: Early overtreatment (low TSH with hyperthyroxinemia) without clinical expression didn´t impair neurocognitive outcome at age 9-10 in our patients. These results have to be taken into account while treating CH, knowing that lowering LT4 dose might lead to an increased risk of undertreatment

P-189 - BUENOS AIRES CITY GOVERNMENT FOR CONGENITAL HYPOTHYROIDISM NEONATAL SCREENING PROGRAM: SETTING CUTOFF

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INTRODUCTION: TSH cutoffs (CO) levels in congenital hypothyroidism(CH) neonatal screening programs (NSP) tend to lower worldwide. Nevertheless, reports on benefits and risks are not clear. The Buenos Aires City Government NSP for CH uses since 2001 a TSH CO of 10 mIU/L blood.
METHODS: A prospective pilot NSP with TSH CO: 8 mIU/L blood (IFMA-DELFIA) was performed from 1/6/2013 to 1/6/2018. DBS were obtained from heel prick at maternity discharge. Newborns with TSH >10mIU/L blood were recalled and usual confirmation procedures were triggered while babies with TSH levels 8-9.9 mIU/L blood assisted to a unique center to be clinically and biochemically evaluated. With serum TSH above the normal age related limit, a TC99 thyroid scintigraphy was performed. Babies were followed up until confirmation or exclusion of CH.
RESULTS: Out of 130.405 newborn screened 496 with TSH >10mIU/L were recalled and 108 CH confirmed (Recall rate (RR): 0.38%).
208 extra babies were recalled with the new cutoff (Overall RR: 0.54%). 206 were localized and evaluated. In 176 (85%) TSH and thyroid hormones normalized within the first month of life. 30% of them reported iodide exposure and 4% were premature.12 (5.8%) were lately localized by social service having already normal thyroid function.
In18 (8.7%) TSH remained high: Nine (1 extreme preterm) confirmed CH (2 goiters with high thyroglobulin, 1 ectopic thyroid gland, 3 eutopic glands and 3 could not be characterized) and were treated (median age: 8 days). Nine (3 exposed to iodide, 1 preterm, 1 with maternal autoimmunity and 4 without relevant history) had persistent hyperthyrotropinemia. At a median age of 13 days their median serum TSH was 12.4 mIU/L with normal Free Thyroxine. All had an eutopic thyroid and when followed up without treatment, 5 normalized TSH levels within the first 3 months, 2 did it after 2 years of follow up and 2 are still in control, all with normal outcomes.
CONCLUSION: In view of the higher detection and still acceptable RR, our screening program decided to keep the lower cutoff. However, the follow up of the detected children will clarify the benefits on their early detection.

P-190 - REVIEW OF THE NEONATAL TSH CUT-OFF IN THE CENTRAL LABORATORY OF THE SAN LUIS HOSPITAL - ARGENTINA

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INTRODUCTION: Congenital Hypothyroidism (CH) is the most frequent endocrinopathy in the neonatal period and one of the most common causes of preventable mental deficiency. Usually it does not present signs or symptoms at the time of birth, reason why its immediate diagnosis through neonatal screening and early treatment are of vital importance.
OBJECTIVE: To compare neonatal TSH recitation rates using two different commercial kits and to adjust the cut-off point currently used by our laboratory.
MATERIALS AND METHODS: 2842 dried blood samples collected on filter paper Whatman # 903 between 48 hours and 5 days of life were analyzed using the QuantaseTM Neonatal TSH Screening Kit (Bio-Rad) (Cut-off: 9 mUI/L). Those samples with TSH above 9 mUI/L were also analyzed using the UMELISA TSH NEONATAL Kit (TecnoSUMA) (Cut-off: 8 mUI/L) and such newborns were recited for the TSH measurement on a second sample collected on filter paper and for the TSH and Free-T4 determinations in serum (Advia Centaur XP autoanalyzer).
RESULTS: Out of the 2842 newborns tested, 49 had TSH higher than 9 mUI/L (Bio-Rad). 40/49 newborns showed normal values in the recitation; 5/49 were confirmed with CH

and 4/49 gave TSH values in the range 10-20 mIU/L, both on filter paper and serum. These newborns were followed by the endocrinologists and before the month of life their values became normal. When the 49 samples with abnormal TSH by Bio-Rad were analyzed using the SUMA technology, the 5 newborns diagnosed with CH showed abnormal results, other 6 gave values higher than the corresponding cut-off, and 38 gave normal values. The recitation rate using the Bio-Rad technique was 1.72%, while in the same period of the previous year the recitation rate using the SUMA technology was 0.55%.

CONCLUSIONS: Due to the higher recitation rate working with the Bio-Rad kit compared to the SUMA technology, we proposed to adjust the Bio-Rad cut-off value to 12.3 mUI/L, which was obtained through a ROC curve analysis with an area below the curve of 0.934 (95% CI 0.857-0.976) with a sensitivity of 83.3 and a specificity of 90.1.

P-191 - INCREASED INCIDENCE OF CONGENITAL HYPOTHYROIDISM NOT RELATED TO LOWERED CUT-OFF VALUES.

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INTRODUCTION: Worldwide incidence of Congenital Hypothyroidism (CH) has been increasing each year due to multiple factors. Lowered cut-off values (CO) are recognized as one of the main causes, but others variables like the increased survival of preterm newborns, iodine deficiency, and other environmental and ethnic factors also play an important role. Newborn screening (NBS) for CH in Buenos Aires Province (BAP) was implemented at request in 1992, and since April/1995 it has been conducted as a program.

OBJECTIVE: To describe the increment on the incidence of CH not related to lowered CO experienced in the BAP-Argentina in the period 2001-2017, and the possible factors influencing the observed behavior.

MATERIALS AND METHODS: NBS for CH was conducted using Delfia Neonatal hTSH and AutoDelfia Neonatal hTSH methods until June/1997 and from then onwards, respectively. On August/2001 the CO was established in 11.0 μU/ml and kept unchanged until present. Annual and cumulative incidences of CH were calculated during the whole NBS period (1992-2017). Annual percentages of preterm newborns diagnosed with CH were determined since 1998 onwards. Percentages of newborns with TSH > 5 μU/ml were calculated in years 2002, 2005, 2009, 2013 and 2017 in order to estimate a potential iodine deficiency. Percentages of transient CH and the etiologies distribution were determined during periods 1998-2004 and 2005-2013.

RESULTS: 3,566,703 newborns were screened during 1992-2017. The annual incidence in the period 2001-2017 was in the range [1: 1,598 - 1: 3,099], but the cumulative incidence increased from 1: 2,428 to 1: 2,037. Percentages of hypothyroid preterm newborns increased from 6.6 to 11.1% in 2004-2017 regarding 1998-2003. Percentages of newborns with TSH > 5 μU/ml were 2.3, 2.9, 3.3, 4.4 and 4.7 in the selected years. Rates of transient CH cases were 4.7 % in 1998-2004 and 4.6 % in 2005-2013. Etiologies were similar in both periods: athyreosis 25.0 %, ectopic disgenetic gland 57.1 %, eutopic disgenetic gland 2.2 %, and eutopic thyroid gland 15.7 %.

CONCLUSIONS: Incidence of CH in BAP has increased significantly in the last 17 years despite the CO remained unchanged, being the increasing preterm newborns survival and a potential development of a mild iodine deficiency in the region the possible reasons for the observed behavior.

P-192 - INCIDENCE OF CONGENITAL HYPOTHYROIDISM AND CONGENITAL ADRENAL HYPERPLASIA IN THE PERUVIAN SOCIAL SECURITY DETECTED BY NEWBORN SCREENING DURING 2008-2018

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INTRODUCTION: Congenital hypothyroidism (CH) is the biggest cause of preventable mental retardation worldwide. Early diagnosis is fundamental because, at birth, most of the patients do not present any signs or symptoms. Congenital adrenal hyperplasia (CAH) is a common and potentially fatal disease that needs early diagnosis. The diagnosis of both diseases is made through neonatal screening of newborns (NBS). In Peru, the Social Security Institute (EsSalud) started the NBS program for CH and CAH in October 2002. National screening of both diseases started in January 2008. Currently, EsSalud is the only center that runs a national NBS program. There are not statistics on nationwide incidences of these diseases.

OBJECTIVE: Determine the incidence CH and CAH among newborns born at EsSalud facilities across the country diagnosed by NBS between 2008 and 2018.

MATERIALS AND METHODS: This study analyzed data from the Neonatal Screening Laboratory at the Edgardo Rebagliati Hospital that operates as the EsSalud national

referral center for the NBS test samples. The blood samples were taken from the heel of the newborns, collected on filter paper and sent to Lima. There, the TSH and 17-hydroxyprogesterone (17OHP) levels were measured by the Tecan Freedom Evo 75 equipment from 2008 to 2016 and by the NS 2400-Labsystems equipment from 2016 to 2018. Positive results were considered when TSH was ≥ 10 mU/L and 17OHP ≥ 20 nmol/L. A second sample was necessary to confirm both diagnosis.
RESULTS: A total of 989 680 neonates born at EsSalud facilities nationwide were screened for CH and CAH between 2008 and 2018. For CH, 319 tested positive, with an incidence rate of 3.2/10 000, and average rate of 1/3 102. At the same time, 55 patients tested positive for CAH, with an incidence rate of 5.55/100 000 live births and an average rate of 1/17 994.
CONCLUSIONS: The incidence of CH in EsSalud was 3.2/10 000 live births, and of CAH was 5.55/100 000 live births. These incidences were similar to international reports. Since EsSalud assists with around 20% of all the births in Peru, these are really important statistics for the country.

P-193 - CONGENITAL HYPOTHYROIDISM: 12 YEARS OF NEONATAL SCREENING EXPERIENCE IN SALTA, ARGENTINA

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INTRODUCTION: Congenital Hypothyroidism (CH) is one of the most common congenital diseases in newborns (NB). It is the most frequent preventable causes of intellectual deterioration, since thyroid hormone plays an essential role in brain development during the first years of life. In Salta, Argentina the CH research began in October 2006 as a provincial program that includes the detection, confirmation, treatment and follow-up of the NB diagnosed in the public sector, but open to general population
OBJECTIVE: To evaluate the frequency of CH in our population and the days of life of the NB at the time of diagnosis and treatment starting.
MATERIALS AND METHODS: Descriptive and retrospective analysis of the program's data.
RESULTS: From October 2006 to December 2018, 227750 NBs were screened, corresponding to 98% coverage of children born in the public sector, in this period, 184 NB were detected and confirmed with CH, the calculated frequency is 1/1238. 50% of the newborns were diagnosed and started treatment before 15 days of age, 36% between 15 and 30 days of life.
CONCLUSIONS: 86% of the newborns were diagnosed and started treatment before the month of life, which is crucial for the normal neurodevelopment of the child. Due to the high frequency of CH in our population, the importance of the fastest treatment initiation to prevent mental retardation and growth associated with CH is highlighted.

P-194 - PREVALENCE OF CONGENITAL HYPOTHYROIDISM IN THE RAFAEL CALVO MATERNITY FROM CARTAGENA-COLOMBIA, DURING THE PERIOD 2005-2018.

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INTRODUCTION: The Rafael Calvo Maternity Clinic located in Cartagena, attends the largest number of births in the city and the department. The Neonatal screening program was implemented on August 17, 2005, developing it within internal and external national and international controls. In Colombia the frequency of Congenital Hypothyroidism is between rates of 1/1886 newborns, 1/2500 and 1/3348.
OBJECTIVES: Establish the number of newborns that were screened for Congenital Hypothyroidism between 2005 and 2018. Determine the number of positive cases and its prevalence.
METHODOLOGY: Observational, Descriptive, Retrospective.
MATERIALS AND METHODS: Umbilical cord blood samples collected from August 17, 2005 to December 31, 2018, were analyzed for TSH using a fluorometric enzyme immuno assay (FEIA).
RESULTS: Number of newborns screened annually: 2005: 2224; 2006: 4866; 2007: 6536; 2008: 7694; 2009: 7986; 2010: 6866; 2011: 9257; 2012: 8260; 2013: 10333; 2014: 8760; 2015: 7249; 2016: 7247; 2017: 7866; 2018: 6249. These figures correspond to 100% of newborns born at the Institution. Currently, congenital hypothyroidism is a notifiable event in Colombia. A total of 101393 newborns were screened, being 2013 the year with the higher and 2006 the year with the lower number of newborns screened.
POSITIVE CASES PER YEAR: 2005, 2006: 0 cases; 2007: 2/6536; 2008: 0 cases; 2009: 0 cases; 2010: 1/6866; 2011: 4 /9257; 2012: 12 /8260; 2013: 3/10333; 2014: 15/8760; 2015: 10/7249; 2016: 5/7247; 2017: 3/7866; 2018 2/7866. 57 Positive cases were confirmed in 13 years of work over a population of 101393 newborns with a general incidence of 1/1779. The year with the higher number of positive cases was 2014 with 15 cases. In 2005, 2006, 2008 and 2009 no case was detected.
CONCLUSIONS: The neonatal screening program of the Maternity Rafael Calvo screened 101393 newborns of the institution for Congenital Hypothytiroidism measuring TSH on umbilical cord blood, achieving 100% of coverage. During the period of time studied, 57 positive cases were found

resulting in 1 case on 1779 live births and keeping the proportion of the national prevalence.

P-195 - TURNAROUND TIMES IN THE PROCESS OF NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM. EIGHTEEN YEARS OF EVOLUTION.

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INTRODUCTION: Early and effective treatments are key components for the success of the newborn screening for congenital hypothyroidism. To achieve it, is essential to control the time of blood sampling and a fast response in the recall process. The use of quality control indicators allows to monitor the activities and take objective actions over the time for the continuous improvements.
OBJECTIVE: To evaluate the evolution of two turnaround times (TAT) covering pre-analytical, and analytical, post-analytical and start of treatment in a subset of congenital hypothyroidism patients at higher risk.
MATERIALS AND METHODS: Newborn babies with serum confirmatory TSH concentrations above 20 uIU/ml were included. Two TAT were used: TAT1 days of life at blood sampling and TAT2 days of life at the start of treatment. The data of each TAT include information of 3 years, starting in 2001 and finishing at December 2018. For each TAT, data of mean and 90th percentile were registered.
RESULTS: 265 congenital hypothyroidism newborns between 2001 and 2018 were included. The number of patients in each time and the mean and 90th percentile for each period for TAT1 and TAT2 were: 2001-2003 (36): TAT1 6.3 and 16.8, TAT2 20.4 and 33.0; 2004-2006 (50): TAT1 4.6 and 12.6, TAT2 14.8 and 23.8; 2007-2009 (33): TAT1 3.3 and 4.6, TAT2 12.1 and 16.2; 2010-2012 (52): TAT1 3.6 and 6.0, TAT2 10.7 and 15.2; 2013-2015 (58): TAT1 3.9 and 8.0, TAT2 10.8 and 17.1; 2016-2018 (36): TAT1 2.7 and 4.0, TAT2 12.6 and 20.0.
CONCLUSION: There were reductions in the turnaround times over the years however for TAT2 in the last three years a slight increase was observed. Efforts are still needed for achieving improvements in the TAT2 indicator.

P-196 - EFFECT OF IMPROVEMENTS IN THE POST-ANALITICAL STAGE OF NEWBORN SCREENING FOR CONGENITAL NEONATAL HYPOTHYROIDISM IN SANTA FE (ARGENTINA)

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INTRODUCTION: In Santa Fe, the Public Health system does not have a Newborn Screening Program for Inborn Errors of Metabolism (IEM), but there is a "Newborn Screening Laboratory Network for IEM" and a "Medical Network of Diagnosis and Therapies" doing transdiciplinary work.
OBJECTIVES: a) To describe the strategy of the post-analytical stage that improved every marker. b) To estimate: 1-Time to diagnosis. 2-Time to treatment starting. 3-Provincial coverage.
METHODOLOGY: 1-We designed algorithms in order to locate patients with positive screening results. 2-Diagnosis procedures were updated in consensus interdisciplinary meetings. 3-Three pediatric coordinators were incorporated to the Network.
Location algorithm for newborns with abnormal results: TSH ≥ 9 µIU/ml (UMELISA TSH-neonatal, Cut-off: 9 µUI/ml, 99% percentile), physician is informed and confirmation is organized. If no response is obtained after 2 (possible case) and 5 days (suspected case), the pediatric coordinator is notified and he locates the child through the Primary Health Care Informatic System (SICAP).
Diagnosis protocol: Serum TSH ≤ 5 µIU/ml and fT4 ≥ 1,4 ng/dl: normal patient; 5 µIU/ml < serum TSH ≤ 9,99 µIU/ml with fT4 ≥ 1.40 ng/dl: repeat the assay between 7 to 15 days of life (same as a normal screening infant of a hypothyroid mother); serum TSH slightly increased with normal fT4: remain under laboratory and medical control for a while to define the case; TSH ≥ 10 µIU/ml, and low values of fT4: patients are referred to an endocrinologist, complementary studies are carried out, and treatment begins (Chemiluminescent immunoassay).
Mean diagnosis time and mean time of treatment starting were calculated for all affected patients in 2017, coverage by statistical records of the laboratory and data from the Direction of Statistics of the Health Ministry.
RESULTS: 28.114 samples out of 27.376 newborns were analyzed. Out of 119 positives: hypothyroids under treatment: 24, controlled hyperthyrotropinemias: 6, normalized: 17. Five borderline newborns with no response were located and studied. False positives: 67. Diagnosis time: 16 days. Time of treatment starting: 19 days. Coverage: > 98%.
CONCLUSIONS: This strategy allowed to locate 100% of newborns with positive screening results and to refer them to specialised medical services.

P-197 - DEMOGRAPHIC AND LABORATORY DATA OF NEWBORNS WITH CONGENITAL HYPOTHYROIDISM DETECTED BY THE NATIONAL NEONATAL DETECTION PROGRAM

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INTRODUCTION: Congenital hypothyroidism (CH) is the main pathology to be included in neonatal screening programs, due to its high frequency of appearance and its good response to treatment. In Paraguay, detection as a pilot project began in October 1999.
OBJECTIVE: To present the demographic and laboratory data of newborns detected with congenital hypothyroidism, between 2015 and 2018 in the National Neonatal Screening Program (NNSP).
METHODOLOGY: The demographic and laboratory data of newborns detected with congenital hypothyroidism were extracted and analyzed, from the NNSP excell data base, from January to December 2015 to 2018.
RESULTS: From January 2015 to December 2018, 350,731 samples of newborns were studied. A total of 148 newborns with CH were detected and confirmed (102 female and 46 male), with an incidence of 1 in 2.421 (36/87.181) in 2015; 1 in 3,074 (28/86,094) in 2016; 1 in 2,046 (44/90,037) in 2017 and 1 in 2,185 (40/87,419) in 2018. In 76% (113/148) the first sample was collected before 10 days of life, in 51% (76/148) of the cases the TSH values were higher than 50 uIU/dl in the first sample, and in 78% (115/148) the treatment was started within the month of life. 16% (23/148) of newborns had gestational age lower than 37 weeks and 5% (7/148) and weight lower than 2,500 grams. 4% (6/148) corresponded to indigenous population. The average maternal age was 27 years (from 15 to 41).
CONCLUSION: The frequency of CH in Paraguay is still one of the highest in the region, which can be explained by its mediterranean nature, also a slight increase in the incidence of CH cases was observed in the last two years of the present study.

P-198 - TEN YEARS EXPERIENCE OF THE NEONATAL SCREENING PROGRAM FOR CONGENITAL HYPOTHYROIDISM IN LA PAZ - BOLIVIA

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INTRODUCTION: Congenital hypothyroidism (CH) is a catastrophic disease when it is not early identified and treated. The untreated CH causes intellectual disability. In La Paz - Bolivia, the Regional Newborn Screening Program (R-NBSP) for urban and rural areas has been leading by Newborn Screening Laboratory (NBSL) of Arco Iris Hospital.
OBJECTIVE: To show the experience of R-NBSP and report the prevalence of CH in La Paz.
MATERIALS AND METHODS: The primary screening for high TSH levels has been the screening approach for CH used by R-NBSP. The hospital and health centers network increased from 8 to 67 in the 2008-2018 period. The NBSL has processed filter paper blood spots from heel samples obtained from each newborn. For term newborns, the sample was collected 24 to 72 hours after birth and for preterm infants, once they reached 40 corrected weeks. All samples were processed using the time-resolved fluorescence immuno assay technology. TSH values above 10 UI/ml were considered suspicious. The complete thyroid profile was performed in serum to confirm each suspicious sample. The false-positive rate was approximately 0.5%. The Pediatric Endocrinologist evaluated all CH patients and started treatment with oral levothyroxine. The Clinical Geneticist evaluated possible syndromic cases. Periodically, they received a clinical and laboratory follow-up.
RESULTS: In total 148853 newborns were screened. Initially, 885 samples were positive. Seventy cases of CH were confirmed. Female cases represent 61%. Newborn screening coverage was 21%. The frequency of CH was 1/2126 live births.
CONCLUSIONS: In Bolivia, there is no official National Program for neonatal screening. The experience accumulated over ten years in this R-NBSP contributes to laying the foundations for the development of a National Neonatal Screening Program for CH. The increase in newborn screening coverage for all newborns should be considered one of the greatest goals to be achieved.

P-199 - EPIDEMIOLOGY OF CONGENITAL HYPOTHYROIDISM IN THE INSTITUTO NACIONAL MATERNO PERINATAL, LIMA-PERU

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INTRODUCTION: The newborn screening program for congenital hypothyroidism started in the Instituto Nacional

Materno Perinatal in 2003 and is mandatory in Peru by Law 29885.
OBJECTIVE: The aim of this study was to investigate the epidemiology of congenital hypothyroidism (CH) in newborns in the Instituto Nacional Materno Perinatal, Lima-Peru.
METHODS: Period: October 2003 to December 2018. Dried blood spots samples were collected from newborns until December 2018. The samples collected from October 2003 to February 2016 were tested by ELISA METHOD: From March 2016 to May 2018 with Time-resolved Fluoroimmuno Assay and subsequently from June 2018 to December 2018 with fluorometric immunoassay. Cutoff value: TSH ≥ 10 uIU/mL. The data were analyzed using SPSS statistics program.
RESULTS: 238 373 infants were screened, of these, 99 cases with CH were detected and 23.9 % of these cases were male and 76.1 % were female. The coverage of the screening program was 80.9 %. Incidence: 3.3 cases for 10 000 live birth. Average newborn weight: 3431.8 ± 526 grams. Average newborn height: 49.8 ± 2.6 cms. TSH levels: 64.5 m IU/L, IQ reange [24.5-102.2]. Average of mothers age: 27.7 ± 6.9 years. Ninety per cent of mothers came from urban areas, and their poverty levels were mostly III and II quintiles. On average, there were higher TSH values in the full-term pregnancies in relation to late-term ones. However, when TSH levels were analyzed according to the classification of term pregnancies in the ANOVA test (p=0.792), there were no statistically significant differences.
CONCLUSION: It is important to study the epidemiology of congenital hypothyroidism (CH) in order to identify the potential risk factors in newborns.

P-200 - NEONATAL SCREENING FOR CONGENITAL HYPOTHYROIDISM: IMPORTANCE OF THE SECOND SAMPLE IN PREMATURE NEWBORNS.

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INTRODUCTION: Hypothyroidism is the situation resulting from a decrease in the biological activity of thyroid hormones at tissue level, either due to poor production or resistance to their action on the target tissues, transportation alteration or metabolism. It can be congenital or acquired. Primary congenital hypothyroidism (CH) is the most frequent cause of newborn (NB) endocrinopathies. About 90% of cases are permanent hypothyroidisms and the rest transient ones.
CH causes mental and growth retardation, preventable through early diagnosis and timely treatment. Its detection is carried out by newborn screening (NBS) programs. The level of thyrotropin (TSH) is determined from whole blood on filter paper (DBS), followed by the measurement of total thyroxine (T4) when TSH is elevated. The blood sample is obtained from the NB heel at 48-72 hours of life. It is recommended to repeat the sample at two weeks in premature infants, critically ill patients, children undergoing surgery and twins in the face of the possibility of late TSH elevations.
OBJECTIVE: To highlight the importance of evaluating a second NBS sample in preterm infants.
MATERIALS AND METHODS: Observational, descriptive, retrospective study. Confirmed cases detected from 2008 to 2018 were analyzed.
The provincial NBS program of Chaco measures first the TSH in DBS with enzyme immunoassay (cut-off value: 8 mUI/mL), requesting a second sample to premature babies and other conditions. The confirmation is done by serum TSH and free T4 analysis. Subsequently, ultrasound, radioisotopic and radiological images are added. The follow-up consists of periodic clinical controls including TSH and free T4 dosage.
RESULTS: Out of 177,518 NB screened, 111 CH cases were detected; 14 corresponded to premature infants, of which two were negative in the first sample and positive in the second, taken between two and four weeks of life.
CONCLUSIONS: We emphasize the importance of taking the second sample in preterm infants for the early detection of CH in order to establish an early treatment and thus, avoid serious consequences in the child.

P-201 - VALUES OF THYROID STIMULATING HORMONE IN NEWBORNS WITH DOWN SYNDROME.

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INTRODUCTION: Down syndrome (DS) is the most frequent autosomal aneuploidy in humans, caused by the trisomy of chromosome 21. Mother´s age > 35 years is considered one of the main risk factors. Children with DS have a higher incidence of endocrine and autoimmune disorders than the general population. Few studies of TSH blood concentrations in newborns (NB) have been done in Mexico.
OBJECTIVE: To know the number of newborns with DS registered on newborn screening identification cards received in a centralized newborn screening laboratory from Mexico and to describe the values of TSH from that population.

MATERIALS AND METHODS: We identified all newborns with DS through the electronic system SySDQM® and analyzed the results of quantification of human thyroid stimulating hormone (hTSH) obtained by fluorometric assay (GSP hTSH kits, Perkin Elmer®) from 415 NB with DS compared to a control group of 1,712,936 NB non-affected with Down Syndrome.
RESULTS: We found 415 cases of NB with DS, finding a prevalence according to maternal age, they were classified as following; 1: 6,142 they were mothers <15 years old, 1: 7,864 were from mothers of 15-19 years old, 1: 5,716 were from mothers 20-35 years old; and in the group of mothers > 35 years old we found 1: 674. The mean of TSH concentration in blood in the group with DS was 1.34 ± 4.96, while in the control group without DS we found an average number of 0.87 ± 3.44 ($p<0.0001$).
CONCLUSIONS: In the studied population 1: 4127 NB presented DS, as expected the higher prevalence is in the group of mothers > 35 years old. The hTSH concentrations in the newborns with DS were higher than in the control group.

P-202 - CONGENITAL ADRENAL HYPERPLASIA; DIFFICULTIES IN THE NEONATAL DIAGNOSIS.

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INTRODUCTION: Two cases about girl´s brothers with Congenital Adrenal Hyperplasia (CAH), whose mothers were prescribed with corticoids in the first months of their pregnancies which could have altered the 17-hydroxyprogesterone (17OHP) values in the newborns.
OBJECTIVES: Report the difficulties that may occur in the 17OHP results interpretation exemplified in the above mentioned clinical cases.
MATERIALS AND METHODS: Two male patients with clinical histories of CAH are presented. The 17OHP dosage on dried blood spots (DBS) was made through a competitive enzyme-immunoassay. The serum dosage was made by radioimmunoassay, using a direct measurement protocol (NE-17OHP) and a post-organic phase extraction protocol (E-17OHP). The molecular study of the 21-hydroxylase (CYP21A2) gene was made at Garrahan Hospital.
RESULTS: Case 1: Female patient´s brother with CAH salt-wasting (SW). His mother was administrated with Dexamethasone during the first months of pregnancy. Full-term newborn, with normal birth weight, normal ionogram and E-17OHP 4.5ng/ml (cut-off: 5.3ng/ml). Clinical control and follow up allow detecting a weight loss. Blood analysis were repeated after 20 days of life: Na+ 134 mEq/l, K+ 7 mEq/l, NE-17OHP >25 ng/ml (cut-off: 21.3 ng/ml), Testosterone 0.9 ng/ml, Δ4-Androstenedione 7.0 ng/ml, and Cortisol 5.9 ug/dl. Molecular studies were not authorized by the family.
Case 2: Brother of two ill sisters, one with CAH simple virilizing and the other with a SW type. His mother was administrated with Dexamethasone until the fifth month of pregnancy. Full-term newborn, normal birth weight, normal ionogram and 17OHP on DBS, NE-17OHP: 12.2 ng/ml, E-17OHP 0.3 ng/ml. At age of 7 months, NE-17OHP > 25ng/ml, E-17OHP 13.9ng/ml. I172N and R356P mutations were found (same mutation in his sisters).
CONCLUSIONS: In spite of corticoid therapy has been described that can only affect neonatal screening in the last month of pregnancy, we found two patients with familiar history of CAH whose mothers were prescribed with high doses of Dexamethasone in their first months of pregnancy. Initially the 17OHP value was normal but lately it increased being difficult to know if it was due to the corticoid therapy or to the own CAH evolution. The utility of early molecular studies would reinforce the diagnosis.

P-203 - NEONATAL SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA: COMPARISON OF METHODS AND DEFINITION OF GESTATIONAL AGE RELATED CUTOFF VALUES

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INTRODUCTION: Congenital Adrenal Hyperplasia screening is mandatory in Argentine since 2007. Neonatal screening in public health system is organized as a network of jurisdictional laboratories supplied by National Secretary of Health. Adoption of a new analytical system (Quantase - BioRad) determined the need to reevaluate cutoff values and compare their performance with a previously known methodology (DELFIA - PerkinElmer) used by the Newborn Screening Program of Buenos Aires City.
OBJECTIVE: To compare both methods and to define cut-off values based on adjusted gestational age (aGA).
MATERIALS AND METHODS: In 9870 dried blood samples from newborns, 17-hydroxyprogesterone (17OHP) was analyzed using two competitive immunoassays: Quantase Neonatal 17-OHP Screening (Evolys TwinPlus equipment) and DELFIA Neonatal α-17OHP (Victor fluorometer). Statistical analyses were performed using MedCalcV13.1.2 software. Linear regression between both analytical systems was done. CDC 17OHP QC material (Atlanta, USA) was evaluated at low, medium and high levels and were used to determine accuracy (Recovery %) and inter-assay precision (CV%). Bland Altman analyses were performed. To define

cut-off values, samples were divided into aGA groups whose mean 17OHP was statistically different. For each one, population parameters mean and 99th percentiles (99p) were evaluated.
RESULTS: a) Regression analysis: $17OHP_{Biorad}$ (nmol/l) = 4.613 + 1.028 $17OHP_{PerkinElmer}$ (nmol/l) 95% CI a: [3.897; 5.3300] and b: [0.9823; 1.0743] p<0.0001, b) CDC 17OHP QC (nmol/L blood): Recovery%: PerkinElmer (n=12) = Low: 89.9, Medium: 111.6, High: 113.3; Biorad (n=9) = Low: 93.7 Medium: 85.9 High: 87.2. CV%: PerkinElmer (n=12) = Low: 13.1, Medium: 12.5, High: 15.6; Biorad (n=9) = Low: 14.2, Medium: 19.3, High: 17.7. c) Limits of agreement from Bland Altman difference and ratio plots: Mean (± 1.96 DS)= -4.9 (-20.6 to 10.6) and 0.7 (-0.4 to 1.8) (nmol/L blood). d) Statistical parameters: F-ratio: 161.3; p<0.001, Scheffé test for all pairwise comparisons: aGA groups (weeks): mean and 99p (nmol/L blood): < 34 (n=206): 56.3 and 291.5; 34 (n=140): 41.1 and 260.6; 35 (n=206): 32.7 and 125.7; 36 (n=413): 22.7 and 71.0, 37 (n=744): 17.9 and 58.6, > 37 (n=8161): 12.8 and 39.9.
CONCLUSIONS: Quantase Neonatal 17-OHP Screening demonstrated good agreement and analytical performance compared to DELFIA. It was able to obtain preliminary cut-off values corrected for aGA.

P-204 - 17OH-PROGESTERONE BIRTH WEIGHT-ADJUSTED CUT-OFF VALUES: THE IMPORTANCE OF THEIR PERIODIC REDEFINITION AND THEIR IMPACT ON THE NEWBORN SCREENING SPECIFICITY.

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INTRODUCTION: Newborn screening (NBS) for Congenital Adrenal Hyperplasia is strongly influenced by gestational age and birth weight (BW). Both variables critically affect the NBS specificity; recall rate (RR) and rate of newborns referred for confirmatory testing (CT). Fundación Bioquímica Argentina implemented a 17OH-Progesterone (17OHP) BW-adjusted cut-off value (CO) for the first time on Dec/1997, having changed it several times in response to changes in the kits reagents design and the methods performance, or due to a periodic plan for CO redefinition.
OBJECTIVE: To describe the performance of the actual 17OHP BW-adjusted CO implemented on Jul/2018 in comparison with the previous CO, in real-time and retrospectively, and their impact on NBS specificity and on the actions required when an abnormal result was obtained.
MATERIALS AND METHODS: 17OHP was measured using the AutoDELFIA Neonatal α-17OH-Progesterone kit. Actual and previous CO were defined analyzing results of 167,264 and 44,172 newborns screened in 2017 and 2009 respectively. Actual-CO: BW < 815 g: 246.0 nmol/l; BW = [815-4270] g: order-6-polynomial function; BW > 4270 g: 23.0 nmol/l. Previous-CO: BW < 900 g: 110.0 nmol/l; BW = [900-3650] g: order-4-polynomial function; BW > 3650 g: 22.3 nmol/l. Newborns screened: Jan-Jun/2018 (Retrospective Evaluation): 87,219; Jul-Dec/2018 (Real-time Evaluation): 83,739. Parameters analyzed: RR and number of newborns requiring collection of a second sample (SS) or their direct referral for CT.
RESULTS: Retrospective Evaluation: using the previous-CO, 377 newborns (0.43 %) showed abnormal results, 358/377 requiring a SS and 19/377 their referral for CT. When these newborns were retrospectively evaluated using the actual-CO, such parameters were 154 (0.18 %), 145/154 and 9/154 respectively. Real-time Evaluation: using the actual-CO, 152 newborns (0.18 %) had abnormal results, 147/152 requiring a SS and 5/152 their referral for CT. When this last population was analyzed using the previous-CO, 195 other newborns became abnormal (total-RR = 0.41 %), 178/195 requiring a SS and 17/195 their referral for CT. A detailed analysis showed that the higher impact of implementing the actual-CO was on newborns ≤ 2500 g with a RR reduction of 90.0 %.
CONCLUSIONS: CO periodic redefinition is a recommended good laboratory practice that improves NBS diagnostic exactitude. Imperceptible day-to-day changes in the population distribution can affect the NBS specificity. More efficient CO definition is possible when large newborn populations are analyzed, especially for low BW newborns.

P-205 - EVALUATION OF CUT OFF VALUES FOR 17a-HYDROXYPROGESTERONE BY TWO METHODOLOGIES IN URUGUAYAN PRETERM BABIES

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INTRODUCTION: Newborn screening tests quantify 17α-hydroxyprogesterone (17-OHP), which is elevated in affected infants with Congenital Adrenal Hyperplasia (CAH). Preterms newborns usually have higher values of 17OHP, so it could cause false positive results. In this study we evaluate the cut off of 17-OHP in preterm infants by two competition assays.
OBJECTIVE: Evaluate the cut off for premature infants by two methodologies and compare them with bibliography.
MATERIALS AND METHODS: Samples from newborns with 36, 35 and 34 weeks of gestational age (WGA) from September to December 2018, were analyzed for 17-OHP using AutoDELFIA (Perkin Elmer) and NeoScreen 4 (Intercientifica). All samples were from whole blood obtained by heel puncture on filter paper Whatman 903, with less than

3 days of life. Calculations were performed using Microsoft Excel.
RESULTS: Cut off values were calculated as 99.5 percentile. During the period studied we received 142 samples from 36 WGA, 85 from 35 WGA, and 40 from 34 WGA. For NeoScreen technology the calculated cut off were: 14 ng/ml, 33 ng/ml, 17 ng/ml for 36, 35 and 34 WAG respectively. Autodelfia shown lower cut off for all the groups: 8 ng/ml, 16 ng/ml and 14 ng/ml.
CONCLUSIONS: Values of 17-OHP cut off from premature babies are lower than expected according to the ones reported in the commercial kit from Perkin Elmer. In all cases cut off for NeoScreen 4 are higher than Perkin Elmer. For 34 and 35 WGA we found an unexpected results, so more samples should be tested to establish the final values.

P-206 - EXPERIENCE IN THE NEONATAL SCREENING FOR CYSTIC FIBROSIS IN THE PUBLIC HOSPITAL DR GUILLERMO RAWSON, SAN JUAN- ARGENTINA.

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INTRODUCTION: Given the possibility of having numerous tools to diagnose Cystic Fibrosis (CF), a diagnostic algorithm, using different strategies of combined methodologies depending on the age of the patient, has been implemented.
OBJECTIVE: Analyze the usefulness of the diagnostic algorithm for CF according to the age of the patient, using techniques available.
MATERIALS AND METHODS: 68291 dried blood specimens were evaluated in newborns (NB), between 2 and 15 days of life, from March 2010 to December 2018. ImmunoChem Trypsin-MW ELISA, MP-Biomedicals was used for the IRT measurement. Positive cases with IRT >130 ng/ml were recited before 30 days and a 2nd IRT was determined.In those NB with IRT > 90 ng/ml in the 2nd sample, Molecular Biology (MB) or Sweat test (ST) was done, depending on their age.
10 mutations were investigated through 2014: DF 508, G542X, G551D, N1303K, 1717-1G - A, W1282X, S1255X, R334W, 3849 + 10 Kb and G85E. Then, 36 mutations were incorporated (CFTR test). The ST was made by iontophoresis (Gibson and Cooke).
RESULTS: Out of 68291 samples, 255 were elevated for 1st IRT, 212 of them were negative in the 2nd IRT. 20 patients were positive for the 2nd IRT, MB was performed and mutations were found in 8 patients (incidence 1 in 8536). There were 12 patients not confirmed, 11 presented IRT near the cut off, concluding that they were false positives for the technique. One showed a value of IRT > 750 ng/ml and did not show any mutation. 23 patients (9%) did not attend to the recitation. One of them came back from clinical service within 18 months. A ST was performed and then an MB test, confirming CF diagnostic.
CONCLUSION: The direct referral of these patients to MB would reduce the age range at the moment of the diagnosis as well as the false negatives in the ST.
The different strategies proposed as diagnostic CF algorithm, will facilitate early diagnosis and adequate procedures depending on the age of the patient, helping to reach an accurate diagnosis, thus collaborating with the implementation of early therapeutic strategies to our hospital population with CF.

P-207 - COMPARISON OF TWO NEWBORN SCREENING ALGORITHMS FOR CYSTIC FIBROSIS

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INTRODUCTION: Despite being a very common hereditary pathology, cystic fibrosis (CF) is difficult to diagnose, and although its inclusion in newborn screening (NBS) improves its detection, it is influenced by pre-analytical, analytical and post-analytical factors. In order to improve diagnostic efficiency, changes have been made to the NBS Provincial Program in Misiones.
OBJECTIVE: To compare results obtained with different NBS algorithms in two periods.
MATERIALS AND METHODS: The following data were analyzed, extracted from the NBS Provincial Program records: number of studied newborns; number of high Immunoreactive Trypsin (IRT); successful recitations by high IRT results in first sample; number of diagnosed patients. These data were compared for the 2012 - 2017 period (IRT/IRT/Sweat Test algorithm, with recitation of patients in charge of Ministry of Health, high IRT > 150 ng/ml); and 2018 (IRT/DF508 in first sample/IRT/Sweat test algorithm with recitation by the laboratory, high IRT > 100 ng/ml). All IRT were analyzed with MP Biomedical colorimetric ELISA kit.
RESULTS: For each period, results were, respectively: analyzed patients, 74655 and 15705; high IRT, 47/year (mean) and 91/year; successful recitations 90 (32% of 282) and 69 (76% of 91); patients diagnosed 9 (1: 8295) and 9 (1: 1745). In the 2018 period, the DF508 mutation was detected in the first NBS sample in 7 patients, 3 in the homozygous state and 4 heterozygotes, representing 55.5% of the alleles.
CONCLUSIONS: Diagnosis of CF from NBS improved markedly with the new proposed algorithm, despite a marked increase in recitations that were maintained at an adequate

level of recall (below 1%). Searching for more CFTR mutations in the first sample and the choice of an IRT cut-off point that decreases recitations without loss of diagnostic sensitivity will make it possible to increase the efficiency of the Provincial Program.

P-208 - STRATEGIES IMPLEMENTED IN PARAGUAY FOR THE NEONATAL DETECTION, DIAGNOSIS AND TREATMENT OF INDIVIDUALS WITH CYSTIC FIBROSIS

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INTRODUCTION: Cystic fibrosis (CF) is an autosomal recessive pathology, capable of being detected neonatally, caused by mutations in the CF transmembrane conductance regulator gene (CFTR), the pathology is multisystemic and early treatment modify the expectation and quality of life of those affected. The incidence in Paraguay for 2017 was 1/5,112 newborns (NB).
OBJECTIVE: Present the main strategies and the results achieved for the detection, diagnosis and treatment of individuals with CF, in the National Neonatal Screening Program.
METHODOLOGY: A review of the annual operating plan, reports, publications and documents issued from 2004 to 2018 was made.
RESULTS: In these 15 years, 16 strategies were implemented that allowed the detection, diagnosis and treatment of individuals affected by CF. Among those that stand out the development of a pilot project for the screening of CF in NB, by means of immunoreactive trypsin (IRT) measurement; delivery of a basic basket of medicines, supplies and equipment for the treatment of individuals with CF detected by the program as well as those previously diagnosed; implementation of the sweat test; preparation of a multidisciplinary Clinical Guide; automation of the IRT analysis that allowed the universalization of the screening, and finally the identification of the mutations present in the affected individuals. In 2015, it was possible to reach 100% coverage of the NBs that attended to the services of the Ministry of Public Health and Social Welfare. From January 2004 to December 2018, 179 individuals received their treatment in the program, 144 of which were detected neonatally.
CONCLUSION: In these 15 years the strategies implemented allowed us to universalize the neonatal detection, which leads to a better quality and life expectancy of the individuals affected by CF. At present, it would only be necessary to implement a Multidisciplinary Care Center for individuals with Cystic Fibrosis.

P-209 - VARIATION IN THE IMMUNOREACTIVE TRYPSINOGEN CONCENTRATION DURING THE NEONATAL PERIOD IN A NEWBORN POPULATION OF BUENOS AIRES PROVINCE, ARGENTINA.

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INTRODUCTION: Cystic Fibrosis (CF) is an autosomal recessive disease with a significant morbidity and mortality. Newborn screening (NBS) offers the best opportunity for early intervention and improved results. NBS programs for CF have evolved rapidly and various algorithms have been implemented trying to increase their diagnostic accuracy, however all of them begin with the Immunoreactive Trypsinogen (IRT) measurement and are influenced by the same variables affecting such measure. Sample collection age (SCA) is one of such variables, and due to the inverse relationship between the IRT concentration and the newborn´s age, to adjust the cut-off value (CO) is recommended in order to avoid false negative results.
OBJECTIVE: To present the results of the statistical evaluation of the IRT distribution in a newborn population of Buenos Aires Province - Argentina during the neonatal period, in order to determine the IRT variation according to the SCA and to establish an adjusted-SCA CO.
MATERIALS AND METHODS: IRT was measured using the AutoDELFIA Neonatal IRT METHOD: A population of 164,593 newborns aged between 1 to 45 days of life (DOL) screened during 2017 was analyzed. Newborns were grouped in 15 DOL ranges. Mean, median, and 99.5 and 99.9 percentiles were calculated. CO was defined considering the 99.5 percentile.
RESULTS: Samples of most newborns (89.9 %) were collected during the first 5 DOL, and 96.4 % during the first 10 DOL. Barely 0.8 % of samples were collected the 1st DOL. IRT mean, median and 99.5 percentile showed a very similar behavior with almost constant values between 1-11 DOL. From 11th DOL onwards IRT showed a marked decrease until it become constant again from 15th DOL onwards. 99.9 percentile was difficult to systematize due to its erratic behavior. The IRT CO was defined at 64.0 and 55.0 ng/ml for newborns $\leq$ 11 DOL and $\geq$ 15 DOL respectively, and adjusted with an order-2-polynomial function in the range 11-15 DOL.
CONCLUSIONS: As expected, IRT concentrations showed a decrease with the newborn´s age during the neonatal period, highlighting the need to use IRT CO adjusted according to the SCA in order to avoid the loss of CF cases.

P-210 - CUT-OFF LEVELS FOR THE IMMUNOREACTIVE TRYPSIN TEST IN A MEXICAN POPULATION OF NEWBORNS

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INTRODUCTION: Cystic Fibrosis (CF) is a genetic, chronic disease that affects multiple organs, a diagnosis of CF has lifelong implications for affected individuals; consequently a timely diagnosis needs to be accurate. CF neonatal screening in Mexico is based on the immunoreactive trypsin (IRT) assay as primary screening. However, if only a single specimen is routinely collected, use of an IRT/IRT algorithm would require for a second dried blood spot specimen at two weeks old approximately. At this age, elevated IRT values are more specific for CF because IRT values decrease in infants.
OBJECTIVES: To present the first IRT cut-off point defined for newborns from two to five days old, and the second cut-off defined for newborns from 15 to 30 days old calculated in order to ensure that any newborn get an equitative test.
METHOD: To calculate first cut-off 500 samples from newborns between two and five days old were analyzed, and using a data set demographic characteristics, specific birth weight, health condition and term infants were examined. The second cut-off was calculated from 133 samples of babies between 15 and 30 days old. Samples were processed with NEONATAL IRT Screening ELISA Kit (Zentech, S.A.), an enzyme linked immunoassay. Assays were read on a spectrophotometer and results concentration of each sample were analyzed in statistical software in order to calculate the cut-off's.
RESULTS: For the first cut off, the result for 99.5th percentile was 85.2 µg/L, and the mean concentration of this population was 38.9 µg/L. The second cut off was 74.5 µg/L. It is important to establish our own cut off points periodically to reduce false positives and negatives, when more newborns are tested.
CONCLUSIONS: These cut off values have been set in an attempt to maximize sensitivity and positive predictive value. Although the initial cut off for IRT/IRT decreased over time from 85.2 µg/L to 74.5 µg/L, in attempts to decrease false negative results in the IRT/IRT, method all abnormal results from the second test it is verified by sweat test.

P-211 - EVALUATION OF CFTR MUTATIONS ANALYSIS AFTER 16 YEARS OF CYSTIC FIBROSIS NEWBORN SCREENING PROGRAM

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BACKGROUND: Cystic fibrosis (CF) newborn screening (NBS) program has been conducted in Buenos Aires city through an IRT/IRT protocol from December 2002 to December 2016, and an IRT/PAP protocol since January 2017, both followed by confirmation with sweat test (ST) and/or genetic analysis.
OBJECTIVE: Describe biochemical results and molecular characterization of CFTR gene in CF patients identified by NBS, and compare different molecular approaches.
METHODS: A retrospective observational study was conducted by analyzing data from 929 samples received from the NBS program. Inclusion criteria: first IRT (DELFIA) measurement ≥60ng/mL and/or meconium ileus. Molecular analysis was performed by screening between 20 and 50 mutations, depending on the kit available at that moment.
RESULTS: Inclusion criteria were met by 799 individuals. Among them, 59 CF patients were identified, 49 bearing two mutations and 10 only one. The most frequent mutations among the 118 CF alleles were F508del (72.9%) and G542X (3.4%). The median value of first IRT measurement was 190 ng/mL, and 180.5 ng/mL (n=43) for the second. PAP measurements were available in 9 patients, and were over the cut-off value. Sweat test, available in 39 patients, was positive in 34, and intermediate in 5. Regarding carrier detection, the median value of first IRT in 34 individuals bearing one mutation was 97.5ng/mL, and 83ng/mL (n=19) for the second. PAP measurements (n=6) were over the cut-off value. Sweat test, available in 24 individuals, was negative in 18, and intermediate in 6. Three molecular approaches were evaluated: analysis of F508del, analysis of F508del and other 6 frequent CF mutations, and analysis of 50 mutations by a commercial kit. Each strategy would detect 73%, 80% and 99% out of 118 affected alleles, and would identify at least one mutation in 91%, 95% and 100% of the CF patients, respectively.
CONCLUSION: Molecular analysis proved to be specially useful in diagnosing CF patients without ST measures or with intermediate results, since it can be performed on blood spot samples. The analysis of 50 mutations currently utilized would have detected at least one mutation in all the patients identified during 16 years of NSB in Buenos Aires city.

P-212 - PERFORMANCE OF GENETIC TESTS IN CYSTIC FIBROSIS (CF) PATIENTS FROM A REFERENCE CENTER IN ARGENTINE

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Cystic Fibrosis is the most common autosomal recessive disease in Caucasians. Latin American populations, including Argentine, are ethnically heterogeneous due to a mixture of European descendants and Native Americans. For this reason, a national panel of mutations is difficult to define.
OBJECTIVE: The aim of this study was to describe genetic mutations found in patients attending an Argentine CF Reference Center, and to assess the sensitivity of the different genetic methods used.
METHODS: the genetic data from patients with confirmed CF diagnosis were analyzed. During the 2006- 2016 period, a panel of 29 mutations was used. Since 2016, Next Generation Sequencing (NGS) and Multiplex Ligation dependent Probe Amplification (MLPA) was introduced. We reviewed all patients with this technique.
RESULTS: 164 patients were included. The most common mutations in our cohort were: p.F508del: 60% (CI95% 54.5-65.4), G542X: 4.5% (CI95% 2.6-7.4), W1282X: 1.5% (CI95% 0.5-3.5), R334W: 1.2% (CI95%0.3-3.1), 1811+1.6 Kb: 1.2% (CI95% 0.3-3.1), 1717 1G-A: 0.9% (CI95% 0.2-2.7) and 2789+ 1G-A: 0.9% (CI95% 0.2-2.7). With the 29 mutation panel and NGS with MLPA, we identified 80.7% (CI95% 76.1-84.9) (265 alleles) and 91.4% (CI95% 87.9-94.3) (300 alleles), respectively. We found both mutations for 67% (CI95% 59.3-74.2) and 86% (CI95% 79.7-90.9) of patients, using the 29 mutation panel and NGS with MLPA, respectively (McNemar test, $p<0.01$). We were not able to identify the both mutations in 6 patients (3.6%) (CI95% 1.3-7.8).
CONCLUSIONS: NGS with MLPA was more sensitivity than the 29 mutation panel to identify both mutated alleles in each confirmed CF patient. Argentine CF patients have a heterogeneous genetic profile.

P-213 - EVALUATION OF A HIGH RESOLUTION MELTING-BASED TEST FOR THE DETECTION OF 18 CYSTIC FIBROSIS-CAUSING MUTATIONS WITH HIGH FREQUENCY IN LATIN AMERICA

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INTRODUCTION: Cystic fibrosis (CF) is the most common life-threatening autosomal recessive genetic disorder caused by mutations in the CF Transmembrane Conductance Regulator (CFTR) gene. A High Resolution Melting (HRM)-based test has been developed for the detection of 18 CF-causing mutations with high frequency in Cuba and Latin America.
OBJECTIVE: To evaluate the analytical parameters of the HRM-based test in samples collected as dried blood spots (DBS) coming from CF patients and their relatives.
METHODS: The HRM-based test allows the detection of mutations G85E, R334W, S466X, I507del, F508del, 1717-1G> A, G542X, R553X, 2183AA>G, 2789 + 5G> A, 3120 + 1G> A, 3272-26A> G, R1066C, Y1092X, R1162X, 3849 + 10KbC>T, W1282X and N1303K. It includes an internal control of PCR amplification. A post-PCR HRM step allows the identification of specific-amplified DNA fragment containing CFTR mutations. A total of 230 samples were evaluated in the HRM-based test and subsequently the results were confirmed by using the CF StripAssay 4-410 test or by automatic DNA sequencing as reference tests. The percentage of concordance between HRM-based test and the reference tests was determined. The clinical and analytical specificity were also evaluated.
RESULTS: A total of 141 mutated alleles were detected, being F508del the predominant mutation. At least one CFTR gene mutation was detected in 88 samples. Out of these 88 samples, 53 had two mutations: 34 compound heterozygotes and 19 homozygous. It was obtained a 100% of agreement between the HRM-based test and the reference tests. The CFTR gene mutations could be detected without cross-reactions and a clinical specificity of 100% was obtained.
CONCLUSIONS: The HRM-based test was able to detect with high specificity 18 mutations of the CFTR gene that cause CF. This method will allow increasing the scope of the molecular diagnosis of CF in Latin America; it is simple, fast and cost-efficient. The test can be used for the genetic characterization of individuals with clinical suspicion of CF and for carrier testing, reducing the risk of having a child with CF.

P-214 - CYSTIC FIBROSIS IN SANTA FE PROVINCE (ARGENTINA)

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IINTRODUCTION: The innovative therapies for genetic disorders that are being designed by the international scientific community depend on the type of mutation rather than the condition of the patient. This imposed the systematic inclusion of DNA analysis in our newborn screening algorithm.
OBJECTIVES: a) To estimate the population incidence, b) To report the allelic frequency found, c) To describe all the

mutations present of the different regions of Santa Fe according to regional ethnic group.
METHODOLOGY: We analyzed the data of live newborns from the public provincial sector by regional genotyping supplied by the Direction of Statistics of the Health Ministry, and records of newborn screening on genetic disorders from 01/01/2011 to 30/04/2018, period in which the mutation panel method was incorporated and sequentially expanded: 2011 PCR allele specific for p.Phe508del, p.Gly542X and p.Asn1303Lys; in 2013 OLA PCR with 32 mutations; in 2016 InnoLipa with 36 mutations and 2018 Elucigen (ARMS) with 50 mutations.
RESULTS: 201.366 newborns were analyzed, 33 patients were diagnosed with cystic fibrosis: incidence: 1/6102. 24 patients (72.7%) presented 2 mutations of those studied, 6 patients (18.2%) 1 alone and, 3 patients (9.1%) did not present any, were diagnosed by the Sweat Test. The allelic frequency of the mutations found were: p.Phe508del: 63.6%, p.Gly85Glu: 6.1%, p.Gly542X: 4.5%, p.Arg1162X: 3.0%, and p.Lys684SerfsX38, p.Asn1303Lys and L49P (de novo mutation): 1.5%. In Rosario Node the mutations found were p.Phe508del, p.Asn1303Lys and p.Gly85Glu; Santa Fe Node: p.Phe508del, p.Gly542X, p.Gly85Glu and p.Arg1162X; Rafaela Node: p.Phe508del and p.Gly542X; VenadoTuerto Node: p.Phe508del; and in Reconquista Node: p.Phe508del, p.Arg1162X, p.Lys684SerfsX38 and L49P.
CONCLUSIONS: The severe mutation classes I and II found in the two alleles of each patient studied, determine severe clinical phenotypes and highlight the genetic heterogeneity of the population in Santa Fe, reassuring the need for molecular diagnosis that allows predicting the course of the disease since the pre-symptomatic stage, and establishing early specific medical therapies that prevent irreversible sequels and improve the quality of life and life expectancy of the patients.

P-215 - EVALUATION OF UMELISA® TIR NEONATAL TESTS IN THE AUTOMATIC ANALYZER SUMAUTOLAB

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INTRODUCTION: The automatic analyzer from SUMA® technology has been extensively tested under routine conditions. SUMAUTOLAB is intended to fully process all newborn screening tests available until now (TSH, T4, 17 OHP, PKU and GAL).
OBJECTIVE: To validate and optimize UMELISA® TIR NEONATAL for the determination of immunoreactive trypsin (IRT) levels in dried blood spots on filter paper using SUMAUTOLAB analyzer.
MATERIALS AND METHODS: Controls were prepared from whole human blood at 55% hematocrit with concentrations between 50 and 160 ng IRT/mL of whole blood and impregnated on Whatman 903 filter paper. Moreover, four controls from the Center for Disease Control and Prevention (CDC), were used to evaluate the performance characteristics. Influence of sample elution, immunoreaction time and interference with other analytes on IRT levels were evaluated. Intra and inter-assay variation coefficients (CVs), were determined from estimating IRT in two replicates of each control, for 30 operating days. CDC controls were measured twofold on 7 consecutive days for evaluating the test recovery. The zero calibrator and 3 samples (31, 15, and 7 ng IRT/mL) were analyzed 40 times to estimate limit of detection (LOD) and limit of quantitation (LOQ). Finally, a comparison between UMELISA TIR semi-automatic test and SUMAUTOLAB was made by linear regression analysis using 1093 newborn dried blood samples.
RESULTS: Best results were achieved for one and half hours of elution with constant agitation and one hour of immunoreaction. Interference with other analytes was not observed. Intra and inter-assay CVs ranged between 3,5-7% and 5-9,5%, respectively. The average percentage of recovery was over 95%, LOD and LOQ were 2,8 and 4,4 ng/mL blood, a good agreement was obtained when comparing the semi-automatic technology with SUMAUTOLAB (r2> 0,8).
CONCLUSIONS: UMELISA® TIR NEONATAL can be performed in the SUMAUTOLAB analyzer. The same reagent kit for semi-automatic technology can be used in the SUMAUTOLAB. Furthermore, the instrument offers advantages, such as, the usage of low volumes of reagents, reduction in the processing time and the number of handling errors by operators, and additional control procedures were included which increase the reliability of the system.

P-216 - PILOT STUDY FOR THE DETECTION OF CYSTIC FIBROSIS IN THE CUBAN NEONATAL SCREENING PROGRAM USING THE ULTRAMICROANALYTICAL SYSTEM

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INTRODUCTION: In Cuba no newborn screening program has been implemented for cystic fibrosis (CF). The UMELISA® TIR Neonatal, has been developed for the measurement of immunoreactive trypsin (IRT) in dried blood spots on filter paper.

OBJECTIVE: To evaluate the analytical performance of the UMELISA® TIR NEONATAL in the national network of SUMA laboratories.
METHODS: Newborn dried blood spots (DBS) were evaluated in sixteen SUMA laboratories from several regions of the country. An IRT/IRT/DNA protocol was followed using a cut-off value of 50 ng/mL. DBS were analyzed to determine the influence of birth weight (BW), gestational age (GA), sex and sample processing time on IRT levels. A t-test was used to compare mean IRT concentrations among groups. A p-value <0.05 was considered as significant.
RESULTS: From January to June 2018, 6470 newborns were studied, obtaining a mean IRT value of 12.1 ng/mL (range 0-358 ng/mL) and a median of 9.0 ng/mL. Fifty-two samples (0.78%) were above the cut off level and sixteen samples (0.24%) were elevated again in the re-screening process. One of these samples was confirmed positive for CF by molecular biology technique (phe508del/c.3120+1G>A), constituting the first newborn screened and early diagnosed in Cuba. Samples were taken on average at 6 days and processed at 9 days. Second DBS samples were collected on average at 14 days and processed at 16 days of birth. Low BW (<2500 grams) and preterm babies (GA<37 weeks) had significantly lower IRT levels (n=518; 10.9 ng/mL and n=352; 10.4 ng/mL respectively). IRT concentrations in females (n=3023; 12.7 ng/mL) were statistically higher than in males (n=3290; 11.7 ng/mL). Lower IRT values were also observed in those samples processed after 10 days of collection (n=123; 10.2 ng/mL).
CONCLUSIONS: Sex, BW, GA and sample processing time lead to differences in IRT concentrations without consequences for the screening algorithm. However, because the sample size is small, further studies evaluating the influence of these factors must be carried out. The performance of UMELISA® TIR Neonatal in the network of SUMA laboratories has been satisfactory, hence CF newborn screening was extended throughout the country from January 2019.

P-217 - FIRST STEPS IN NEONATAL SCREENING FOR CYSTIC FIBROSIS IN CORRIENTES, ARGENTINA

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INTRODUCTION: Cystic fibrosis (CF) is a severe recessive genetic disease, with a high incidence in the Caucasian population. Early diagnosis in the neonatal period can reduce morbidity and early mortality.
OBJECTIVE: To evaluate the incorporation of neonatal screening for CF for the provincial program through two determinations of immunoreactive trypsinogen (IRT) and sweat test as diagnostic confirmation.
MATERIALS AND METHODS: Of 8536 samples of newborns (NB) (dried blood on filter paper) received for metabolic screening, 5872 were studied from July 2018 to January 2019, through the quantification of IRT by ELISA method micro-immuno assay. Selection criteria: NB up to 7 days of life and less than 15 days of transit in the first sample, cut-off: 100 ng/ml. The samples with higher values were recalled. Second samples collected before 25 days of age, cutoff: 70 ng/ml. Patients with higher values were analyzed with sweat test. Positive patients were referred to molecular analysis.
RESULTS: 2664 NB were not investigated for not fulfil the selection criteria. 30 NB (0.51%) presented values higher than the cutoff point in the first sample, 4 NB (0.07%) were positive in the second sample. 1 NB with cystic fibrosis was confirmed at 27 days of age. Among the false positives: 1 trisomy 18, 1 trisomy 21 with renal failure, 1 premature with respiratory and gastric involvement (deceased)
CONCLUSIONS: Actions for newborn screening for CF in all newborns should be implemented. The local availability of IRT test and the sweat test along with the good response of the provincial network made early detection possible. The sweat test and IRT/IRT protocol were useful for the early detection of CF

P-218 - GALACTOSEMIA IN COSTA RICA: MOLECULAR CHARACTERIZATION OF 22 CHILDREN IDENTIFIED BY NEWBORN SCREENING IN 2001-2018.

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INTRODUCTION: Galactosemia is an autosomal recessive inborn error of metabolism of carbohydrates. This pathology is caused by the deficiency of any of the following enzymes of galactose metabolism: galactokinase 1 (GALK1), galactose-1-phosphate uridylyltransferase (GALT) and UDP-galactose-4-epimerase (GALE). Newborn screening (NBS) for galactosemia has been done in Costa Rica for 18 years (2001-2018).
OBJECTIVE: This study presents data about GAL mutations, and describes the genotype and estimate the frequency of the mutations encountered among our galactosemic patients confirmed, after 18 years of NBS implementation in Costa Rica.

MATERIALS AND METHODS: Total galactose (TGal) concentration was determined by fluorescent galactose oxidase method (2001-2013: Victor 1420-TM, and 2014-2018: GSP), with Neonatal Total Galactose kit, PerkinElmer, Inc. The cut off value was 12.8 mg/dL (trust interval of 99.2%). Confirmatory tests included: thin layer chromatography and molecular analysis of GALK1, GALT and GALE genes, by Sanger sequencing.
RESULTS: Throughout 18 years of NBS, 1 118 625 babies have been screened, where 32 of them had positive confirmatory test for galactosemia. Molecular analysis confirmed the diagnosis of 19 patients, in 3 cases a single variant was identified and finally in 10 cases no variants were detected. Among patients in whom some variant was identified, 9 were in GALT and 13 in GALK1.
In GALT (NM_000152.3) 2 patients were homozygous (p.Q188R) (c.[563A>G];c.[563A>G]). Five patients were compound heterozygous, where c.[-119_-116delGTCA;940A>G] (Duarte variant);[563A>G] genotype was the most frequent (3 patients), the other 2 patients were c.[-119_16delGTCA;940A>G];[c.584T>C] (p.L195P). Finally, in 2 cases just a single variant was detected, these patients carried c.[-119_-116delGTCA;940A>G] and c.512T>C variant (p.F171S).
Furthermore, 9 patients were homozygous for a GALK1 (NM_000154.1), c.[1144C>T];[1144C>T] (p.Q382*).Three cases were compound heterozygous c.[766C>T] (p.R256W);[1144C>T], and one patient carried a single variant , c.1144C>T.
CONCLUSIONS: The variants found most frequently in GALT and GALK1 were c.[-119_-116delGTCA;940A>G] and c.1144C>T, respectively. Further analysis are required in order to confirm or rule out the diagnosis in heterozygous patients, and in those where no variants were detected. In those patients, where no variants were detected, closer follow-up should be recommended in order to identify which clinical factors produce increases in TGal determination.

P-219 - CLASSIC GALACTOSEMIA IN TWO ISOLATED NATIVE POPULATIONS FROM SOUTHERN BRAZIL: PHENOTYPICAL AND GENETIC CHARACTERIZATION

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INTRODUCTION: Classic galactosemia is an inherited condition that can result in complications as hepatocellular damage, failure-to-thrive, developmental delay, cataracts and premature ovarian failure. Diagnosis is established by detection of high levels of galactose-1-phosphate; reduced activity of galactose-1-phosphate uridyltransferase (GALT); and/or by identification of pathogenic variants in GALT gene. It is possible to perform newborn screening (NBS) for this condition, though it is not part of public NBS program in Brazil. Treatment consists on a lactose-restricted diet which is life-saving but cannot prevent long-term complications. Out ot the ten individuals with classic galactosemia followed at Hospital de Clínicas de Porto Alegre, four are from two native indigenous populations.
OBJECTIVES: To characterize a cohort of patients with Classic Galactosemia from two native populations from Southern Brazil.
MATERIALS AND METHODS: Clinical data was obtained through file's review. DNA was extracted from blood samples. After PCR amplification of individual exons and related intronic boundaries, direct sequence analysis of GALT gene (GenBank NG_009029.1) was performed.
RESULTS: Four individuals from three different families were included in the study (male: 3; mean age at inclusion: 6 years). All presented reduced GALT enzyme activity (mean: 2.87 μmol/h/gHb; range: 2-5; NRV: 33-67). They came from isolated populations from Southern Brazil and identified themselves as Native American from two distinct ethnic groups [Guarani (n=1) and Kaingang (n=3)]. Three individuals started symptoms during the first week of life. The mean age of diagnosis was 3.68 years (Range: 0.25-10). Manifestations included developmental delay (3/4); hepatic failure (2/4); feeding problems (2/4); failure-to-thrive (2/4); microcephaly (2/4); extrapyramidal findings (1/4); cataracts (1/4) and cirrhosis (1/4). Besides Classic Galactosemia, one patient also presented with oculocutaneous albinism, deafness and autism, and had normal karyotype. All patients are homozygous for two novel mutations in GALT gene: c.90_91insG (p.His31Alafs*9) and c.529A>G (p.Met177Val). Concerning the second mutation, bioinformatic analyses revealed that it may affect the splicing mechanism, thus being most probably also a pathogenic mutation.
CONCLUSIONS AND DISCUSSION: Our data suggest a higher incidence of Classic Galactosemia among Guarani and Kaingang indigenous peoples from South Brazil is possibly related to endogamy. However, the presence of the same variants in both groups is intriguing.

P-220 - MAPLE SYRUP URINE DISEASE IN COSTA RICA: MOLECULAR CHARACTERIZATION OF 30 CHILDREN IDENTIFIED BY NEWBORN SCREENING IN 1990-2018.

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INTRODUCTION: Maple syrup urine disease (MSUD) is an autosomal recessive inborn error of metabolism caused by an altered function of branched-chain α-ketoacid dehydrogenase (BCKD) complex. Mutations in subunits E1α (BCKDHA), E1β (BCKDHB) and E2 (DBT) cause the disease. Newborn screening (NBS) for MSUD has been done in Costa Rica for 28 years.
OBJECTIVE: The aim of this work is to describe the genotype and estimate the frequency of the mutations encountered among our MSUD patients after 28 years of NBS implementation in Costa Rica.
METHODS: Bacterial inhibition test (Guthrie) was used for NBS from 1990 to 2005. From 2006 onwards amino acids quantification is done by tandem mass spectrometry (MSMS). Molecular analysis of BCKDHA, BCKDHB and DBT genes was performed by Sanger sequencing, using specific primers for coding exons and its intronic flanking regions.
RESULTS: To 2018, 1.828.312 babies have been screened, where 43 affected individuals have been identified, 21 by Guthrie test and 22 by MSMS. The estimated prevalence is 2 affected individuals per 100.000 live births (1: 42519). Here we describe 30 out of 43 detected patients, since 13 of them died before sequencing analysis implementation. All cases were confirmed by molecular analysis, and the variants detected were in BCKDHA (6 patients) and BCKDHB (24 patients) genes.
In BCKDHA (NM_000709.3) the most frequent genotype was: c.[117delC];[117delC] (4 patients) and the rest were: c.[484+1G>A];[484+1G>A] and c.[661_664delTACG];[1234G>A]. The c.117delC variant was the most frequent (67%), whereas c.484+1G>A is a novel variant, according to our literature review.
Furthermore, 17 patients were homozygous for a BCKDHB (NM_183050.3), c.[564T>A];[564T>A] (1 patient) and c.[853C>T];[853C>T] (16 patients, including 2 brothers). Seven patients were compound heterozygous where c.[564T>A];[853C>T] genotype was the most frequent (4 patients, including 2 brothers), the others carry c.853C>T variant in trans configuration with c.564T>A, c.633+1G>A and c.832G>A. As observed, the most frequent variant found in BCKDHB was c.853C>T (82%).
CONCLUSIONS: In Costa Rica MSUD prevalence is 2: 100.000 live births and is caused by mutations that affect function mainly of E1β subunit, followed by E1α. In our sample, the most frequent genotype was NM_183050.3(BCKDHB): c.[853C>T];[853C>T]. Furthermore, NM_000709.3(BCKDHA): c.484+1G>A variant is likely pathogenic.

P-221 - BIOTINIDASE DEFICIENCY: INCIDENCE AND CORRELATION BETWEEN ENZYMATIC ACTIVITY AND MOLECULAR FINDINGS IN A POPULATION OF MEXICAN NEWBORNS

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INTRODUCTION: Biotinidase deficiency (BIOT) is an inborn error of metabolism with an estimated incidence of 1 in 61,000 newborns (NB). BIOT impairs biotin recycling and diminishes its bioavailability, leading to neurocutaneous manifestations, ketolactic acidosis, as well as organic aciduria. To prevent such manifestations, newborn screening (NBS) allows timely detection and early treatment. Therapeutic decisions are currently based on enzymatic activity, as no clear genotype-phenotype correlation has been established for BIOT, due to the heterogeneity in clinical presentation described among patients.
OBJECTIVES: To estimate BIOT incidence in a Mexican NB population, and to demonstrate a correlation between enzymatic activity and genetic findings in BIOT NBS referred patients.
MATERIALS AND METHODS: We analyzed 249,442 NBS reports performed by Genomi-k from July 2005 to December 2018. Presumptive positives cases, previously assessed by semi-quantitative fluorometric assay, were requested for serum enzymatic activity and BTD gene sequencing. A normal enzymatic activity was considered above 5 nmol/min/ml. The biochemical phenotype under the limit was classified in: profound deficiency (<0.75), partial deficiency (0.75-2.25), and false positive (2.26-4.9) characterized by low-activity and lack of symptoms.
We applied the Mann-Whitney U test to analyze the genotype-phenotype impact (i.e. variants and enzymatic activity, respectively) between group 1 (D444H/D444H; n=8) and group 2 (D444H/pathogenic variant; n=7).
RESULTS: Overall, we identified 8 NB for partial BIOT, with an estimated incidence of 3.2: 100,000 NB, no NB for profound BIOT, and 21 false positive cases. Furthermore, D543E, Q456H, D444H (most frequent variant), F443Y, F403V-D444H, R211H, K176N, A171T-D444H, and C33Ffs variants were identified.
The statistical analysis concluded a significant effect between enzymatic activity and genotype (mean of groups 1 and 2 was 4.2 and 11.3 respectively; $U = 1.5$, $z = -3.067$, $p = 0.001$, $r = 0.792$).
DISCUSSION AND CONCLUSIONS: Our estimated incidence is comparable to the U.S. and Spain (3.9 and 3.3:

100,000 NB, respectively). Furthermore, D444H/pathogenic variant had a significant impact, causing lower enzymatic activity than D444H/D444H. Therefore, molecular findings may help in defining the biotin dose in ambiguous cases, supporting current literature.
NBS is of paramount importance to detect patients for this condition and start promptly their appropriate therapeutic approach.

P-222 - FIVE YEARS EXPERIENCE OF NEWBORN SCREENING FOR MEDIUM CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY.

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INTRODUCTION: The newborn screening for MCADD was added to our program after the set-up of the mass spectrometry (LC-MS/MS) technology in 2014. It is the seventh disease that is screened in our program.
OBJECTIVE: to describe the results of the MCADD newborn screening at 5 years of its implementation.
MATERIALS AND METHODS: Beginning in January 2014 MCADD screening was conducted in every newborn of our program. Blood samples were collected on filter paper Whatman 903 within 2-5 days of life. Non derivatized reagent from PerkinElmer and Chromsystems were used over the five yerars on API 3200 LC-MS/MS instrument from ABSciex. Primary marker used was Octanoylcarnitine (C8), cut off value of 0.28 uM (99.9 th percentile) Since July 2014 it was added the informative ratio C8/C10 with a cut off value of 1.0. Since that moment, babies with C8 and C8/C10 ratio above cut off values were recalled. Since January 2016, C8 cut off value of 0.21 uM and C8/C10 ratio of 1.0 using Chromsystems reagents were implemented. Confirmatory studies include acylcarnitines profile, Urine organic acids and molecular studies.
RESULTS: The total number of newborns tested until December 2018 was 119,353, the total number of recalled babies was 31, Recall rate 0.026%. Five babies were confirmed with MCADD, positive predictive value at screening was 16.1 %. Mean days of life at newborn sampling was 2.8 days and mean days of life at physician visit for confirmatory testing was 9.2 days. All the patients were asymptomatic at their first physician visit and had good evolution.
CONCLUSION: The introduction of this new disease at our program, allow the detection of patients with medium chain acyl coA dehydrogenase deficiency on a timely manner with acceptable recall rate and good evolution.

P-223 - RAPID DETECTION OF A 3-HYDROXY-3-METHYLGLUTARYL-COA LYASE DEFICIENCY CASE THROUGH A SIMULTANEOUS NEONATAL SCREENING IN BLOOD AND URINE.

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INTRODUCTION: Traditional newborn screening for the detection of inborn errors of metabolism (IEM) is done analyzing dried blood samples on filter paper, however these require further analysis to confirm or discard the disease. An alternative to speed up the diagnosis could be the simultaneous analysis of dried blood and urine samples on filter paper.
OBJECTIVE: To present a case of a 3-hydroxy-3-methylglutaryl-CoA lyase deficiency quickly diagnosed by simultaneous analysis of dried blood and urine on filter paper.
MATERIALS AND METHODS: The dried blood sample impregnated on filter paper from a male newborn weighing 2,750 g, size 50 cm and 40 weeks of gestation was analyzed by Waters® MS-MS using a triple quadrupole and the dried urine sample on filter paper was analyzed by GC-MS of Agilent Technologies®.
RESULTS: High concentrations of C5OH were found in the blood screening: 5.10 µmol/L (normal value < 0.64 µmol/L), C6DC: 0.21 µmol/L (normal value <0.24 µmol/L), C5OH/C8 ratio: 51.00 (normal value < 2.13), C5OH/C0 ratio: 0.43 (normal value < 0.01). In the urine, the following urinary organic acids were identified: 3-hydroxymethylglutaric acid, 3-methylglutaconic acid, 3-methylglutaric acid, 3-hydroxyisovaleric acid and 3-methylcrotonylglycine. Both results confirm the diagnosis of 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. The time from sample arrival to the laboratory until the notification of diagnosis was 3 days.
CONCLUSIONS: IEM can be detected promptly with the simultaneous analysis of dried blood and urine samples on filter paper.
The simultaneous analysis of samples in the neonatal screening could represent a great breakthrough alternative for the diagnosis of metabolic disorders in a shorter period of time and transcending the possibility of offering a better quality of life for screened newborns.

P-224 - EXPANSION OF NEWBORN SCREENING IN QATAR TO INCLUDE SICKLE CELL, THALASSEMIAS AND OTHER HAEMOGLOBINOPATHIES

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INTRODUCTION: Haemoglobinopathies are a group of disorders which have abnormal production or structure of hemoglobin molecules. They are inherited as autosomal recessive. Qatar has a diverse population with more than 70% expats, predominantly from southeast Asian countries, middle east, Africa and Mediterranean countries.
OBJECTIVES AND METHODS: Newborn screening for Sickle cell in Qatar was performed for two common mutations by molecular genetics. Since June 2018, we have expanded the screening to include thalassemias (α/β), Hemoglobin C/D/E using Bio-Rad VARIANTnbs in biochemical genetics. The new method uses high performance liquid chromatography.
RESULTS: The switch of method from molecular to biochemical screen was done in collaboration of all the laboratory teams (genetics, biochemistry, hematology) with clinical teams (newborn screening unit and paediatric hematology). A total of 19,462 screens were performed on dried blood spots (DBS) from June 2018 to Jan 2019. During this 8 month period, we have identified 13 cases of sickle cell disease, 7 β thalassemia major, 5 hemoglobin D disease and 3 alpha thalassemia major. We also diagnosed 167 sickle cell traits, 90 Hemoglobin D traits, 35 Hemoglobin E traits and 18 Hemoglobin C traits. The confirmation is done by recall of the babies by newborn screening unit to collect whole blood for hemoglobin electrophoresis performed in hematology. The incidence of Sickle cell disease is 1 in 1500 livebirths (LB), β-thalassemia major 1 in 2800 LB, Hemoglobin D disease 1 in 3900LB and α-thalassemia major 1 in 6500LB.
CONCLUSIONS: With the molecular screen, we were only able to detect sickle cell traits and sickle cell disease. The new method has helped us identify thalassemia major (α/β), Hemoglobin C/D/E traits and diseases which are highly prevalent in our population of Qatar. The limitation of new method is it cannot distinguish HbE from HbA2, as they produce peaks with same retention times; the latter is raised in β thalassemia. We are looking to introduce 2nd tier test on DBS using electrophoresis to distinguish the two peaks. This will avoid recall of the babies for collection of whole blood for electrophoresis. Also the method cannot identify Thalassemia traits (α/β) with sufficient sensitivity.

P-225 - MOLECULAR CARACTERIZATION OF RARE HEMOGLOBINES FOUND BY NEWBORN SCREENING

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INTRODUCTION: In 2013, Uruguay started a nonselective pilot program for newborn screening for hemoglobinopathies. Since then, many variant trait hemoglobin have been found by CE-HPLC. Many clinical complications have been reported due to the presence of rare hemoglobins, even thought if it were found as a trait. This fact gives the importance of their characterization. In consequence, Newborn screening Laboratory in Uruguay is evaluating the incorporation of molecular studies for α and β gen as part of the diagnosis.
Objetive
Present the results obtained from samples analyzed as a pilot program for molecular studies of rare hemoglobin.
MATERIALS AND METHODS: Molecular studies were performed on seven patients detected by Newborn Screening. All of them presented a HPLC profile of carriers of a rare hemoglobin. Genomic DNA was extracted from the same samples used to the screening studies, obtained from heel prick on filter paper Whatman 903.
All exons from β, α1 and α2 and its corresponding intronic sequences were amplified by PCR (polymerase chain reaction), purified and analyzed in an automatic sequencer ABI 310 from Applied Biosystems. Every mutation profile was compared with the databases Ensembl and HGMD.
RESULTS: We found five mutations on β gene of hemoglobin chain, one in α1 and one in α2. In gene β we found three different mutations, 20 A>T (Glu6Val) present in three cases, 19 G>A (Glu6Lys) and 23 A>G (Glu7Gly). Moreover, 137A>G (His45Arg) was present in α1 exon 2, and 134C>G (Pro44Arg) in α2 exon 2. All mutations were detected in heterozygosis as newborn screening suggested.
These hemoglobins were found in databases like Hb S, Hb C and G-San José, Hb Fort de France, Hb Kawachi respectively.
CONCLUSION: Rare hemoglobins are frequent in Uruguayan population, so molecular studies are very important and helpful to characterize these cases. However, to complete the molecular profile is necessary to incorporate thalassemia studies.

P-226 - GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY AND NEWBORN SCREENING – 6 YEARS EXPERIENCE IN THE FEDERAL DISTRICT PUBLIC HEALTH SYSTEM

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INTRODUCTION: The Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is a widespread inherited enzyme deficiency that causes neonatal hyperbilirubinemia and hemolytic anemia. The early diagnosis allows parents orientation and prevents negatives outcomes. In Brazil, the Newborn Screening Nacional Program offers to the whole country a six diseases newborn screening test which does not include the G6PD deficiency. The Federal District, Brazil's capital, has its own laws and provides to the population a newborn screening test for 30 diseases including the G6PD deficiency.
OBJECTIVE: Presents the Federal District's experience in 6 years of newborn screening for G6PD deficiency.
METHODS: Data were collected from the software that runs the neonatal screening laboratory.
RESULTS: From January 2012 to December 2018, 309.346 newborns were screened by fluorimetry (normal reference range: > 22 U/dl Hb). All the positive samples were confirmed by a second one, until the 30th day of life. The disease's incidence is 3% of the population. There is also a whole blood third sample, measured by UV kinetic method (normal reference range: > 6,7 U/g Hb) at the age of 2 years old to assure the diagnosis. The diagnosis was confirmed in 96,5 % of these samples. All the parents receive the proper orientations at an educational lecture when they are informed about the clinical characteristics of the disease and learn to avoid the anemia hemolytic triggers. The patients follow up is carried out by the Primary Care where the physicians were trained to identify the signals and symptoms of the hemolytic anemia. If one of them goes to hemolytic anemia, the physicians from Primary Care refer them to the pediatric hematologist.
CONCLUSION: As long as G6PD deficiency is a very common disease, it would be a great challenge to provide individual assistance to each committed child in a public health system with limited resources. But the early diagnosis, the parent's group orientations, the primary care asymptomatic patients follow up and the pediatric hematologist support, enabled the provision of adequate and qualified care to these children.

P-227 - COMPARISON OF FDA-CLEARED NEWBORN SCREENING PLATFORMS FOR LYSOSOMAL STORAGE DISORDERS - POMPE AND MPS I

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INTRODUCTION: As Latin American countries seek to expand newborn screening to include lysosomal storage disorders (LSDs), prospective results from active LSD screening programs can be used to compare the performance of available screening methodologies. Two FDA-cleared platforms are currently available for LSD enzyme testing from dried blood spot specimens – tandem mass spectrometry (MS/MS) and digital microfluidic fluorometry (DMF). Both methods are currently being actively used for newborn screening (NBS) of Pompe disease and Mucopolysaccharidosis Type I (MPS I) in several states and both platforms offer FDA-cleared specific reagent kits that use synthetic substrates and have the ability to screen for multiple LSDs in a single run. The ability of each method to discriminate normal from affected samples must take into account the multiple sources of variability (biological/genetic variability, DBS sample quality, gestational age at sampling, for example) that exist between newborn samples.
OBJECTIVES: We will use published data sets from active LSD screening programs to evaluate the clinical performance of MS/MS and DMF for Pompe and MPS I newborn screening.
RESULTS: Substantial data sets are available from the prospective LSD screening programs in the United States from the states of Missouri (N=441,000 infants screened using DMF) and Illinois (N=220,000 infants screened using MS/MS). The data sets do not show significant differences between the two testing platforms in terms of the positive predictive value (PPV). It is clear, however, from these and other data, that further testing algorithms are required to improve the PPV of both the MPS I and Pompe disease screening tests using any of the currently available platforms.
CONCLUSIONS: We conclude that the active and pilot LSD screening programs in the United States are excellent, unbiased resources for those interested in initiating NBS for LSDs into their laboratories. The emerging clinical results from these prospective screening programs reflect the real world performance of each platform and should be considered alongside the associated costs (equipment, maintenance, personnel, etc.) and workflow of each platform to determine the best fit for each NBS laboratory.

P-228 - NEWBORN SCREENING FOR SIX LYSOSOMAL DISEASES: PILOT STUDY IN BRAZIL

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INTRODUCTION: Lysosomal storage disorders (LSDs) are inborn errors of metabolism caused by excessive accumulation of undegraded metabolites due to the deficiency of soluble lysosomal hydrolases, membrane proteins or accessory proteins that lead to an impaired turnover of complex macromolecules, including glycosaminoglycans, proteins and lipids. Many LSDs already have specific therapies, and in most cases the earlier introduction of therapy provides better outcomes. However, patients are usually diagnosed only after a long "diagnostic odyssey", with therapies introduced when irreversible manifestations are already present.
OBJECTIVE: This project aims to evaluate the feasibility of newborn screening (NBS) for selected LSDs in Brazil, using a tandem mass spectrometry (MS/MS) platform with a 6-Plex kit (supplied by PerkinElmer).
MATERIALS AND METHODS: The study includes the screening for Gaucher, Fabry, Pompe, Krabbe, Niemann-Pick A/B and Mucopolysaccharidosis I. This is a prospective study in 20,000 unselected newborns from the state of Bahia, Brazil. The newborns with low enzyme activity are further evaluated by biochemical and molecular genetics methods until the diagnosis is confirmed and are referred for treatment as appropriate. All lysosomal enzymes were analyzed with NeoLSD MS/MS kit (Perkin Elmer) on a Waters Xevo TQ-S Micro.
RESULTS: Validation of the method was conducted in dried blood spots provided by the supplier and from unselected newborns. Instrument optimization was conducted in order to increase the signal and to decrease the in source fragmentation. Initial cutoffs were established as percentage of median in nmol/h/mL, as 0.8 (Gaucher), 1 (Fabry), 1.6 (Pompe), 0.8 (MPS I), 0.46 (Krabbe) and 0.9 (Niemann-Pick A/B).
CONCLUSIONS: Further positive samples will be included in order to confirm the cutoffs. This validation of the MS/MS method enabled the beginning of a pilot study, which, when completed, will include 20,000 newborns and will provide important information about the feasibility of a NBS for LSDs in Brazil.

P-229 - PRECISION EVALUATION OF THE MULTIPLEX NEOSCREEN4 KIT

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INTRODUCTION: NeoScreen 4 from Intercientifica is a fluorimetric assay on xMAP platform that allows simultaneous quantification, from a single spot of whole blood, of 4 parameters: 17OHP, IRT, TSH and T4. The assay uses high specificity proteins coupled to magnetic microspheres of different colors associated to the biochemical marker to quantify. T4 and 17OHP are analyzed in solution by a competition assay, while IRT and TSH in a like-sandwich assay. In 2018 our laboratory introduced this technology to newborn screening program. Precision was established by CV% calculation.
OBJECTIVE: Evaluate the precision of a multiplex kit for TSH, 17OHP, IRT and T4.
MATERIALS AND METHODS: Two levels of CDC control (low and high for each biomarker) and the three internal controls provided with the commercial kit, were used to establish the precision of the METHOD: Determination of the four biomarkers was carried out during 20 days. All samples were whole blood on filter paper Whatman 903. Calculations were performed using Microsoft Excel.
RESULTS: Coefficients of variation were calculated for each biomarker in both groups of controls. In all cases commercial kit controls showed lower CV% (from 8% to 22%) than CDC Controls CV% (from 11 to 33%). In both types of controls used, T4 and 17-OHP presented lower precision than IRT and TSH. Higher variability is shown in the biomarkers determined by competition assay.
CONCLUSIONS: The different behaviors observed between both types of controls support the need of run a third part quality control to validate each batch. To complete de evaluation of this method it will be necessary to continue with complementary studies and comparison with other methodologies.

P-230 - DEVELOPMENT OF A HEAVY METAL FREE FILTER PAPER DEVICE FOR SCREENING NEWBORNS FOR LEAD, MERCURY, AND ARSENIC POISONING

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INTRODUCTION: Lead poisoning is serious, underdiagnosed and preventable, damaging many organ systems. Even exposures resulting in blood levels below the current United States `action' level (5 µg/dl) can cause cognitive impairment. The fetus and newborn are most vulnerable.
Argentina banned leaded gasoline in 1996, but lead contained in leaded paint, water pipes, and atmospheric lead from mining remain problems.
Current tests for lead require venipuncture and 0.5-3.0 ml blood therefore testing is delayed or omitted, precluding treatment and environmental actions.

METHODS: EnMed has developed a filter paper that is lead free and protects sample from environmental contamination allowing precise quantification. It requires only 1 drop of blood.
A protective housing and built in desiccant allow easy transport. DBS specimens are analyzed using Inductively Coupled Plasma Mass Spectrometry, permitting sensitivity to trace levels. Three isotopes were scanned (mz 206, 207, 208). Validation studies for certification of a new DBS screening test were carried out.
RESULTS: 49 de-identified newborn DBS specimens were analyzed. Median lead value was 13.3 ppb while blank was 5.7 ppb. Analysis of 82 matched venous blood and finger stick DBS from untreated cards were significantly correlated, but with a relatively weak R2 value of 0.022. When lead free card was used, correlation became highly significant with an R2 of 0.99. Calibration curves were run with spiked internal standards and NIST external standards. Reproducibility was demonstrated using 9 DBS from the same patient (median 1.9932 µg/dl – range 1.828-2.185). 96 newborn DBS samples were screened without special precautions to prevent environmental contamination. 69 were below the recommended cutoff of 5.00 µg/dl; 13 5.00-9.99; 14 10.00-44.00; and 0 >44.00. This illustrates the need to use not only lead-free filter paper, but a collection device that protects from environmental contamination.
DISCUSSION: Mining lead in Latin America carries risk of environmental lead exposure, increasing risk of infants prenatally and postnatally. Population-based screening of gravid women and/or their newborns should be considered in mining regions. A lead-free filter paper, protected from environmental contamination, can be used to collect DBS as a minimally-invasive alternative to venipuncture to estimate lead exposure.

P-231 - DETERMINATION OF CUT OFF VALUES FOR: TSH, T4, IRT AND 17OHP USING MULTIPLEX METHODOLOGY IN URUGUAY.

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INTRODUCTION: In 2018 we evaluated a new technology based on multiplex determination. NeoScreen 4 from Intercientifica is a fluorimetric assay on xMAP platform that allows simultaneous quantification of 4 parameters: 17OHP, IRT, TSH and T4. In order to get simultaneous results, the assay uses high specificity proteins coupled to magnetic microspheres of different colors associated to the biochemical marker to quantify. The reactions are carry out on solution, T4 and 17-OHP are analyzed by a competition assay, while IRT and TSH in a like-sandwich assay.
This technique has the advantage that use a single whole blood sample on filter paper for the four determinations.
OBJECTIVE: Evaluate the cut off for TSH, T4, IRT AND 17OHP with multiplex technology.
MATERIALS AND METHODS: During September 2018 we processed 1098 samples of whole blood obtained from heel prick on filter paper Whatman 903 of newborns with 2 days of life. All the samples were from babies with more than 37 weeks of gestational age.
The samples were analyzed using multiplex technology: Neoscreen 4 kit, Hamilton automatic robot Nimbus and Magpix detector from Luminex.
RESULTS: The cutoff values were calculated as 99 and 99.5 percentile to compare. For 99 percentile the results were: 17OHP 9 ng/ml, IRT 70 ng/ml, TSH 8.3 uIU/ml and T4 1.7 ug/dl. For 99.5 percentile the results were: 17OHP 19 ng/ml, IRT 84 ng/ml, TSH 8.6 uIU/ml and T4 1.4 ug/dl.
CONCLUSIONS: The cutoff values calculated for our population correspond with the ones reported in the instructions of the commercial kit. To be conservative, in this first period, 99 percentile was establish as the cutoff.

P-232 - MANUFACTURE AND EVALUATION OF A DEVICE TO VERIFY MINIMUM QUANTITY OF SAMPLE REQUIRED FOR ANALYSIS IN NEWBORN SCREENING

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INTRODUCTION: In Costa Rica, there has been a steady increase of unsatisfactory samples, for newborn screening since 2013. Insufficient quantity of sample to carry out the corresponding analyzes is the main cause.
AIM OF THE STUDY: The aim of this study is to evaluate if the prototype device assures the minimum amount of blood sample required, at the time of collection, to perform all the downstream analysis related to newborn screening. At the same time the device is also useful to evaluate correct sampling by health workers in medical facilities.
MATERIALS AND METHODS: The prototype device consists of a plastic transparent sheet (120x40 mm), with an 8 mm diameter opening in the center. The area of the opening is compared to the area of the sample obtained by capillary puncture. If the area of the sample is greater than the opening in the device, the sample is satisfactory. On the contrary, if the area of the sample is less than the opening on the device, the sample is considered unsatisfactory.
A total of 280 devices were distributed in 36 collection centers throughout the country.

RESULTS: After a follow-up regarding the production of unsatisfactory samples, we found that in 30 centers, the percentage of unsatisfactory samples had decreased, only 5 centers had increased and in 1 center the same percentage did not change.
CONCLUSIONS AND DISCUSSION: The extended distribution of this device throughout sample collecting medical facilities will have a favorable impact in decreasing the percentage of samples classified as insufficient. This tool will complement the use of other resources such as statistical monitoring and training.

P-233 - ECONOMIC EVALUATION OF A HEEL INCISION DEVICE COMPARED TO A PUNCTURE LANCET DEVICE FOR SAMPLE COLLECTION BY HEEL STICK IN NEWBORNS

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INTRODUCTION: Every infant born in Mexico is screened at around three to five days after birth using heel-stick blood spots collected with a sterile puncture lancet device (PLD) or a heel incision device (HID), to detect a variety of congenital conditions. Incision devices were specifically designed for sampling blood from newborn's heel; however, in most public screening programs in Mexico, PLD are still used, although these require a greater number of heel sticks and the procedure is more traumatic than with a HID. Several studies have reported that pain, puncture frequency, duration of procedures and tissue damage are significantly reduced with the use of HID, since they have a higher efficacy than PLD. This analysis was performed to determine whether using HID is cost-effective in Mexico.
OBJECTIVE: To carry out a complete economic assessment regarding cost-effectiveness for a public newborn screening program in Mexico.
MATERIALS AND METHODS: Efficacy data for heel-stick performed by different nurses using a HID or a PLD, was obtained in the literature. A random effect model was used obtain the mean of the number of required punctures and the probability of repeating the blood sampling with each device. A decision model explained the associated probability of having to repeat the blood sampling in newborns with each alternative. A univariate sensitivity analysis on the price of the alternatives and the measures of effectiveness was performed. The chosen option was the one that showed the lowest incremental cost-effectiveness ratio (ICER) among the alternatives.
RESULTS: Sample collection data from 520 neonates were evaluated, 259 procedures were made with PLD and 261 with HID. 96.2% of procedures with HID, required only one puncture to obtain a suitable blood sample, compared to 68.0% of procedures with PLD. The total cost of a newborn screening procedure in a public institution in Mexico, with a HID is lower, compared to the PLD, due to the greater efficiency that HID present. ICER obtained was US-$7.44 per patient.
CONCLUSION: The use of HID represents a cost-saving strategy when used to perform heel sticks in public health institutions in Mexico, compared to PLD.

P-234 - ANALYTICAL PERFORMANCE EVALUATION FOR NEONATAL TSH IN THE BUENOS AIRES CITY NEONATAL SCREENING PROGRAM USING AN EXTERNAL QUALITY CONTROL PROGRAM

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INTRODUCCION: The Neonatal Screening Program (NSP) of the Buenos Aires City Government has four laboratories in networking. Given the importance of the comparability of the results, the Sigma (σ) metrics is a useful tool for evaluating the analytical performance of the process.
OBJECTIVE: To evaluate the analytical performance of neonatal TSH (nTSH) for the four laboratories by calculating the overall σ index of each panel of dried blood samples, in the 2016 - 2018 period.
MATERIALS AND METHODS: The nTSH results of 32 External Quality Control Program (EQCP) samples (16 panels) provided by the Argentine Biochemical Foundation, were evaluated for the 4 NSP laboratories. The interlaboratory σ (σi) was calculated for each sample using: An Allowable Total Error (ATE%) of 54%, interlaboratory BIAS% and CV% (BIASi%, CVi%), according to σi = (ATE% - |BIASi%|)/CVi%. The percentage of adherence to the EQCP and the degree of compliance in terms of the maximum allowed BIAS% (BIAS%m) established by EQCP of ± 22.5% were calculated. The four laboratories use DELFIA (Perkin-Elmer) **METHOD**: The calculations were made using data of the peer group. The sigma analysis criteria consider σ>4 as optimum while σ<2 shows a need for improvement.
RESULTS: The overall compliance of the NSP to the EQCP was 95.3%. The overall compliance to the BIAS%m was 79.2 %, whereas it was 68.7 % for samples between 7 and 15 µUI/ml (which includes our cut-off stablished in 8 µUI/ml blood). σi index was calculated in 32 samples (range= 0.4-9.9):

12.5 % of them had σ<2, 43.7 % had 2<σ< 4 and 43.7 % had σ>4. In those samples between 7 and 15 µUI/ml (n=7), 14.3 % had σ<2, 57.1 % had 2<σ<4 and 28.6 % had σ>4.
CONCLUSION: The low number of samples offered by the provider close to our cut-off in the analyzed period is a certain limitation of this study. However, the results show that the analytical performance of the NSP is acceptable. Our data shows an opportunity for improvement and the need to keep monitoring the analytical performance of our Program.

P-235 - EXTERNAL QUALITY ASSURANCE PROGRAM FOR NEONATAL SCREENING IN LATIN AMERICA: PITFALLS AND ERRORS IN THE MEASUREMENTS AND REPORTING RESULTS.

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INTRODUCTION: External Quality Assurance (EQA) is an essential component of the Laboratory Quality System. The EQA Program for Neonatal Screening (PEEC-PN) of the Fundación Bioquímica Argentina was implemented in 2000. It distributes bimonthly control materials for Phenylalanine, TSH, IRT and Galactose to more than 190 Laboratories from 13 countries from Latin America.
OBJECTIVE: To describe the main pitfalls and errors made by the participants in the measurement and reporting results of Phenylalanine and TSH in the period Jun/17-May/18.
MATERIALS AND METHODS: Surveys #103 to #108 for Phenylalanine and TSH were included in the analysis. Parameters evaluated: number of registered Laboratories; number of results received after the deadline; shipping time of controls; time of analysis; time of reporting results; outliers; percentages of: units expression (UE), transposition results (TE), and results interpretation (IE) errors; and false negatives (FN) and false positive (FP) rates.
RESULTS: 194 laboratories participated in the 6 surveys, 92/194 (47.4 %) had perfect attendance, but 13/194 (6.7 %) did not send any result. 23 new laboratories applied for registration and 17 were deregistered. 898 results (84.4 %) were received. 177/898 (19.7 %) were received after the deadline, but they equally were included in the specific survey evaluation. Mean shipping time was 8.2 and 28.2 days for Argentina and the rest of the countries, respectively. Mean times of analysis and reporting results were 7.2 and 9.4 days, respectively. $Outliers_{Phe}$ = 2.3 %, $Outliers_{TSH}$ = 4.2 %; UE_{Phe} = 0.0 %, UE_{TSH} = 1.9 %; TE_{Phe} = 0.5 %, TE_{TSH} = 0.7 %; IE_{Phe} = 0.5 %, IE_{TSH} = 1.0 %; FN_{Phe} = 3.3 %, FN_{TSH} = 1.9 %; FP_{Phe} = 5.6 %, FP_{TSH} = 3.7 %. Percentages of Laboratories without FN results for Phe and TSH were 95.1 % in both cases, while they were 94.4 and 93.3 % in the case of FP, respectively.
CONCLUSIONS: The scenario of the EQA in Latin America pose different aspects that require to be improved: the continuous replacement of Laboratories (registration/deregistration), the lack of compromise of some participants who do not report any result, the logistic of shipments to countries out of Argentina, the constant presence of non-analytical errors caused by inattention in the reporting results (TE and IE), and the poor knowledge about the units used by the reagent manufacturers to assign values to the calibrators (UE), are the main topics to work.

P-236 - EXTERNAL QUALITY ASSESSMENT OF NEONATAL SCREENING WITH ULTRAMICROANALYTIC SYSTEM IN LATIN AMERICA. GENERAL EVALUATION OF MORE THAN TWO DECADES OF WORK.

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INTRODUCTION: For more than two decades Cuba has been facilitating an External Quality Assessment Program (EQAP) as an important analytical support to more than a hundred laboratories that carry out neonatal screening (NS) in Latin America, using the Ultramicroanalytic System (SUMA® technology).
OBJECTIVES: The aim of this study is to present the results of the implementation of this EQAP and its influence on the quality of NS program with SUMA® technology in these countries.
MATERIALS AND METHODS: Controls with different concentration levels for each analyte (TSH, T4, 17-OH Progesterone, Galactose and Phe) are provided to each participant on a quarterly basis. The results of variables such as the Average Variation Index (AVI) and the Average Accuracy Index (AAI) are statistically evaluated per month with a software designed for this purpose. The evaluation is made according to the results of AVI obtained by the laboratory; when AVI is 100, the evaluation is Very Good; in case of AVI from 100 to 200, it is Good; from 200 to 250 it is Regular; so, greater than 250 it is Deficient.
RESULTS: With analytical and technical assistance these indexes have progressively improved in more than 90 % of participants corresponding to a Very Good AVI results, resulting in better intra and interlaboratory precision, with coefficients of variation lower than 10% and 15%, respectively.
CONCLUSIONS: Our results confirm the relevance of the application of this quality control scheme as an additional component to support the screening program of the SUMA®

network of laboratories outside Cuba, guaranteeing a means of monitoring analytical performance and improving their quality.

P-237 - EXTERNAL QUALITY ASSESSMENT FOR TSH ON DRIED BLOOD SPOTS: INFLUENCE OF RESULTS´ EXPRESSION ON SCREENING INTERPRETATION.

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Proficiency testing is required for certification/accreditation as part of the quality management system of clinical laboratories and is a powerful tool for methods´ evaluation.
Our EQAS (ProgBA) provides laboratories dried blood spot materials that mimic newborn specimens, monthly statistics and cumulative reports to help participants maintain accurate and reliable testing practices. Newborn screening analytes (TSH, 17OHProgesterone, Phenylalanine, Immunoreactive Trypsin, Galactose, Biotinidase) are under the scope of ISO/IEC17043: 2010 since 2014.
TSH results are expressed in serum equivalent or whole blood units. Different cutoffs are used by individual labs, triggering difficulties in interpretation.
We present data for TSH. ProgBA distributed 12 samples prepared out of 7 pools to 50 laboratories (2017-2018 surveys); target values for interpretation were assigned as > 80% consensus. Homogeneity and stability of samples were checked before distribution. Results were evaluated using measured concentrations, cutoffs informed by each participant lab, expressed in whole blood or serum equivalent units, and positive ratio (PR) values and interpretation (recall patient or not). Major methods for TSH used were ELISA (MP-Biomedicals, n=48 (39%); Tecnosuma, n=31 (25%); BioRad, n=3 (2%); Monobind, n=14 (11%)) and DELFIA (PerkinElmer®, n=26 (21%)).
TSH results (Median [interquartile ranges] in mUI/mL and median PR) for a positive sample, >80% general and within-method consensus, were: MP-Biomedicals 80 [60-91], 4.4; Tecnosuma 65 [49-77], 6.5; BioRad 49 [45-58], 4.5; Monobind 48 [45-57], 3.2; Delfia 64 [57-67], 6.8. Results for a TSH borderline sample (47% general consensus) were (Median [interquartile ranges] and median PR): MP Biomedicals 18 [15-24], 0.98; Tecnosuma 7.4 [4.6-9], 0.68; BioRad 16 [15.6-17], 1.5; Monobind 11 [9.4-13], 0.74; Delfia 11 [10.7-12.7], 1.25. %Concordance with positive screening obtained for this sample was: Delfia 76%, BioRad 83%, Monobind 12%, MP-Biomedicals 47%, Tecnosuma 18%. Cutoffs used (mUI/mL) by Labs were for: Delfia=8 (35%), 9 (18%), 10 (35%), 15 (12%), BioRad=10 (67%), 20 (33%), Monobind=15 (92%), 25(8%), MP-Biomedicals=10(16%), 15(6%), 20(78%), Tecnosuma=8(29%), 9(12%), 10 (53%), 15 (6%).
Within-method differences in %concordance may be due to the use of different individual cutoff values and use of blood or serum equivalent units. Harmonization of results´ expression is of outmost importance to get comparable results in newborn screening.

P-238 - NEONATAL SCREENING REFERENCE MATERIALS. QUALITY ASSURANCE OF KITS PRODUCED IN THE IMMUNOASSAY CENTER

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INTRODUCTION: The development of today's society requires increasingly accurate and precise measurements as a fundamental attribute of product and service quality offered on the market.
OBJECTIVE: To reflect the results in the preparation and evaluation of the Working Reference Materials (WRM) used in the quality control of neonatal kits manufactured in the ImmunoAssay Center (IAC) and utilized in neonatal screening.
MATERIALS AND METHODS: The Secondary Reference Materials (SRM) were produced from acquired National Institute for Biological Standards and Control (NIBSC) Primary Reference Materials (PRM). Those tests that do not have PRM use commercial stock solutions as raw material for the WRM, prepared by gravimetric methods at three levels concentration: low, medium and high controls in dried blood on filter paper which are verified according to a calibration curve prepared from the secondary standard of each test. The WRM are evaluated with diagnostic batches and a statistical analysis is performed using STATGRAPHICS PLUS 5.0 and Microsoft Excel programs.
RESULTS: The percentages of relative accuracy of the WRM were between 10% (optimal value) and 20%. Besides, the slope values estimated in the linear regression significance tests were higher than 0.05, the level of significance established for the test; uncertainty limits were established for the WRM between two standard deviations, with a coefficient of variation ≤ 15%. In UMTEST BIOTINIDASA, visual observation of results was obtained with expected coloration. Tests used in the certification of the UMTEST GAL, PKU and Biotinidase kits, and so in the UMELISAS T4 Neonatal, TSH Neonatal, and 17OH Progesterone ones, are stable and will emit results of greater reliability and traceability for quality control.

CONCLUSIONS: The use of WRM has allowed the opportune detection of out-of-specification results, constituting a practical, direct and reliable tool in the quality certification of each kit batch, reducing also the costs and time used in the quality assurance of the IAC productions.

P-239 - ANALYTICAL VERIFICATION OF THE NEWBORN SCREENING TESTS TO EVALUATE THE PROCESS COMPETENCE.

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INTRODUCTION: The laboratory quality standard implementation is an efficient and useful way to demonstrate and attest competence, through better processes and high quality of results, which provide to the experts of different tools for reliable interpretation. The Ensayos y Tamizajes de México, newborn screening laboratory, accredited in the semi-quantitative neonatal tests: TSH, T4, TGAL and PKU from Tecnosuma; IRT, G6PD, and Biotinidase from Zentech; GALT from Astoria Pacific; as well as the qualitative tests hemoglobins variants from Bio-Rad and Biotinidase from Tecnosuma, under the Mexican standard NMX-EC-15189-IMNC-2015, ISO 15189: 2012.
OBJECTIVE: Verify the compliance of the newborn screening tests supported by analytical evidence to confirm their analytical performance when applied under the operating conditions of the laboratory, to confirm their performance against validation specifications of the manufacturer, to determine the tests are suitable for the intended use.
METHOD: For the verification we use "validation and verification of quantitative methods perform by clinical laboratories" as guide, from the standard NMX-EC-INMC-2015. All the tests were processed according with the analytical protocols described in the insert of each test. For semi-quantitative tests linearity, precision intra-assay and inter-assay, veracity and uncertainties were calculated; and for qualitative tests sensitivity, specificity, kappa index, positive predictive value and the negative predictive value were calculated. To calculate those parameters, controls from Centers for Disease Control and Prevention (CDC Atlanta) and calibrators from the commercial kits were used.
RESULTS: For IRT the correlation coefficient obtained was 0.99 against of the manufacturer 0.99, the precision intra-assay (% CV) obtained was 9.98 % the manufacturer was 15.07 % and the precision inter-assay (% CV) obtained was 2.35 % the manufacturer was 8.56 %. The verification performance for all test approved the acceptance criteria of the measured and calculated parameters, ratified their performance against validation specifications of the manufacturer and was suitable for the intended use.
CONCLUSIONS: Each clinical laboratory has to verify the performance of the reagent to determine the tests are suitable for the intended use. The verification process supports all the results emmited by the Ensayos y Tamizajes laboratory and provides a certainty in the quality of the results.

P-240 - QUALITY INDICATORS IN A PROGRAM OF METABOLIC DISEASES

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INTRODUCTION: The Metabolic Diseases Program (PEM) has been in place for 9 years, performing studies for the prevention of endocrine-metabolic diseases, in compliance with the laws in force.
To ensure the quality and efficiency of the post-analytical stage, indicators are used to monitor compliance with the process.
OBJECTIVE: To analyze the most relevant indicators in the post-analytical stage, such as: response time (TAT), index of recall (IR), recovery percentage of recall (RR) and diagnostic time (DT).
MATERIALS AND METHODS: We analyzed 151788 samples on filter paper from 2013 to 2018, with a processing frequency of 2 days a week for phenylalanine (fluorometric), thyrotropin (DELFIA), immunoreactive trypsin (ELISA), 17OHProgesterone (DELFIA), biotinidase (colometric) and galactose (fluorometric). The following quality indicators were calculated: 1) TAT: time between receiving the sample in the laboratory and sending the result, 2) IR: Number of recalls/Number of total samples, 3) RR%: Total number of recalls/Number of recalls received*100, 4) DT: time between the date of birth and the diagnosis of the disease evaluated.
RESULTS: The average TAT obtained was 72 hours, the general recall rate 1.7% and the recovery percentage 95%.The age of newborns at diagnosis of the diseases were: Congenital hypothyroidism 10 ± 2 days, Congenital adrenal hyperplasia 10 ± 2 days, Phenylketonuria 12 ± 2 days, Galactosemia 12 ± 2 days, Cystic fibrosis 16 ± 2 days and Biotinidase deficiency 15 ± 2 days.
CONCLUSIONS: According to the results obtained, the response time was acceptable. A stable total recall index has been achieved over the years that has allowed us to detect methodological and/or sample quality related deviations. The recall percentage received was very good, which allows us to achieve a high attendance rate. The age of newborns at treatment starting for each disease was optimal allowing newborns to receive their treatment in a timely manner. We consider that the use of these indicators is extremely important to evaluate the Metabolic Disease Program in a comprehensive

manner in order to implement corrective actions for continuous improvement.

P-241 - NEONATAL SCREENING PROGRAM KEY INDEXES IN A NEONATAL INTENSIVE CARE UNIT (NICU)

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INTRODUCTION: There is scarce information about Neonatal Screening Program Key Indexes applied to babies in a neonatal intensive care unit (NICU).
OBJECTIVE: The purpose of this study was to compare retrospectively the rates of recall (RR) and detection (DR) observed in the NICU with those of general public maternities from Buenos Aires City.
MATERIALS AND METHODS: Newborn screening for Congenital Hypothyroidism (CH) (TSH), Hyperphenylalaninemia (HPA) (Phenylalanine), Cystic Fibrosis (CF) (IRT/IRT), Congenital Adrenal Hyperplasia (CAH) (17OHP), Galactosemia (Gal) (Total galactose) and Biotinidase Deficiency (BIO) was done in 27.842 newborns from 2 maternities (96%) (G1) and in 1.238 from NICU (4%) (G2). RR and DR from 2009 to 2017 were calculated and compared (Fisher t test and chi2 test).
RESULTS: In G1, with a median age of sampling of 3 days, RR due to preanalytical causes was 2.1% (0.15% inadequate samples and 1.95% other causes (medication, blood transfusions, fasting). Positive screening results led to a RR of 2.7% (CH: 0.29%; CF: 1.18%; HPA: 0.03%; CAH: 0.49%; Gal: 0.47% and BIO: 0.22%). Global DR was 0.13% (1/752), detecting: 25 CH (1/1.114), 6 CF (1/4.640), 3 CAH (1/9280) 1 Gal, 1 BIO and 1 HPA with a median age of diagnosis confirmation and treatment (MADT) for CH: 14 days (range 6-25), CF: 29 days (20-60), CAH: 4 days (3-11), Gal: 6 days, BIO: 30 days and HPA: 12 days.
In G2 median age of sampling was 14 days. RR for preanalytical causes was 20.6% (inadequate samples 1,86%, and other 18,8%) ($p< 0.01$ vs. G1). A positive screening result triggered a RR of 11.6% (4.5 times higher than G1) (CH: 1.05%, CF: 4.38%; HPA: 0.32%; CAH: 3.29%; Gal: 1.05%; and BIO: 1.53%).
Global DR was 0.73% (1/137), ($p< 0.01$ vs. G1) identifying 7 CH (1/176), 2 CF (1/619) and 1 CAH (1/1.238) with a MADT of 32 days (13-52) for CH, 31 days (30-33) for CF and 3 days for CAH.
CONCLUSIONS: Neonatal screening in the NICU is complex with higher RR for either causes but also a higher DR. In our NICU population RR for CF and CAH were very high and need revision.

P-242 - IMPROVEMENT IN RECALL EFFECTIVENESS IN THE BUENOS AIRES CITY NEONATAL SCREENING PROGRAM (PPN)

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INTRODUCTION: The recall procedure in a neonatal screening program requires an effective strategy in order to timely get in contact with families whose babies are suspected to have the screened disorders. This allows confirming the disease and eventually implementing the treatment.
Our neonatal screening program has 3 organized levels to carry on the recall task. Initially, recall is triggered by the screening laboratory, if it fails the social service makes another call and finally the intervention of the Minority General Tutelary Advisory (AGAM) and the Primary Health Assistance are required.
OBJECTIVE: To evaluate the effectiveness of the recall procedure over the years.
MATERIALS AND METHODS: We analyzed the effectiveness of localization of the recalled newborn coming from 12 public Maternities of Buenos Aires City. In them, screening for Congenital Hypothyroidism, Phenylketonuria, Cystic Fibrosis, Congenital Adrenal Hyperplasia, Galactosemia, Biotinidase Deficiency, MCADD and MSUD is performed in 4 laboratories.
Out of 246274 screened babies from 2010 to 2018, 11377 were recalled for either cause.
In order to diminish the rate of lost babies since 2016 the program implemented educational procedures organizing meetings where neonatologists, nurses, biochemists, disease specialists and program referents were asked to participate.
RESULTS: During the whole studied period, 9521 out of 11377 recalled babies (84%) were retrieved by the laboratories, 1138 (10%) came after the intervention of social services and 347 (3%) did it by means of the AGAM citation.

Only 371 children (3.3%) were not found after all. From 2010 to 2016 the number of lost babies ranged from 2.4% to 5.1% (mean 3.9%). During 2017-2018 with the educational intervention and the personal contact with caretakers this rate diminished to 1,0 % ($p<0.01$)
CONCLUSIONS: The interdisciplinary strategy, enhanced communication between the different levels within the neonatal screening program and the active involvement of neonatal caretakers, resulted in an increased effectiveness in the recall.

P-243 - EXPANDED NEWBORN SCREENING IN THE FEDERAL DISTRICT: SEVEN YEARS OF EXPERIENCE IN PUBLIC HEALTH NETWORK

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INTRODUCTION: The Expanded Newborn Screening, for Treatable Hereditary Metabolic Diseases, using Tandem Mass Spectrometry (MSMS), began in 1990 and became widely used worldwide. Between 2001-2008, the Newborn Screening in the Federal District followed the National Newborn Screening program of the Ministry of Health tracking four diseases. District law 4190 of August 28, 2008, established the Extended Neonatal Screening in the Federal District (TNNA-DF), aimed at the newborns of the Public Health System for the purpose of screening at least for thirty treatable diseases.
GOAL: To report the paradigm shift of the Newborn Screening in Federal District with the implementation of the MSMS to perform the TNNA-DF and the results obtained after seven years.
MATERIALS/METHOD: We retrospectively analyzed the results of the DF Newborn Screening Program (PTN-DF) from 2011-2017.
RESULTS: Between 2008 and 2011, there was a transition period, with the elaboration of projects for PTN-DF paradigm changes. The blood samples collection started to be performed at the public maternities, and all blood samples were transported in thermal boxes to the Reference Center of newborn screening. These changes were possible by the introduction of high sensitivity technologies, especially the MSMS, modifying the form and time of collection of the samples in filter paper. Between 2007 and 2017, 453.980 children were screened and from January, 2011 to December, 2017, 309.428 children were evaluated in an expanded way. The expected coverage of 100% of the newborns reached 109.4% in 2017 due to the attendance of the cities of the environment and private hospital network. The collection period reached 96.4% with 05 days of life and 100% with 7 days of life. Number of diagnoses per disease (2011-2017): congenital hypothyroidism: 98, hyperphenylalaninemias: 22, hemoglobinopathies: 252, congenital adrenal hyperplasia: 14, biotinidase deficiency: 22, galactosemia: 63, others inborn errors of metabolism: 145, glucose-6-phosphate deshydrogenase deficiency: 7133, congenital toxoplasmosis: 103.
CONCLUSION: Newborns with positive and confirmed results are immediately referred to the multiprofessional clinics of the genetics unit. TNNA-DF represents a major prevention project in primary health care for the child and high complexity care in the treatment of positive cases, favoring a decrease in infantile mortality.

P-244 - EXPANDED NEWBORN SCREENING IN A POPULATION AT RISK OF VALLE DEL CAUCA- COLOMBIA

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INTRODUCTION: Inborn Errors of metabolism (IEM) are a set of conditions characterized by the accumulation of toxic substances usually produced by an enzymatic defect that cause serious consequences in the newborn. Likewise, congenital hypothyroidism (CH), due to hormonal déficit, causes intellectual disability and dwarfism, a consequence that could be avoided with early detection. The incidence of IEM in Colombia is approximately 1/3000 live newborns and 50% develop the disease during the neonatal period. Their diagnosis and treatment has not been completely standardized, so the patients affected with these alterations are not being detected opportunely. The measurement of neonatal thyroid stimulating hormone (TSH) in umbilical cord for early detection of CH is the only legislated in the country but there is no infrastructure and equipment that allows to perform an expanded neonatal screening by tandem mass spectrometry, impeding the opportunity for newborns to have access to this program.
OBJECTIVES: To check the usefulness and efficiency of expanded newborn screening using analytical tests for the detection of IEM.
METHODS: Five Health Services Providing Institutions were included in the Department of Valle del Cauca-Colombia.

1000 baby samples were taken, with signs or symptoms that generated a medical suspicion of the presence of IEM. Blood samples were collected on filter paper for convenience, and analytical tests were performed to quantify TSH by immunoenzymatic tests, hyperphenylalaninemia by phenylalanine quantification by fluorometric ultramicroassay, Biotinidase deficiency by colorimetric ultramicroassay, congenital adrenal hyperplasia by quantification of 17-hydroxyprogesterone by immunoenzymatic tests and galactosemia test by fluorometric enzyme assay.
RESULTS: The results of the tests carried out, showed that 2 newborn had TSH concentrations of 358 umol/L and 184.6 umol/L, respectively. In addition, 2 tests of phenylalanine with values of 497.2 umol/L and 289.6 umol/L were found.
CONCLUSION: The increased in newborn screening by ultramicroanalytical tests allowed the early detection of patients affected by EIM. The patients in this study were confirmed and treatment was started. This technique is an effective and efficient alternative that, despite its limitations, achieves its objectives in the absence of most advanced technologies in our country.

P-245 - NEWBORN SCREENING OUT OF A PROGRAM IN ARGENTINA

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INTRODUCTION: Newborn screening (NBS) involves more than a single laboratory test; it's a program in which the detection of patients at risk is just one link in a chain.
In Argentina, the public health system runs a National Strengthening Program but both the city and the Province of Buenos Aires have different programs for children born in public hospitals.
Private hospitals, conversely, do not run any program and reduce NBS to a single lab test without proper confirmation or patients' follow-up.
Our Center, as a reference institution in the diagnosis of inborn errors of metabolism (IEM) has been informally taking the role of confirmatory center for patients with inconclusive NBS results generated in the private sector.
OBJECTIVE: Describe the consequences of not being part of a universal screening program in the population consulting our center.
MATERIALS AND METHODS: Revision of medical records from 2007 to 2018.
RESULTS: We received 15 neonates with inconclusive NBS results: 7 were false positives (FP) for PKU, 1 FP for MSUD, and 7 were true positives for PKU. On the other hand we evaluated 11 children from 2 months to 11 years with signs or symptoms of IEM, all of them were false negative (FN) for PKU. All patients were screened at birth in private labs or maternities.
DISCUSSION: There is no control of NBS in private institutions in Argentina but children born in public institutions are covered by the NBS program.
Families coming to our Center with non-specific NBS results are filled with anguish about this proceeding. The NBS program should include all Argentine children alike.

P-246 - RESULTS OF A MEXICAN NEWBORN SCREENING PROGRAM: GLOBAL INCIDENCE COMPARISON

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INTRODUCTION: Newborn screening (NBS) is fundamental for early diagnosis of inborn errors of metabolism (IEM) and other disorders. Although, these are known as rare, as group they become a relevant cause of morbidity and mortality. The disparity in the NBS performed, different laboratory methodologies, and suboptimal coverage, among others, explain the international statistics' variability.
OBJECTIVE: To analyze and compare the incidence obtained by a Mexican NBS program with the described in the world literature.
MATERIALS AND METHODS: We reviewed 199,065 NBS reports performed by Genomi-k's NBS program from January 1, 2008 to January 31, 2018. All newborns (NB) were screened for 68 pathologies; 62,584 were also evaluated for SCID and 56,979 for six lysosomal storage diseases. We collected and filtered the published data per screened diseases. Further, we estimated their incidence and compared it with our results.
RESULTS: An overall incidence of 48.3 affected NB and 101.6 heterozygotes per 10,000 screened NB (from the latter, 63% for Hb S) was found. Particularly, the IEM incidence that could be compared to previous studies was 5.8: 10,000 screened NB. The five most frequent diagnosed pathologies comprehend 89% of the positive results. These were: glucose-6-phosphate dehydrogenase deficiency (G6PD), congenital hypothyroidism (CH), Fabry disease, Cystic Fibrosis (CF), and Pompe disease.
DISCUSSION AND CONCLUSIONS: Overall, the incidence we estimated exceeded other countries' incidence by more than 100%. This could be explained by the consideration of more diseases besides IEM (42.5: 10,000 NB). Even though, IEM's incidence is one of the highest, like the described in Spain and United Kingdom (6.4 and 6.5: 10,000 NB, respectively).

Our estimated incidences are generally greater than those presented in the literature. This proves that the data variability is due to the number of biomarkers, the NBS methodology, and the population distribution. We highlight the frequency of G6PD, CH, and Fabry disease in the studied population. Since the patient's prognosis is proportional to early diagnosis and treatment, we recommend the inclusion of these biomarkers within any NBS program in Mexico.

P-247 - IMPLEMENTATION OF AN INTEGRAL EXPANDED NEWBORN SCREENING PROGRAM IN SOUTHERN MEXICO: AN ELEVEN YEARS EXPERIENCE.

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INTRODUCTION: In the state of Yucatán, México, they have been doing the integral expanded newborn screening program for the detection of congenital metabolic diseases continuously for 11 years, which represents the longest experience of this type in the country.
OBJECTIVE: To report the results from the integral expanded neonatal screening program in the state of Yucatan, Mexico.
MATERIALS AND METHODS: Retrospective analysis of the data of the integral expanded newborn screening program of the health services of the state of Yucatan. Blood samples were obtained by puncture of the heel of newborns (NB), which were impregnated on filter paper cards and studied in a highly automated analytic platform conformed by fluorometric assay, tandem mass spectrometry, isoelectric focusing and high performance liquid chromatography. The program logistics included a professional service for notification, localization and confirmation of suspected cases and monitoring of medical follow-up for 5 years.
RESULTS: From January 2008 to December 2018, with the participation of 148 health centers, 7 hospitals and 27 mobile units distributed in five routes, they screened 174,307 NB, having a coverage of 96.6 %. There were 1,525 suspected cases (0.87% repetition rate), they confirmed 311 cases (1: 560 NB), with 1189 false positives (0.68%). 9 patients were not located (0.52% error rate) and 16 died before the second sampling. Those confirmed included: 194 cases of endocrinopathies (1: 898 NB); 15 of organic acidemias (1: 11,620 NB); 13 of amino acids (1: 13,408 NB); 76 hematological disorders (haemoglobinopathies and glucose-6-phosphate dehydrogenase [G6PD] deficiency) (1: 2,294 NB); 13 cases of other metabolic diseases (1: 13,408 NB) and 678 carriers of hemoglobinopathies (1: 257 NB).
CONCLUSIONS: The population studied showed a high prevalence of birth defects (1: 560 NB), being thyroid defects (1: 1,050 RN) and hematological disorders the most common (1: 2,294 NB). The majority of the affected children was opportunely evaluated and began treatment before 20 days of age. Parents received training for the manage and care of the children as well as the accompaniment in the medical follow-up for 5 years.

P-248 - EXPANDED NEWBORN SCREENING PROGRAM IN THE HEALTH SERVICES OF THE MEXICAN NAVY: A 6-YEAR EXPERIENCE.

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(1) Secretariat of the Navy of Mexico. (2) TamizMas Screening Center de Químicos Maldonado, Yucatán, México.

INTRODUCTION: The purpose of an expanded newborn screening program is the early detection of congenital metabolic disorders that otherwise could produce serious clinical consequences. Nowadays, newborn screening is part of the health care system of a large number of countries and institutions. Since 2012, the Secretariat of the Navy of Mexico has implemented a program for the detection of these conditions in newborns.
OBJECTIVE: To report the results obtained in the expanded neonatal screening program of the Secretariat of the Navy of Mexico.
MATERIALS AND METHODS: From July 2012 to December 2018, blood samples were taken from the newborn's heel (NB) in 32 medical units of the Mexican Navy, located in 18 states of Mexico. All samples were analyzed by immunofluorometric analysis (AutoDELFIA © / GSP ©), tandem mass spectrometry, isoelectric focusing and high performance liquid chromatography.
RESULTS: 16,781 NB were screened; 61.22% of the samples were taken between 3-5 days of life, (0.9% of the samples were considered inadequate), 249 samples were considered as suspected cases, 90.8% were located and re-examined. Sixty-one cases were confirmed, with a false positive rate of 0.95%. The detected diseases were 24 cases of endocrinopathies, 33 cases of hemoglobinopathies and other hematological disorders (230 carriers of Hb), 1 case of organic acidemia and

3 cases of other congenital metabolic diseases. All confirmed cases initiated specialized medical treatment at an average of 16 days of age. All affected families received genetic counseling.
CONCLUSIONS: In the studied population, the prevalence of congenital metabolic defects was 1/275 NB. The most prevalent ones were Congenital Hypothyroidism (1: 1,199 NB) and Glucose 6 Phosphate Dehydrogenase Deficiency (1: 524 NB). The expanded screening program allowed the early detection of 61 affected newborns.

P-249 - USHUAIA NEWBORN SCREENING: QUALITY INDICATORS

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INTRODUCTION: The estimated population of Ushuaia is 65,000 people. There are about 1200 births per year and 51.2% of the total number of births takes place in public hospitals. Public health institutions participate in the National Strengthening Program (Programa Nacional de Fortalecimiento de la Detección Precoz de Enfermedades Congénitas), send samples to NBS Laboratory of Hospital "Prof. Dr. Juan P. Garrahan" in Buenos Aires (3099 km away) and have current coverage of approximately 98.15% of newborns.
OBJECTIVE: Our aim is to improve the quality of the NBS in the Ushuaia´s public hospital.
MATERIALS AND METHODS: Retrospective and descriptive study to evaluate quality of NBS in Ushuaia´s public hospital. We determined program, pre-analytical, analytical and post-analytical quality indicators (PQIs, Pre-AQIs, AQIs and Post-AQIs respectively). PQIs: Total births per year, coverage rate. Pre-AQIs: median age at specimen collection, percentage of specimens in transit for 8 days or less, percentage of unsuitable samples. AQIs: recall rate. Post-AQIs: percentage of recall specimens in transit for 8 days or less, median age at diagnostic confirm.
RESULTS: PQIs: Total births in 2016 was n: 717, NBS n: 702, coverage rate 97.9% vs. Total births in 2018 n: 612, NBS n: 609, coverage rate 99.5 %.
Pre-AQIs: Median age of specimen collection was 48.5 h, with 98% collected between 48 and 72 hours of age (target 95% collected between 48 and 72 hours of age). Percentage of specimens in transit for 8 day or less was 44% in 2016 vs. 72% in 2018 (target was 95%). Percentage of unsuitable samples was 0.64% in 2016 vs. 0.13 % in 2018 (target less than 0.5%).
AQIs: Recall rate was 4.4% in 2016 vs. 6.6 % in 2018.
Post-AQIs: Percentage of recall specimens in transit for 8 days or less was 57.7 % in 2016 vs. 74.71 % in 2018. Median age at diagnostic confirmation was 12 days of age (n: 2. Diagnostic CH)
CONCLUSIONS: According to these data, we emphasize that there is still a need for system-wide assessment and improvement. Pre-analytical, analytical and post-analytical stages must be monitored frequently to ensure children receive optimal health care.

P-250 - NEWBORN SCREENING AND SELECTIVE SCREENING FOR CONGENITAL METABOLIC DISEASES IN A PEDIATRIC HOSPITAL, MENDOZA-ARGENTINA

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(1) Programa Provincial de Pesquisa Neonatal. Centro de Prevención Enfermedades Inaparentes de la Infancia (CE.P.E.I.I.). (2) Servicio de Endocrinología. (3) Servicio de Crecimiento y Desarrollo. Hospital Pediátrico Dr. Humberto J. Notti. Mendoza-Argentina. amguercio@intramed.net.ar

INTRODUCTION: Its important that the detection, diagnosis, treatment and follow-up of congenital endocrine-metabolic diseases are developed in Reference Centers. Therefore, our Program covered two areas of work: a) Newborn screening (NBS): primary congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), phenylketonuria, galactosemia, biotinidase deficiency (BTDdef), cystic fibrosis (CF). b) Selective Screening (SS): for some non-mandatory congenital metabolic diseases (CMD).
OBJECTIVES: Present results and indicators of NS and SS.
MATERIALS AND METHODS: a) From 1999 to 2009, NBS for CH and Phenylketonuria; in 2010 NBS for CAH, Galactosemia, BTDdef, CF was added. Analytical process in two stages, 1st stage: [Phenylalanine, Galactose, Biotinidase]: colorimetry; [TSH, 17OHP, IRT]: ELISA; 2nd stage: re-evaluation of samples with "border-line and positives" results: [Phenylalanine, Galactose, Biotinidase]: fluorometry; [TSH, 17OHP, IRT]: DELFIA. b) Since 2016, by medical order, SS CMD, prior to send samples to specialized centers in Argentina located 700-1100 km from our Hospital. Biochemical parameters: [Leucine-Isoleucine-Valine]: fluorometry, home-made methodologies; Amino Acids in plasma-urine and Monosaccharides in urine: TLC and Gal-1-phosphate-uridyltransferase: fluorometry.
RESULTS: a) NBS, 1999-2018 = 410925 newborns (NB) (2010-2018 = 210921 NB). Indicators, mean, 2017-2018: Days of life (DOL) to the sample collection= 2. Time of transit of the sample from the Maternities to CE.P.E.I.I.= 3 days. DOL to get the result= 7. DOL to deliver the report= 9.

Diagnosis and start of Treatment= 14 days. Rejected and Insufficient samples= 0.49%. Recall rate: Total/NB gestational age ≥ 37 weeks= 3.2%/2.1%; 99% of the NB were located. Coverage; Publics hospitals/Private= 99%/13%. Children in treatment-follow-up= 200 CH (Incidence= 1/2055); 9 Phenylketonuria and 18 persistent Hyperphenylalaninemias (Incidence= 1/15219); 15 CAH (Incidence= 1/14061) and 28 CF (Incidence= 1/7533). b) SS, 2016-2018: evaluation of 83 samples, patients admitted to our Hospital and outpatient. Results, average time= 3 days in CE.P.E.I.I., versus 30 days by referral of samples to specialized centers. SS= 2 children with MSUD.
CONCLUSIONS: In the context of a Reference Center and cost-effectiveness: a.improved NS indicators, from sample collection to diagnosis and treatment b.the study of new CMD, SS, was expanded with acceptable costs for the validation of home-made methodologies and reduction of screening and diagnostic times.

P-251 - RESULTS OF THE NEONATAL SCREENING PROGRAM IN CUBA. 33 YEARS OF EXPERIENCE.

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INTRODUCTION: The Neonatal Screening Program in Cuba began in 1986 with the study of congenital hypothyroidism. In 2000 was included the early diagnosis of Phenylketonuria and in 2005 the detection of congenital adrenal hyperplasia, Galactosemia and Biotinidase Deficiency. These tests guarantee the screening of inborn errors of metabolism to more than 100,000 children each year.
OBJECTIVE: Evaluate the results of the Program and its impact on the National Health System. METHODS: A retrospective descriptive study was conducted in the period 1986-2018 of the statistical reports of medical records, analyzed the program's effectiveness indicators and evaluated the performance of SUMA services, according to the results of the External Quality Control. Statistical methods were applied for the analysis of the results.
RESULTS: In 33 years, 11.115.382 newborn exams have been performed, of which 1077 children with different metabolic disorders have been diagnosed and treated in time. From these, 942 with congenital hypothyroidism and an incidence 1: 4532; 38 cases of Phenylketonuria for an incidence 1: 51064; 68 cases of Congenital adrenal hyperplasia, incidence 1: 24301; 18 children with Biotinidase Deficiency, incidence 1: 91375, and 11 with Galactosemia and an incidence 1: 146152. The follow-up of the indicators of effectiveness showed in 2018 that more than 95% of the samples were collected before the sixth day of birth, transferred to the laboratories before 72 hours and tested immediately. The coverage of the program reaches 99% of the children born, and it extends to 169 Specialized Centers of Integral Active Research (CEPAI), that participate in the program of external evaluation of the quality and are located with technological support, in the National Network of the National Health System.
CONCLUSIONS: Since the beginning of the program, life has been saved and guaranteed normal neurocognitive development for all children diagnosed; A high level of well-being has been guaranteed to the family and society as a whole. It has achieved the necessary technological sovereignty that allows strengthening and giving continuity to the national program with excellent results in the indicators of effectiveness. The external control program monitored the work of the laboratory network, giving credit to the results.

P-252 - NEWBORN SCREENING IN GUATEMALA: NEW STRATEGIES IN PUBLIC HEALTH

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INTRODUCTION: Newborn screening (NS) in Guatemala has been done since three decades ago in two national hospitals (Hospital Roosevelt and Hospital General San Juan de Dios) covering births only in these hospitals. In 2018, new strategies began with the objective of completing the basic panel of tests and linking Latin-American methodologies.
OBJECTIVES: Expose the current situation in Guatemala and make evident the need of support from the Government for the establishment of a National Newborn Screening Program.
MATERIALS AND METHODS: Diagnostic algorithms were updated. In 2017, the samples collection was done between 24 and 28 hours after birth, and due to the little capacity of bedding, the samples collection changed to 72 hours after birth. An information network was created for professionals to socialize the importance of NS with the population.
Incidence for each illness was established in 2017 and 2018 unifying both hospitals. Coverage percentage was compared for both years to evaluate the effectiveness of the new strategies.
RESULTS: In 2017, 18725 newborns (NB) were screened, with a coverage percentage of 98.2 %. The incidences were: Congenital Hypothyroidism (CH) 1: 2675, Congenital Adrenal Hyperplasia (CAH) 1: 3520, and Cystic Fibrosis (CF) 1: 5798. In 2018, 10263 NB were screened, having a coverage percentage of 47.8 %, obtaining incidence of CH 1: 1140,

CAH 1: 2053, CF 1: 10263 and Galactosemia 1: 5132, with no report of Phenylketonuria cases.
DISCUSSION AND CONCLUSIONS: New strategies allowed to implement the detection of Galactosemia and Phenylketonuria. Coverage decreased in 50.3 % because of the difficult access to public transportation and low financial resources. Although, incidences gave evidence of the importance to seek metabolic illnesses in NB and adjust the rates with a bigger population. Coverage percentage is alarming showing the need to establish a national level program in which multidisciplinary groups may be in charge of active seeking of cases.

P-253 - COVERAGE AND FOLLOW-UP OF REGIONAL NEONATAL SCREENING SERVICE OF THE AMAZONAS STATE BETWEEN 2016 AND 2018

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INTRODUCTION: The National Neonatal Screening Program in Brazil functions as a transversal agenda and is complementary to other actions of the Unified Health System. Its mission is: "To promote, to implant and to implement the Neonatal Screening actions in the scope of the brazilian public health service, aiming universal, integral and equitable access, focusing on prevention, early intervention and permanent monitoring of people with diseases included in the program." Neonatal screening occurs throughout the country for 6 diseases: phenylketonuria, congenital hypothyroidism, hemoglobinopathies, cystic fibrosis, congenital adrenal hyperplasia and biotinidase deficiency. In Amazonas, the screening for all those diseases has been implemented since 2016, with 22 new cases diagnosed.
OBJECTIVES: Report cases diagnosed by the Regional Neonatal Screening Service of Amazonas (RNSSA) between 2016 and 2018.
METHODOLOGY: Descriptive observational study performed at the public health system of the state.
RESULTS: Live births registry in Amazonas has varied within 75000 to 80000 per year. In 2016 the RNSSA registered one patient with congenital adrenal hyperplasia, using laboratory dosage of 17-hydroxyprogesterone; one patient with cystic fibrosis, screened by reactive immunoreactive trypsin and confirmed by sweat test; and one patient with biotinidase deficiency, dosed by time-resolved fluorimetry. In 2017, one patient with cystic fibrosis was diagnosed; three patients with congenital adrenal hyperplasia and seven patients with congenital hypothyroidism, diagnosed by elevated TSH levels. In 2018, three new cases of congenital adrenal hyperplasia and five new cases of congenital hypothyroidism were diagnosed.
CONCLUSIONS: and discussion: The coverage of the program is not yet possible due to the lack of registration of live births in official sources. Since 2016 no new cases of phenylketonuria have been diagnosed and this data deserves investigation. Cases of congenital adrenal hyperplasia, cystic fibrosis and biotinidase deficiency indicate the relevance of their research in neonatal screening. The early diagnosis and follow-up of these patients minimizes the repercussions of the diseases, provides quality of life, guarantees adequate neuropsychomotor development and strengthens the physician-patient relationship, also present enough data for planning public health policies and resource use, essential for the health public service maintenance and the benefit of the general population.

P-254 - APPROACH TO INTERNATIONAL BIOETHICAL CONTROVERSIES OF NEONATAL SCREENING: THE COLOMBIAN EXAMPLE

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INTRODUCTION: There is an agreement in neonatal screening about aspects such as equity of access, confidentiality of results and privacy of samples. However, there are controversies in other topics related to bioethical aspects.
OBJECTIVE: To understand, how international bioethical controversies of neonatal screening are addressed in the Colombian context.
METHODOLOGY: It was applied a survey to officials of the Colombian National Institute of Health involved in surveillance or coordination of research or public health programs, through a form of 13 questions built with international bioethics controversies of neonatal screening.
RESULTS: The survey was filled out by 85 of the 127 officials. Regarding to test of proved benefit for the newborn, there is a high percentage of agreement among officials in the obligation of their offer by the State. There is also a high percentage of agreement in trusting on parents and health record to keep the information with confidentiality. In contrast, there is less agreement about the need of detailed information for each screened anomaly and in the need of consent to authorize the screening. However, there is a higher percentage of agreement in the utility of the informed consent for the research use of the screening results and the residual samples.

CONCLUSIONS: There are international controversies that are solved without discussion but others that persist without agreement in the Colombian context. Cultural and legal aspects help to solve some of them but there is a necessity of a bioethical analysis to solve others, thus making relevant their discussion in both developed and developing countries.

P-255 - RETROSPECTIVE REVIEW STUDY ON THE IMPLEMENTATION OF INBORN ERRORS OF METABOLISM SCREENING IN THE COLOMBIAN CAPITAL: A STUDENTS' DISSATISFACTORY POINT VIEW

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INTRODUCTION: In 2013, the Ministry of Health of Colombia published a Clinical Practice Guide (GPC) which focuses on the early detection of congenital anomalies in neonates at term; by recommending the screening of the following inborn errors of metabolism (EIM): congenital hypothyroidism, congenital adrenal hyperplasia, phenylketonuria, biotinidase deficiency, galactosemia, medium-chain acyl-CoA dehydrogenase deficiency, propionic and methylmalonic acidemia.
OBJECTIVE: To discuss the degree of knowledge and the perception of metabolic neonatal screening implementation by undergraduate students of Medicine in the fourth year of the Military University of Nueva Granada (Bogotá, Colombia).
MATERIALS AND METHODS: Descriptive qualitative study to assess the degree of knowledge regarding the neonatal screening of EIM, in addition to the perception of their implementation in centers of hospital practice (CPH) of the Colombian capital, that through a virtual survey filled by undergraduate students. The survey was applied to 173 students in three academic semesters in the years 2014, 2015 and 2018. One analysis was withdrawn due to inconsistencies in the information, for a total of 137 participants.
RESULTS: The degree of knowledge about screening was categorized subjectively into "poor", "sufficient" and "detailed" giving as results: 4.4%, 21.2%, and 74.2% respectively. 94.2% of students commented that in their care rotations at CPH, the implementation of metabolic screening is incorrectly performed. It was found that only congenital hypothyroidism was evaluated at birth, without testing for other pathologies.
CONCLUSIONS/DISCUSSION: In the medical and teaching CPH medical students describe that the recommendations and algorithms of the Colombian CPG do not apply. The screening tests of seven EIMs are omitted and only performed for congenital hypothyroidism in umbilical cord blood samples. The results obtained in 2018 are similar to those observed in the first and second year after the publication of the CPG. In retrospect, it can be concluded that efforts should be increased from the academy both in the theoretical and practical component in the training of health professionals. On the other hand, a real commitment is required in the generation of public policy for the implementation of EIM screening.

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