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BOOK OF ABSTRACTS - X Latin American Congress of Inborn Errors of Metabolism and Neonatal Screening

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(P-1) Poster Session With Authors I

P001 - Multiplex Analysis Using a Totally Automated System for Newborn Screening of Congenital Hypothyroidism, Congenital Adrenal Hyperplasia, and Cystic Fibrosis in the Northeast of Brazil

Sampaio Filho (jr), C.(1); Frias, F.(1); Veturiano, R.(1); Assunção Do Amor Divino, S.(2); Andrade Sousa, M.(2); Conceição Da Purificação, A(2)

(1): INTERCIENTIFICA, S.J.Campos, Brasil
(2): APAE-SALVADOR, Salvador, Brasil

Introduction: The Northeast of Brazil represents 27.7% of population with 9 States and approximately 690.000 newborn screening samples per year. The State of Bahia began to offer newborn screening in 1992. APAE-SALVADOR is the reference institution in the State processing 12.000 samples per month. During the last years, the inclusion of new markers by the Brazilian Newborn Screening Program, quantification of 17OH and analysis of Biotinidase activity has generated a significant increase in the number of assays. The impact is considered important inside the lab, since changes or limitations in infrastructure, human resources, punching sample process, data analysis can affect a critical parameter inside the Newborn Screening Program, the time from processing the sample to the results. Development of advanced technologies according the Brazilian Newborn Screening Program is needed to minimize the impact in the implementation of new markers. **Materials and Methods:** Lab of APAE-SALVADOR used a totally automated system (Nimbus NeoMAP) with multiplex assay (NeoMAP 4plex). Approximately 20.000 samples collected from 417 cities in State of Bahia have been analyzed during last 2 months in the routine. In the same study we evaluated the application of an additional feature offered with the use of the multiplex system, the analysis of the results by percentile instead the fixed cut-offs. DBS from positive samples (diagnostic confirmed) were used as controls in the study. **Results:** The time from receiving the sample to delivery of the results has been reduced 3 times using the multiplex technology. The use of NeoMAP 4plex Kits associated with totally automated equipment, Nimbus NeoMAP, reduced 75% the sample punching process. The use of percentiles has reduced the number of false positive samples and the potential false negatives in the routine compared to fixed cut-off. The results are presented in tables for each marker. **Conclusion:** The development of new technology that is focused on the requests and needs of the state newborn screening programs are essential for evolution of prevention in addition of new screening diseases and more sustainable public health system.

P002 - Newborn Screening for Biotinidase Deficiency Using a Totally Automated System and Enzymatic Analysis With Results Expressed in nmol/min/mL

Sampaio Filho (jr), C.(1); Frias, F.(1); Veturiano, R.(1); Silva, V.(1); Gallo, B.(1); Bernardes, F.(1); Boalento, J.(1); Massi, A.(1); Lira, J.(1)

(1): INTERCIENTIFICA, S.J.Campos, Brasil

Introduction: Newborn Screening for Biotinidase Deficiency has been implemented in the Brazilian Newborn Screening Program (PNTN) since 2012. Since 1999 INTERCIENTIFICA offers the NeoLISA BIO kit using an enzymatic colorimetric method that differentiates the enzyme's activity by the color produced in the end of the reaction. The national legislation accepts the use of qualitative methods in Newborn Screening for Biotinidase Deficiency but the market requests new protocols with reduced times, totally automated processes and results reported in numeric values. **Materials and Methods:** The NeoLISA BIO Kits associated with Nimbus NeoLISA have been used to develop a totally automated system to determine the enzymatic activity of Biotinidase in numeric values (nmol/min/mL). Standards and Internal Controls with different levels of Biotinidase activity, plus external quality control materials, have been used for this study. The protocol of the assay takes 4 hours instead the 18 hours of the qualitative protocol. The results are compared between the protocols and are presented in tables. **Results:** The new protocol demonstrates the same confidence and quality results expected from a product used by the Brazilian market for more than 15 years. Therefore, the protocol with 4 hours reduces substantially the time process of the samples in the routine. The analysis demonstrated comparable results using the protocol for 18 hours in a manual process against the protocol for 4 hours in totally automated system, Nimbus NeoLISA. **Conclusion:** The NeoLISA BIO kit using an automated system, Nimbus NeoLISA, with a protocol of 4 hours has shown excellent concordance compared with traditional method in 18 hours protocol. The new assay protocol considers the needs of the Brazilian market to promote innovation according market needs. The results presented can be considered evidence that this product keeps the same level of confidence and quality expected for newborn screening programs.

P003- Newborn Screening for Maple Syrup Urine Disease (MSUD) Using a Totally Automated System

Sampaio Filho (jr), C.(1); Frias, F.(1); Veturiano, R.(1); Silva, V.(1); Bernardes, F.(1); Boalento, J.(1); Massi, A.(1); Lira, J.(1)

(1): INTERCIENTIFICA, S.J.Campos, Brasil

Introduction: In the last years the organization called Rede DXB, an MSUD workgroup of specialized professionals in Brazil, has produced actions for development of research and diagnosis of MSUD. MSUD is not mandated by the Brazilian Newborn Screening Program but published data reveals an incidence 5 times higher than expected. The Brazilian industry, looking to meet the requests and needs of the Newborn Screening Program, has developed a totally automated system for the detection of MSUD. **Materials and methods:** This study was developed using NeoLISA MSUD kit, routine newborn screening samples from different labs in Brazil, positive confirmed samples, internal controls and external quality control materials. The assay is enzymatic colorimetric and the procedure occurs in a totally automated system. The system takes 1 hour to run about 500 samples but can perform almost 800 samples per routine, or 3000 samples per day per equipment. **Results:** The results demonstrated the reproducibility of samples and controls used in the study including the external quality control materials. All positive samples were correctly classified as positives by NeoLISA MSUD. These samples were previously confirmed by HPLC method associated with clinical diagnosis. **Conclusions:** The enzymatic colorimetric method (NeoLISA MSUD Kit) associated with totally automated system (Nimbus NeoLISA) is an excellent alternative to meet the needs of the Brazilian Newborn Screening Program. The use of tMS/MS for MSUD and other diseases has been studied by many labs in Brazil. High cost associated with the equipment and accessories, human resources, infrastructure of the labs, and technical support are considered problematic and usually associated with the negative perspective to introduce MSUD testing. The use of NeoLISA MSUD meets the perspective proposed by the studies of Rede DXB with development of newborn screening program recognizing the professional's efforts to prevent deleterious consequences in non-treated MSUD patients.

P004 - Importance of Individualized Nutritional Calculation in Nephropathic Cystinosis: Comparison of Two Cases

Guillén López, S.(1); Belmont-martínez, L.(2); Vela-amieva, M.(2); Juárez-cruz, M.(3)

(1): Instituto Nacional de Pediatría, D.F., México
(2): Instituto Nacional de Pediatría, D.F, México
(3): Instituto Politécnico Nacional, D.F, México

Introduction: Nephropatic cystinosis is a metabolic disease involving cystine accumulation in different organs and tissues due to a defect in lysosomal transport. The usual treatment for this disease involves oral cysteamine, however there are no specific dietary recommendations and sometimes nutrition therapy is not considered as priority or important in these disorder. **Objective:** To compare 3 years of the serum creatinine determinations in two patients with nephropatic cystinosis treated with cysteamine, with and without early dietary management in relation to the amount of protein in the diet. **Material and Methods:** Retrospective study of two patients with confirmed diagnosis of nephropatic cystinosis in which serum creatinine was assessed for the last 3 years of their treatment. Both patients started taking cysteamine around one year of age. The amount of protein from dietary recalls was calculated in both patients during treatment of the past three years in one of them 7 dietary recalls were analyzed and in the other patient 6 of them. Serum creatinine concentrations were recorded, in one patient 16 determinations were collected and in the other one only 8. **Results and Discussion:** One of the patients received nutritional guidance and diet calculated with the recommended daily intake (RDI) of protein to meet their biological age and sex requirements, after these diet plan, creatinine levels in the last three years were measured. Creatinine remained in intervals below 1.18 mg/ dl, the lowest value was 0.87 mg/dl. From the 7 dietary recalls analyzed, on average protein intake was 0.95 g/kg/d, her specific recommendation was 1 g/kg/d. However in the other patient who was not following any diet, the amount of protein on average per day was 3 g/kg, three times higher than the RDI value for her biological age of 1.1g / kg / d according to her dietary recalls. The highest creatinine value was 2.8 and the lowest was 0.57 mg/dl. **Conclusion:** On time nutritional guidance in patients with cystinosis may be one of multiple factors that could prevent the development of kidney damage based on creatinine levels.

P005 - Biochemical Diagnosis of Non-Ketotic Hyperglycinemia in Cuba

Contreras Roura, J.(1); Camayd Viera, I.(1); Nogueras Rodríguez, L.(1); Padrón Díaz, A.(1); Martínez Rey, L.(1); Teixidor Llopiz, L.(1); González Reyes, E.(2)

(1): Centro Nacional de Genética Médica, La Habana, Cuba
(2): Centro de Inmunoensayo, La Habana, Cuba

Introduction: Non-ketotik hyperglycinemia (NKH) is an inborn error of Glycine metabolism, due to a deficit in the glycine cleavage system. The accumulation of abnormally large quantities of glycine in tissues, blood, cerebrospinal fluid and urine is a distinctive feature of this disorder. Main clinical symptoms are seizures and the central nervous system damage. There are three variants: the classic form, the atypical variants and the transitory form. Biochemical diagnosis consists of plasma and CSF glycine quantification; simultaneous urine organic acid analysis should also be performed. **Aim:** The objectives of this work were to implement a protocol for the biochemical diagnosis of NKH in Cuba and describe clinical and biochemical findings from two patients with a suspicion of inborn error of NKH. **Material and Methods:** A cross-sectional study was performed in 139 patients under clinical suspicion of IEM amino acids in 2014. Glycine was quantified in blood and CFS by HPLC in those patients who showed hyperglicinemia and a normal organic acids profile. **Results:** Two patients with treatment refractory seizures showed high glycine levels in urine and plasma and normal organic acid profiles. In both of them, the glycine CFS/plasma ratios were

positive. Considering the clinical symptoms and the age of symptoms onset, a neonatal classic NKH and an infantile variant were diagnosed. **Conclusion:** A protocol for the biochemical diagnosis of NKH in Cuba was implemented.

P006 - Mitochondrial Myopathy: TK2 Gene Depletion Syndrome

Chacin Hernandez, J.(1); Costagliola Martorona, A.(2); Miranda Contreras, L.(2); Torres Chirinos, Y.(2); Ocando Pino, L.(3); Mahfoud, A.(4)

(1): Universidad del Zulia, Maracaibo, Venezuela
(2): Universidad del Zulia
(3): Fundación Hospital de Especialidades Pediátricas
(4): Instituto de Estudios Avanzados

Introduction: Mitochondrial myopathies are a group of muscle diseases that are characterized by being slowly progressive, with muscles weakness, poor growth and multisystem involvement. They are etiology heterogeneous groups of disorders and they can be caused by mutations of genes encoded by either nuclear or mitochondrial DNA (mtDNA). The protocol diagnostic involves multisystem management and intervention of different study groups. **Patients and Methods:** Male patient, 13 years old, born and from Venezuela, with progressive muscles weakness from 3 years old and poor growth, his parents are not consanguineous with 4 children. He underwent clinical evaluation, neurophysiologic studies, biochemical tests, muscle biopsy and molecular analysis. **Results:** Physical exam at age 13. Weight: 24 kg (P <3) Height: 158 cm (P: 25-50) CC: 53 cm (P: 50). Poor muscle and adipose tissue. Neurological exam: Bilateral eyelid ptosis, tetraparesis with normal reflexes and waddling. Appropriate language and cognitive skills. Exams: Nerve conduction velocity normal, electromyography with myopathic features. MRI: Normal results. Visual and auditory evoked potentials: normal. Low carnitine levels. Normal lactate. Comparison of the relationship of lactic acid and pyruvic acid: normal levels. Urine organic acids, long chain fatty acids and blood aminoacid in normal concentration. Alpha Glycosidase activity: normal. Muscle biopsy by trichrome stain showed ragged red fibers, SDH stain showed number increased of mitochondria, COX and COX / SDH stain evidenced COX negative fibers. DNA genetic study: depletion of 60% mtDNA. Molecular study of *TK2* gene: Mutation p.K202 del and p.R130W. **Conclusion:** This myopathy is due to mutations in the *TK2* gene, located on the long arm of chromosome 16 (16q22-q23.1). This gene encodes thymidine-kinase 2 enzyme found within mitochondria, which is involved in the production and maintenance of mtDNA, playing a role in nucleotide recycling so that errors in mtDNA replication can be repaired and new healthy molecules appear. They have identified more than 30 mutations in the gene TK2. All mutations lead to a decrease in enzymatic activity, damaging recycling mtDNA nucleotide. Further depletion of mtDNA tends to cause more severe signs and symptoms. This disease is inherited in an autosomal recessive pattern.

P007 - Workflow Improvements Obtained With Automation of Traditional Newborn Screening Assays on the Perkinelmer GSP® High-Throughput System

Furu, P.(1); Merio, L.(1); Kerokoski, P.(1); Karunen, J.(1); Seppala, J.(1)

(1): PerkinElmer Diagnostics, Turku, Finland

Introduction and aim: The performance and workflow improvements of nine fully automated screening assays developed for the Genetic Screening Processor (GSP®) high-throughput system were evaluated. The analytes included TSH, T4, GALT, TGAL, 17OHP, IRT, Phe, BTD and G6PD. The assays are intended for determination of the before mentioned analytes as an aid in newborn screening of blood specimens dried on filter paper using the GSP® instrument. **Methods and results:** The GSP® instrument uses time resolved fluorescence, prompt fluorescence, and absorbance measurement technologies to support determination of traditional screening analytes in parallel on one platform. GSP is designed to measure reliably dried blood spot samples by utilizing several novel controls steps, i.e. Elution control, Floating disk control and Disk detection steps. The instrument is capable of processing 26 plates simultaneously and is designed for continuous loading of reagents and plates for added flexibility. For ease of use and error proofing, all the reagents are barcoded and usage is automatically monitored by the system. The GSP® instrument contains cooled storage for assay reagents, which improves onboard stability for up to 14 days. The calibration curve is valid for 24 hours (excluding GSP TGAL assay which requires plate specific calibration), indicating robust chemistry and minimal variation between the sample plates. The automated GSP® instrument requires less time for both daily instrument operation and maintenance tasks due to online water and waste connections, automated maintenance, and ready-to-use reagents. The GSP® instrument offers significant workflow improvements and reduction of technician hands-on time for the classically manual assays for biotinidase deficiency, galactosemia, glucose-6 phosphate dehydrogenase deficiency and phenylketonuria screening. **Conclusion:** The GSP® reagent kits together with the easy-to-use and high-capacity GSP® instrument offer a comprehensive test panel with reliable performance for newborn screening laboratories.

P008 - Creatine Kinase Muscle Isozyme Immunoassay for the Newborn Screening of Duchenne Muscular Dystrophy

Furu, P.(1); Korpimaki, T.(1); Makinen, P.(1); Merio, L.(1); Airenne, S.(1); Polari, H.(1); Hakala, H.(1)

(1): PerkinElmer Diagnostics, Turku, Finland

Introduction: Duchenne muscular dystrophy (DMD) is a X-linked disorder, affecting 1 in 3600-6000 live male births.

The skeletal muscle damage caused by DMD releases intracellular creatine kinase of predominantly the muscle isozyme type (CK-MM) to the circulation. Thus CK-MM is a biomarker useful for the screening of DMD. **Aim:** Our objective is the development of an immunoassay for measuring CK-MM from dry blood spots (DBS), intended for screening neonates for DMD. The assay is designed to run in the GSP® high throughput analyzer system (PerkinElmer) making it completely automated after DBS punching from plate loading to result generation. **Methods:** Using a prototype version of the assay under development, we tested the specificity of the assay for the different creatine kinase isozymes. We also tested the preliminary sensitivity and DMD screening performance of the assay by measuring a panel of 10 unaffected adult, 18 unaffected neonatal and 10 DMD affected neonatal DBS samples. **Results:** The specificity of the assay for creatine kinase isozymes was: CK-MM 100%, CK-MB (cardiac) 25% and CK-BB (brain) 0%. The assay was able to measure CK-MM concentration from all of the unaffected samples, even the lowest adult sample (16 ng/mL). There was a complete separation between the DMD affected samples (all >1000 ng/mL) and the unaffected samples (all <1000 ng/mL). **Conclusion:** The results demonstrated that the prototype assay under development had good specificity to CK-MM, good enough sensitivity to get a reading from all of the tested DBS samples and ability to separate the DMD affected from unaffected. These properties add to the usability of the assay in DMD screening of neonates.

P009 - Validation of Prescan Function of Autodelfia Software

Borrajo, G.(1); Gómez, F.(1); Di Carlo, C.(1)

(1): Detección de Errores Congénitos. Fundación Bioquímica Argentina, La Plata, Argentina

Introduction: AutoDELFIA Prescan function has been intended with the purpose of detecting possible missing dried blood spots (DBS) in microplates run in AutoDELFIA instruments. It works based on an adaptive algorithm that uses a special measurement protocol in which transmittance of the buffer containing the eluted DBS is measured. However, in practice is usual to find the message ''blood spots possible missing'' (BSPM) when DBS are really placed in the well. **Objective:** To present the results of the AutoDELFIA Prescan validation, working on the TSH measurement. **Materials and Methods:** The validation was made in 5 different TSH routine runs, in each one of them 12 standards, 11 controls and 818 newborn samples on average were analyzed. In order to check the Prescan function, 68 selected samples were analyzed in singlicate or duplicate, that include: filter paper blank disks (FPBD), DBS recently prepared (hematocrit adjusted from 25 to 55%), autoclaved DBS, and newborn DBS of different ages (from 15 days to 7 years old). Additionally, fresh liquid whole blood adjusted to 25 and 50% hematocrit were analyzed dispensing 3 ul in wells added of one FPBD. Finally, 17 newborn samples detected in daily routine as ''BSPM'' were also analyzed. The variables intended to evaluate were: presence or absence of paper disc, presence of blood, blood hematocrit, blood elution efficiency, and potential obstruction of the optical way by paper disk in absence of elution. **Results:** The only cases in which Prescan consistently reported ''BSPM'' were empty wells and blank disks and, in a lesser grade, autoclaved DBS, demonstrating the elution role in fulfilling its purpose. All DBS samples younger than 3 years always were detected as blood spot present, independently of the hematocrit. DBS older than 3 years showed an erratic behavior, 10/42 showing BSPM in only one replicate or in the first run but not in the repetition, evidencing a potential combined effect of poor elution plus optical obstruction. **Conclusions:** The Prescan function is a useful tool to detect BSPM, however false BSPM are observed in samples that elute normally and in some fixed samples that randomly showed a BSPM.

P010 - Experience With Sapropterin Treatment in PKU Patients

Fraga, C.(1); Valle, G.(1); Enacan, R.(1); Mendez, V.(1); Prieto, L.(1); Chiesa, A.(1)

(1): Fundacion de Endocrinologia Infantil, CABA, Argentina

Introduction: Tetrahydrobiopterin (BH4) allows certain PKU patients to increase their phenylalanine tolerance, enabling them to interrupt or reduce their dietary restriction. **Objectives:** To asses BH4 response of a group of PKU patients and to analyze the evolution of those selected for Sapropterin treatment. **Patients and methods:** 48 hs tests with 20mg/kg/day of Sapropterin were performed in 16 early detected PKU, median age 14.2 years old (range (R) 5.3-17.9 years), (10 males, 5 prepubertal). A positive response was considered with a phenylalanine blood level decrease of ≥30% from basal.13/16 were selected due to potentially responding genotype, 1/16 due to moderate-mild PKU phenotype and 2/16 due to severe family difficulties and psychiatric problems that would ameliorate with a therapy change. **Results:** 25% (n: 4) of patients did not respond (including 2 chosen by social reasons), 19% (n: 3) showed a 30-50% response and 56% (n: 9) respond >50%. Treatment with 10 mg/kg/day was proposed to the latter. One of them refused to try the new treatment continuing the classic one, another one stopped diet keeping optimal blood levels without any treatment and a third one accepted but did not start yet. The remaining 6 received treatment for (median) 3 years (R: 1-4). 4/6 reached adequate nutrient intake and blood phenylalanine levels exclusively with Sapropterin and 2/6 needed also protein substitute (30 and 10% of the previous intake respectively). All of them increased phenylalanine intake (median) 3 times (R: 2-6) and natural protein (median) 3 times (R: 1.5-5).Blood phe levels lowered 40% of previous ones in 1 patient, remained the same in 2 and in three patients a 30 to 40% increase was noticed. Although higher, 2 of them kept

levels in the safe control range but in 1 levels were above the recommendations. **Conclusions:** The parameters of selection (genotype and phenotype) allowed the identification of patients in which BH4 was an efficient therapeutic option. All patients improve dieťs protein quality. The false subjective feeling of healing produced by diet relaxation, affected the control frequency and quality in some patients.

P011 - BONE Mineral Density in Children With Maple Syrup Urine Disease (MSUD)

Campo Perez, K.(1); Castro, G.(1); Hamilton, V.(1); Bravo, P.(1); Arias, C.(1); Cabello, J.(1); Cornejo, V.(1)

(1): INTA, SANTIAGO, CHILE

Introduction: MSUD is caused by a blockage of the catabolic pathway of branched chain amino acids (BCAA). The disease leads to neurological damage through leucine and other metabolites accumulation. Treatment consists of a leucine restricted diet plus consumption of a special formula without BCAA, leading to supplement with minerals that can become deficient because of the diet, such as calcium. There are few investigations of bone mineral density (BMO) in this population. **Objective:** Describe and report data of bone mineral density of MSUD patients. **Methods:** Cross-sectional study of a sample of MSUD patients between 5-18 years of age (n=20), in which bone mineral density was evaluated by X-ray absorptiometry dual energy (DEXA). **Results:** About 30% of children have risk of osteopenia/osteoporosis (BMO $\leq$ -1 Z score). The rest, has an adequate BMO distributed 50% above Z Score $\geq$ 0 and 50% between 0 and -1 Z Score. **Conclusion:** These data should be considered to design future studies to evaluate other parameters involved in bone health such as vitamin D levels, physical activity, frequency of fractures and other clinical data in order to propose adjustments in the treatment protocols for MSUD children regarding calcium supplementation and to assess other strategies related to these variables that could be implemented.

P012 - Genotype Analysis OF Phenylketonuria in Chile

Hamilton, V.(1); Santamaria, L.(1); Cornejo, V.(1)

(1): INTA, Universidad de Chile, santiago, Chile

Introduction: Phenylketonuria (PKU, OMIM 261600) is caused by a mutation in Phenylalanine Hydroxylase (*PAH*) gene situated in chromosome 12q22-q24.2. This gene has 13 exons and 12 introns. Up to date 885 mutations have been described. The genotype is one of the main factors that determine the phenotype of this disease. In Chile, we have a national Newborn Screening program for PKU since 1992 with more than 350 patients detected with PKU and Hyperphenylalaninemias (HPhe). **Methods:** We selected 40 PKU patients to study the *PAH* gene by restriction fragment length polymorphism (RFLP) and sequencing techniques to identify the genotype, previous exon and intron amplification through PCR technique. Classification of the phenotype according to Guldberg predicted value. **Results:** We present the different mutations found, allele frequency and phenotype classification according to their genotype (Guldberg predicted value). **Conclusions:** The implementation of molecular study will allow the characterization of the phenotype according to their mutations, to develop a genotype/phenotype correlation in the Chilean PKU population and to evaluate the possible inclusion of new therapies for treatment.

P013 - Evaluation of DNA Extraction Method and 11 Most-Common Mutations in the CYP21A2 Gene From Neonatal Dried Blood Spots Samples as a Confirmatory Method in Neonatal Screening (NS)

Marino, S.(1); Dratler, G.(1); Ramirez, P.(1); Perez Garrido, N.(1); Galeano, J.(1); Juanes, M.(1); Touzon, S.(1); Glikman, P.(2); Junco, M.(2); Maccalini, G.(3); Aranda, C.(3); Pasteris, E.(4); Campi, V.(5); Vaiani, E.(1); Marino, R.(1); Belgorosky, A.(1)

(1): Hospital de Pediatria SAMIC Dr JP Garrahan, Buenos Aires, Argentina
(2): Hospital Ramos Mejia, Buenos Aires, Argentina
(3): Hospital Durand, Buenos Aires, Argentina
(4): Hospital Materno Infantil, Salta, Argentina
(5): Maternidad Provincial 25 de Mayo, Catamarca, Argentina

Background: Neonatal dried blood spots (DBS) represent an inexpensive method for long-term biobanking. Congenital adrenal hyperplasia (CAH) neonatal screening has a low positive predictive value (about 1%), which leads to many follow-up evaluations that have negative results. The positive predictive value might be improved by second-tier screening using DNA-based methods. Besides, genotyping using DBS samples is very useful for sample transportation from different geographical regions, specially when it is difficult for the patient to travel for a suitable blood collection, and also allows for a retrospective study of the disease. **Objective:** To evaluate a DNA extraction method and 11 most-common mutations screening in CYP21A2 gene from DBS samples as a confirmatory method in CAH neonatal screening. **Methods:** Twelve neonatal dried blood spots (DBS) from 5 different NS laboratories conserved at room temperature between 2010-2015 which were presumably pathological for CAH in neonatal screening were analyzed. DNA extraction was performed with a commercial extraction kit (QIAamp DNA Mini Kit, Qiagen). DNA quality was assessed based on spectrophotometric measurements, DNA detectability by PCR and DNA integrity by gel electrophoresis. 11-most-common mutations described in CYP21A2 gene were analyzed by automated sequencing and MLPA analysis. **Results:** 260/280 ratio was found to be 1.72 ± 0.11. DNA integrity was fairly

satisfactory and detectability by PCR and sequencing was successful in all the samples. In 10 from 12 samples, CAH diagnosis was confirmed while 2 patients turned out to be false positive cases, in agreement with molecular studies performed in DNA extracted from blood samples. **Conclusion:** Early confirmation of the diagnosis by molecular studies without the request of a second sample is very important to improve the clinical management of the patient, preventing salt-wasting crises and incorrect sex assignment. In this study we showed that DNA extracted from DBS is a useful tool for 21-hydroxylase deficiency diagnostic confirmation for newborn screening programs. Moreover, DBS represent an inexpensive method for long-term biobanking and for possible use in retrospective studies.

P014 - Evaluation Of Neolisa® MSUD Kit in Maple Syrup Urine Disease Child Monitoring in a Reference Service for Newborn Screening

Santos Calmon, L.(1); Da Anunciação Do Espírito Santo, D.(1); Efigenia De Queiroz Leite, M.(1); Amaral Boa Sorte, N.(2); Kraychete Costa, B.(2); Amorim, T.(2)

(1): APAE/UFBA, Salvador, BRASIL
(2): APAE/UNEB, Salvador, BRASIL

Introduction: MSUD patients require regular monitoring of serum leucine, isoleucine and valine, measured by high-performance liquid chromatography (HPLC), not easily available in Brazil public health services. NeoLISA® MSUD kit (MSUD kit) performance was analyzed, comparing it to HPLC. **Methods:** We evaluated medical records of 32 pairs of tests (MSUD kit/HPLC) obtained from 9 patients with MSUD treated in Bahia until July/2015. MSUD kit results expressed combined amounts of leucine and isoleucine (iso/leu) obtained from dried blood spot samples on filter paper. Leucine (leu) and isoleucine (iso) quantification was performed by HPLC in plasma collected in the same moment and forwarded to Inborn Errors of Metabolism Network Brasil (www.redeeimbrasil.ufrgs.br). They were classified as normal or elevated. Spearman correlation, kappa and predictive values were used in the comparison of the laboratories procedures. Iso/leu values (MSUD kit) were compared with leucine and isoleucine values obtained by HPLC, as well as the sum of leucine and isoleucine (iso + leu). **Results:** There were no differences in mean (SD) of iso + leu and leu [345.6 (175.1) versus 321.2 (517.0); p = 0802]. According to the kit MSUD, 12 (37.5%) of dosages were abnormal, while 13 (40.6%) of HPLC examinations showed leucine>216 micromol/L. Correlations observed between iso/leu values (MSUD kit) and leu, isoleu and iso + leu (HPLC) were 0.680; 0.530 and 0.746 (p <0.001), respectively. With the removal of a pair of outlier values (n=31), correlations were 0.649; 0.655 and 0.722, respectively. The kappa obtained was 0.241 (95%CI:-0.108-0.590), with 64.5% agreement. When considering abnormal values of leucine and/or isoleucine the kappa reached 0.323 (95% CI:0013-0633). In that case, the positive and negative predictive values were 75.0% and 60.0%, respectively. Among the tests with leucine above 500 micromol/L, MSUD kit identified 80% (4/5) of patients. **Conclusions:** The MSUD kit showed good correlation with the gold standard (HPLC) and good agreement, and may be useful for immediate assessment of MSUD patients, especially in more severe situations. However, HPLC testing remains mandatory.

P015 - Congenital Hypothyroidism. Progression of the Neonatal Screening Program in the Department of La Paz, Bolivia

Jove, A.(1); Salvatierra, I.(1); Siacar, S.(2)

(1): Hospital Arco Iris, La Paz, Bolivia
(2): Hospital Materno Infantil, La Paz, Bolivia

Introduction: Neonatal screening (NS) for congenital hypothyroidism was established by the laws of public health in Bolivia. Nevertheless, Bolivia does not have a national program. We present regional data of the Department of La Paz, with data from the Arco Iris Hospital, (private Hospital that applies public policies) and the Maternal-Infantile Hospital of the Social Security (CNS). **Objective:** To analyze the results of three years of congenital hypothyroidism (CH) screening and their impact in our health system. **Methods:** We included all newborns in the period of June 2012 to June 2015. Dried blood spot filter paper samples from a heel prick were analyzed for TSH levels, using the DELFIA (time-resolved immunofluorometric) assay. All TSH values above 10 μUI/mL were considered suspicious and were confirmed by a complete study of the thyroid (ultrasensible TSH, T3, T4 and free T4 by DELFIA). **Results:** 67000 newborns were screened in that period of time, 24 cases of congenital hypothyroidism were confirmed. The patients receive treatment and have periodical follow-up. The CH prevalence is 1:2792 with a coverage of 82% for the areas of service of the Arco Iris Hospital and Maternal-Infantile Hospital. **Conclusions:** Congenital hypothyroidism neonatal screening has been progressively increased with the incorporation of the Social Security, obtaining the mentioned coverage at the area of service of our two hospitals. Nevertheless, the official data of the number of births of the Department of La Paz shows approximately 53000 births per year in the province, and 73000 in the whole Department, for approximately 150000 births in the province and 22000 in the Department of La Paz. It is urgent to establish a comprehensive regional and national program for appropriate prevention of the intellectual disabilities associated with congenital hypothyroidism.

P016 - Distribution of the C.60+5G>T Danish Pathogenic Variant of PAH Gene Among Latin American PKU Patients and Phenotype Description of Resulting Homozygous State

Fernández-lainez, C.(1); González Del Ángel, A.(2); Alcántara-ortigoza, M.(2); Ibarra-González, I.(3); Vela-amieva, M.(2)

(1): Instituto Nacional de Pediatría, Mexico DF, Mexico
(2): Instituto Nacional de Pediatría, Mexico DF
(3): Instituto de Investigaciones Biomédicas, Mexico DF,

Introduction: Defects on the *PAH* gene are causative of phenylketonuria (PKU), an intellectual disabling inherited metabolic disorder. Recently, it has been reported that, unlike European population, splicing mutations are the most frequent among a Mexican population studied, being the c.60+5G>T variant the most frequent one, its predicted effect is a decrease in the affinity of the natural splicing site, which classifies it as a severe, null enzymatic activity and non-BH4 responding variant; furthermore, this mutation, which is of Danish origin, has a low incidence worldwide and was found to have a possible founder effect in a particular region of Mexico named "Los Altos de Jalisco". **Objective:** To investigate the allelic frequency of c.60+5G>T Danish mutation in Latin American studies of *PAH* gene mutational spectrum and to describe the phenotype associated to homozygous state. **Material and methods:** Exhaustive literature revision of PKU Latin American genetic studies in PubMed, Scopus, Scielo, and Imbiomed, with the terms *PAH*, PKU mutational spectrum, and Phenylketonuria, in Spanish, English and Portuguese languages. **Results:** Mutational spectrum and case reports were found from Spain, Cuba, Venezuela, Brazil, Chile, México, Argentina and Costa Rica. The c.60+5G>T variant was found to be the most frequent in México, followed by Costa Rica, Spain and Brazil with allelic frequencies of 20.8, 16.6, 1.36 and 0.42% respectively. There were no presence of c.60+5G>T variant in Chile, Argentina, Venezuela and Cuba. The only population in whom this variant was found in homozygous state was the Mexican, where the phenotype corresponded to classical PKU. **Conclusions:** The c.60+5G>T variant, as in the rest of the world, has a low frequency among Latin American PKU patients, except for Mexico, where a possible founder effect has been documented.

P017 - Evaluation of Homocysteine Levels in Cuban Patients With Homocystinuria and Methylmalonic Aciduria

Concepción Alvarez, A.(1); Camayd Viera, I.(1); Nuevas Paz, L.(1); Martínez Rey, L.(1); González Reyes, E.(2)

(1): Centro Nacional de Genética Médica, La Habana, Cuba
(2): Centro de Inmunoensayos, La Habana, Cuba

Introduction: Homocysteine (Hcy) is a nonessential amino acid that links the methionine and the folate cycle. Hcy levels are increased in genetic disorders such as classical homocystinuria, homocystinuria combined with methylmalonic aciduria and megaloblastic anemia. Therefore, Hcy quantification is included among the first recommended steps for differential diagnosis and management of these disorders. The diagnosis of classic homocystinuria in Cuba is routinely carried out by a qualitative test, which does not have the necessary sensitivity to detect milder Hcy elevations in combined methylmalonic acidurias (MA). The aim of this work is to validate a High Performance Liquid Chromatography (HPLC) method to quantify Hcy and to introduce it in the assessment in patients with high urine methylmalonic acid levels or clinically suspected to have classic homocystinuria. **Material and Methods:** A method to quantify Hcy levels in plasma by HPLC was developed and validated. We determined the following validation parameters: specificity, linearity, precision, accuracy, limit of detection and quantification. The method was applied in 14 patients with suspicion of homocystinuria and MA in a period of two years. **Results:** The method allowed the identification and quantification of Hcy. A lineal behavior was observed with an $r2 = 0.9967$. In the precision and accuracy studies the coefficients of variation obtained were below 5%. The limits of detection and quantification obtained were 3.12 μM and 6.25 μM, respectively. Of the 14 studied patients, one of them showed elevated Hcy levels suggesting a homocystinuria. In addition, three out of five patients with MA, showed elevated Hcy levels, indicating the presence of a MA combined with homocystinuria. In one of these patients after starting treatment, a decrease of Hcy levels was observed, which was correlated to a successful evolution after starting the treatment. The remaining two patients had normal Hcy levels and were described as isolated MA. **Conclusions:** The method validated for the quantification of Hcy in plasma fulfills the requirements for analytical validation of methods in clinical chemistry. Its use allowed the diagnosis and follow-up of patients with homocystinuria and methylmalonic acidurias.

P018 - Organic Acidurias in Chile: Evaluation After a Year of Implementation of Urinary Organic Acids Test by Gas Chromatography-Mass Spectrometry (GC-MS)

Fuenzalida, K.(1); Betta, K.(1); Arias, C.(1); Sanchez, M.(1); Valiente, A.(1); Cornejo, V.(1); Cabello, J.(1)

(1): Instituto de Nutrición y Tecnología de los Alimentos. Dr. Fernando Monckeberg, Santiago, Chile

Introduction: Urinary organic acid (UOA) analysis by gas chromatography-mass spectrometry (GC-MS) is one of the essentials analytical procedures for the laboratories focused in investigation and diagnosis of the inherited metabolic disorders. Our center has implemented a year ago the analysis of UOA excretion profiles following a qualitative methodology. The information content of the profile is high and the complexity of the interpretation mainly relies on more than of 200 metabolites that could be find in urine, taking this into consideration in 2014 we started to participate in the educational program of UOA Qualitative Scheme from ERNDIM, (European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism). **Results:** During the past year the laboratory has received and analyzed 168 urine patient samples 4,76% had an abnormal excretion pattern of organic acids that was characteristic for one of the classic profile of organic acidemias or another metabolic disorder. The

confirmatory diagnostic was based on the compatibility of chromatographic UOA findings profile and clinical manifestation of the patients. The age of patients at the time of diagnosis ranged from one month of age to 3 years and 2 months, with an average time in the notification of the result of five days. ERNDIM evaluation was successful from this period of time. **Conclusion:** After a year working as a specialist laboratory for analysis of organic acid analysis, we could evaluate the overall performance as positive. The recognition of this test as an invaluable tool for the diagnosis of several inherited metabolic disorder, greater accessibility for the regional health care centers and a prompt response time could be the main factors that account for this achievement. The relationships between laboratory findings and clinical data are essential for correct interpretation of this results.

P019 - Transient Congenital Hypothyroidism due to Biallelic Defects in DUOX2 Gene

Enacan, R.(1); Masnata, M.(1); Papendieck, P.(1); Belforte, F.(2); Targovnik, H.(2); Gruñeiro-papendieck, L.(1); Rivolta, C.(2); Chiesa, A.(1)

(1): CEDIE-CONICET-FEI-División de Endocrinología, Hospital de Niños R. Gutiérrez, CABA, Argentina
(2): Catedra de Biologia Molecular. Facultad de Farmacia y Bioquímica UBA, CABA, Argentina

Introduction: Dual oxidases (DUOX1 and 2) are components of the thyroid hydrogen peroxide (H2O2) generating system needed for the thyroid hormone organification. Mutations in the *DUOX2* gen have been described in transient and permanent congenital hypothyroidism (CH) presenting with goiter and positive perchlorate discharge test. **Subjects and Methods:** We report two siblings born from unrelated healthy parents. The oldest was detected through neonatal screening with slightly elevated TSH. When she was 30 days old, the treatment with LT4 began. TSH was 32 mUI/l, T4 13 ug/dl, FT4 1.46 ng/dl and TG 266 ng/dl (RV 30-100) and she had goiter in the Tc99 scan. Treatment was withdrawn at 2.9 years of age when she showed normal TSH, T4 and FT4 levels and TG:41,7 ng/dl (NRV 6-30). Perchlorate discharge was 17% (Normal <15%). Treatment was restarted two months later and stopped again at 7 years. A month later, thyroid profile was normal, perchlorate test negative and TG: 51.2 ng/dl. She is now 12 years old, grows normally, undergoes normal puberty and keeps euthyroid. Her brother also tested positive for CH at screening and the treatment started at 15 days of life (TSH 33 mUI/l, T4 7.9 ug/dl, FT4 0.9 ng/dl and TG 666 ng/dl). Reevaluation at 3.3 years showed normal thyroid profile and negative perchlorate test. At 7 years of age, he is euthyroid and grows normally. With suspicion of organification disorder, all 17 exons of the TPO gene and the 33 exons of the DUOX2 gene were studied by SSCP. **Results:** SSCP revealed no abnormalities in the *TPO* gene. In both patients, the study of the *DUOX 2* gene revealed a novel deletion in exon 9 (c.1057_1058delTT, p.F353 fsX388) in the paternal allele and an already described mutation in exon 11 (c.1271t>g,p.Y425X) in the maternal allele. Their healthy brother harbored only the exon 11 mutation. **Conclusion:** Molecular *TPO* and *DUOX* evaluation should be carried out when permanent or transient organification disorders are suspected. As our findings confirm, the magnitude of the defect is not related to the number of inactivated alleles. Biallelic defects of *DUOX2* in transient CH infers compensatory mechanisms in the peroxide supply.

P020 - Cobalamine C Deficiency. A Case Detected by Newborn Screening

Lemes, A.(1); Zabala, C.(1); Machado, M.(1); González, F.(1); Cabrera, A.(1); Queijo, C.(1)

(1): Instituto de Seguridad Social-BPS, Montevideo, Uruguay

Introduction: The metabolic pathway of vitamin B12 (cobalamin) is fundamental to cell metabolism through the production of two essential cofactors: methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl). The cobalamin type C deficiency (CblC, OMIM 277400) is the most common inborn error of cobalamin metabolism. It is a panethnic and recessively inherited disease, with an estimated incidence of approximately 1:100,000 live births. CblC deficiency produces a combination of methylmalonic aciduria (uMMA) and hyperhomocysteinemia (pHcty). It seems that the treatment with high dose of hydroxycobalamin (OHCbl) has better results than cyanocobalamin (CNCbl). The long-term follow-up of early-onset patients is often unsatisfactory, with progression of neurological and ocular impairment. **Objective:** to present our first case of CblC deficiency detected by newborn screening and treatment with CNCbl that has acceptable biochemical response. **Case report:** 7 months of age male patient. Newborn screening sample (40 hours of life) showed elevated C3 and ratios C3/C2 and C3/C16. Afterwards, the following studies were performed: basal uMMA and pHcty with elevated results and plasma vitamin B12 with normal value. After parenteral administration of 1 mg of CNCbl (two consecutive days), the patient uMMA and pHcty decreased 69% and 49% respectively from the baseline sample. From the clinical point of view, before parenteral vitamin B12, the patient presented generalized hypotonia that improved after starting 1mg once a week administration, but he still has slight hypotonia. He is not receiving betaine yet. Two known pathogenic mutations were identified in the *MMACHC* gene. The mother studies showed normal values of plasma B12 and pHcty. **Conclusion:** we report on a patient with cobalamin type C deficiency detected through newborn screening that improved biochemically and clinically after initiating once-a-week parenteral CNCbl treatment.

P021 - Neonatal Screening of Persistent Hyperphenylalaninemia: Strategies and Cut-Off Values

Guercio, A.(1); Villarías, N.(1); Lobato, V.(1); Castro, B.(1); Bassino, S.(1); Valle, S.(1)

(1): Programa Pesquisa Neonatal-CEPEII. Hospital Pediátrico Dr. Humberto Notti, Mendoza, Argentina

Introduction: The performance of the methods in detecting concentrations of phenylalanine (Phe) close to 2 mg/dL is critical in the neonatal screening (NS) for persistent hyperphenylalaninemia (HPA). **Objectives:** to ensure NS for HPA and to reduce the recall using an analytical algorithm in stages with different cut-off values. **Methods:** Statistical parameters related to internal and external quality controls of samples with Phe close to 2 mg/dL were analyzed. Alarm-alerts in control cards and "no clinical acceptability" of results due to negative percentage relative deviations in respect of median consensus were recorded. Taking into account the availability of reagents in our program, we decided to perform the analytical process in two stages with fluorometric methods:-1st stage, all samples of newborn (NB) were analyzed with SUMA (SU) reagents, cut-off value Phe $\geq$ 1mg/dL. -2nd stage, samples that presented in the previous stage values $\geq$ 1 mg/dL were reprocessed with the Perkin Elmer (PE) reagents, cut-off value $\geq$ 2 mg/dL. We used MedCalc®v15.6.1 to evaluate the performance of the tests and ROC curves. **Results:** 2013-2014. -1st stage, with SU reagents, we analyzed dried blood spot samples from 46528 NB, average three days of life: 959 samples (2,06%) that presented Phe values $\geq$ 1 mg/dL. 2nd stage, these samples were reprocessed with the PE reagents: 26 had Phe values $\geq$ 2 mg/dL (0,06%). Positive cases of HPA: 5 NB; Phe average values: 1,84 mg/dL SU / 3,40 mg/dL PE; incidence 1:9306. ·Performance of the SU test with different cut-off values in 46528 NB; Phe $\geq$ 2 mg/dL vs Phe $\geq$ 1 mg/dL: true positives, NB=2/5; false negatives, NB=3/0; false positives, NB=154/954; sensitivity (S) %=40/100; specificity %=99,67/97,95; positive predictive value %=1,28/0,52; negative predictive value %=99,99/100; Positive likelihood ratio=121/49; Negative likelihood ratio=0,60/0,00. ·Analysis of ROC curves with S=100%, to 959 samples processed by two methods; compared SU/PE: AUC=0,61/1,00; Phe cut-off value: > 1,1mg/dL / > 2,2mg/dL. **Conclusions:** In 2013-2014, the analytical process in two stages with different reagents and cut-off values guaranteed the NS of 5 NB with HPA and reduced the recall from 2,06% to 0,06%.

P022 - Cognitive Assessment and Stimulation in Patients With Glutaric Acidemia Type I, With Severe Neurological Impairment, by Using Technological Platform Games

García Valdés, M.(1); Arias, C.(1); De La Parra, A.(1); Solares, C.(2); Olguín, P.(2); Bunster, J.(2); Grez, O.(2)

(1): LabGEM del INTA, Universidad de Chile, Santiago, Chile
(2): Cedeti P. Universidad Católica de Chile, Santiago, Chile

Introduction: The present study shows the results obtained in the assessment of children with Glutaric Acidemia type 1 (GA-1) with severe neurological impairment and the impact of an educational intervention mediated by technology. GA-1 is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan metabolism. Patients with GA-1 have a particularly high risk of permanent cerebral damage from a metabolic crisis. Severe disability, including motor, cognitive and speech functions have been reported but little information is available regarding the cognitive profile of these patients due to lack of proper instruments to asses cognitive functioning in patients with severe motor and speech limitations. **Material and Methods:** A qualitative study was structured in three phases (1) cognitive assessment of children with GA-1 with neurological impairment (2) a personal work plan was designed for each child according to age and cognitive development status to promote the cognitive abilities development, mainly attention, working memory and specific learning, for which the child's caregiver was trained (3) During the third phase children were reassess to evaluate the programs impact. 8 children between ages 3 and 9 participated of the project during a four month period. Also quality of life and family perception of the intervention was assess. **Results and Discussion:** The initial assessment was used to describe baseline abilities in each of the children. We found great variability among the participants in evaluated abilities, degree of formal of schooling, family support and comorbidity with other pathologies. The final evaluation showed progress in control and sustained attention, inhibitory control and visomotor abilities, but these results were not statistically significant. In specific learning, progress was identified in grapheme-phoneme association, number acquisition, color identification or beginning of reading and writing, according to developmental profile of each participant. From a quality of life perspective, parents reported communicational enhancement, increased frustration tolerance and self-regulation. The project shows the importance of adequate cognitive assessment and how technological instruments that can be easily access can promote childs development in GA-1 patients with severe neurological impairment. Further research should be conducted with a larger number of participants and a longer intervention period.

P023 - Glutaric Aciduria Type I (GA1), Clinical Characterization and Genetic Study of 11 Chilean Children

Troncoso, M.(1); Santander, P.(1); Ruiz, I.(1); Yáñez, C.(1); Troncoso, L.(1); Barrios, A.(1); Tello, J.(1); Guzmán, G.(1)

(1): Hospital Clínico San Borja Arriarán. Servicio Neuropsiquiatria Infantil, Santiago, Chile

Introduction: GA1 is a metabolic disorder produced by a defect on glutaryl CoA dehydrogenase (GCDH) enzyme, in the GCDH gene localized in 19p13.2 chromosome. **Objective:** To analyze clinical manifestations, neurologic evolution, imagenologic characteristics and type of mutations found in children with diagnosis controlled in our service. **Materials and Method:** Retrospective-descriptive study and prospective analysis of 11 children diagnosed in our center in the last 17 years, with positive genetic study. **Results:** Of a total of 11 patients, six were male. Eight debuted

with an encephalitis-like episode at a mean age of 9,9 months. The three remaining patients debuted with psychomotor delay (mean age 4 months) with two of them presenting an encephalitis-like crisis later. Three patients progressed with macrocephaly. One patient presented mild, two moderate and eight severe disability. Cerebral RM in acute episode showed basal ganglia and white matter compromise, bifrontotemporal atrophy, progressing to striatal atrophy. Residual enzymatic activity was deficient in four patients who were studied. Mutations found were heterozygous to R161Q/R402W, Y133H/R161Q, Y133H/R402W, V133/A385V and homozygous to R402W/R402W, A293T/A293T, Y113H/Y113H. No relationship was found between neurologic severity and specific genotype. **Conclusion:** In our series, the most frequent presentation was an encephalitis-like episode. The most invalidating symptoms were extrapyramidal and neuroimages were distinctive. The homozygous and heterozygous mutation in Y113H and R402W are frequent in chilean population, being Y113H exclusive in this population. The biochemical genotype and phenotype did not predict clinical course. In conclusion, pre-symptomatic diagnosis of this affection allows an appropriate management with a favorable evolution.

P024 - Frequency Analysis of the N370S and L444P Mutations in Gaucher Disease Patients From Pará-Northern Brazil

Franco, F.(1); Pereira, L.(1); Amaral, C.(1); Trindade, S.(2); Santana Da Silva, L.(1)

(1): Universidade Federal do Pará, Belém, Brazil
(2): Fundação Centro de Hematologia e Hemoterapia do Pará, Belém, Brazil

Introduction: Gaucher disease (GD) is an autosomal recessive disorder caused by the deficiency of glucocerebrosidase, a lysosomal enzyme that catalyzes the hydrolysis of the glycolipid glucocerebroside to ceramide and glucose. Lysosomal storage of the substrate in cells of the reticuloendothelial system leads to multisystemic manifestations, including involvement of the liver, spleen, bone marrow, lungs, and nervous system. Almost 300 unique mutations have been reported in the glucocerebrosidase gene, with a distribution that spans the gene. **Material and methods:** Mutation analysis was performed on 13 unrelated GD patients from Belém—PA, Brazil, which the diagnosis of GD was established by demonstration of low glucocerebrosidase activity in leukocytes. Genomic DNA was prepared from peripheral blood leukocytes and screened for two known missense mutations (N370S and L444P) in the glucocerebrosidase gene by PCR amplification and direct sequencing. **Results:** The mutation N370S was present in 23% (6/26 of alleles) and the mutation L444P in 15% (5/26) of the patients with GD. No was identified patients homozygous for this mutations. **Conclusions:** The identification of different genetic modifiers and the mechanisms of their effects on the phenotypes seen in GD will significantly improve our understanding of genotype–phenotype relationships both in GD and in other Mendelian disorders.

P025 - Objectives and Quality Requirements in Neonatal Screening Programs. A Relevant Tool in Public Health

Eguileor, I.(1); Dulín, E.(2); Espada, M.(2); Zubizarreta, R.(2)

(1): AECNE-ASOCIACION ESPAÑOLA DE CRIBADO NEONATAL, Madrid, España
(2): AECNE-ASOCIACION ESPAÑOLA DE CRIBADO NEONATAL, Madrid,

Introduction: The growing demand for new diseases to be included in Neonatal Screening Programs (NSP) and their public funding have forced Governments to establish a basic portfolio of diseases that must be screened within a country. Such minimum offer must ensure that all NSP operating in a country fulfill some basic organizational requirements to guaranty an efficient service provided to population. **Material and methods:** The information of Preanalytical, Analytical and Postanalytical indicators of the 18 Neonatal Screening Programs within the country was studied exclusively for Phenylketonuria and Congenital Hypothyroidism. **Results:** Consistent results among all NSP were observed in population coverage (> 99% of NB) and quality of the analytical methods (> 95% of satisfactory performance in external quality assurance scheme (EQAS)). However other basic indicators showed great variability in mean values. For example: - Age at sampling: 2-8 days; - Transport time: 2 to 7 days; - Inadequate samples: 0.1% to 10.8% NB; - Analysis time: 1 to 8 days;- New sample request on doubtful result: 0.06% to 7.8% NB. The Scientific Society established recommendations on basic indicators for NSP with optimal levels of service delivery. Among others, organizational requirements for the previous examples were set. For example:- Age at sampling: 99th percentile <3rd day; - Transport time: 95th percentile <3 days, 99 percentile <4days; - Inadequate of samples: <0.5% NB; -Analysis time: 99th percentile <2days. - New sample request on doubtful result: <1% NB. Subsequently, the State Government has taken into account these recommendations and made them mandatory requirements for all NSP over the country. **Conclusions:** the availability of quality indicators for all key stages of a NSP is essential to assess its effectiveness and ensure compliance with its objectives. In addition, the establishment of these indicators as mandated in a country avoids inequalities and ensures access of the population to this basic public health prevention service.

P026 - Neonatal Screening Program (NSP) in Zulia—Venezuela: Evaluation of Twelve Years of Experience

Costagliola Martorona, A.(1); Chacin Hernandez, J.(2); Ocando Pino, L.(3); Mejìa Villan, I.(4); Torres Quevedo, E.(3); Torres Chirinos, Y.(3); Picado Gutierrez, J.(3)

(1): Fundacion Hospital De Especialidades Pediatricas, Maracaibo, Venezuela

(2): La Universidad del Zulia; Instituto de Investigaciones Genèticas, Maracaibo
(3): Fundacion Hospital de Especialidades Pediatricas; Laboratorio de Salud Pùblica, Maracaibo
(4): Fundacîon Hospital de Especialidades Pediatricas, Maracaibo,

Introduction: The Neonatal Screening Program (NSP) in Zulia state began in 2003 with the aim to prevent deleterious sequelae resulting from inherited metabolic diseases such as congenital hypothyroidism (CH) and phenylketonuria (PKU). The objective of this work is to evaluate 12 years of NSP with quality indicators, from dried blood spots on filter paper Whatman 903. **Materials and Methods:** The levels of TSH and phenylalanine (Phe) were determined by UMELISA Test, cut-off: CH 10 mIU / and Phe: 2mg / dL. Patients were classified according to their status: Suspected, confirmed, discarded and probable cases with first positive sample but unreachable. The percentage of coverage and the percentage of recalls of suspected cases were determined. **Results:** A total of 282 576 newborn samples were analyzed. There were 85 confirmed cases with CH and 2 cases with PKU; centers trained 88%, active centers 86%. During first quarter of 2015 the NSP achieved 66.66% coverage; suspected 30 cases, confirmed 3 cases for CH, dismissed 25 cases and found 2 probable cases; with 43.3% recall (1-5) range, positive response called 93%, incomplete data 20%, Leasehold drop filter 65%. Pre-analytical period 5 days, analytical period 2 days and post-analytical period 2 days. **Conclusion:** The coverage achieved for the first quarter of 2015 was 66.66% for all newborns in Zulia state. It is necessary to intervene with training of human resources to overcome the evidenced quality deficit and to get 100% of demographic data completed on the screening card data. The promotion of NSP is necessary to shorten response times.

P027 - Newborn Screening Experience for Galactosemia in México

Mendiola Ramírez, K.(1); Gonzalez Guerrero, J.(1); Delgado Gonzalez, E.(1); Burciaga Torres, M.(1); Ferrer Arreola, L.(1)

(1): Instituto Mexicano del Seguro Social, Coordinación de Atención Integral a la Salud en el Primer Nivel, México D.F., Mexico

Introduction: The detection of classic galactosemia was included in the Newborn Screening Institutional Program nationally in April 2012. Approximately 450,000 infants are screened annually in 1499 Family Medicine Units and 271 Secondary Hospitals and 10 Tertiary Hospitals. **Objective:** To evaluate the coverage, index of suspicion, positive predictive value, cumulative incidence, opportunity of diagnosis and analysis of patients screened in the period from 2012 to 2014. **Methodology:** A cross-sectional study was conducted with collected samples and processed during the period 2012 to 2014. Total galactose (TGal) was determined by enzyme immunoassay (UMTEST GAL) in dried blood spots collected on filter paper. If the first sample showed a high result, a second sample was requested and in the case of obtaining an elevated result, this is considered a probable case. The cutoff was defined as values of TGal higher than 10 mg / dL (> 0.56 mmol / L). The epidemiological indexes were evaluated in the epidemiological surveillance system (SIVE). **Results:** In the period 2012-2014, we processed 1,363,135 samples, thus the coverage was 98.9%. There were 187 probable cases and 35 confirmed cases by spectrophotometry and fluorometric assays in plasma, with an index of suspicion of 0.01%. We identified a positive predictive value of 18.72; cumulative incidence of 1: 39.385 live births, an opportunity in the diagnosis within 30 days of 17.14%, an average of days to the final diagnosis to 62.57 days, classification by type of galactosemia: 32 (91.42%) cases of classic galactosemia, 2 (5.71%) cases of Duarte galactosemia and 1 (2.85%) for deficiency of galactose kinase (GALK). **Conclusions:** The incidence is similar to that reported in other countries. We observed higher prevalence of cases in the Bajio states. We consider maintaining an active surveillance system to improve the opportunity of diagnosis and treatment of these patients.

P028 - Neuronal Ceroid Lipofuscinosis-2 (CLN2) Disease, a Type of Batten Disease Caused by TPP1 Enzyme Deficiency: Current Knowledge of the Natural History From International Experts

Guelbert, N.(1); L Cohen-pfeffer, J.(2); Crystal, R.(3); De Los Reyes, E.(4); Eto, Y.(5); Héron, B.(6); Mikhailova, S.(7); Miller, N.(8); Mink, J.(9); Socorro Perez-poyato, M.(10); Simonati, A.(11); Sims, K.(12); Williams, R.(13); Schulz, A.(14)

(1): Hospital de Niños de Cordoba, Cordoba, Argentina, CORDOBA, Argentina
(2): BioMarin Pharmaceutical Inc., Novato, CA, USA, Novato, USA
(3): Department of Genetic Medicine, Weill Cornell Medical College, New York, NY, USA, New York, USA
(4): Department of Pediatric Neurology, Nationwide Children's Hospital, Columbus, OH, USA, COLUMBUS, USA
(5): Advanced Clinical Research Center, Southern Tohoku Brain Research Center, Kawasaki, Japan, Kawasaki, Japan
(6): Service de Neuropédiatrie, CHU Paris Est—Hôpital d'Enfants Armand-Trousseau, Paris, France, PARIS, FRANCE
(7): Department of Medical Genetics, Russian Pediatric Regional Hospital, Moscow, Russia, MOSCOW, RUSSIA
(8): Biomarin, Novato, USA
(9): Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA, ROCHESTER, USA
(10): Unit of Pediatric Neurology, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spa, CANTABRIA, SPAIN
(11): Department of Neurological and Movement Sciences-Neurology, University, VERONA, ITALY
(12): Department of Neurology, Massachusetts General Hospital, Boston, MA, USA, BOSTON, USA
(13): Children's Neurosciences, Guy's and St Thomas' NHS Foundation Trust, London, UK, LONDON, USA

(14): 13Department of Paediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, HAMBURG, GERMANY

Background/Objectives: The neuronal ceroid lipofuscinoses (NCLs) are the most common group of neurodegenerative disorders in children and adolescents. CLN2, a type of NCL caused by TPP1 enzyme deficiency, is characterized by seizures, rapid deterioration of language, cognition, motor skills and vision, and premature death. Our aim is to describe expert knowledge of CLN2 disease. **Methods:** 18 international NCL experts answered a survey on CLN2 natural history. **Results:** Clinical suspicion for CLN2 is low due to its rarity and non-specific presenting symptoms. A 1-4 year delay was reported between first onset of symptoms and diagnosis. Speech delay/decline, developmental delay/regression and seizures/epilepsy were identified as initial presenting symptoms. Symptom onset typically occurs between 1.5-5 years of age, but may occur later (9-12 years). Myoclonic epilepsy was the most commonly reported seizure type. Notably, seizures are refractory oftentimes requiring polytherapy. Cardiac rhythm anomalies, not previously associated with CLN2, were also identified. **Conclusions:** CLN2 is a severe, progressive, pediatric-onset neurodegenerative disease. Disease awareness is low, causing delays in diagnosis. Seizures associated to a regression of language and/or motor milestones should raise suspicion for CLN2. Knowledge of CLN2 is paramount to ensure timely diagnosis and to enable early initiation of future therapies.

P029 - A Study on the Effects of Interrupting Enzyme Replacement Therapy on a Lysosomal Storage Disorder

Schneider, A.(1); Baldo, G.(1); Pasqualim, G.(2); Tavares, A.(3); Giugliani, R.(3); Matte, U.(3)

(1): Hospital de Clínicas de Porto Alegre/ Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
(2): Hospital de Clínicas de Porto Alegre, Porto Aleg, Brazil
(3): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Introduction: There are reports in the literature of enzyme replacement (ERT) interruption/ withdrawal in lysosomal storage disorders (LSD), due to medical recommendation (in case of pregnancy, for example), to shortage in the production of a recombinant enzyme, or other reasons. In all these cases, some level of deterioration was observed in the patients. However, due to differences in phenotypes even within the same disease, it is hard to obtain accurate data on which organs/systems are more or less affected when treatment is interrupted. **Objective:** In the present work we aimed to study the effects of ERT withdrawal and reintroduction of therapy in an animal model of Hurler syndrome (MPS I). **Methods:** Animals were divided in 4 groups: Normal and MPS I untreated mice, MPS I mice treated from neonatal period without interruption (ERT-neo, 1,2 mg/kg of Laronidase® every 2 weeks) and MPS I mice treated from birth with treatment interrupted from 2 to 4 months of age (ERT-stop) and then reintroduced. All animals were sacrificed at 6 months. **Results:** Urinary Glycosaminoglycans (GAG) levels were reduced in both treated groups and surprisingly did not increase during the interruption period. Tissue GAG in organs such as the liver and kidney were normalized in both treated groups. ERT-stop mice had heart and lungs GAG levels still slightly elevated at 6 months, indicating that GAG storage in these organs may be harder to correct after interruption. GAG levels were increased in MPS I mice aortas, and were only partially restored in treated groups. Also, only ERT-stop mice had increased aortic wall distention compared to normal mice ($p < 0.05$), suggesting a deleterious effect of ERT interruption. Echocardiography analyses revealed that most parameters were normalized in both treated groups (ejection fraction and heart dilatation) but parameters of pulmonary vascular resistance were corrected only in ERT-neo mice. Neonatal treatment prevented antibody formation against the enzyme, and the immune tolerance was maintained even if treatment was interrupted and reintroduced. **Conclusions:** Treatment interruption may have deleterious effects in particular organs and should be avoided in LSDs. Urinary GAG levels should be carefully analyzed and may not reflect disease status.

P030 - Nutritional Status and Carnitine Levels in Patients With Nephropatic Cystinosis

Guillén López, S.(1); Belmont-martínez, L.(2); Ibarra-gonzález, I.(3); Juárez-cruz, M.(4); Vela-amieva, M.(2)

(1): Instituto Nacional de Pediatría, D.F., México
(2): Instituto Nacional de Pediatría, D.F, México
(3): Instituto de Invetigaciones Biomédicas, D.F, México
(4): Instituto Politécnico Nacional, D.F, México

Introduction: Nephropathic Cystinosis is an autosomal recessive disorder that causes defect in cystine transport with subsequent accumulation in almost all body tissues, especially kidneys. There are few studies regarding the nutritional status assessment of patients with cystinosis. It has been reported that patients with cystinosis showed increased urinary losses of carnitine, resulting in plasma and muscle carnitine deficiency also increased metabolic requirements of carnitine in cystinosis have also been proposed, but to date carnitine supplementation is controversial. **Objective:** The aim of this study was to perform an assessment of nutritional status in patients with nephropathic cystinosis and to determine its blood free carnitine concentrations. **Material and Methods:** Anthropometric assessment and nutritional diagnosis of 12 patients with cystinosis which included measurement of weight, height, mid upper arm circumference and triceps skinfold thickness. This assessment was performed by qualified, standardized dietitians. Calculation of Body Mass Index was done using actual weight and height, cut off values for patients under 18 years old were according OMS percentiles: < 5 malnutrition, 5-85

normal, 85-95 overweight and > 95 obesity, and for adults OMS values were <18.5 malnutrition, 18.5- 24.9 normal, > 25 -29.9 overweight and >30 obesity. Free carnitine was measured by tandem mass spectrometry in fasting blood samples. **Results and Discussion:** 7/12 had normal BMI, 3/12 were classified as malnourished with low weight and height and 1/12 was diagnosed as overweight and only 1/12 with obesity. Mid upper arm circumference was used as an indirect measure of skeletal muscle protein reserves and in 6/12 of the patients was below 5th percentile and only one patient had an excess of lean mass above 85th percentile, the other 5 fall on normal percentiles. Triceps skinfold thickness percentiles were below 15th in 5/12 of the patients, 5/12 were normal and 2/12 had an excess of fat mass. Serum free carnitine levels were low in 10/12 patients. **Conclusion:** In this study, serum free carnitine levels were low in 83% cystinotic patients. From the 12 patients 25% of them were malnourished and 16.6% were overweight-obese. Nutritional assessment in this disease is required and carnitine supplementation most be considered.

P031 - Recommendations for Enzyme Replacement Therapy in Classical Phenotype of Fabry Disease in Latin America

Politei, J.(1)

(1): Fundación para el Estudio de las Enfermedades Neurometabólicas (FESEN), quilmes, ARGENTINA

Authors: JUAN POLITEI, on behalf of Latinamerican study group for the recommendations of enzyme replacement therapy in Fabry Disease

Introduction: Fabry disease is a rare X-linked inherited disorder due to deficient or absent lysosomal α-galactosidase A activity, resulting in an excessive glycosphingolipid deposit and early mortality due renal, cardiac and neurological cause. Currently, there are some controversies regarding the right moment for the initiation of enzyme replacement therapy (ERT), even when an early indication is linked with a better outcome. **Aim:** to present a recommendation for the initiation of ERT in Fabry patients with classical phenotype, based in the knowledge and expertise of a group of Latinamerican practitioners involved in daily care for Fabry patients. **Methods:** For the first round, a background document was compiled by the study coordinator (J.P.) with information on national and local treatment protocols and an overview of inclusion criteria applied in other international guidelines. Subsequently, an online questionnaire was set up by the study team to discuss initiation criteria. The participants were asked to assess criteria on a 4-point scale (1 = strongly agree, 2 = agree, 3 = disagree and 4 = strongly disagree) and were invited to add suggestions. A criterion was used in the treatment recommendations only if there was at least 66% agreement (1+2). **Results:** Forty eight practitioners responded to the online survey. The group agreed that a differentiation should be made between male and female patients. The criteria were divided in five main sections, with a consensus in all of them. (see table 1).

	No signs or symptoms	Renal involvement	Cardiac involvement	Central nervous system inv.	Peripheral nervous system inv.	Gastro-intestinal involvement
males	If ≥ 16 years of age	- Microalbuminuria - Proteinuria - Glomerular filtration rate <90 - GI3 deposits and foot process effacement in kidney biopsy	- Cardiac hypertrophy (IVS or LVPW > 12 mm) - signs of cardiac rhythm disturbances - Fibrosis in cardiac resonance (even without LVH)	- white matter lesions in MRI - clinical stroke/ TIA	- Neuropathic pain, even if completely controlled (not interfering with daily activities) with pain medications. - sudden or progressive hearing loss	- abdominal pain, nauseas, vomits and/or frequent diarrhea
females		- Microalbuminuria - Proteinuria - glomerular filtration rate <90 - GI3 deposits and foot process effacement in kidney biopsy	- Cardiac hypertrophy (IVS or LVPW > 12 mm) - signs of cardiac rhythm disturbances - Fibrosis in cardiac resonance (even without LVH)	- white matter lesions in MRI - clinical stroke/ TIA	- Neuropathic pain, even if completely controlled (not interfering with daily activities) with pain medications. - sudden or progressive hearing loss	- abdominal pain, nauseas, vomits and/or frequent diarrhea

P032 - Regulation of the Antioxidant Enzymes Catalase and Glutathione Peroxidase 1 by Kinase C-ABL in Neuronal Models of Niemann-Pick C Disease

Rojas, C.(1); Marín, T.(1); Castro, J.(1); Contreras, P.(1); Alvarez, A.(1); Zanlungo, S.(1)

(1): Pontificia Universidad Católica de Chile, Santiago, Chile

Introduction: Niemann-Pick C (NPC) disease is a genetic lysosomal storage disease characterized by cholesterol accumulation and progressive neurodegeneration. We have previously reported that oxidative stress is the main upstream stimulus activating the proapoptotic c-Abl kinase in NPC neurons. Interestingly, dysregulation of the antioxidant enzymes

catalase and glutathione peroxidase activities mediated by c-Abl has been reported in several cell types, but not in neurons. Aim: to analyze if c-Abl regulates the levels of catalase and glutathione peroxidase in NPC neuronal models. **Materials and methods:** We used two in vitro neuronal NPC models; 1) pharmacological: HT22 neuronal hippocampal cell line treated with the U18666A (U18) drug and 2) genetic: stable Npc1 knockdown in the HT22 cell line. We treated both models with the c-Abl inhibitor, Imatinib, and evaluated: i) the levels of catalase and glutathione peroxidase 1 (gpx1) by western blot and ii) the association between the antioxidant enzymes and c-Abl through immunoprecipitation studies. **Results:** Imatinib increased the protein levels of catalase and gpx1 in both NPC neuronal models. In addition, we found that c-Abl associates with both antioxidant enzymes and that these interactions increased with Imatinib. **Conclusions:** C-Abl inhibition using Imatinib increases the levels of catalase and gpx1 and the association with the antioxidant enzymes and c-Abl in NPC neuronal models. These results could be potentially relevant for the therapeutic treatment of NPC disease.

P033 - Sphingomyelin Metabolism and Fibrosis Development in Livers of Niemann–Pick Type B Disease Patients and the Mouse Model

Acuña, M.(1); Benítez, C.(1); Arrese, M.(1); Miquel, J.(1); Mabe, P.(2); Schuchman, E.(3); Zanlungo, S.(1)

(1): Pontificia Universidad Católica de Chile, Santiago, Chile
(2): Hospital Exequiel González Cortés, Santiago, Chile
(3): Icahn School of Medicine at Mount Sinai, New York, Estados Unidos

Introduction: Niemann-Pick type B (NPB) disease is a hereditary disorder caused by mutations in the acid sphingomyelinase (ASM) gene and secondary accumulation of sphingomyelin in the lysosome. The p.Ala359Asp mutation has been identified only in Chilean patients. Homozygosis for this mutation confers a high risk of liver cirrhosis. Goal: To evaluate the sphingomyelin metabolism and fibrosis markers in liver biopsies of p.Ala359Asp homozygous patients and to correlate the pathological findings with the development of fibrosis in the NPB knockout mouse model (ASMKO). **Methods:** The lipids and mRNA expression of enzymes related with sphingomyelin metabolism were evaluated in liver biopsies from one NPB p.Ala359Asp homozygous patient. The mRNA and protein expression of markers for hepatic fibrosis were measured in liver biopsies of two p.Ala359Asp homozygous patients and in the ASMKO mice of five, seven and nine months of age (n=3 of each condition). **Results:** We found increased levels of sphingomyelin, ceramide and sphingosine and changes in the expression of some enzymes involved in sphingomyelin metabolism in the liver biopsies of the NPB patient. The levels of markers for hepatic fibrosis were increased in the patient's liver and also in the ASMKO mouse, in which further damage was found with increasing age of the mice. The ASMKO model showed hepatic increased macrophages infiltration and fibrosis. **Conclusions:** The p.Ala359Asp mutation correlates with changes in sphingomyelin metabolism that could be related to the liver damage found in patients. Homozygous p.Ala359Asp patients and ASMKO mice present increased markers for hepatic fibrosis. The ASMKO mouse is a useful model to understand the mechanisms involved in the liver damage in NPB patients. Supported by FONDAP CGR 15090007.

P034 - Development of a New 17OH Progesterone Neonatal Umelisa Using Monoclonal Antibodies on the Solid Phase

González Reyes, E.(1); Morejón García, G.(1); Castells Martínez, E.(1); García De La Rosa, I.(1); Rubio Torres, A.(1); Frómeta Suárez, A.(1); Pérez Moras, P.(1); Del Río Fabre, L.(1); Tejeda Gómez, Y.(1); Segura González, M.(1); Almenares Guasch, P.(1); Quintana Guerra, J.(1); Rosabal Polonshkov, A.(1)

(1): Centro de Inmunoensayo, La Habana, Cuba

Introduction: Since 2005, a National Neonatal Screening program for congenital adrenal hyperplasia (CAH) using a simple and rapid competitive ultramicroELISA for detecting 17-hydroxyprogesterone (17OHP) was initiated in Cuba. A new 17OH Progesterone Neonatal UMELISA based on competition between 17OHP-alkaline phosphatase conjugate the steroid in blood specimens for a limited number of binding sites on a specific monoclonal antibody (MAb) against 17OHP has been developed. The aim of this study is to describe the main analytical performance characteristics of this assay for newborn screening purposes. **Materials and Methods:** In the Immunoassay Center, a hybridoma secreting anti-17OHP MAbs has been generated. These MAbs are highly specific and have an affinity of 1.7×109 L/mol. A new formulation of the solid phase was carried out by pre-coating white opaque 96-well polystyrene ultramicroplates, first with a sheep anti-mouse IgG polyclonal antibody and finally, with the specific monoclonal. Studies of precision, accuracy, cross-reactivity, limits of detection (LoD) and quantification (LoQ) were developed. Newborn dried blood samples (DBS) were analyzed to determine preliminary 17OHP threshold levels (99th percentile) according to gestational age (GA) and birth weight (BW). **Results:** The new assay with a measuring range of 4-320 nmol/L, provides a lower background (at least 2 fold) and better sensitivity in the range of the curve with higher concentrations, with respect to the commercial available kit. The intra- and inter-assay coefficients of variation were 5.4-7.8% and 6.6-8.0%, respectively, depending on the 17OHP concentrations. The recovery with CDC quality controls was about 100%. The calculated LoD and LoQ were 2.0 and 4.0 nmol/L, respectively. The major cross-reactivity with possible interfering steroids were hydrocortisone (5.7%), progesterone (3.0%), Reichstein's substance

(2.7%) and 17-hydroxypregnenolone (2.5%). The mean 17OHP concentration in 6157 DBS was 20.1 nmol/L, with significantly higher levels in newborns with lower BW and GA. 17OHP threshold levels for BW were <2500 g (173 nmol/L) and >2500 g (75 nmol/L) while according to GA, were <37 weeks (204 nmol/L) and >37 weeks (73 nmol/L). **Conclusions:** These results indicate that the new 17OHP NEONATAL UMELISA has a high sensitivity and adequate specificity for detection of 17OHP and it is suitable for neonatal screening of CAH.

P035 - Standardization of a Molecular Method for Mutations Detection in the CFTR Gene in Patients With Cystic Fibrosis Suspicion in Southern Brazil

Castro, S.(1); Rosseti, L.(2); Dornelles, C.(2); Grandi, T.(2); Filippon, L.(3); Rispoli, T.(4)

(1): Serviço Referência Triagem Neonatal RS/Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil
(2): Centro de Desenvolvimento Científico e Tecnológico (CDCT)—Fundação Estadual de Produção e Pesquisa, Porto Alegre, Brasil
(3): Serviço de Referência em Triagem Neonatal RS (SRTN)/PMPA, Porto Alegre, Brasil (4): Centro de Desenvolvimento Científico e Tecnológico (CDCT)—FEPPS/UFRGS, Porto Alegre, Brasil

Introduction: Cystic fibrosis (CF) is an autosomal recessive genetic disease of high incidence in euro-descendant populations (1: 2500 live births) and is caused by mutations in the *CFTR* gene (Cystic Fibrosis Transmembrane Conductance Regulator). Approximately 2,000 mutations have been identified, the most prevalent being F508del. These mutations cause dysfunctions in the CFTR protein that regulates the movement of chlorine and sodium across cell membranes, leading to different degrees of clinical manifestations. In 2012, studies for CF screening were implemented in Rio Grande do Sul (RS), southern Brasil, just for the F508del mutation. Therefore it becomes necessary to search for molecular methods that enhance the detection of other mutations. **Objective:** To standardize a molecular detection method of thirteen mutations (R1162X, G85E, R117H, 2789 + 5G> A, G542X, R334W, W1282X, R553X, 1717-1G> A, 3120-1G> A, G551D, N1303K and F508del) in *CFTR* gene and evaluate the frequencies in patients with CF suspicion coming from Newborn Screening Reference Service of Rio Grande do Sul (SRTN/RS-Brazil). **Materials and methods:** The genetic material was extracted from whole blood using the salting out technique. Then, a method was developed in-house using the single base extension technique (Multiplex Kit SNaPshotTM), for the detection of the 13 mutations of interest. The external primers for multiplex PCR, and internal primers for the single base extension were designed using Primer3 software. Also genotyping was performed by commercial assays (Inno-LiPACFTR19 and CFTR17+Tn) and sequenced in order to validate this methodology. **Results:** standardization of an in-house method for 13 mutations detection, with 100% agreement with the techniques evaluated in 96 genotyped patients. Among these, 22 patients had at least one of the mutations investigated: 1 F508del/F508del, 9 Wt/F508del, 1 G542X/G542X, 2 Wt/G542X, 2 Wt/W1282X, 2 Wt/1717-1G>A, 2 Wt/3120-1G>A, 1 Wt/R334W and 1 Wt/N1303K. **Conclusion:** Through this study it was possible to standardize a molecular detection method for 13 mutations in the CFTR gene that, once implemented in the routine of SRTN/RS-Brazil, will allow better targeting of the treatment, genetic counseling, prognosis and better quality of life for patients.

P036 - Validation of the GSP 2021® for the Performance of Newborn Screening Tests in Southern Brazil

Castro, S.(1); Macedo, J.(2); Canto, A.(2); Filippon, L.(2)

(1): Serviço Referência Triagem Neonatal RS/Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil
(2): Serviço Referência Triagem Neonatal RS/HMIPV/PMPA, Porto Alegre, Brasil

Introduction: The analytical validation of a methodology requires knowledge of the equipment performance, including accuracy and precision analysis, in order to measure the total analytical error in the medical decision range. The quantification of a given analyte, especially in newborn screening (NBS), makes it extremely important that the methodology has a high sensitivity, minimizing the occurrence of false negative results, i.e, failure to identify a possible patient with the disease. Dried blood spots (DBS) used in NBS have qualitative restrictions, such as hemolysis, supersaturation, presence of clots and insufficient amount of blood which can also lead to analytical error and erroneous results. **Objective:** Determining the Total Analytical Error of GSP 2021® equipment, compared to the performance of AutoDELFIA 1235® and Victor 2D® equipments, for NTSH, NIRT, N17OHP and Phenylalanine (PKU) assays, based on the precision and accuracy of the method. **Materials and Methods:** In order to analyze the accuracy (systematic error) of NTSH, NIRT and N17OHP tests, 48 samples were processed in the AutoDELFIA® and GSP® equipments, and the results were compared. For the precision analysis (random error), 20 replicates of a sample were processed for intra- and inter-assay analysis. The same pattern of analysis was used to compare the GSP® and Victor 2D® equipments for evaluation of phenylalanine (PKU). **Results:** Comparing the GSP® and AutoDELFIA® equipments, analysis of Total Analytical Error showed the following results: NTSH = 13.07%, NIRT = 7.23% and N17OHP = 7.73%. For the PKU test, the Total Analytical Error, when comparing results between GSP® and Victor 2D® equipments, was 0.57%. **Conclusion:** Through statistical analysis, we concluded that the GSP® equipment is suitable for implementation in the NBS routine. Furthermore, the equipment has advantages when compared with AutoDelfia®, such as methodology with more specificity, reduction in the processing time and randomized routine. This helps promoting faster dynamic technical processes and faster reports generation.

P037 - Peroxisomal Disorders With Neonatal Presentation: Clinical Features, Imaging Findings and Lab Tests in a Series of Chilean Patients

Troncoso, M.(1); Barrios, A.(1); Balut, F.(1); Ruiz, I.(1); Hidalgo, M.(1); Muñoz, D.(1); Parra, P.(1); Sáez, C.(1); Nilo, K.(1); Carrera, J.(1); Guerra, P.(1)

(1): Hospital Clinico San Borja Arriaran, Servicio Neurología Infantil, Santiago, Chile

Introduction: Peroxisomal disorders are an heterogeneous group of inborn errors of metabolism. One of these are the Peroxisome biogenesis disorders, which includes Zellweger syndrome spectrum (ZSS) that is a continuum of three phenotypes of increasing severity: Infantile Refsum disease, Neonatal adrenoleukodystrophy (NALD) and Zellweger syndrome (ZS). Both, NALD and ZS, may present in neonatal period, characterized by severe hypotonia, seizures and dysmorphic features, among other conditions. An elevation of plasma very long chain fatty acid (VLCFA) levels is compatible with a defect in peroxisomal fatty acid metabolism. **Objectives:** Report the experience of patients diagnosed in our center with Peroxisomal disorders of neonatal presentation, analyze the spectrum of clinical features and diagnostic tests. **Material and methods:** Retrospective study. Clinical analysis, evolution and study of VLCFA. **Results:** Series of 7 patients, all coming from different regions of Chile, all born at term, 3 males and 4 females. Three of the cases were relatives, 2 sisters and one cousin. Before the first 20 days of life, all patients present severe hypotonia, hypoactivity, swallowing problems and seizures with poor response to treatment. Four cases have dysmorphic facial features, with large anterior fontanelle. Four evolve with hepatomegaly and three with jaundice. Three cases require ventilatory support. One patient have kidney impairment with multiple renal cysts. In 5 cases the brain images showed alterations, 4 cases have hypomyelination, 4 have polymicrogyria, 1 case corpus callosum agenesis and other with severe thinning of it. Elevation of plasma concentrations of VLCFA was consistent with a defect in peroxisomal fatty acid metabolism in all cases. **Conclusions:** All the cases described in this series presented severe neonatal hypotonia, epilepsy and multisystem involvement, with alteration in the magnetic resonance, hypomyelination and polymicrogyria. All findings mentioned allowed suspicion of a peroxisomal disorder, which was confirmed in all cases by the elevation of the plasma concentrations of VLCFA. All these characteristics are compatible with ZSS of neonatal presentation that could correspond with high probability to a ZS or NALD.

P038 - Biochemical and Genetic Diagnosis in Congenital Disorders of Glycosylation

Asteggiano, C.(1); Papazoglu, G.(2); Suldrup, N.(3); Ng, B.(4); Dodelson De Kremer, R.(5); Freeze, H.(6)

(1): CONICET/CEMECO/UNC/UCC Hospital de Niños Sma Trinidad, Córdoba, Argentina
(2): CONICET/Centro de Estudio de las Metabolopatías (CEMECO) UNC/Hospital de Niños Sma Trinidad, Córdoba, Argentina
(3): Dpto. Metabolopatías, IACA Laboratorios, Bahía Blanca, Argentina
(4): Human Genetics Program, Sanford-Burnham Medical Research Center, San Diego (CA), United States (USA)
(5): Centro de Estudio de las Metabolopatías (CEMECO) UNC/Hospital de Niños Sma Trinidad, Córdoba, Argentina
(6): Human Genetics Program, Sanford-Burnham Medical Research Center, San Diego (CA), United State (USA)

Introduction: Congenital Disorders of Glycosylation (CDG) are human genetic diseases due to defects in the attachment of glycans to proteins, lipids and proteoglycans in the lumen of the endoplasmic reticulum (ER) and their elaboration in the Golgi apparatus. More than 110 affected genes have been described as N- or O-glycosylation disorders, encompassing CDG 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. They can affect nearly all organs and systems, but it is often associated with neurological impairments. Serum transferrin (Tf) is a key glycoprotein for the study of N-glycosylation diseases. **Objective:** To increase the detection of inherited glycosylation disorders in Latin American patients. **Methodology:** To study N-glycosylation disorders, serum transferrin (Tf) was analyzed by Isoelectric Focusing (IEF), High Performance Liquid Chromatography (HPLC), Capillary Electrophoresis (CE) and Mass Spectrometry (MS). Sanger sequencing and Whole Exome Sequence (WES), were carried out in gDNA to detect the affected gene. **Results:** A multisystem clinical phenotype was observed in five CDG-I (cytosolic or ER defects) and in one CDG-II (Golgi defects) patients. We detected three PMM2-CDG patients and two ALG2-CDG siblings by exome sequencing and confirmed by Sanger sequencing. We also identified *COL6A2* mutations in a patient with CDG-II Tf pattern, with autosomal recessive myosclerosis myopathy, rather than a CDG disease. One CDG-IIx patient requires further analysis to detect the gene alteration. **Conclusion:** PMM2-CDG, the most frequent CDG, leads to the loss of phosphomannomutase 2 activity and presented clinical features highly variable (from a multisystem stage to a severe neurological presentation). ALG2-CDG, a rare form of CDG, was reported only in one patient deficient in alpha 1,3 mannosyltransferase presenting refractory epilepsy, maturation and mental disability, severe hypotonia, facial dysmorphia, weak tendon reflexes and c. Six from seven Argentinean CDG-x patients carried mutations in genes that alter glycosylation pathway. We highlight a broad screening of clinical features to suspect CDG in patients with inherited disorders and to develop Next Generation Sequence methods to discover new genes involved in CDG. Supported by CONICET/FONCYT/UCC/Sanford-Burnham Research Institute.

P039 - Biochemical and Genetic Screening in ATP6V0A2-CDG Patients

Lopez Valdez, J.(1); Bahena-bahena, D.(2); Raymond, K.(3); Salinas-marín, R.(2); Ortega-garcía, A.(2); Ng, B.(3); Freeze, H.(4); Ruiz-garcía, M.(5); González-palacios, J.(6); Patiño-félix, F.(6); Arenas-velazquez, E.(6); Martínez-duncker, I.(2)

(1): CENTENARIO HOSPITAL MIGUEL HIDALGO, AGUASCALIENTES, MEXICO
(2): HUMAN GLYCOBIOLOGY LABORATORY, SCIENCE FACULTY, MORELOS STATE AUTONOMOUS UNIVERSITY, MORELOS
(3): MAYO CLINIC, ROCHESTER, USA
(4): SANFORD BURNHAM MEDICAL RESEARCH INSTITUTE, LA JOLLA, USA,
(5): INSTITUTO NACIONAL DE PEDIATRÍA, DISTRITO FEDERAL
(6): CENTENARIO HOSPITAL MIGUEL HIDALGO, AGUASCALIENTES,

Introduction: Cutis laxa (CL) is an inherited or acquired disorder characterized by abnormal elastic fibers resulting in furrow, loose, redundant and hypoelastic skin. Inherited forms are rare with a prevalence of 1:4,000,000 but the most frequent are autosomal recessive CL (ARCL). ARCL-IIA harbor mutations in *ATP6V0A2* gene and characteristically presents a combined glycosylation defect affecting N-linked and O-linked glycosylations, classifying it as a Congenital Disorder of Glycosylation (ATP6V0A2-CDG). We present the clinical, biochemical and molecular studies in three patients with ARCL-IIA. **Material and methods:** After informed consent obtained in three patients with clinical phenotype of CLAR-IIA we performed in serum a transferrin isoelectric focusing (IEF), mass spectrometry for transferrin (Tf) and apolipoprotein CIII (ApoCIII). DNA from peripheral blood of patients and their parents and mRNA was isolated from fibroblasts obtained from patients and sequenced cDNA from *ATP6V0A2* gene by conventional techniques. **Results:** We studied three male patients under 3 years of age with cutis laxa, distinctive facial features, delayed closure of the fontanelles, hyperextensible joints and another multisystemic manifestations included ventricular septal defect (VSD) and cerebral malformations. The skin biopsy demonstrated an abnormal elastic fiber structure. In the patients the IEF revealed an abnormal type II profile, the mass spectrometry confirming the hypoglycosylation of serum transferrin and ApoCIII except in one patient with normal glycosylation of ApoCIII. Mutational studies revealed in patient 1 a previously reported mutation c.187CNT (p.R63X) associated with a novel clinical finding of VSD and hypospadias. In patient 2 we found a homozygous c.2293CNT (p.Q765X) mutation previously reported but found that it also altered RNA processing generating a novel transcript not previously identified. Screening of parental genomic DNA confirmed the recessive transmission. Patient 3 is currently being studied at the genetic level. **Conclusion:** Clinical and molecular findings described expand knowledge of CDG. We propose in all patients with CL and development delay to be screened with serum transferring because ApoCIII is a less reliable marker of hypoglycosylation in patients with ATP6V0A2-CDG. Further, the transcript studies are important to understand these heterogeneous disorders. The CDGs are underdiagnosed diseases that must be sought in all patients with development delay and multisystem disease.

P040 - Analysis of Allelic Variant R347P of Exon 7 of the Gene CFTR in Patients Diagnosed With Cystic Fibrosis

Albrekt, A.(1); Trigo, C.(2); Tiscornia, M.(2); Guastavino, M.(3); Malvasi, G.(3)

(1): Programa Provincial de Pesquisa Neonatal Misiones, Posadas, Argentina
(2): Instituto de Biotecnología Misiones "Dra Maria Ebe Reca" Universidad Nacional de Misiones, Posadas, Argentina
(3): Facultad de Ciencias Exactas, Químicas y Naturales, Universidad Nacional de Misiones, Posadas, Argentina

Introduction: Cystic Fibrosis (CF) is the most common autosomal recessive genetic disease in the Caucasian population, with an incidence of 1: 2000 to 1: 3,500 in newborns. This condition is caused by mutations in the regulatory gene cystic fibrosis transmembrane conductance (CFTR), located on chromosome 7, which codes for a protein whose most important function is to be a chloride channel. Currently, there are 1.988 mutations and 200 polymorphisms are known, being DF508 the most common worldwide mutation. **Aim:** The aim of this study was to analyze the allelic variant R347P of exon 7 of the gene *cftr* in patients diagnosed with Cystic Fibrosis. **Methods:** 13 pediatric patients diagnosed with Cystic Fibrosis who attended different healthcare centers during 2010-2014 period, and 15 adult individuals no fibrocystic as negative controls was studied. DNA was extracted from EDTA anticoagulated whole blood by using the *salting-out* method, modified. To carry out the study of R347P mutation, fragments containing exon 7 were amplified by using the PCR technique (polymerase chain reaction), taking primers of the bibliography. After that, RFLP technique (Restriction fragment length polymorphism) was carried out using Hha1 restriction enzyme (cut plain exon), and analysis was performed in polyacrylamide gels 8% nondenaturing, colored with Silver nitrate. **Results:** It was possible to standardize the PCR amplification of exon 7, resulting in a fragment of 647 base pairs. After to analyze the exon by RFLP technique in fibrocystic patients and controls not fibrocystic it was found out that both populations were normal for the R347P mutation featuring 2 fragments 258 and 359 bp. **Conclusion:** The mutation R347P did not detect any patients, probably due to their low frequency worldwide and the few samples tested. Therefore, further study of this variant should be continued, analyzing a larger sample in order to estimate their frequency in our region and for both diagnosis and detection of healthy carriers.

P041 - Nine Year Experience of a Provincial Newborn Screening Program

Albrekt, A.(1); Czubarko, L.(1); Klein, P.(1)

(1): Programa Provincial de Pesquisa Neonatal Misiones, Posadas, Argentina

Introduction: The Provincial Newborn Screening Programme (PNSP) was implemented in January 2006 with provincial funding, and began working with the National Program to Strengthen Early Detection of Congenital Diseases since June 15 of that year. It provides reagents for the detection of congenital hypothyroidism (CH), phenylketonuria (PKU), congenital adrenal hyperplasia (CAH), biotinidase deficiency (BIO) and galactosemia (GAL). The provincial government is responsible for providing reagents for Cystic Fibrosis (CF) screening, thus fulfilling the Extended Newborn Screening (Law No. 26279/2007) from that date. It is intended primarily to provide coverage for all newborn (NB) in the public health subsector, representing approximately 60% of births, and patients who need on-demand testing. **Aim:** To present coverage results, diagnosed cases and frequency of screened diseases after nine years of program implementation. **Methods:** Data from the Program from January 1, 2006 to June 30, 2015 were reviewed. **Results:** In this period 122200 patients were tested, achieving the coverage: 28.4% (2006), 58.6 (2007) 82.2% (2008), 78.9% (2009), 100% (2010) 112.4% (2011) 97.08% (2012), 101.5% (2013) 96.2% (2014), 104.2% (2015); the highest coverage to 100% due to on-demand tests from patients who are not the main subjects of the program. 57 CH, 5 PKU, one benign hyperphenylalaninemia (HPA), 5 CAH, 13 CF, 2 BIO, 2 GAL were detected. The calculated frequencies of the screened diseases were CH, 1: 2144; PKU, 1: 24400; CF, 1: 9400; CAH, 1: 24400; BIO, 1: 61100; GAL, 1: 61100. **Conclusions:** PNSP access to the National Program for Strengthening allowed the gradual expansion of coverage and ensured early diagnosis with timely delivery of reagents, sampling cards and other inputs. It also contributed to the diagnostic confirmation in cases that cannot be done in the province and offered the possibility of assistance in the treatment and monitoring of diagnosed patients.

P042 - Cystic Fibrosis: Experience of the Newborn Screening Program of Costa Rica (2009-2015)

Rodríguez Araya, A.(1); Obando Rodríguez, S.(1); Chaves Guzmán, I.(1); Alvarado Romero, D.(2); Jiménez Hernández, M.(2); Saborio Rocafort, M.(2)

(1): Asociación Costarricense para el Tamizaje (ASTA), San José, Costa Rica

(2): Programa Nacional de Tamizaje Neonatal (PNT), San José, Costa Rica

Introduction: The Newborn Screening Program (NSP) of Costa Rica conducted a pilot project (2009-2013) to detect Cystic Fibrosis (CF) by the quantification of immunoreactive trypsinogen (IRT/IRT) in neonatal samples. As a result, CF became part of the 29 diseases currently screened by NSP. This paper presents the analyzed data showing the disease prevalence; positive and negative predictive value, the IRT average value, mutations and allelic frequency found between November 2009 and May 2015. **Methods:** IRT levels in blood were determined using AutoDELFIA and GSP fluoroimmunoassays (PerkinElmer). If the first sample tested above 70 ng/mL and the second sample above 60 ng/mL, these newborns were evaluated by the Pneumology Department. Mutation analysis (CFTR gene), was achieved by using Oligonucleotide Ligation Assay (OLA) (Abbott). **Results:** A total of 261.653 neonatal samples were processed. CF was diagnosed in 17 cases out of the 35 samples with positive consecutive IRT test, with an average of 156.1 ng/mL in the first sample and 173.8 ng/mL in the second one. An exception was a single newborn diagnosed with CF with negative neonatal screening results, with a total of 18 patients and a prevalence of 1: 14,536. The applied protocol revealed 48.6% of PPV and 99.9% of NPV. In confirmed CF cases, nine mutations associated with the disease were detected. The most frequent mutations were: G542X, delF508 and 711 + 1G>, with an allelic frequency of 28%, 22% and 14% respectively. The remaining 36% is distributed among the following mutations: 3120+1G>A, S549R, 3876delA, delI507, N1303K and 2789+5G>A. The most identified genotypes were delF508 and G542X mutations in homozygous state in 3 patients each, 6 had compound heterozygous, 1 homozygous for the mutation 711 + 1G> T and in 5 cases only one mutation was identified from the 32 analyzed. **Conclusion:** The results showed that the protocol used is effective detecting CF in the neonatal population. It also reaffirms the need to include genetic confirmation which will allow appropriate genetic counseling to affected families and expand the knowledge of the mutations in the population.

P043 - Galactosemia and Pregnancy Report of a Case

Carrillo Estrada, U.(1); Zayas Torriente, G.(2); Torriente Valle, J.(3); Henriquez Daudinot, L.(1); Abreu Soto, D.(3)

(1): Hospital Docente Marfan-Borrás, La Habana, Cuba

(2): Instituto nacional de Higiene, epidemiologia y microbiología, La habana, Cuba

(3): Instituto Nacional de Higiene, Epidemiología, La habana, Cuba

Introduction: The classic galactosemia is a severe inborn error in galactose metabolism caused by alterations in galactose-1-phosphate enzyme uridyltransferase (GALT). The symptoms of this acute condition caused by the accumulation of galactose and its metabolites, completely back under galactose-free diet. Despite a fulfillment of the right diet, patients often develop long-term complications, such as detection of growth, reduced bone mass, delayed speech development, or other neurological signs Whereas these complications occur in both sexes, gonadal toxicity appears to be limited to the ovary, because galactosemic show no abnormalities in male fertility has long

recognized that female patients with galactosemia are at high risk of premature ovarian failure with an estimated prevalence between 67% and 96% so it raises the question of their future fertility and the chances to preserve it. The complete or almost complete loss of GALT may be the main cause of a neonatal disorder endangering life when vomiting, abnormal prosperity of pregnancy, liver failure, cataracts, neurological disorders and anxiety are included. **Objective:** To present a spontaneous pregnancy in a patient with classic galactosemia Methods: Center Secondary health care: Patient with classic galactosemia: classified by galactose-1-phosphate in erythrocytes uridyltransferase (GALT) and strict adherence to a diet free of galactose. Weight measurements were taken; size; arm circumference and skin to assess nutritional status by BMI at different stages of pregnancy folds and weight gain; evolutionary quantification in blood galactose; amniocentesis and genetic markers for achieving pregnancy. **Results:** In the 3 quarters quantification of galactose in blood was found in the range of <3 mg/dl; negative genetic markers; proper weight gain; norm weight nutritional status. Amniocentesis negative embryopathy. **Conclusions:** With proper nutritional management of galactosemia since the beginning of the disease, it is possible to achieve a pregnancy without complications.

P044 - Lysinuric Protein Intolerance and Liver Transplantation: A Case Description

Bravo, P.(1); Carolina, A.(1); Pilar, P.(1); Barbara, O.(2); Carolina, A.(2); Juan Francisco, C.(1)

(1): LabGEM INTA, Santiago, Chile
(2): Hospital Van Buren, Valparaiso, Chile

Introduction: Lysinuric Protein Intolerance (LPI) is a rare genetic error, which affects cationic transmembrane transport of amino acids as lysine, arginine and ornithine. Even though it was considered a mild urea cycle disease, nowadays macrophage activation and unknown mechanisms shows to be implicated in a complex multisystemic compromise. Hepatomegaly is well described but liver function compromise is not well understood. Since is a transport defect, it is not predicted to be affected by liver transplantation. **Methods:** A case of 8 year old male neonatal diagnosed as IPL because of family history and failure to thrive, hematological compromise and hyperammonemia is described. His progress to a severe hepatosplenomegaly and liver insufficiency undo liver transplantation is presented. **Results:** The liver transplant was indicated because of acute liver insufficiency. Postransplantation ammonia levels decreased temporarily. Protein restriction and arginine and citrulline supplementation has been maintained until 9 months after transplantation. As we supposed it, liver function is recovered but the disturb on the arginine and citrulline metabolism persisted. **Conclusions:** Liver transplantation does not seem to affect the IPL metabolic disturbance. A longer follow-up and additional case reports could give us more data to increase the understanding of the IPL physiopathology.

P045 - A Patient With OTC Deficiency That Also Has a Mutation on CPT2 Gen

Piñeros-fernandez, M.(1); Rivera-nieto, C.(1); Lozano, M.(1); Aguilera, S.(1); Leal, M.(1); Londoño, C.(1)

(1): Fundacion Cardioinfantil, Bogota, Colombia

Introduction: We present a girl with a non-classical OTC deficiency disease. **Material and methods:** The patient is a 5-year-old female of Colombian origin, born after a term pregnancy. Delivery was performed via cesarean section. Her (30) father and 28 (mother) years old, were healthy and not known to be consanguineous, but three maternal uncles died within the first 48 hours of life without diagnosis. At the age of four years she presented with episodes of headache, fluctuating dysarthria, behavioral changes, aggressiveness bursts, episodes of staring in blank, fatigue. One day remained deeply slept for more hours than usual so her mother decided to bring her to our Hospital ER and then the patient was admitted to the PICU. The patient began a diet with protein restriction, treatment with oral sodium benzoate was initiated. She improved, became alert and orientated with normal behavior. **Results:** On biochemical investigation: Hemogram, liver function tests were normal. Ammonia level was on 305 . After the fourth day of hospitalization, ammonia levels descended to 182. Following amonio remains about 50.Urine amino acids chromatogram (qualitative): abnormal glycine, serine and glutamine bands. Plasma amino acids chromatogram (qualitative) and Quantification of plasma and urine amino acids and acylcarnitines (MS/MS) were normal. A brain MRI: normal. Ammonia control exams were below 50. Genetic Testing for Hyperammonemia was performed (Commercial Panel). The heterozygous variant c.583 G>A (p.Gly195Arg, G195R) was found in the *OTC* gene, it was described previously as disease causing. The heterozygous variant c.631 C>A (p.Pro211Thr, P211T) in the *CPT2* gene was also found. it was not described previously as disease causing. **Conclusion:** Clinical presentation in this case was the clue to suspect a metabolic disorder. Our patient surprisingly has two mutations for inborn metabolic errors, the first is causing OTC deficiency described previously and the second mutation on CPT2 gen in a heterozygous fashion non causing disease reports at this moment. The patient presents intolerance to exercise but she has normal CPK levels; we cannot affirm that it is due to the mutation in *CPT2*. Mutations in *CPT2* gene have to be homozygous or compound heterozygous to be damaging.

P046 - HPLC For Confirmatory Diagnosis and Biochemical Monitoring of Cuban Patients With Hyperphenylalaninemias

Contreras Roura, J.(1); Alonso Jiménez, E.(1); Fuentes Smith, L.(1); González Reyes, E.(2)

(1): Centro Nacional de Genética Médica, La Habana, Cuba
(2): Centro de Inmunoensayos, La Habana, Cuba

Introduction: Hyperphenylalaninemias are inborn errors of phenylalanine metabolism caused by deficiency of L-phenylalanine hydroxylase, resulting in increased serum phenylalanine. Phenylketonuria (PKU) is the most common form. Untreated PKU is associated with progressive neurodevelopmental delay, evolving towards intellectual impairment. Cuba introduced a national newborn screening program for PKU in 1986. It has enabled early diagnosis and initiation of dietary treatment, reducing appearance of intellectual impairment in these patients. Originally, confirmatory diagnosis was done only by quantifying serum phenylalanine. In 2010, an HPLC method for quantifying serum phenylalanine and tyrosine simultaneously was validated at the National Medical Genetics Center, to perform confirmatory and differential diagnosis of hyperphenylalaninemias, as well as biochemical monitoring of patients diagnosed. The objectives of this study were to describe experience using HPLC confirmatory diagnosis for positive cases from Neonatal Screening (NS) for Phenylketonuria and in biochemical monitoring of diagnosed patients after initiation of dietary treatment. **Materials and Methods:** A descriptive retrospective case-series study was conducted from June 2010 through June 2012. The study population comprised 531 infants who tested positive in the NS for Phenylketonuria. Variables used were serum phenylalanine concentration and tyrosine, phenylalanine/tyrosine ratio, both detected by reverse-phase HPLC. **Results:** Of the samples, 97.7% were confirmed as false positives, and 10.4% had transient neonatal tyrosinemia. Hyperphenylalaninemia was diagnosed in 12 infants (2.2%): 1.3% presented classical PKU, with 34.7 $\pm$ 14.7 mg/dL phenylalanine in serum and phenylalanine/tyrosine ratio of 18.9 $\pm$ 12.7; and 0.9% had persistent hyperphenylalaninemia, with 8.9 $\pm$ 3.4 mg/dL of phenylalanine and phenylalanine/tyrosine ratio of 4.5 $\pm$ 1.6. Matanzas Province contributed more cases than any of Cuba's 14 other provinces (25%) and there was a slight predominance of male sex (58.3%). During biochemical monitoring, 83.3% of patients reduced their levels of phenylalanine. The incidence of neonatal hyperphenylalaninemias was 1/22,503 live births and 1/38,577 for classical PKU. **Conclusions:** HPLC for simultaneous quantification of phenylalanine and tyrosine in serum meets the needs of a confirmatory test for patients testing positive in Cuba's NS for Phenylketonuria. It has enabled the introduction in Cuba of a second PKU diagnostic criterion of positivity for both the classification of hyperphenylalaninemias and the biochemical monitoring of diagnosed patients.

P047 - Sumautolab: Automatic Analyzer of Suma® Technology for Neonatal Screening

Frías Figueroa, G.(1); Toledano Hernández, A.(1); Iglesias Benitez, A.(1); Arce Quintana, J.(1); Pico García, J.(1); González Aguilera, D.(1); García Álvarez, M.(1); Frómeta Suárez, A.(1); González Reyes, E.(1); Carlos Pías, N.(1); Wong Matos, F.(1)

(1): Centro de Inmunoensayo, La Habana, Cuba

Introduction: SUMA® (Ultra Micro Analytical System) Technology emerged as a semi-automatic technology mainly intended for laboratories of low and medium sample processing capacity. Centralization of screening laboratories increases the amount of samples to be processed, and it has made necessary the automatization of this technology. In this work, the characteristics of a new automated analyzer and its performance evaluation during processing the neonatal assays, are described. **Material and Methods:** The instrument consists of a robotic arm for liquid handling with four stainless steel tips coated with ceramic, a second robotic arm to transport the plates to the various devices, incubators with programmable temperature, shakers, plate washer and a fluorescence reader. The equipment is controlled by a software that schedules the different tasks optimally and provides the necessary information both in preparation and during the run. Technical procedures were defined and evaluated with the SUMA Technology assays for neonatal screening: UMELISA TSH NEONATAL, UMELISA T4 NEONATAL, UMELISA 17OH Progesterone NEONATAL, UMTEST GAL and UMTEST PKU. **Results:** The great challenges of using very low volumes of samples and reagents, between 10 and 70 μL per well, were successfully faced. Processing time of kits was reduced without affecting the performance of the assays, which is an improvement over the semi-automated procedure. This allows the analyzer processes 12 plates per run, in any combination of neonatal assays. The average percent recovery for each test was over 90% with individual percentages fluctuating between 90 and 109%. The intra and inter-assay CVs were 4 to 9% and 5 to 11%, respectively. These values are similar to those obtained with the semi-automatic technology. **Conclusions:** SUMAutoLab is a reliable and accurate automatic analyzer that can be used for neonatal screening purposes. This new technology uses low volume of reagents, allows efficient increase in the volume of sample processing, and drastically reduces the number of handling errors by operators.

P048 - Confirmatory Diagnosis OF Biotinidase Deficiency in the National Centre of Medical Genetics: 2006-2013

Moreno Arango, J.(1); Texidor Llopiz, L.(1); Camayd Viera, I.(1); Valdes Fraser, Y.(1); Gámez Torres, G.(1); Martínez Rey, L.(1); Suárez Besil, B.(1)

(1): Centro Nacional de Genética Médica, La Habana, Cuba

Introduction: In Cuba, the program for early diagnosis of inborn errors of metabolism has contributed significantly to their prevention and treatment, from its origins to the present day. Biotinidase Deficiency (BD) is a disease of autosomal recessive inheritance where the affected patients may present seizures, hypotonia, ataxia, alopecia and others neurological problems. In our country, we have been performing neonatal screening for BD using SUMA's technology since 2005, while performing the cBD confirmatory analysis at the National Centre of Medical Genetics. The objective of this

study is to describe the results obtained in the confirmatory diagnosis of biotinidase deficiency in the National Centre of Medical Genetics, in the period 2006-2013. **Materials and methods:** The method used was described by Wolf and associates in 1983 and it is based on the spectrophotometric determination of the levels of p-aminobenzoic acid, released product of the hydrolytic action of the enzyme. In the evaluated period we analyzed 906 samples of patients, who were screen-positive in the neonatal screening program for biotinidase. **Results:** We confirmed 10 positive cases (1.10%), distributed between the provinces of Artemisa, Havana, Matanzas, Cienfuegos, Villa Clara, Holguín, Santiago de Cuba and Guantanamo. **Conclusions:** The confirmatory analysis constituted an important key for the diagnosis of this disease, reporting 10 patients with biotinidase deficiency. It allowed the timely implementation of treatment, genetic counseling to parents for the next pregnancy and a certain diagnosis of cases with suspicion of genetic risk.

P049 - Propionic Acidemia and Humoral Immune Deficiency

De Oliveira Poswar, F.(1); Farret Refosco, L.(1); Wajner, M.(1); Sitta, A.(1); Nori Rodrigues Taniguchi, A.(1); De Sampaio Leite Jobim Wilson, M.(1); Fischinger Moura De Souza, C.(1); Pinto E Vairo, F.(1); Doederlein Schwartz, I.(1)

(1): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil

Introduction: Propionic acidemia (PA) is an organic acidemia caused by the deficiency of propionyl-CoA carboxylase. Immune deficiency is an unusual presentation of PA. We report a case of a patient with PA associated with humoral immune deficiency. **Materials and Methods:** Chart Review. **Results:** A 6-month-old male was referred for investigation of immune deficiency. He is the first son of a non-consanguineous couple. Prenatal and birth were uneventful. However, at the first days of life, he started with hypoactivity and was admitted with 23 days old in his home town for somnolence, poor suction and vomiting after feeding. During the hospitalization, he presented pulmonary sepsis with positive culture for *Pseudomonas*, seizures and pancytopenia. He was discharged, and then hospitalized two more times with similar symptoms. In the last admission, he presented low levels of CD19 positive cells (152/mcL; reference range (ref): 955-2596) and immunoglobulins (IgA: <10 mg/dL—ref: 40-350; IgG: 369.3 mg/dL—ref: 650-1600; IgM: 30.8 mg/dL—ref: 50-300). He received intravenous immunoglobulin (IVIG) and was transferred to our center. At our first evaluation, it was noticed microcephaly, low weight and length, axial hypotonia and ankle clonus. Considering the neurological clinical picture and the history of pancytopenia, it was suspected of an organic aciduria. Acylcarnitines profile and organic acids were compatible with PA diagnosis and specific treatment was started, including IVIG infusions of 500 mg/kg/dose. Bone marrow biopsy showed only reactive changes. MRI showed enlarged subarachnoid spaces and ventricular system and lesions in the putamen and the globus pallidus. After 28 days of treatment, the IgG levels were higher (524 mg/dL) and the CD19 positive cells increased to normal levels (1019/mcL). On the last evaluation, at 8 months old, in spite of remaining microcephalic, the patient was stable, with improvements in neurological development and weight and was maintained with IVIG infusions every 21 days. **Conclusion:** The association of PA and humoral immune deficiency is rare but well described. There is little experience in the use of IVIG in PA. The present case reinforces the need of considering the diagnosis of organic aciduria in patients with immune deficiency, pancytopenia and neurological findings.

P050 - Hereditary Fructose Intolerance: Clinical Diagnosis in Patient With One Novel Missense Mutation in the Aldolase B Gene

Gonzalez, N.(1); Beltrán, O.(2); Marquez, W.(3)

(1): Universidad Militar Nueva Granada, Bogota, Colombia
(2): Universidad Militar Nueva Granada, Fundación HOMI Hospital de la Misericordia, Bogota, Colombia
(3): Fundacion HOMI Fundación HOMI Hospital de la Misericordia, Bogota, Colombia

Introduction: Hereditary fructose intolerance (HFI) is a pathology with autosomal recessive inheritance by deficiency of the enzyme aldolase B, thus prevents the transformation of fructose-1-phosphate into fructose 1-6 diphosphate dihydroxyacetone phosphate and glyceraldehyde inhibiting glucose production. **Materials and methods:** Description of a female infant of 4 years old affected with HFI by two different mutations, a nonsense mutation and a novel missense mutation in the aldolase B gene. **Results:** Patient was born from healthy non-consanguineous parents, pregnancy was normal and perinatal follow without complications. At 4 months old, she presented seizures by hypoglycemia to intake fruit compote. Physical examination showed hepatomegaly without ophthalmic anomalies, with which liver biopsy diagnosing moderate fibrosis. Further, test of cystic fibrosis, urine reducing sugars, and organic acids were normal. Her neurodevelopmental has been normal with rejection meals with fruits and aversion to fruits. Molecular analysis of the gene detected in compounds heterozygous ALDOB gene, missense mutation c.102T>A (p.Asp34Glu) and nonsense mutation c.178C>T (p.Arg60Ter). **Conclusions:** HFI is evident in childhood when fructose or sucrose is introduced in the diet, starting as vomiting, nausea, abdominal pain, lethargy and hypoglycemia can be fatal and long-term can cause liver failure, renal tubulopathy and delayed growth. The c.178C>T (p.Arg60Ter) mutation is a nonsense mutation which cause a change of cytosine for thymine producing in the protein the change of arginine at position 60 by a premature stop codon causing an incomplete and non-functional protein, this mutation was already described in cases with HFI. While c.102T>A

(p. Asp34Glu) mutation is a missense mutation not previously reported producing in a different amino acid aspartate for glutamate at position 34. In silico for functional analysis predicted which may cause an aldolase B protein unable to fulfill its function. However, our case meets clinical and histopathological findings of HFI, considering that this mutation was correlate with the pathology. Functional genomics studies are need to confirm the mutation effect. This case highlights the importance of early diagnosis of HFI to start a diet proper with strict restriction of fructose and identification healthy carrier in the related family to prevention of new cases through genetic counseling.

P051 - Clinical, Biochemical and Molecular Characterization of an Argentinean Patient With Niemann Pick Type B Disease

Martínez, L.(1); Giner-ayala, A.(2); Oropeza, G.(3); Grinberg, D.(4); Dodelson De Kremer, R.(1)

(1): Centro de estudio de las Metabolopatías Congénitas, CEMECO. Facultad de Ciencias Médicas- UNC, Córdoba, Argentina
(2): Centro de estudio de las Metabolopatías Congénitas, CEMECO. Facultad de Ciencias Médicas-UNC, Córdoba, Argentina
(3): Servicio de Gastroenterología. Hospital Infantil., Córdoba, Argentina
(4): Departament de Genética, Facultat de Biología, Universitat de Barcelona, Barcelona, España

Introduction: Niemann-Pick type B (NP-B) is an autosomal recessive lysosomal storage disorder caused by a deficiency of acid sphingomyelinase coded by *SMPD1* gene. NP-B is a multisystem disease with progressive hepatosplenomegaly and gradual deterioration of pulmonary function, most type B patients have little or no neurologic involvement and survive into adulthood. **Aim:** to report the clinical, biochemical and molecular studies for the characterization of patients, in the context of a systematic research protocol of this pathology in Argentina. **Methodology:** a) Case report b) Research Protocol: 1- compatible patients selection, 2- histological and biochemical studies 3- enzymatic determinations (acid sphingomyelinase and chitotriosidase), 4- molecular analysis. **Results:** A 6 years-old female of nonconsanguineous parents, presented a previous history of hepatosplenomegaly. She didńt had any neurological symptoms. The liver electron microscopy indicated the presence of electron-lucent vacuoles and electron-dense membranes in hepatocytes. Bone marrow biopsy show foam cells. The general laboratory analyses showed hypertriglyceridemia and elevated transaminases. The plasma chitotriosidase was slightly increased. Sphingomyelinase enzyme level was 0.46 nmol/ 17 hour/ mg protein (Range: 8- 47 nmol/ 17 hour/ mg protein). The *SMPD1* gene sequencing revealed that the patient is compound homozygote for the previously described mutation, p.R608del. and the diagnosis of NP-B was established. **Conclusion:** This study indicates that the clinical heterogeneity and biochemical required of a research protocol aimed at identifying patients with NP disease. Genotype-phenotype correlations were established for this mutation. Moreover, enzyme replacement therapy with recombinant sphingomyelinase is currently studied as potential treatment for NP-B.

P052 - Molecular Characterization of Phenylketonurics in Uruguay

Méndez, S.(1); Lemes, A.(1); Queijo, C.(1)

(1): Instituto de Seguridad Social—BPS, Montevideo, Uruguay

Introduction: Phenylketonuria (PKU) is an autosomal recessive disorder caused by a deficiency of phenylalanine hydroxylase. This enzyme is encoded in the PAH gene, causing an elevation in phenylalanine blood levels as well as a decrease of tyrosine concentrations. The mutational spectrum of this gene is large, and a wide variation of genotypes have been identified distributed along its 13 exons. The identification of PAH genotype provides the information needed to provide genetic counseling to the patients, genotype-phenotype correlations and in some cases treatment adjustments. Since 2007 our country has a National Newborn Screening Program (NNSP) that includes detection of PKU by MS/MS. At present we have diagnosed 17 patients with PKU, all of them with molecular studies. **Materials and methods:** Genomic DNA was obtained from dried blood spots on Whatman 903 filter paper of 17 PKU patients detected by our NNSP. At the first step, exons 7, 10 and 11 and their surrounding introns of PAH gene were amplified, looking for, at least, the presence of two mutations responsible for disease. If the mutation was not found, the others exons were amplified. All amplified products were purified, sequenced and analyzed using an ABI 310 (Applied Biosystems) Genetic Analyzer. **Results:** The results allowed the full molecular characterization of 17 PKU patients. The mutational spectrum encompasses 18 distinct mutations, with 168+19 T>C (29,4%), 353-22 C>T (23,5%), 441+5 G>T (23,5%), 168+5 G>C (17,6%) and 1066 -11 G>A (17,6%) being the most frequent. Moreover, from the 17 patients, 3 were homozygous for the 168+19T>C mutation, 1 homozygous for 353-22C>T, 2 homozygous for 441+5G>T and 1 homozygous for 168+5G>C. **Conclusions:** Most of the mutations were not found in exons 7 and 11 as we expected according to published reports. From our 17 patients, 12 combinations have not been described in BIOPKU database. Only 5 patients show reported combination. From this last group we found that one patient with 1162G>A/194T>C mutation will be potentially benefit from BH4 therapy.

P053 - Incidence of Phenylketonuria in the Peruvian Social Security Institute Detected by Newborn Screening During 2012-2014

Morales Acosta, M.(1); Dueñas Roque, M.(1); Arteaga Cano, M.(1); Lavado Ariza, M.(1)

(1): Hospital Nacional Edgardo Rebagliati Martins, Lima, Perú

Introduction: The Social Security Institute of Peru (EsSalud) began a pilot Newborn Screening (NBS) Program for congenital hypothyroidism and congenital adrenal hyperplasia at the Hospital Edgardo Rebagliati Martins of Lima in October 2002, spreading nationwide since January 2008. In the same year, screening for phenylketonuria and galactosemia began only at the Rebagliati Hospital and its affiliated medical centers, and expanded to all Lima medical centers in 2010. In September 2011 the NBS program became nationwide and included four diseases: congenital hypothyroidism, galactosemia, phenylketonuria and congenital adrenal hyperplasia, with a coverage of 100% of the insured population. The samples are processed by the Mother-Child Laboratory at the Edgardo Rebagliati Martins Hospital. Our objective is to report the incidence of Phenylketonuria in the Peruvian Social Security during the period 2012-2014. **Material and methods:** Phenylalanine levels in newborns were measured by a fluorescent method (UMTEST) in dried blood spots collected on filter paper. The cut point was phenylalanine >3mg/dL (>180 umol/L). A second assay was necessary to confirm diagnosis in positive cases. **Results:** NBS was performed to a total of 281,128 neonates with a coverage of 100%. A number of 179 were identified as probable cases, and 8 were confirmed. The incidence of PKU in the period 2012-2014 in Social Security was 1 in 35,141 live births. The confirmed cases were from the metropolitan Lima (3), other provinces of Lima (2), Cusco (1) Ucayali (1) and Tumbes (1). **Conclusion:** The incidence observed in the Peruvian Social Security Institute (EsSalud) was 1: 35,141 live births, which is less than that reported in the international literature. This is the first report of PKU incidence in Peru.

P054 - Phenylketonuria Newborn Screening Experience In México Epidemiological Overview

González Guerrero, J.(1); Delgado González, E.(1); Burciaga Torres, M.(1); Mendiola Ramirez, K.(1); Ferrer Arreola, L.(1)

(1): Instituto Mexicano del Seguro Social, Coordinación de Atención Integral a la Salud en el Primer Nivel, México D.F., Mexico

Introduction: The neonatal screening to detect phenylketonuria was started in our institution in 2005. Approximately 450,000 newborns throughout the country are screened yearly. Our neonatal screening program has a surveillance system (SIVE) that identifies areas of opportunity and it is applicable to all states. **Objective:** This study was done to evaluate the coverage, index of suspicion, positive predictive value, cumulative incidence, opportunity of diagnosis and analysis of means for Phenylketonuria (PKU) patients detected during the period from 2005 to 2014. **Methodology:** Cross-sectional study. Cases were identified by fluorescence assay (UMTEST) in dried blood spots, collected on filter paper. Probable cases were defined with Phe levels greater than 4 mg/dL (240 umol/L) and confirmed cases with Phe levels in plasma by high performance liquid chromatography greater than 7 mg /dL. Confirmed cases were identified as benign hyperphenylalaninemia (levels 2 to 7 mg/dl), mild PKU (> 7 to 20 mg/dl), moderate PKU (> 20 to 30 mg/dl) and severe PKU (> 30 mg/dl). We used the SPSS statistical package to obtain the epidemiological indexes. **Results and Discussion:** 4,348,721 screening tests were made, with average coverage of 94.2%. 201 probable cases were identified, with index of suspicion of 0.005; and 43 were confirmed (PPV: 20.48%), the cumulative incidence was 1: 101.133 live births. The diagnostic opportunity before 30 days was 23.3% and the date at which the final diagnosis was established was 52 days. Confirmed cases have only been reported in Aguascalientes. Baja California Sur, Chihuahua, México City, Guanajuato, Guerrero, Jalisco, Mexico State, Nayarit, Nuevo Leon, Tabasco, Veracruz and Zacatecas. HPA benign cases were 13.3%, mild PKU 26.67% moderate PKU 20% and severe PKU 40%. **Conclusions:** The incidence of phenylketonuria found in our institution in Mexico is lower than reported internationally; we observed higher prevalence of cases in Bajio states. It is necessary to maintain an active surveillance system to improve the opportunity of diagnosis and treatment of patients.

P055 - Hyperactivity: A Nearly Feature of Homocystinuria, Case Report

Porras, L.(1); Sierra-ramírez, A.(2); Silvestre, J.(3); Muñoz, N.(4)

(1): Clínica Comfamiliar Risaralda, Pereira, Colombia
(2): Colciencias
(3): Universidad de las Americas
(4): Metabolic Therapies

Inherited metabolic disorders comprehend a several diseases more commonly thoughtful in the setting of an acute illness with clinical decompensation. However they could have more insidiously presentation, with behavioral and psychiatric manifestations delaying the identification of the subjacent disorder. Homocystinuria is a chronic and disable illness, which classically has been taken into account their manifestations ophthalmologic, cardiologic and skeletal as marfanoid habit and in general its systemic commitment, neglecting behavioral and psychiatric manifestations, which could be the initial feature of this disorder. In this case report, we are going to describe two siblings diagnosed with homocystinuria, both patients with behavioral disturbances and academic concerns. Patient number one, she was referred to a medical examination because academic concerns, unnoticed the possible diagnoses of inherited metabolic disorder, despite that her parents were consanguineous and she had severe myopia. Only two years later, when she debuted with *ectopia lentis* the diagnoses was made, it showing as that this patients could be consulting for academic concerns without this kind of etiologies are taken into account. The diagnoses in patient number two is

carried out to study in the family, without the features of classic homocystinuria that direct as to thing in this entity. But when the boy is subjected to all examinations, we found the ADHD joined by high levels of homocysteine. Both patients started treatment with nutritional intervention (a controlled-protein diet and a special formula free from methionine) and cofactors (Pyridoxine and Betaine). Patient one, had an undernutrition (BMI: −2.13.SD), not patient two (BMI: −1.50 SD); one year after, both improve nutritional indicators (BMI: −1.84 and −1.40), respectively. The adherence of treatment has been a problem for us, it could be for the age of the patients (a school boy and a teenage girl) and/or their behavioral problems. We arise to suspect inherited metabolic disorder in evaluating children with behavioral or academic concerns

P056 - Mitochondrial Diseases Series of Case Reports

Pereyra, M.(1); Gatica, C.(1); Gamboni, B.(1); Guercio, A.(1); Mayorga, L.(2); Szlago, M.(3); Carbajal, B.(1); Elescano, A.(1); Dri, J.(1)

(1): Hospital Pediatrico Dr. H. J. Notti, mendoza, Argentina
(2): CONICET-UNCuyo, mendoza, Argentina
(3): Hospital Italiano, buenos aires, Argentina

Introduction: We present the clinical and molecular presentation of 4 patients with Mitochondrial (mt) disease followed in a Childreńs Hospital. **Materials and Methods:** Case reports 1) Boy born from a non-consanguineous couple. Bilateral neurosensorial hypoacusia (BNSH) failure to thrive, progressive external ophthalmoplegia (PEO), ptosis and complete atrioventricular block that required a permanent pacemaker. His brain MRI showed hyperintensity of the basal ganglia. He had lactic acidosis and organic acids with Krebs cycle metabolites. Kearns Sayre Syndrome(KSS) was suspected and confirmed by Southern Blot analysis on leukocyteś DNA performed at Baylor College of Medicine(USA) that detected a large mitochondrial DNA (mtDNA) deletion. He died at age 8. 2) Casés 1 15 year-old twin sister with similar clinical findings plus Diabetes mellitus(DM) since age 5 with a bad metabolic control. Multiplex ligation-dependent Probe Amplification(MLPA), using the P125 mtDNAkit (MRC-Holland®) was performed on leukocyteś DNA at the Instituto Histología y Embriología seeking for a mtDNA deletion. However, this was negative probably due to the expected low heteroplasmy in blood. Muscle biopsy was not performed. 3) 18 year-old girl, born to a consanguineous couple and then adopted. Failure to thrive. BNSH. PEO, ptosis, pigmentary retinopathy and complete atrioventricular block, permanent pacemaker. DM since age 14. Progressive swallowing difficulties. Brain CT: hypodensity of the lenticular ganglia. mtDNAMLPA was performed on leukocytes DNA finding a mtDNA deletion from MT-ATP6 to MT-CYTB in a 23% heteroplasmy level confirming KSS. 4) 12 year-old girl with a background of seizures, mental retardation, failure to thrive. She has persistent lactic acidosis with stroke-like episodes. Her family background was consistent with maternal inheritance: mother and 2 sisters with strokes. MLPA P125 was performed on leukocytes DNA, confirming the m.3243A>Gmutation (MELAS). **Conclusions:** Mt diseases diagnosis is always a challenge due to their complex clinical presentation and different inheritance patterns. Syndromes due to large mtDNA deletions are usually sporadic. The 3 KSS cases presented here are particular because of their recurrence in siblings(case 1, 2) or background of consanguinity(case 3). They could be due to nuclear gene mutations like in the RRM2Bgene. Finally, patient 3 and 4́s genetic diagnosis was achieved locally, something not possible a few years ago.

P057 - Hypercalciuric Normocalcemia and Mild Hypoparathyroidism With Pathologic Fracture in a Child: Suspected Dysfunction CASR?

Ramirez Rey, A.(1); Salgado, P.(2); Beltran, O.(3)

(1): Organizacion Sanitas Internacional. Universidad Militar Nueva Granada, Bogota, Colombia
(2): Universidad Militar Nueva Granada, Bogota, Colombia
(3): Organizacion Sanitas Internacional. Universidad militar nueva granada. Fundacion Homi, Bogota, Colombia

Introduction: Disorders of calcium metabolism can be associated with mutations in the calcium-sensing receptor (CASR). In kidney, CASR activation inhibits reabsorption of calcium in the thick ascending limb and water reabsorption in the collecting duct. CASR is also expressed in thyroidal C cells, parathyroid gland, osteoclasts and brain. **Materials and methods:** We report the case of child with possible mutation in CASR with atypical presentation. **Results:** The proband a 5-year-old male referred for investigation of femur diaphyseal fractures, was the second child of non-consanguineous parents. Parents and sibling are healthy, but his maternal uncle has history of seven femur fractures from 13 years of age. His medical record not indicated history of bone disease, he has normal height and development for age. At 2 years old presented low energy trauma that results in a right femur fracture and subsequently suffers refracture two years later in the same place. He had experienced no clinical symptoms attributable to hypercalcemia or hypocalcemia. Paraclinical exams shows upper limit normocalcemia (10.9mg/dl), mild hyperphosphatemia (6.48mg/dl), hypercalciuria (209mg/24h) and low levels of parathyroid hormone (PTH:3.0 pg/ml). The initial treatment was supplementation with vitamin D and intake of five glasses of milk per day and hydrochlorothiazide. At 3 months follow up he has asymptomatic nephrocalcinosis evident by renal ultrasonography; therefore it was decided to suspend intake of vitamin D and calcium intake is restricted to 400mg/day. During the most recent clinical monitoring the bone mineral density of the lumbar spine showed evidence of low bone mass.

Laboratory tests revealed hypocalciuria, PTH rising but below the reference limits (5,87 – 8.25 and 6.68 pg/ml), with normal serum calcium (Ca), sodium (Na), chloride (Cl),1,25-dihydroxyvitamin D3 and alkaline phosphatase (ALP) levels. Renal function are normal (creatinine 0,31 mg/dl and urea nitrogen 11.3 mg/dl). **Discussion:** CASR modulate synthesis and secretion of PTH and renal calcium excretion. Mutations in the CARS gene can lead a gain or loss of receptor function. **Conclusion:** It is suspected mutation in the CASR gene with atypical clinical features present with hypercalciuria, upper limit normocalcemia and mild hypoparathyroidism, that are not the typical clinical features reported in the CASR mutations.

P058 - Fundación De Endocrinología Infantil (FEI): 30 Years of Experience in Newborn Screening

Prieto, L.(1); Mendez, V.(1); Enacan, R.(1); Bergadá, I.(1); Chiesa, A.(1); Gruñeiro-papendieck, L.(1)

(1): Fundacion de Endocrinologia Infantil, CABA, Argentina

Introduction: In August 1985, the Fundación de Endocrinología Infantil (FEI) started a Neonatal Screening Program for Congenital Hypotiroidism (CH) and Phenylketonuria (PKU). Neonatal screening for Cystic Fibrosis (CF), Galactosemia (GAL), and Congenital Adrenal Hyperplasia (CAH) were begun in 1997, Biotinidase Deficiency (BD) in 2006 and Leucinosis (MSUD) in 2013. **Objective:** To communicate the results of the FEI neonatal screening program during the period 8/1985-5/2015. **Materials and Methods:** screening was performed in dried blood spot samples obtained by newborn heel prick between 36 hours and 7 days of life. Biochemical markers for detection were: 1) CH: TSH with Delfia-IFMA assay from 1997 to 2003 (cutoff 15 mUI/L) and 10 mUI/l onwards (double sample strategy in prematures < 33 weeks of gestational age (GA)); 2) PKU: Phenylalanine with fluorometric assay since 1990 (cutoff 2.5mg/dl); 3) CF: Immunoreactive trypsinogen IRT (Delfia –IFMA) with IRT/IRT strategy (cutoff 70 ng/dl); 4) GAL: Total Galactose enzymatic colorimetric method (cutoff 12mg/dl); 5) CAH: 17 hydroxyprogesterone (Delfia-FIA) with cutoff adapted for GA and chronological age; 6) BD: Biotinidase activity (colorimetric method); 7) MSUD: Branched chain amino acids (enzymatic colorimetric assay) for MSUD (cutoff 4 mg/dl). The Program included the confirmation procedures in the detected newborn and started treatment in those affected continuing their follow up or referring them to the respective specialist. **Results:** The table shows the detection results. Mean age of sampling was 3 days and treatment was indicated timely. **Conclusion:** Detection was carried out properly with adequate parameters of analytical performance. Our screening program as conceived was responsible for the confirmation and appropriate treatment of screened newborns preventing the deleterious consequences inherent to these diseases. Moreover, our data provide information about the incidence and characteristic of these diseases in our country.

P059 - Expanded Newborn Screening Experience in the Health Services of the Mexican Army

Madrigal Mendoza, L.(1); Vela Amieva, M.(2)

(1): Secretaría de la Defensa Nacional, Ciudad de México, México
(2): Hospital Infantil de México, Ciudad de México, México

Introduction: In 2013, the Mexican Ministry of Health published a new regulation that established mandatory expanded newborn screening in Mexico. To meet the new requirements, the Health Services of the Mexican Army decided to implement a new screening program for metabolic congenital diseases. **Objective:** The aim of this work is to present the results of new neonatal screening program implemented in 2013. **Methods:** Retrospective analysis of the newborn screening database of the Health Services of the Mexican Army. All samples were obtained by heel puncture, deposited on filter paper cards and analyzed by Auto-DELFIA, tandem mass spectrometry and isoelectric focusing or high-performance liquid chromatography techniques. **Results:** From December 2013 to July 2015, and with the participation of 38 military medical units distributed in 24 of 32 Mexican States, a total of 13,814 newborns were screened. 123 samples were considered suspect (recall rate of 0.89%), 29 cases were confirmed (1:476 NB), with 94 false positives (0.68%). The detected diseases were: 11 cases of glucose 6-phosphate dehydrogenase deficiency (1:1,256 NB); 11 cases of congenital hypothyroidism (1:1,256 NB); 4 patients with congenital adrenal hyperplasia (1:3,454 NB); two patients with hemoglobinopathies (one sickle cell anemia and one with HbS/beta thalassemia) (1:6,907 NB) and one case of hyperphenylalaninemia (1:13,814 NB). Additionally, 3 cases of transitory hyperthyrotropinemia were detected (1:4,605 NB), but they are not considered in the overall prevalence. All the affected children were timely evaluated and began treatment before 20 days of life. **Conclusions:** The studied population showed a high disease prevalence (1:476 NB), being thyroid defects the most prevalent.

Disease	CH	PKU	CF	CAH	GAL	BD	MSUD
Number of samples	1.483.976	1.494.142	576.994	467.378	475.559	391.056	44.639
Detected	744	124 (50% HPA)	93	40 (2/3 Salt wasting)	19	3	–
Incidence	1:1994	1:12.049	1:6.204	1: 11.684	1:25.029	1:130.352	–
Recall rate	0,59%	0,12%	0,51%	0,55%,	0,012%	0,02%.	0.27%
Diagnostic Efficiency	0,13	0,02	0,05	0,011	0,34%	0,075	–

P060 - Results of Expanded Newborn Screening in the Health Services of the Mexican Navy

De La Torre García, O.(1); Trigo Madrid, M.(2)

(1): Secretaria De Marina Armada De México, Mexico D.F., México
(2): Secretaria De Marina Armada De México, Mexico D.F., México

Introduction: The main goal of newborn screening is timely detection, diagnosis and intervention for genetic disorders that may otherwise produce serious clinical consequences. Nowadays newborn screening is part of the health care system of a high number of countries and institutions. Since 2012, in the Mexican Navy (Secretaría de Marina—Armada de México), an expanded newborn screening program was implemented. **Objective:** To describe the birth prevalence of the congenital defects detected by the expanded newborn screening program from the Mexican Navy and to analyze the main performance indicators. **Materials and methods:** From July 2012 to July 2015, blood samples from heel pricks were taken in Medical Units of the Mexican Navy, located in 18 states of Mexico. All samples were analyzed by AutoDELFIA, tandem mass spectrometry and isoelectric focusing or high-performance liquid chromatography techniques. The number and type of congenital diseases were evaluated. **Results:** A total of 8,212 newborns were screened; 74.36% of the samples were taken between the 3-5 day of life, and 2.6% of the samples were considered inadequate. A total of 108 samples were considered as suspect and all newborns were located and retested. Fourteen cases were confirmed, with a false positive rate of 1.13%. The detected diseases were: 7 glucose 6-phosphate dehydrogenase deficiency, 3 congenital hypothyroidism, 2 congenital adrenal hyperplasia, 1 hemoglobinopathy and 1 case of 3-methylcrotonyl-CoA carboxylase deficiency. All the cases arrived to the appropriate medical protocol evaluation before 16 days of life. All affected families received genetic/reproductive professional counseling. **Conclusions:** In the studied population, the birth prevalence of metabolic defects was 1:587 newborns. The expanded newborn screening program allowed their early identification, with the aim of preventing disability and death.

P061 - Advances to Improve Scientific Knowledge and Practice on Rare Diseases Into Higher Education in Latin America

Cismondi, I.(1); Kohan, R.(2); Pesaola, F.(3); Guelbert, N.(2); Becerra, A.(2); Rautenberg, G.(4); Oller-ramìrez, A.(2); Noher De Halac, I.(5)

(1): CEMECO-Hospital de Niños- Facultad de Odontologia-Universidad Nacional de Cordoba, Córdoba, Argentina
(2): CEMECO-Hospital de Niños, Córdoba, Argentina
(3): CEMECO-Hospital de Niños y CONICET, Córdoba, Argentina
(4): CEMECO-Hospital de Niños, Cordoba, Argentina
(5): CEMECO-Hospital de Niños y CONICET, Cordoba, Argentina

Introduction: Rare diseases (RD) are collectively common in the general population with 1/17 people affected by a RD in their lifetime. Inherited defects in genes involved in metabolism are the commonest group of RD with over 8000 known inborn errors of metabolism. The majority of these diseases are neurodegenerative with a remarkable impact on public health. There remains a gap in medical knowledge about RD among clinical practitioners, both because of their rarity but also because of the lack of emphasis in medical training. Our aim is to improve scientific knowledge and practice in higher education and continuous learning programs in Latin America. **Methods:** 1) An international panel of experts discussed in a workshop held in Cordoba 2014 the current global state and the gaps of education and training on RDs, and proposed an agenda of solutions 1.2) A literature search via PubMed using the key words ''rare diseases'' and ''medical education'' covering ten years of publication starting in 2004. 3) A network proposal in the frame of the International *Redes VIII* Program of Argentinean Universities. **Results:** 1) Consensus was achieved on the innovative integration of RDs into the Medicine Studies, Continuing Professional Development, and Continuing Medical Education. 2) The citations on RDs Education in the last 10 years numbered only 377 with very low relevance. 3) A proposal on RD education emerged in Argentina through an international Network effort (REDES VIII-2015) approved by the University Rectors Conference of Argentina with the participation of three National Universities http://portales.educacion.gov.ar/spu/noticias/redes-internacionales-8-resultados/. **Conclusions:** Including RD education in university curricula should reflect its complex nature. Any professional training program on RD in Health Sciences curricula must take into account the medical, social and economic burdens related to RDs and be treated in an integrated manner, not only in terms of specific medical issues associated with the use of sophisticated diagnostics, but also as complex challenges to institutions and society as a whole. The *Redes VIII* proposal intends to advance in that direction in Latin America. Ref: 1 Cismondi IA, Kohan R, Adams H, Bond M, Brown R, Cooper JD, Krupnik de Hidalgo P, Kleine Holthaus S, Mole SE, Mugnaini J, Oller Ramirez AM, Pesaola F, Rautenberg G, Platt FM, Noher de Halac I. Guidelines for incorporating scientific knowledge and practice on rare diseases into higher education: neuronal ceroid lipofuscinoses as a model disorder. Biochim Biophys Acta. 2015 Jun 24. pii: S0925-4439(15)00184-2. doi:10.1016/j.bbadis.2015.06.018.

P062 - Nutritional Status and Body Composition of Patients With Hepatic Glycogen Storage Diseases

Nalin, T.(1); Bento Dos Santos, B.(1); Castrogrokoski, K.(1); Schweigert Perry, I.(2); Farret Refosco, L.(3); Pinto E Vairo, F.(3); Fishinger Moura De Souza, (3); Doederlein Schwartz, I.(1)

(1): Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil
(2): Universidade do Extremo Sul Catarinense, Criciúma, Brasil
(3): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil

Background: The hepatic Glycogen Storage Diseases (GSD) comprise a group of rare inherited diseases caused by abnormalities of the enzymes that regulate the glycogen metabolism. The main treatment consists of the administration of uncooked cornstarch throughout life. The objective of this study is to evaluate the nutritional status and the body composition of patients with hepatic GSD through bioelectrical impedance (BIA). **Materials and methods:** This is a transversal and controlled study, matched by sex. Anthropometric measurements (weight and height) were verified in patients and controls and body mass index (BMI) was calculated. Body composition data were assessed by performing BIA in both groups. **Results:** Thirty-one patients with hepatic GSD were included (type I – 24 patients, type III – 4 patients, type IX – 2 patients, type not defined – 1 patient), mean age of 11 $\pm$ 6 years (range: 3–32 years). Also, thirty-one healthy controls were included, mean age of 14 $\pm$ 5 years (range: 4 to 31 years). Regarding BMI classification, among patients, nine (29%) were considered eutrophic, eight (26%) overweight and fourteen (45%) obese. In the control group, nineteen (61%) were considered eutrophic, one (3%) with low weight, seven (23%) overweight and four (13%) obese. As for body composition, the average fat mass in patients was $26.6 \pm 8.6\%$, among the controls this value was $22.0 \pm 8.1\%$ ($p=0.037$). **Conclusion:** The results of this study reinforce the literature findings, which indicate that patients with hepatic GSD are frequently overweight. This excess weight also reflected in the fat mass accumulation, which is significantly higher in patients than in healthy controls. These data may be associated with administration of high daily doses of cornstarch, used in the treatment of hepatic GSD. Support: CNPq, FAPERGS.

P063 - Targeted Metabolomics Reveals Changes Caused by Biotin Deprivation in Rats

Ibarra-gonzález, I.(1); Hernández-vázquez, A.(1); Vela-amieva, M.(2); Velázquez-arellano, A.(1)

(1): Instituto de Investigaciones Biomédicas—UNAM, México D.F., México
(2): Instituto Nacional de Pediatría, México D.F., México

Introduction: Certain inborn errors of metabolism result from deficiencies in biotin (BT) containing enzymes. These disorders are mimicked by dietary absence or insufficiency of Bt. Biotin is a water-soluble vitamin and an essential prosthetic group of the carboxylase enzymes, propionyl-CoA carboxylase (PCC), pyruvate carboxylase (PC) 3-methylcrotonyl-CoA carboxylase (MCC) and acetyl-CoA carboxylase (ACC) that have important roles in tricarboxylic acid cycle anaplerosis, gluconeogenesis, fatty acid synthesis and amino acid and odd-chain fatty acid catabolism. To obtain a better understanding of Bt deficiency and its influence on the metabolism, we utilized a target metabolomics approach to explore the metabolic alterations caused by nutritional biotin deficiency in rats. **Methods:** Wistar male rats, aged 21 days and 80–90 g of weight, were made Bt deficient by feeding commercial diet (TD 81079 HARLAN Teklad. Madison, WI) supplemented with 30% white egg as source of avidin. Control rats were of similar gender, age and weight, and fed with the same commercial diet, supplemented with 4mg/kg biotin (TD. 97126 Harlan 324 Teklad. Madison, WI). Rats were housed individually in air-filtered cages, and were exposed to 12h light/dark cycles with free access to food and water. After 4 weeks of Bt deprivation Dried blood spots were collected from all rats on Whatman 903 filter paper and concentrations of free amino acids and acylcarnitines were determined by electrospray tandem mass spectrometry using isotope dilution methods in both groups of animals. Multivariate statistical analysis was used. **Results and Discussion:** The supervised analysis of dataset showed a different metabolite pattern associated with Bt deficiency rats compared to the controls, remarkably we found not only the classical biomarkers of biotin deficiency (3-hydroxyisovalerylcarnitine, and propionylcarnitine) furthermore acetylcarnitine (C2) and b-OH-butyrylcarnitine (C4OH), a strong marker of b-oxidation and ketone metabolism, both were markedly decreased in Bt deficiency rats, the alterations in the amino acid levels suggested the increased protein turnover in the Bt deficient group. **Conclusion:** The metabolomics approach can be applied to identify biotin deficiency biomarkers and reveals impaired metabolic pathways in response to specific dietary modifications and can be used to analyses the interaction between nutrients and metabolism.

P064 - Triheptanoin as a Potential Treatment for Genetic Disorders of Energy Metabolism

Marsden, D.(1); Kakkis, E.(2)

(1): Ultragenyx Pharmaceuticals, Novato, United States
(2): Ultragenyx Pharmaceuticals, Novato, United States

Introduction: Triheptanoin (UX007) a 7-carbon medium chain triglyceride metabolized to ketones and TCA cycle intermediates as well as supporting gluconeogenesis, is being investigated as an alternate substrate for genetic disorders of energy metabolism. Loss of TCA cycle intermediates (cataplerosis) may contribute to the pathogenesis of many such disorders. Ketones are important sources of energy for heart, liver and brain. Medium even chain triglycerides (MCT) are ketogenic, providing acetoacetate to the TCA cycle, generating energy, and may bypass the enzyme deficiencies in long chain fatty acid oxidation disorders (LC-FAODs) but do not provide TCA cycle intermediates. Likewise, the ketogenic diet has been used to treat seizures in glucose transporter 1 deficiency syndrome (Glut 1 DS). In contrast, triheptanoin is metabolized to acetyl

CoA, providing energy, and has the unique feature of producing propionyl CoA, regenerating TCA cycle intermediates via succinyl CoA (anaplerosis), and the potential to yield net production of glucose. **Methods:** A PubMed search was performed for publications using the search terms "triheptanoin", "triheptanoin AND treatment", "triheptanoin AND therapy", "anaplerotic therapy" "anaplerotic AND diet". ClinicalTrials.gov was searched for trials with triheptanoin that were "Completed", "Active", "Recruiting," "Not Yet Recruiting". **Results:** Between 2000-2015, 19 papers were found describing treatment with triheptanoin in humans: 6 LC-FAODs, 3 Glut-1DS, 3 pyruvate carboxylase deficiency, 1 anaplerotic molecules, 1 anaplerotic diet therapy, 1 Adult Onset Polyglucosan Body Disease (APBD), 2 Huntington disease (HD), 2 mitochondrial disorders. 17 clinical trials were listed: 7 Glut 1DS, 4 LC-FAOD, 2 HD, 1 glycogen storage disease type V (GSD V), 1 Alternating Hemiplegia, 1 APBD, 1 Heart failure. The publications suggest that treatment can improve energy metabolism and multiple associated clinical symptoms but substantial controlled clinical studies are necessary for conclusive evidence. **Conclusion:** There are currently limited clinical data on the use of triheptanoin; however, emerging clinical data suggest that triheptanoin may provide an alternate substrate for genetic disorders of energy metabolism. Multiple clinical trials are underway or planned to further investigate triheptanoin, suggesting that there is much interest in the potential therapeutic benefit of this investigational product.

(O-1.1) Oral Communications I—NBS

O01 - Neonatal Screening Program for Central Congenital Hypothyroidism

Braslavsky, D.(1); Prieto, L.(2); Keselman, A.(1); Gruñeiro-papendieck, L.(1); Enacan, R.(2); Méndez, V.(2); Saveanu, A.(3); Reynaud, R.(3); Brue, T.(3); Bergadá, I.(1); Chiesa, A.(1)

(1): CEDIE- CONICET-FEI- División de Endocrinología, Hospital de Niños R. Gutiérrez, Buenos Aires, Argentina
(2): Fundacion de Endocrinologia Infantil, Buenos Aires, Argentina
(3): Hôpital Conception, Service d'Endocrinologie, Diabète et Maladies Métaboliques, Marseille, Francia

Introduction: Congenital hypothyroidism (CH) is a heterogeneous entity that includes disorders of the hypothalamo-hypophyseal system. Many patients are missed on TSH-based screening programs leading to increased morbidity and mortality. Additional T4 determination allows an early detection of CH of central origin (CH-C). **Aim:** To report the findings of a neonatal screening program based on determination of TSH and T4 for early detection of CH-C. **Population and methods:** From June 2014 to June 2015, 37045 term newborns aged 2-7 days were included. Screening was carried out with TSH (IFMA Delfia; cutoff 10mUI/L) and T4 [FIA Delfia, cutoff 4.5 ug/dL (-2.3 SDS)] in filter paper blood samples. Infants suspected of having CH-C were referred to a pediatric endocrinologist. They underwent a thorough clinical assessment and determinations of serum TSH,T4,FT4,T3, thyroglobulin, antithyroid-antibodies, cortisol, GH, prolactin, LH, FSH and testosterone (boys). Serum TBG was measured in patients likely to have hypoTBGemia. Brain imaging and studies of transcription factors involved in hypophyseal development were performed. **Results:** Twenty three (1:1610) infants had primary hypothyroidism (TSH 10.4->100 mUI/L). Twenty four patients with only low T4 were recalled. Fourteen of these had transient hypothyroxinemia (13 non-thyroidal illness; 1 healthy). One additional multimalformated patient died at 3 days of life. Five boys had hypoTBGemia (mean T4 2.6 ug/dL; TBG <3.5 ug/dl). Three had permanent CH-C (mean T4 3.9 ug/dl) due to a hypothalamo-hypophyseal disorder (1:12348) and had not been discharged due to morbid conditions (one hypernatremia; two hypoglycemia). All of them had combined pituitary hormone deficiency. MRI showed midline defects (n=2); *LHX4* and *HESX1* mutations were excluded. *POU1F1* heterozygous mutation (c.811C>T,p.Arg271Trp) was found in one patient. One additional patient normalized T4 but remained with isolated ACTH deficiency. Hormonal replacement was instituted at a mean age of 12.2 days. **Conclusions:** T4 determination allowed us to identify CH-C as a prevalent condition and to detect T4 transport defects. It is important to highlight that this screening strategy requires an experienced specialist to confirm the diagnosis of CH-C as well as to rule out transient disorders with low T4. In CH-C infants, the detection of other life-threatening hormone deficits facilitated a timely treatment preventing major morbidity.

O02 - Etiology and Evolution in Newborns With Congenital Hypothyroidism and Mildly Elevated TSH Screening Cut-Off

Signorino, M.(1); Sobrero, G.(1); Testa, G.(1); Boyanovsky, A.(1); Silvano, L.(1); Collet, I.(1); Martin, S.(1); Franchioni De Muñoz, L.(1); Miras, M.(1)

(1): Hospital de Niños de la Santisima Trinidad, Córdoba, Argentina

Introduction: To minimize the risk of not detecting newborns with congenital hypothyroidism (CH), screening programs have gradually lowered TSH cut-offs, which has generated discussions about the contribution to the increase in CH incidence and the possible etiology of mild forms of this condition. **Objective:** To describe the clinical, biochemical and diagnosis imaging parameters contributing to etiological diagnosis and evolution in newborns with CH detected by neonatal screening with mildly elevated TSH values. **Methods:** Medical records of 212 infants with CH detected by neonatal screening from Córdoba, Argentina between 1996-2013 were analyzed. Incidence:1:2000. Those cases whose TSH levels:10-20 uUI/mL (ELISA Tecnosuma) in whole

blood samples collected in filter paper between 2nd-10th day after birth were selected. Diagnosis was performed by serum TSH, total T4, freeT4, T3, TPO Ab, Tg Ab antibodies, Thyroglobulin (ECLIA Roche). Contributions of neck ultrasound and Tc-99 scintigraphy were evaluated. Children presenting eutopic gland of normal size were reevaluated at 3 years of age due to transient hyperthyrotropinemia. **Results:** The sample comprised 32 full-term newborn appropriate for gestational age, F/M: 1,2/1. The 50% of them presented eutopic thyroid gland, with serum TSH: 13.5-321 uUI/mL; Total T4 3-14 ug/dL and free T4 0.26-1.8 ng/dL. The serum Tg (ng/ml) was normal according to regional reference values in 5 newborns (Tg:60-100), was high in 10 (Tg:156-1000) and without data in 1. The TPO Ab and Tg Ab antibodies were negative in all samples. Thyroid dysgenesis was observed in 50% of the patients with serum TSH: 11-250 uUI/mL; total T4: 5-13 ug/dL; free T4: 0.5-1.6 ng/dL; Tg 49.5-1000. Three children with eutopic thyroid gland were reevaluated, and one of them had to restart treatment. Congenital anomalies were reported in 10 patients (3%): Down syndrome (n=6), isolated congenital heart disease (n=3) and Frasier syndrome (n=1). **Conclusion:** Our results do not show differences in the proportion of eutopic and dysgenetic glands in newborns with mildly increased TSH levels, indicating the importance of generating complementary data for the etiological diagnosis of this condition, as well as the need to have appropriate biochemical reference values in the first days of life, which contribute to the diagnosis of thyroid dysfunction.

O03 - Cuban National Newborn Screening Program for Congenital Adrenal Hyperplasia From 2005-2014: A Reality

Carvajal Martínez, F.(1); González Reyes, E.(2); Espinosa Reyes, T.(1); Frómeta Suárez, A.(2); Castells Martínez, E.(2); Arteaga Yera, A.(2); Pérez Moras, P.(2); Carlos Pías, N.(2); Fernández Yero, J.(3)

(1): Instituto de Endocrinología, La Habana, Cuba
(2): Centro de Inmunoensayo, La Habana, Cuba
(3): Grupo de las Industrias Biotecnológica y Farmacéuticas, La Habana, Cuba

Introduction: In 2005, a newborn screening program (NSP) for congenital adrenal hyperplasia (CAH) was introduced in Cuba. CAH represents a family of autosomal recessive endocrine disorders caused by different enzyme deficiencies affecting the adrenal steroid biosynthesis of cortisol and aldosterone, increasing secretion of 17-hydroxyprogesterone (17OHP) and androgens. This work shows the major results of 10 years of Cuban NSP for CAH. **Material and Methods:** NSP for CAH is managed by the Ministry of Public Health where the National Institute of Endocrinology coordinates the actions for the diagnosis, confirmation, control of cases, treatment, follow-up of patients and attention to families. 17OHP quantification is performed using the 17OHP Neonatal UMELISA, in dried blood samples collected on the 5th-7th day using a national network of 200 laboratories. Serum confirmatory test (without extraction) is performed to those neonates with 17OHP values above 55 nmol/L blood. All newborns with a positive screening test are referred for biochemical, clinical confirmation and follow-up at the Regional Paediatric Endocrinology Centers. Treatment with hydrocortisone is begun in all newborns with 17OHP $\geq$40 ng/mL serum and clinical or biochemical signs of CAH. Patients with suggestive salt-wasting crises are given fludrocortisone doses. **Results:** From January 2005 to December 2014, 1,140,882 newborns were screened and 56 CAH cases were confirmed, for an incidence of 1:20,373. About 75% (43 newborns) were diagnosed as classical forms, with a salt-wasting/simple virilization ratio of 1.15. Additionally, thirteen non-classic forms were identified. Coverage of the program reached 99.34%. A recall for suspected CAH was performed in 19,503 cases (1.70%). Specificity of the program is in accordance with the expected value by choosing a unique and low cut-off (calculated for the 98th percentile). However, after a decade, a new screening algorithm that includes adjusted cut-offs for birth-weight and/or gestational age should be implemented to reduce the percentage of recalled babies. Therapy in classical CAH patients was started at the mean age of 22 days. **Conclusions:** In Cuba, the NSP has proved to be useful in detecting CAH cases, has increased the knowledge of the disease and made possible a consensus for its treatment and follow-up.

O04 - Continuous Improvement in the Newborn Screening Program of the State of Rio De Janeiro, Brazil

Introduction: The Rio de Janeiro State Newborn Screening Program, Programa Primeiros Passos, in April 2015 implemented Congenital Adrenal Hyperplasia and Biotinidase Deficiency screening as a complimentary and evolutionary step (FASE IV) of the Brazilian Newborn Screening Program. The introduction of new markers has had a significant impact with approximately 30.000 extra analyses in the lab routine per month. During the last months, the lab team evaluated the routines for positive samples, time collection and confirmed cases. **Materials and Methods:** Samples collected from 728 public health units of Rio de Janeiro State were analyzed for Congenital Hypothyroidism, Congenital Adrenal Hyperplasia, Cystic Fibrosis, Phenylketonuria and Biotinidase Deficiency. The screening results were confirmed in partnership with other reference institutions of the State of Rio de Janeiro, as Instituto Fernandes Figueiras. Newborn Screening for Hemoglobinopathies, and diagnostic and related clinical support, are done by HEMORIO, a partner institution inside the Programa Primeiros Passos. Sample collection time is monitored with the objective to maintain sample collection between 3-5 days, reduce usual pre analytical interferences and perform corrective action plan in public health units. **Results:** Congenital Hypothyroidism, Congenital Adrenal Hyperplasia, Cystic Fibrosis, Phenylketonuria and Biotinidase Deficiency screening positives are reported with confirmed cases. The sample collection time was analyzed, collection during 3-5 days was 22% of the samples

received. 74% of the samples received were collected with 4-30 days and 4% over 30 days. **Conclusion:** The Programa Primeiros Passos is committed with FASE IV of the Brazilian Newborn Screening Program to introduce new markers and analysis, as well as performing an integration of actions with other important reference institutions with the objective to prevent, treat, and offer total support to patients and parents. Time of Collection is considered critical and the challenge is a continued process of training and monitoring 728 public health units to obtain better coverage (3-5 days) and help our lab minimize potential false-positive and false-negative cases.

O-1.2 - Oral Communications I—EIM

O05 - Phenylalanine Hydroxylase (PAH) Production in L. Plantarum as a Potential Orally Administered Enzyme Replacement Therapy

Ramírez, A.(1); Rodriguez, A.(1); Ardila, A.(2); Sanchez, O.(3); Almeciga, C.(1)

(1): Pontificia Universidad Javeriana, Bogota, Colombia
(2): Hospital Universitario San Ingacio, Bogota, Colombia
(3): Purdue University, West Lafayette, Estados Unidos

Introduction: Phenylketonuria (PKU) is the most frequent aminoacidopathies among Caucasians, occurs due to a defect phenylalanine hydroxylase (PAH), which catalyzes the conversion of phenylalanine (Phe) to tyrosine (Tyr). Defective PAH causes the accumulation of Phe that can cause severe neurological damage owed to Phe accumulation in brain. Treatment for this disease includes life-long diets that are hard for patients to maintain, supplementation with tetrahydrobiopterin depending on the mutation (not all are responsive), or very expensive and tedious parenterally administered enzyme replacement therapy (ERT). The aim of this work is to evaluate the production of recombinant PAH (rPAH) in a *L. plantarum* strain modified with a signal peptides that facilitates its transport across the intestinal epithelial barrier. **Methods:** The *PAH* gene was designed as a fusion protein along with an enhanced green fluorescent protein (EGFP), and peptides for: 1) secretion from Lactobacilli, 2) transport across gastrointestinal membrane, and 3) cell capture by liver cells. This construct was inserted into the expression plasmid pSIP501. *L. plantarum* cells were transformed by electroporation, and cultured in MRS culture media. Expression of the EGFP-fusion protein (EGFP-rPAH) in the culture extract was evaluated by fluorospectrometry. The best-clone culture extract was tested in CaCo2 cells cultured in Tanswell plates (1x104 cells per well) to evaluate the capacity of the rPAH to cross the epithelial membrane. Finally, rPAH was assayed *in vitro* for its capacity to reduce plasma Phe concentration. **Results and conclusion:** The *L. plantarum* strain successfully produced and secreted the recombinant EGFP-rPAH, which was able to cross at a low protein concentration through a monolayer of CaCo2 cells. We expect then that the recombinant protein will be able to cross through the intestinal epithelial membrane in-vivo. In addition, this suggests that the transport might be mediated trough a receptor sensitive to protein concentration and susceptible to saturation. It is noteworthy that rPAH reduced Phe levels in a plasma sample from a PKU patient. These results support the ability of recombinant proteins produced in probiotic bacteria to be used in ERT due to their capacity to cross the gastrointestinal barrier.

O06 - Epigenetic Alterations in Niemann-Pick Type C Models: Neuronal Gene Repression Mediated by the C-ABL/HDAC2 Pathway

Contreras, P.(1); González-zuñiga, M.(1); González-hódar, L.(2); Alvarez, A.(1); Zanlungo, S.(2)

(1): Cell Signaling Laboratory. Biological Sciences Faculty. Pontificia Universidad Católica de Chile., Santiago, Chile
(2): School of Medicine, Pontificia Universidad Católica de Chile., Santiago, Chile

Introduction: Niemann-Pick type C (NPC) disease is a neurodegenerative lysosomal cholesterol storage disorder resulting from loss-of-function mutations in either the *Npc1* or *Npc2* genes. Recently, histone deacetylases (HDAC) inhibitors have emerged as possible cholesterol lowering drugs for NPC treatment due to the expression induction of several genes involved in cholesterol metabolism and neuronal function. Previously, our laboratory has shown that c-Abl activity is increased in NPC and Alzheimer's disease (AD) models and stabilizes HDAC2 levels in AD models. Our principal objective was to evaluate if c-Abl activity induces upregulation of HDAC2; and in this way the inhibition of neuronal genes expression in NPC models. **Methods:** We used different NPC-models: i) pharmacological models: primary cultures of hippocampal neurons (7DIV), Hepa 1-6 and neuronal HT22 cells were treated with U18666A (U18); ii) genetic models: NPC1 null fibroblasts and NPC1 null mice. We treated the cells and animals with the c-Abl inhibitor, Imatinib, and evaluated: 1) HDAC2 levels by immunoblot and immunofluorescence, 2) the recruitment of HDAC2 in the promoter of neuronal genes (GluR1, NR2a, Synaptotagmin I and Synaptophysin) by chromatin immunoprecipitation assay, 3) the expression of these neuronal genes by real time PCR and 4) cholesterol levels by filipin staining. **Results:** We found increased HDAC2 levels in both U18-treated primary hippocampal neurons and the cerebellum and brain of NPC1 null mice. Treatment with Imatinib: i) induced a decrease in HDAC2 levels, ii) prevented HDAC2 recruitment on neuronal gene promoters and iii) reduced neuronal gene repression. Interestingly, c-Abl inhibitor reduced cholesterol accumulation in Hepa 1-6 and neuronal HT22 U18-treated cells and in the fibroblast NPC1 genetic model. **Conclusions:** c-Abl induces an increase of HDAC2 levels promoting the repression of neuronal genes. Moreover, c-Abl inhibition reduces cholesterol accumulation. With these novel data we suggest that c-Abl/HDAC2 pathway is a possible target for NPC treatment.

O07 - Identification of Modifiable Epitopes for the ARSB Enzyme by a Computational Approach

Olarte, S.(1); Rodriguez, A.(2); Alméciga-diaz, C.(2)

(1): Universidad Colegio Mayor de Cundinamarca, Bogota, Colombia
(2): Pontificia Universidad Javeriana, Bogota, Colombia

Introduction: Mucopolysaccharidoses VI (MPS VI) is a lysosomal storage disorders (LSD) caused by deficiency of N-acetylgalactosamine-4-sulfate (Arylsulfatase B, ARSB). The Enzyme replacement therapy (ERT) is available for this disease as treatment but 98% of patients develop anti-antibodies that can limit the efficacy or produce Infusion Related Reactions. **Objective:** In this study, we present a computational approach for the identification of human ARSB antibody epitopes or complex major histocompatibility II (CMH II) epitopes and the possible residues that can be modified as a strategy to decrease the antigenicity of the protein used in the ERT. **Methodology:** The antibody epitopes were evaluated using Epitopia Server and ElliPro tool while the CMH II epitopes using NetMHCII 2.2 server. Amino acids more antigenic were assessed by conservativeness evolutionary in other species and in PolyPhen 2 tool. **Results:** Twelve antibody epitopes were identified in the primary sequence and tertiary structure of ARSB. In addition to N-terminal and C-terminal domains, residues 217 to 231 and 246 until 265 have highly immunogenic antibody epitopes. The epitope of the sequence 175 to 195 has several of the individual residues more antigenic in the analysis of the tertiary structure for antibody epitopes. The epitope (217 to 231) and the C-terminal domain (471 to 508) were the more antigenic for CMH II epitopes and the motive 227 to 231 was the sequence more frequent in the epitopes for the HLA-DRB and HLA-DPA. Twenty-seven changes of antigenic amino acids by other residues present in ARSB of six different species did not have affects on protein function according to Poplyphen2 analysis. **Conclusion:** The identification of antigenic amino acids in ARSB can be useful for the identification of potential residues that can be modified to decrease the immunogenicity without affect the conformation structural of the protein. This is the first step in the computational analysis for the design of an ARSB less immunogenic as a therapeutic alternative for the MPS VI and as strategy for other mucopolysaccharidoses.

O08 - Production of Human Recombinant Iduronate-2-Sulfatase in Two Microbial Hosts

Pimentel-vera, L.(1); Bonilla, Y.(1); Rodríguez, A.(1); Diaz, D.(1); Espejo, Á.(1); Poutou-piñales, R.(2); Alméciga-diaz, C.(1); Barrera, L.(1)

(1): Instituto de Errores Innatos Del Metabolismo; Pontificia Universidad Javeriana, Bogota, Colombia
(2): Grupo de Biotecnología Ambiental e Industrial (GBAI); Pontificia universidad Javeriana, Bogota, Colombia

Introduction: Hunter Syndrome (MPS II, OMIM 30990), is an X-linked lysosomal storage disease originated in the deficiency of iduronate-2-sulfatase (IDS, 3.1.6.13). Currently, MPS patients are treated by enzyme replacement therapy (ERT) with recombinant enzymes produced in mammalian cells. Recent studies for the lysosomal enzymes have shown the potential of microorganisms as host for the production of recombinant lysosomal enzymes. In this study, we used bacteria (*E.coli*) and yeast (*Pichia pastoris*) to produce human recombinant IDS. Recombinant IDS was purified and some physicochemical properties were studied. **Materials and Methods:** Native human IDS cDNA was cloned into pGEX-3X or pPIC9 vectors for expression in *E. coli* BL21(DE3) or *P. pastoris* GS115, respectively. Clones were screened at 100 mL scale and those with the highest activity were selected for recombinant enzyme production at bioreactor (1.65) L scale. Recombinant IDS was purified by ion-exchange chromatography, and used to evaluate pH, and serum stability. **Results and conclusions:** Several *E. coli* BL21(DE3) clones were screened at 100 mL with a highest enzyme activity of 2.3 U/mg in the intracellular fraction, while no enzyme activity was detected on the extracellular fraction. A different profile was observed at bioreactor scale, where the highest enzyme activity was 0.4 U/mg after 24 h induction in the extracellular fraction, which was significantly higher than that of the intracellular fraction. For *Pichia pastoris*, IDS production was monitored at the extracellular fraction due to the presence of a secretion signal peptide. At 100 mL scale the highest enzyme activity was 1.0 U/mg. At bioreactor scale, the highest enzyme activity values (1.58 U/mg) were observed under oxygen-limited conditions. Purified recombinant IDS produced both in *E. coli* and *P. pastoris* showed the maximum stability at pH 7.0 and pH 6.0, respectively, suggesting that N-glycosylations affect pH stability. It is noteworthy that at pH 5.5 IDS produced in *E. coli* showed 50% of the activity observed at pH 7.0, Recombinant IDS produced in both expression systems remained relatively constant during the 8 h of evaluation on serum; suggesting that the rIDS produced in *E. coli* or *P. pastoris* could be stable relatively long time in circulation.

(P-2) Poster Session With Authors II

P065 - Expanded Newborn Screening Program in One Center in Santiago De Chile: 8 Year Experience and Challenges

Valiente, A.(1); Pinto, M.(2); Cabello, J.(1)

(1): INTA, Universidad de Chile, Santiago, Chile
(2): Clinica Las Condes, Santiago, Chile

Introduction: Clinica Las Condes (CLC) is one of the main private health centers in Santiago de Chile. We decided to start an expanded newborn screening program (ENBSP) in 2007 in a partnership with the Metabolic Disease Laboratory at the Nutrition and Food Technology Institute (INTA), University of

Chile. **Material and methods:** We collected a heel sample from every newborn whose family agreed to send a sample for ENBSP. We performed Tandem Mass Spectrometry (MS/MS) for amino acids and acylcarnitines profiles; immunofluorometry for TSH, immunoreactive trypsinogen and 17-OH progesterone; and fluorometry for total galactose, biotinidase activity, and galactose-1-phosphate uridyltransferase activity. **Results:** We analyzed 11.128 samples between July 2007 and February 2014, representing 83% of the deliveries in our Clinic. We found 285 abnormal results and/or insufficient sample (2,35%). In the second call sample, we were able to confirm the following cases: 1 MCAD deficiency, 1 classic PKU and 1 Hyperphenylalaninemia, 3 Congenital Hypothyroidism and 2 Cystic Fibrosis, and 1 Congenital Adrenal Hyperplasia. This represents an incidence of 1:1.236 newborns detected. **Discussion:** This is the first ENBSP established in a private institution in Chile. Data obtained during 8 years allowed us to encourage the Ministry of Health authorities to start with this expanded program along the country. We need to improve coverage in CLC with education campaigns, to decrease the recall percentage and to improve the follow up of those patients, especially in immunoreactive trypsinogen and TSH.

P066 - Review of the Immunoreactive Trypsinogen (IRT) Cutoff Value For Neonatal Screening of Cystic Fibrosis (CF)

Odriozola, A.(1); Junco, M.(2); Gotta, G.(2); Dratler, G.(2); Smithuis, F.(2); Hunt, M.(2); Marino, S.(2); Gonzalez, V.(2); Teper, A.(2); Muntaabski, P.(2); Aranda, C.(2); Glikman, P.(2)

(1): Programa de Pesquisa Neonatal. Gobierno de la Ciudad de Buenos Aires, Buenos Aires, Argentina
(2): rograma de Pesquisa Neonatal. Gobierno de la Ciudad de Buenos Aires, Buenos Aires, Argentina

Introduction: The algorithm we are using for CF screening in our Neonatal Screening Program is IRT/IRT followed by confirmation of positive cases with sweat test and their characterization by molecular biology. During the year 2013 we began to use the kit DELFIA Neonatal IRT modified by the manufacturer (version A005-110 replaced by A005-210). **Objective:** 1) to review the IRT cutoff value (CO) using the latest version of the IRT kit, by studying IRT distribution in our population of term newborns (NB) in 2014 and to compare it with results from the previous version of the kit used in 2012; 2) to analyze the impact on recall rate (RR) of an eventually new CO. **Materials and Methods:** We retrospectively analyzed IRT results of the first samples obtained from healthy term NB, 3-7 days old, in dried blood spots using Whatman #903 paper, from first semester 2014 (n=5645) vs first semester 2012 (n=3836). IRT was measured by DELFIA Neonatal IRT (PerkinElmer) version A005-110 for 2012 and A005-210 for 2014 samples. Statistical analysis: Median (M) and Percentiles (P99, P995) of the distributions were calculated and compared. RR was calculated using the P99 from both periods. **Results:** The distribution of IRT (ng/mL) in 2012/2014 were: M:16.3/14.9, P99:60/50; P99.5:70/60. IRT range data from confirmed CF babies were in 2012 / 2014: n=3 (87-209.2) / (n=4) (65-327). The RR (%) in 2014 using the new P99 would increase from 0.6 to 0.9%. **Conclusions:** Distribution of IRT shifted to lower values with the new version of the neonatal IRT kit. We propose to decrease the IRT cutoff to 50 ng/mL (P99); the RR still remains acceptable for a neonatal screening program. The impact of this analytical change in the cutoff deserves further evaluation and correlation with additional clinical findings.

P067 - Qualitative Survey Tool to Evaluate Neonatal Screening Centers: Neonatal Screening Program (NSP) Zulia-Venezuela Experience

Costagliola Martorona, A.(1); Chacin Hernandez, J.(2); Ocando Pino, L.(3); Mejia Millan, I.(4); Torres, E.(3); Torres Chirinos, Y.(3); Picado Gutierrez, J.(3)

(1): Fundacion Hospital De Especialidades Pediatricas, Maracaibo, Venezuela
(2): La Universidad del Zulia; Institito de Investigaciones Geneticas, Maracaibo, Venezuela
(3): Fundacion Hospital de Especialidades Pediatricas; Laboratorio de Salud Publica, Maracaibo, Venezuela
(4): Fundación Hospital de Especialidades Pediatricas, Maracaibo, Venezuela

Introduction: Zulia has a population of nearly five million inhabitants with an average of 5000 newborns per month; the health system has 295 outpatient centers and 30 hospitals. 88% of these centers are included in the NSP. On the fifth day of life (or seventh and twenty day of life from premature newborn), a few drops of blood from eutocic newborns' heel are taken. These samples are received weekly, with the basic package of neonatal screening. Having an instrument for monitoring screening centers during the pre-analytical period is vital to the timely intervention of problems. We aim to show the usefulness of a Qualitative Survey (QS) applied prospectively. **Materials and Methods:** QS applied upon receipt of samples during the first half 2015. **Contents:** List of centers, qualified/not; active/not; timely transfer of sample-taking shows/5th eutocic day, 7th and 21vo in premature/no; record full/no data, contact phones present/absent, address present /absent; Mother authorizing signature, drop of blood transferred paper/not; using circle full/not, status and condition of screening cards satisfactory/no, matching identification number and samples list and develop letter. **Results:** 86% of centers are active in NSP. 81% timely transfer of samples, 80% shot shows / date of birth eutocic/preterm infant timely, complete data record 76%, 60% drop of blood transferred paper, use 75% of full circles. 100% match between number and identification of samples. After the application of the instrument data are analyzed, identified neonatal screening centers situation to intervene, effectively improving the

pre-analytical processes allowing the identification of future recidivism. **Conclusion:** The design and implementation of an assessment instrument with qualitative techniques for the pre-analytical period is necessary for timely corrective action to and ensure the effectiveness and efficiency of the NSP.

P068 - Phenylketonuria: Analysis of Adiponectin, Biomarkers and Anthropometric Parameters

Hack Mendes, R.(1); Castro, K.(2); Nalin, T.(3); Tonon, T.(4); Siebert, M.(5); Chrisostomo, P.(5); Poloni, S.(1); Oliveira, F.(1); De Souza, C.(5); Vairo, F.(5); Schwartz, I.(5);

(1): PPGBM-UFRGS—Pós Graduação em Genética e Biologia Molecular, Porto Alegre, Brasil
(2): PPGSCA-UFRGS—Pós Graduação em Saúde da Criança e do Adolescente, Porto Alegre, Brasil
(3): PPGBM-UFRGS—Pós Graduação em Genética e Biologia Molecular (Av. Bento Gonçalves, 9500, Porto Alegr, Porto Alegre, Brasil
(4): PPGCM-UFRGS—Pós Graduação em Medicina: Ciências Médicas, Porto Alegre, Brasil
(5): SGM-HCPA—Serviço de Genética Médica-Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil

Introduction: Phenylketonuria (PKU) is an inborn error of phenylalanine (Phe) metabolism, associated with a decrease of catecholamines biosynthesis, treated with a low-Phe diet. To assess the concentration of adiponectin and biomarkers in patients with PKU accompanied the Inborn Errors of Metabolism Clinic (EIM) of Hospital de Clínicas de Porto Alegre, Brazil. **Material and Methods:** Cross-sectional study, sampling for convenience and including 27 PKU patients older than 5 years. The analysis of adipokines also involved 27 controls matched for age and sex with patients. Measurements of weight and height were carried out on the day of blood collection to measure adiponectin, and chart review to obtain the concentration of biomarkers [hemoglobin (Hb), albumin, ferritin, vitamin B12, calcium, total cholesterol (TC), LDL, HDL, triglycerides (TG) and the concentration of Phe, more recent. The analysis of adiponectin was performed by ELISA. **Results:** Regarding PKU group, 51.9% were male and the mean age, weight and height were, respectively, 14.2 $\pm$ 4.3 years, 47.8 $\pm$ 15,9kg, and 150 $\pm$ 10 cm. Regarding the classification of the type of PKU, 59.3% of the patients had classic PKU and 40.7% mild PKU. BMI mean was 20.04 kg/m^2 (14.70 to 31.16) and 20.69 kg/m^2 (14.00 to 28.73), for PKU patients and control group, respectively. Regarding the BMI, classification, 74.1% of the patients had normal weight, 14.8% overweight and 11.1% obese. In the control group, 85.2% were eutrophic, 11.1% overweight and 3.7% obese. The mean Hb was 13.44 $\pm$ 1.05 g / dL, and the median of Phe was 18.40 mg / dL. (IQ 5.72 to 48.70). The most of the patients had CT (70.8%), LDL (88.9%) and TG (88%) in the adequate values; however, for HDL, 73.9% had borderline values. Difference was found between adiponectin levels (median = PKU 124,26ng / mL; controls = 10.34; $p = 0.000$). **Conclusion:** Patients included in this study present, mostly adequate nutritional status. The increase of adiponectin in patients with PKU is probably related to low levels norepinephrine and dopamine levels acting directly on adipocyte of adiponectin production and/or release in blood stream.

P069 - Phenylketonuria: Analysis of Gut Microbiome Using Next-Generation Sequencing

Oliveira, F.(1); Refosco, L.(2); Dobbler, P.(3); Vairo, F.(2); Mendes, R.(1); Roesch, L.(3); Schwartz, I.(2)

(1): Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil
(2): SGM-HCPA—Serviço de Genética Médica-HCPA, Porto Alegre, Brasil
(3): Universidade Federal do Pampa, São Gabriel, Brasil

Introduction: The human gastrointestinal tract harbors a large microbial community composed approximately by 10.000.000.000.000 microorganisms and changes in composition and functional characteristic may be associated with pathophysiology of several diseases. The aim of this study was to characterize the structure and diversity of gut microbiome in patients with phenylketonuria (PKU), an inborn error of metabolism defined by inability to convert phenylalanine (Phe) in tyrosine, whose treatment is based on dietary Phe restriction. **Material and Methods:** Stool samples were collected from 9 PKU patients on treatment (median age: 2.6 years; IQ: 1 to 10.7, mean Phe concentration: 5.6 + - 3.25 mg / dL) and 12 healthy controls (median age: 4.83 years; IQ: 1.91 to 16.66). PKU patients had a median intake of 250 mg (IQ: 162.5 to 337.5 mg) of Phe in diet, while normal individuals have over 1000 mg of Phe on diet. Bacterial DNA was extracted and 16S rRNA gene was sequenced on PGM Ion TorrentTM. Bioinformatics analyses were performed following recommendations of the Brazilian Microbiome Project. **Results:** Differences in gut microbiome were observed between PKU patients and controls (pseudo $F = 39.5$; $p = 0.001$). PKU patients showed an increase in the amount of bacteria belonging to Prevotella and Akkermansia genus and Peptostreptococcaceae family. Meanwhile, gut microbiome in control group was enriched by bacteria belonging to Clostridiales class, especially Ruminococcus, Coprococcus, Odoribacter, Dorea, Bilophila and Lachnospira genus. **Conclusion:** These differences also reflected in small number of genes involved in starch and sucrose metabolism in microbiome of PKU patients compared with control group. The Prevotella genus is involved in the metabolism of complex glycans, including plant polysaccharides, and is associated with low consumption of animal protein and saturated fats. Ruminococcus are also associated with metabolism of plant polysaccharides, especially starch. These results indicate a loss of diversity in the bacterial flora of patients with PKU, which may reflect the effects of dietary treatment in these patients.

P070 - BH4 Loading Test for Evaluation of Neonatal Hyperphenylalaninemia

Specola, N.(1); Núñez Miñana, M.(1); Muschietti, L.(1); Borrajo, G.(2); Procopio, D.(1)

(1): Hospital de Niños, La Plata, Argentina
(2): Fundación Bioquímica Argentina, La Plata, Argentina

Introduction: The outcome of various forms of Hyperphenylalaninemia (HPA) depends on early diagnosis and treatment. Neonatal screening test must be followed by confirmation and variant's diagnosis (PKU—no PKU HPA—biopterin deficits). It means a timely analyze of aminoacids, biopterin profile and dihydropteridin reductase (DHPR). In Latin America, where biopterin profile is not regularly performed, Tetrahydrobiopterin (BH4) neonatal test is useful to reduce time of diagnosis and treatment. **Methods:** After BH4 was approved in our country for treat PKU patients, it was decided to perform a short BH4 test (8 hs) to newborns with positive screening test, the day they come to hospital for confirmation. Inform consent was signed for each family. Phenylalanine (Phe) levels were measured with 2 to 4 hs fast at 0 - 4 - 8 hs. After T0 20 mg/kg of BH4 (Kuvan, Merck-Serono) was administered as a single oral dose. At T0 filter paper blood samples for DHPR and biopterins were also obtained. 18 neonatal tests were done and compare with a similar test of a patient previously diagnosed with pyruvoyl tetrahydrobiopterin synthase (PTPS) deficiency. Patients were classified according to % of Phe decreased as BH4 non responders NR (< 30%), responders R1 (30 - 80%), responders R2 (> 80%). Classification of HPA patients (T0 Phe levels with normal diet): classical PKU > 20 mg/dl, moderate PKU 10-20 mg/dl, mild PKU 6-10 mg/dl, HPA nonPKU 2-6 mg/dl and biopterin deficiencies. **Results:** Biopterin profile and DHPR were normal in the 18 patients. 66% were NR. 33% were R1. Only PTPS patient were R2. The 7 patients with classic PKU were among the NR group. Group R1 gather moderate and mild forms. Patients of this group decreased Phe levels faster to reached target level. All the patients continued with Phe restricted diet. Bh4 was well tolerated. **Conclusions:** BH4 test proved useful and safe in reducing diagnostic time, allowed to suspect biopterin deficits, that must be completed with DHPR activity and biopterin profile. This short test does not exclude PKU BH4 responsive.

P071 - Molecular Analysis for Galactosemia Was Implemented in the Neonatal Screening Program of the Province of Santa Fe, Argentina

Maggi, L.(1); Cabrera, A.(2); Fain, H.(2); Benetti, S.(3)

(1): Laboratorio Provincial de PN de ECM de Santa Fe, Santo Tome, Argentina
(2): Hospital Vilela, Rosario, Argentina
(3): Cemar, Rosario, Argentina

Introduction: Classic Galactosemia (G/G), a metabolic disorder of autosomal recessive heredity, is caused by a mutation in the galactose-1-phosphate uridyltransferase gene, which encodes the homonymous enzyme (GALT) and is located at the short arm of chromosome 9 in position 13. More than 180 mutations of the GALT gene have been identified. These mutations are responsible for the lack of enzymatic activity or its reduction in the case of the Duarte variety (G/D), causing accumulation of toxic substances that damage tissues and organs. **Goal:** To present every result from studies conducted on two GALT positive-testing cases, from the development of genetic analysis within the province of Santa Fe. **Material and methods:** For the study, for neonatal screening (NS), dried blood spot samples on filter paper Whatman 903 were used, and ultra micro analytical fluorescent enzyme assays performed, ratio: 10 mg%, for confirmation: GALT's enzymatic activity (EA) on heparinized red blood cells, spectrophotometric method, reference values (rv); 0-0.5 U/g Hb: Galactosemia (G), 0.5-1.5 U/g Hb: possible G, intermediate values: heterozygous patient, over 18: normal, and molecular study through sequencing of GALT gene 1-to-11 exons. **Results:** Newborn (NB)1: female, normal weight, gestation weeks (GW): 40, no family history. First NS high, 10.05 mg%, second sample with a 3 hour fast, positive 24.50 mg%; GALT EA: 1.1 U/g Hb and heterozygous mutation M142K/normal. NB2: Male, good height and weight progress, jaundice that disappears spontaneously, without hepatomegaly. Three studies were made which produced high results: 1st: 27 mg%, 2nd: 16 mg% and 3rd: 14 mg%, GALT EA: 2.3 U/g Hb and heterozygous, mutation Q188/N314D. **Conclusions:** Both diagnosed children are under control and monitoring. NB1, classic mutation, it is yet to be defined whether she is carrier or there is another associated mutation responsible for her symptoms; and NB2 shows signs of the Duarte variant.

P072 - Evaluation of a New Algorithm for Cystic Fibrosis in Neonatal Screening

Maggi, L.(1); Benetti, S.(2); Arguellles, A.(1); Flaherty, P.(2)

(1): Laboratorio Provincial de PN de ECM de Santa Fe, Santa Fe, Argentina
(2): Cemar, Rosario, Argentina

Introduction: Neonatal screening gives a better life quality prognosis to timely identified and treated children. The diagnosis time index (60 days) in our Provincial Net, was better than the 4-month national average up to the end of 2013. Nevertheless, in order to start therapy in the pre-symptomatic stage, it was necessary to optimize all process times. **Objective:** To evaluate whether the implemented algorithm had: a- Diminished diagnosis time index, b- Increased affected alleles detection when going from 3 to 32 analyzed mutations. **Materials and Methods:** Dried blood samples on filter paper, Immunoreactive Trypsinogen (IRT) ELISA assay, with a cut off for the first sample (36-72 hours old) of ≥150 ng/ml, P99; 2nd sample (20-25 days old), cut off ≥ 100 ng/ml, P 99. "Gibson & Cook" sweat test (ST), chlorides < 30 mEq/l normal, between 30 and 60 mEq/l equivocal and

≥ 60 mEq/l positive; molecular biology (MB), sample on paper, PCR technique, "Ola Cystic Fibrosis Assay" method, 32 mutations. **Results:** Every patient with 1st and 2nd elevated IRT was referred to Cystic Fibrosis Units (CFU) for clinical evaluation and simultaneous determination of ST and genetic tests, as well as every 1st IRT higher than 200 ng/ml of newborn without injury, base disease or family history. Two positive ST and/or patient with two mutated alleles confirmed CF; ST with equivocal result and/or MB: mutation/normal, newborn under control and monitoring and 2 negative ST with MB without mutation, normal patient. The diagnosis average time was 30 days and from 30.417 examined patients 145 had 1st positive IRT, 117 attended to make 2nd IRT, from which 99 were normal, 6 fibrocystic patients, 4 homozygous (D508/D508), 1 heterozygous (D508/normal) and 1 meconium ileus; 13 children continue on study, control and monitoring. **Conclusions:** This algorithm made it possible to diminish diagnosis time, determine the CFTR gene allelic heterogeneity and guarantee the patient's prompt access to the CFU.

P073 - Endocrinopathies Detected by Newborn Screening: Epidemiological Overview

Burciaga Torres, M.(1); Delgado González, E.(1); González Guerrero, J.(1)

(1): Instituto Mexicano del Seguro Social, Coordinación de Atención Integral a la Salud en el Primer Nivel, México D.F., Mexico

Introduction: Endocrinopathies are the most common group of diseases detected by newborn screening. Their detection in the first month of life is very important to prevent various sequelae and complications, and even death in affected children. In Mexico, screening for Congenital Hypothyroidism (CH) has been carried out since 1994 and for congenital adrenal hyperplasia (CAH) since 2005. We have a special surveillance system at all three levels of care, as well as an evaluation system of quality indicators, for monitoring of detected cases. **Objective:** To analyze the coverage of detection of CH and CAH, the index of suspicion, positive predictive value (PPV), sensitivity and specificity of screening, state and national cumulative incidence, and quality indicators over a period of 10 years (2005-2014). **Methodology:** Epidemiological study of a 10-year period; special information system for epidemiological surveillance of CH and CAH was obtained. Frequencies, crosstabs, means analysis and incidences were obtained using the SPSS statistical package. **Results:** In the period studied, 4,801,973 newborn screening samples were analyzed, with an average coverage of 96% of newborns. 6,611 probable cases of CH and 16,723 of CAH were detected (index of suspicion: 0.14% and 0.38% respectively). 2,112 cases of CH (PPV: 31.95%) and 522 of CAH (PPV 3.12%) were confirmed. The cumulative incidence was 1:2,304 and 1:8,840 for CH and CAH respectively). The states with the highest incidence of CH were Mexico State, Nuevo Leon, Tamaulipas and Nayarit, Oaxaca Sonora for CAH. The opportunity for diagnosis for CH was 58.0% and 31.5% for CAH. The average days to diagnosis were 28 and 46 respectively. **Conclusions:** The endocrinopathies are the most common diseases detected by neonatal screening in Mexico. However it is still necessary to strengthen the training of health personnel to improve the timeliness of diagnosis within 30 days to avoid the occurrence of complications.

P074 - First Year of Metabolic Control Guidelines and its Impact on Future Metabolic Control and Cognitive Performance in Children Affected With PKU

De La Parra, A.(1); García, M.(1)

(1): LabGEM INTA, Santiago, Chile

Introduction: Phenylketonuria (PKU) is a hereditary metabolic disorder that causes elevated blood phenylalanine (Phe). PKU patients' left untreated exhibit intellectual impairment. Early diagnosis and treatment enables normal development. Recommended Phe levels during the first years of life are between 2-6mg/dl in most countries. In Chile since 2010 the recommended Phe levels are between 2-4mg/dl during first year of life. This study analyzes the impact of targeted first year metabolic control on psychomotor development, cognitive performance and metabolic control during following years. **Sample and Methods:** A total sample of 77 children diagnosed with PKU through neonatal screening and that participated of the follow up program were included in the sample. Only children with Phe>18mg/dL at diagnosis where include, to exclude milder variants of the condition. Psychomotor development was assessed with Bayley-II at 12 and 36 months of age, and cognitive performance at preschool age and school age with Wechsler Scale. Children were grouped according to metabolic control during first year of life into two groups, mean Phe <4mg/dL (n=38, Phe=2,84) and Phe ≥4mg/dl (n=39, Phe=5,72). Results were compared in between both the two groups. **Results:** When comparing the group with mean Phe<4mg/dL (Group A) to the group with average Phe≥4mg/dL (Group B) during the first year of life significant differences where identified in metabolic control during the second (p=0,0001), third (p=0,041), fourth (P=0,037), fifth and sixth (p= 0,003) year of life. Infant in Group B performed significantly better in Motor Development Index (PDI) at 12 months (average PDI 89/79, p=0,001). At preschool age results were significantly higher in Performance IQ (PIQ) in group A (PIQ 101/94, p=0,03). At school age results were significantly higher in group A in Verbal IQ (VIQ 99/91, P=0,005) Motor IQ (MIQ 97/88, P=0,01) and Total IQ (TIQ 98/89, p=0,003). When dividing and comparing the group with average blood Phe during first year of life, between averages Phe≥4mg/dL<6,0mg/dl and Phe>6,0mg/dl during first year, no significant differences were identified in analyzed variables. **Conclusions:** Average Phe plasmatic levels < 4mg/dl during the first year might increase the odds of better treatment compliance in following years and protect cognitive development.

P075 - Energy Expenditure in Children With Maple Syrup Urine Disease (MSUD)

Campo Perez, K.(1); Castro, G.(1); Valerie, H.(1); Arias, C.(1); Cabello, J.(1); Cornejo, V.(1)

(1): Inta, Santiago, Chile

Background: Maple syrup urine disease (MSUD) is caused by a blockage of the catabolic pathway of branched chain amino acids. The disease leads to neurological damage through leucine and metabolite accumulation. Evaluation of expenditure and energy requirements for MSUD patients is necessary for metabolic balance and proper growth, however, information is limited. **Objective:** To determine if basal/total energy expenditure (BEE/TEE) is comparable between different determination methods and if values agree with recommendations of energy in MSUD children, and whether they relate to nutritional status. **Methods:** case-control study between MSUD (n=16) and healthy children (n=11) aged 6-18 years. Current nutritional status, physical activity level, body composition by DEXA and BEE/TEE by indirect calorimetry (BEEr) and predictive equations (FAO/WHO/ONU –WHO– and Schofield) were assessed; STATA 2013 (p<0,05). **Results:** When comparing the energy expenditure variables there was no significant difference between groups (*P=0,5212; 0,5052; 0,4897)*. Moreover, compared to BEEr, equations underestimate: in the study group 9,5% vs 10,4% and in control group 7,5% vs 9,4% according to BEE WHO and Schofield, respectively (*P=0,0008; 0,0208*). The WHO equation for energy expenditure had lower average calorie difference, greater concordance correlation and association with indirect calorimetry compared to the Schofield equation for both groups, being the best predictor of the BEE for MSUD group. **Conclusion:** Energy recommendations for MSUD children are according to energy expenditure, thus the use of WHO equation is a clinically and statistically feasible tool for its determination.

P076 - Anthropometric Assessment in Children and Adolescents With Classical Phenylketonuria

Zayas Torriente, G.(1); Torriente Valle, J.(2); Carrillo Estrada, U.(3); Díaz Fuentes, Y.(1); Abreu Soto, D.(4); Martínez Rey, L.(5)

(1): Instituto Nacional de Higiene, Epidemiología, La Habana, Cuba
(2): Instituto Nacional de higiene, epidemiología y Microbiología, La Habana, CUBA
(3): Hospital pediátrico marfan-borrás, La habana, Cuba
(4): Instituto nacional de Higiene, epidemiología y Mirobiología, La Habana, Cuba
(5): Centro Nacional de Genética Médica, La Habana, Cuba

Introduction: PKU is an Inborn Error of Amino acid Metabolism. The flaw resides in deficiency of the activity of the hepatic enzyme phenylalanine hydroxylase (FAH). This produces a blockage in the conversion of phenylalanine to tyrosine and causes increased levels of phenylalanine in blood. The disease is clinically manifested in different ways according to the degree of residual enzyme activity. This determines if it is classical PKU or variants of Hyperphenylalaninemias (HFA). In untreated patients is observed irreversible mental retardation, low intelligence quotient (IQ); neurological abnormalities, hyperactivity, and seizures. Early diagnosis and comprehensive assessment of nutritional status of the patient by clinical, anthropometric, biochemical and dietary indicators help establish an effective treatment and prevent sequelae of the disease. **Objectives:** To carry out the assessment of nutritional status by anthropometric a group of patients with classic phenylketonuria indicators. **Methodology:** A descriptive cross-sectional study was conducted. The population consisted of 12 patients between 1 and 18 years diagnosed with classical phenylketonuria who serve in the office of national reference. Weight, height, arm circumference, triceps skinfold: anthropometric assessment for the following measurements were used. Indices of weight / height, height / age, weight / age and body mass index were calculated. To assess adiposity indices muscularity and muscle area and arm fat was calculated. Breakpoints and reference standards for the Cuban people less than 20 years were used. **Results:** By: Weight / Size: Thin 1 (8.3%), Normal 7 (58.3%), overweight one (8.3%), obesity 3 (25%), Weight / Age: normal weight 7 (58.3%), high weight 5 (41.6%), height / age: Normal-11 (91.6%), high Size 1 (8.3%), BMI: Normal 7 (58.3%), overweight 2 (16.6%), obesity 3 (25%), muscular area arm: Normal 8 (66.6%) Excessive 4 (33.3%), Fat area arm: Normal 9 (75%) Excessive 3 (25%) **Conclusions:** The majority of patients with classical phenylketonuria have an adequate nutritional status. There are patients with overweight or obesity, which could be related to food free from phenylalanine in the diet. This is a factor to control in the prevention of non-communicable diseases.

P077 - Study of Three Years of Newborn Screening for Cystic Fibrosis in the Public Health System in Southern Brazil

Castro, S.(1); Rispoli, T.(2); Dornelles, C.(3); Chapper, M.(4); Fischer, G.(4); Malerba, H.(4); Fillipon, L.(5)

(1): Serviço Referência Triagem Neonatal RS/UFRGS, Porto Alegre, Brasil
(2): Centro de Desenvolvimento Científico e Tecnológico (CDCT)—FEPPS/UFRGS, Porto Alegre, Brasil
(3): Centro de Desenvolvimento Científico e Tecnológico (CDCT)—FEPPS, Porto Alegre, Brasil
(4): Serviço de Referência em Triagem Neonatal do Rio Grande do Sul, Porto Alegre, Brasil
(5): Serviço de Referência em Triagem Neonatal RS, Porto Alegre, Brasil

Introduction: Cystic fibrosis (CF) is a genetic disease, whose clinical manifestations result from dysfunction of the CFTR protein. Measurement of immunoreactive trypsin (IRT) is an

indirect indicator of the disease and has been used for screening tests in DBS. The newborn screening accuracy can be increased by combining the sweat test and genotyping in newborns that present elevated levels of IRT, in order to identify at least the most common mutation, F508del. **Methods:** A cross-sectional study of newborns who had abnormal results of IRT screened in the Newborn Screening Reference Service in RS in the period of June 2012 to May 2015. In the public health system of RS State the reference values for IRT are less than 70 ng/mL, and the sweat test and the analysis of F508del are the confirmatory tests for CF. **Results:** In three years 318,142 newborns were screened, of which 1,561 (0.5%) were referred for confirmatory tests with clinical or laboratory suspicion of CF. Of these, 31 newborns (1:10,263) were confirmed with a diagnosis of CF, including 2 cases that were negative for screening and diagnosed from clinical suspicion. Deaths occurred in 91 (5.8%) cases before the end of the investigations and 1,439 (92.2%) did not present CF or were considered inconclusive until the end of this study. The median age and interquartile range of newborns with CF at the time of collecting of the first and second samples was 6.0 (5-8.5) and 15.0 (13-21) days, respectively. The median value of IRT in the first sample was 156 (109.5-198) and 82.2 (74.2-97.3) ng/ml, and in the second sample was 148 (115-200) and 34.1 (22.6-49.4) ng/mL, among ill patients and newborns that did not have the disease (P<0,001). The average time for performing the sweat test was 34 $\pm$ 6 days in the suspected newborns. Of the 31 children diagnosed with CF, 19 (61.3%) were homozygous for the mutation F508del, 11 (35.5%) were heterozygous to F508del or other mutations (G542X, 711+1G>T, 3120+1G>A, N1303K) and 1 (3.2%) did not present any studied mutation. **Conclusion:** The implementation of the newborn screening test for CF contributes to the diagnosis in asymptomatic stages of the disease, allowing an early and appropriate therapeutic approach for the newborns in the RS State.

P078 - Statistical Analysis for the Preanalytical Stage Sampling for Newborn Screening in Costa Rica

Obando Rodriguez, S.(1); Jimenez Hernandez, M.(2); Saborio Rocafort, M.(2)

(1): Asoc. Costarricense Para El Tamizaje, San Jose, Costa Rica
(2): Hospital Nacional De Niños, San Jose, Costa Rica

Introduction: In Costa Rica, the National Newborn Screening Program was implemented 25 years ago and currently contributes to the detection of 29 diseases through the implementation of six different analyses. In 2014, the national coverage reached 98.3% . Until June 2015, it had the active participation of 840 specimen collection centers nationwide (centers of public and private health, comprising a participation rate of 92.5% and 7.5% respectively). This work aims to show the results obtained by focusing on the pre analytical step, corresponding to the process of sampling during the period from May 2012 to May 2015, from the children population of Costa Rica that underwent the newborn screening program. **Material and Methods:** The statistical study included a population of 232,510 samples, which were received in the period between May 2012 to May 2015. Based on laboratory data and using the informatic system STARLIMS v10.1, the following indicators were determined: age at the collection, transit time of the samples, age of babies at the time of the sample in the laboratory. The following statistical calculations were applied: average and percentiles 25-50-75-95-99.5 and the percentage of unsatisfactory samples was calculated, which were classified according to two general parameters: quality and quantity. The first refers to features related to the total rejection of the sample, the second describes those samples that are suitable for one or more tests, but its amount does not fulfill the necessary conditions to determine all analyses. **Results:** On average, 95% of the samples received at the laboratory were taken before the seventh day of life, before they were transported and processed. Unsatisfactory samples represent 2.4% of total samples received, among them, 94.2% were suitable from one to five tests, thus 5.8% was totally rejected for not meeting quality requirements. **Conclusion:** The frequent monitoring of quality indicators in a newborn screening program is very important as it allows to timely implement preventive and corrective actions that promote continuous improvement in the daily work flow.

P079 - Prevalence of Hemoglobin Patterns in Newborns Screened in the Public Health System in Rio Grande Do Sul State, Southern Brazil, From 2004 to 2014

Castro, S.(1); Grandi, T.(2); Diedrich, V.(3); Filippon, L.(3); Weber, C.(3); Macedo, J.(3)

(1): Serviço Referência Triagem Neonatal RS/Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil
(2): Centro de Desenvolvimento Científico e Tecnológico (CDCT)—Fundação Estadual de Produção e Pesquisa, Porto Alegre, Brasil
(3): Serviço Referência Triagem Neonatal RS, Porto Alegre, Brasil

Introduction: Hemoglobinopathies are genetic disorders resulting from mutations in the genes responsible for globin synthesis and show significant morbidity worldwide. In Brazil, the Ministry of Health mandates the diagnosis of newborn metabolic abnormalities, including screening for hemoglobinopathies in the National Newborn Screening Program (PNTN). **Objective:** To evaluate the prevalence of hemoglobin patterns in newborns screened in the public health system in Rio Grande do Sul state. **Materials and Methods:** Blood samples from newborns collected by heel prick on filter paper Whatman 903 were collected from January 2004 to December 2014. The methodologies used to screen the samples were High Performance Liquid Chromatography (HPLC) and/or isoelectric focusing (IEF). **Results:** A total of 1,161,066 neonates were analyzed. Of these, 17,562 (1.51%) presented an abnormal hemoglobin pattern: 160 cases of sickle cell syndromes (95 Hb FS, 44 Hb FSA, 19 Hb FSC, 01 Hb FSD and 01 Hb FS/E-Saskatoon) and other hemoglobins variants (18 FAH, 05

Hb FCA, 02 Hb FC, 01 Hb FVA, 01 Hb FCD). Among those who were heterozygous, 14,224 Hb FAS, 2,259 Hb FAC, 456 Hb FAD and 435 carriers of hemoglobin rare variants were detected. For the study of rare variants, 42 DNA samples were obtained for sequencing and were characterized 23 alpha chain variants (3 Hb Woodville, 1 Hb Chad, 2 Hb Hasharon, 3 Hb G-Phil, 4 Hb G-Pest and 10 Hb Stanleyville) and 19 beta chain (11 Hb E-Sakatoon, 1 Hb Osu-Christiansborg, 1 Hb Richmond, 1 Hb O-Arab, 1 Hb J-Guantanamo, 1 Hb Shelby, 1 Hb Beckman, and 2 Hb Hope). **Conclusion:** Newborn screening allows early diagnosis of sickle cell syndromes and the inclusion of the carriers in prevention and treatment programs, reducing the morbidity and mortality in childhood. The variability of hemoglobin patterns identified in this sample reflects the heterogeneity of the southern population of Brazil. These data provide indicators that can be used in public health policies for improving the life quality of this population.

P080 - Anthropometric State Evaluation of Children Diagnosed With Maple Syrup Urine Disease (MSUD) Attended in a Reference Service in Newborn Screening in Salvador, Bahia, Brazil

Santos Calmon, L.(1); Da Anunciação Do Espírito Santo, D.(1); Efigenia De Queiroz Leite, M.(1); Cristian Amaral Boa Sorte, N.(2); Kraychete Costa, B.(2); Amorim, T.(2)

(1): APAE/UFBA, Salvador, BRASIL
(2): APAE/UNEB, Salvador, BRASIL

Introduction: MSUD is an inherited metabolic disorder associated to leucine, valine and isoleucine accumulation. Treatment consists in reducing serum concentrations of those amino acids, enabling affected children normal development and growth. **Objective:** Evaluate anthropometric status of MSUD patients treated with protein-restricted diet in Bahia. **Method:** Retrospective study with MSUD patients until July 2015. Data obtained from medical records review. Anthropometric status assessment used the indicators: height/age (H/A), weigh/age (W/A) and weight / height (W/A), to <05 years and for > 5 years the BMI / age (BMI/A) and height / age (H/A) with z-score value as the cutoff point according to WHO classification, 2006.Data was analyzed using EpiData software (v3.1). **Results:** Among nine patients studied, 55.6% (05) were girls with a mean age of 39 months (SD ± 34.78), ranging from 4 to 120 months. Six had MSUD classic form, two intermediate and one, non-determinate. Diagnostic age average was 23.38 days (SD ± 10.45) with symptoms onset mean age of 07 days (SD ± 4.04). One patient had severe short stature (H/A = -4.36) since admission and three had low height for age and all had adequacy W/H. At the end of the first year was observed worsening of the H/A with 71.42% (5/7) of severe short stature and 14.28% (1/7) of short stature, deficit W/H in two patients and one case of overweight. At the end of the second year there was improvement in growth, with only 50% (3/6) of short stature and adequacy of W/H for all the patients. At three years 01/04 child remained severe short stature and 02/04 short stature and all kept adequacy W/H. One child had obesity at 07 years of life keeping short stature. **Conclusion:** The disease has an important impact on linear growth already observed at the end of the first year of life. After this age, there is a growth recovery and maintenance of appropriateness of weight for height. This situation can be strongly associated with adequate nutritional therapy and multidisciplinary monitoring.

P081 - Clinical and Laboratory Characterization of Patients With Maple Syrup Urine Disease Followed in a Reference Service for Newborn Screening in Salvador, Bahia, Brazil

Santos Calmon, L.(1); Da Anunciação Do Espírito Santo, D.(2); Efigenia De Queiroz Leite, M.(2); Cristian Amaral Boa Sorte, N.(3); Kraychete Costa, B.(3); Amorim, T.(3)

(1): APAE-SALVADOR, Salvador, BRASIL
(2): APAE/UFBA, Salvador, BRASIL
(3): APAE/UNEB, Salvador, BRASIL

Introduction: Maple Syrup Urine Disease (MSUD) is an inherited metabolic disorder of leucine, valine and isoleucine, whose accumulation leads to toxicity to central nervous system. Most frequent symptoms in the classic form are poor appetite, lethargy, neurological disorders, characteristic odor, seizures, hypothermia and coma. The Newborn Screening allows early diagnosis and treatment essentials to improve the clinical profiles. **Objective:** To characterize aspects of the diagnosis, treatment, and laboratory tests of MSUD patients attended at the Reference Service of Newborn Screening in Bahia-Brazil. **Method:** Retrospective study that evaluated patients diagnosed with MSUD until July 2015. Data obtained from medical records. Metabolic control tests were performed using the NeoLISA®MSUD kit and High Performance Liquid Chromatography (HPLC) and/or Tandem Mass Spectrometry (MS/MS). Data were analyzed using EpiData software (v3.1). **Results:** From nine patients studied, 55.6% (05) were female with average age of 39 months (SD ± 34.78), ranging from 4 to 120 months. Six had classical form of the disease, two intermediate form and in one the form was not determined. The average age of diagnosis was 23.38 days (± 10.45) with mean age of symptoms onset 07 days (± 4.04). Only 02 patients were diagnosed before developing clinical symptoms. The main symptoms at the first visit were poor suction (77.78%), seizures (66.67%), hypertonicity (55.56%) and skin lesions (55.56%). Seven patients were diagnosed by the combined dosage Leucine-Isoleucine with average of 1056.0 micromol/L (SD± 374.7) and median of 1083.0 micromol/L (755,0-1449.9), ranging from 427, 0 to 1479.8 micromol/L (VR 57.1 to 287 micromol/L). After completing six months of life was noted improvement in metabolic control in all patients.

Conclusion: Appropriate classification of clinical picture of disease and laboratory monitoring are important tools for clinical practice and dietary prescription for MSUD patients, allowing better matching of conducts to each patient tolerance.

P082 - Description of Nutritional Deficiencies in Children With Maple Syrup Disease (MSUD) in Dietary Treatment Attended in Reference Service of Newborn Screening in Salvador, Bahia, Brazil

Santos Calmon, L.(1); Da Anunciação Do Espírito Santo, D.(1); Efigenia De Queiroz Leite, M.(1); Cristian Amaral Boa Sorte, N.(2); Kraychete Costa, B.(2); Amorim, T.(2)

(1): APAE/UFBA, Salvador, BRASIL
(2): APAE/UNEB, Salvador, BRASIL

Introduction: MSUD is an inborn error of metabolism caused by deficiency of dehydrogenase enzyme complex activity that leads to leucine, valine and isoleucine tissue accumulation. Treatment consists of protein restriction and supplementation with metabolic formula valine, leucine and isoleucine free. It may lead to essentials vitamins and minerals deficient supply. **Objective:** To describe nutritional deficiencies or disorders in MSUD patients accompanied in reference service in Bahia-Brazil. **Methods:** Retrospective study analyzed MSUD patients until July 2015. Recommended criteria by WHO (WHO, 2011) was used to identify anemia, considering hemoglobin(Hb) <11.0g/dL in children up to 59 months of life, and Hb <11,5g/dL for children between 5 and 11 years. For vitamin and minerals dosage was considered laboratory cutoffs. Serum lipids assessment considered the reference values recommended by the I Directive of Atherosclerosis Prevention in Childhood and Adolescence (2005). Data were obtained from medical reports and analyzed using EpiData software (v3.1). **Results:** From nine patients, 55.6% (05) were female with an average age of 39 months (SD ± 34.78), ranging from 4-120 months. Six had classic form of MSUD, two intermediate and one non-determinate. Average diagnostic age was 23.38 days (SD ± 10.45) with average age of symptoms onset of 07 days (SD ± 4.04). Average hemoglobin was 11.6 (SD ± 1.2) g/dL ranging from 9,4-13,6g/dL, with three anemic patients, and one with hypochromic/microcytic anemia and normal ferritin. Four patients had creatinine low concentration with average of 0.38mg/dL (SD ± 0.05) and 50% (4/8) patients showed alkaline phosphatase elevation with average of 621U/L (SD ± 186.15) ranging from 300- 942U/L (VR to 645). None had hypoalbuminemia, folate, cyanocobalamin or vitamin D deficiency, abnormal levels of sodium or potassium. All evaluated patients had HDL low levels (VR>45mg/dLl). High values of triglycerides were found in 16.7%, and 50.0% had borderline values. **Conclusion:** Adequate dietary management prevents nutritional deficiencies. Although patients follow animal fat low diet and vegetable fat rich diet, it was noted changes in lipid profile, especially in relation to HDL levels.

P083 - Cystic Fibrosis Birth Prevalence Diagnosed by Expanded Neonatal Screening in Yucatan, Mexico

Campos García, F.(1); Contreras Capetillo, S.(2); Loría Fernández, J.(1); Martínez Cruz, P.(3); Maldonado Solís, F.(1); Salazar Escalante, R.(1); Ibarra González, I.(4); Vela Amieva, M.(4)

(1): Tamiz Ampliado de Yucatán, Mérida, México
(2): Hospital General "Dr. Agustín OHorán", Mérida, México
(3): Tamizaje Plus, Villahermosa, México
(4): Instituto Nacional de Pediatría, D.F., México

Introduction: Yucatan is a peninsula located in south of Mexico and its population has a high degree of Mayan ancestry with low European admixture. An expanded newborn screening program that includes cystic fibrosis (CF) detection has been routinely performed in Yucatan since 2008. Although CF is a worldwide disease, traditionally it has been considered more prevalent in European descendants, but its prevalence in populations with indigenous Mayan ancestry is unknown. **Methods:** Immunoreactive trypsinogen (IRT) was determined through fluorometric immunoassay in dried blood spot samples collected from 100 public health centers distributed in the state of Yucatan, Mexico, from May 2008 to July 2015. All newborns with a suspicious result (cut-off IRT: >90 ng/mL) were retested. Sweat chloride tests were performed in those subjects with persistent IRT elevation (cut-off >60 mmol/L), along with a genetic mutation panel searching for the 32 most frequent CF mutations recommended by the ACMG. **Results:** The IRT determination performed on 71,888 newborns showed 132 suspected CF samples (0.18%); all suspected subjects were contacted and 131 of them accepted diagnostic protocol and follow up. Seven patients met the FQ diagnostic criteria and were confirmed after medical evaluation by an experienced pediatrician; 6/7 patients had *CFTR* molecular study, with p.[Phe508del] being the most frequent mutation (33.3%), followed by p.[Gly542Ter] (16.6%); in 50% of alleles, the pathogenic variation could not be identified in the recommended ACMG genetic mutation panel. **Conclusions:** The prevalence of CF in Yucatan, Mexico is 1:10,270 newborns, slightly higher than the reported for Hispanic Americans in the United States (1:13,500). CF is a worldwide disease that is also present in populations with Amerindian admixture. It is important for appropriate CF mutational analysis, to consider panels that includes the pathogenic *CFTR* variants described in the Mexican population by other authors, or using whole exome sequencing studies to identify all the mutations, including the new ones.

P084 - External Quality Assessment for the Detection of Phenylketonuria: Results of the Buenos Aires Programme

Vilche Juarez, A.(1); Farquharson, V.(1); Del Vecchio, L.(1); Torres, M.(1)

(1): CEMIC. Centro de Educación Médica e Investigaciones Clínicas " Norberto Quirno", Ciudad Autonoma de Buenos Aires, Argentina

Introduction: In Argentina, national law N° 26,279 –concerning newborn screening tests– governs the detection and treatment of galactosemia, congenital hypothyroidism, phenylketonuria, cystic fibrosis, congenital adrenal hyperplasia, biotinidase deficiency, retinopathy of prematurity and congenital Chagas disease and syphilis. The Buenos Aires Programme for External Quality Assessment has established, since 1999, an annual plan to determine galactose, TSH, phenylalanine, IRT, 17OH progesterone and biotinidase in blood samples on filter paper. **Aims:** The aim of this work was to prove the homogeneity and stability of the samples prepared on filter paper for the external assessment of newborn screening tests and to evaluate the performance of the participants who carry out the phenylketonuria detection. **Materials and methods:** Samples were prepared by enriching analyte-free blood to obtain the different concentrations. The samples used were prepared at different times of the year, to compare stability and batch homogeneity. The samples and the processing instructions were distributed to 50 laboratories, from September 2013 to August 2014. The results were first analyzed in aggregate and then sorted according to the reagent used. **Results:** For a positive sample distributed in previous periods, there was a general concordance >80% in the interpretation of the results ("positive" screening). The ANOVA of the results from the 3 periods showed no significant differences ($p>0.6$); nor were there significant differences when sorted by reagent. For a negative sample, the interpretation had a general concordance >80% ("negative" screening). For a 3.8 mg/dl sample (borderline, at the moment of preparation), there was a concordance <80% due to the different cut values used in the different laboratories. **Conclusion:** The results retrieved for the "clearly positive" and "clearly negative" samples showed a concordance of >80%. They had both been used in previous rounds and had proved the eligibility and homogeneity of the preparation. The <80% concordance for the sample with the closest value to the cut level, revealed the different performance of the available reagents and the use of different cutoff values. The interpretation of the results allowed each participant laboratory to compare their performance to that of others and assess the quality of their service in the screening for phenylketonuria.

P085 - Glucose-6-Phosphate Dehydrogenase Deficiency: Three Years Experience in Neonatal Screening Program and its Incidence in Federal District, Brazil

Reis, B.(1); Viegas, M.(2); Toledo, L.(1); Teixeira, R.(1); Vasconcelos, G.(1); Adjuto, G.(1); Cardoso, M.(1); Thomas, J.(1)

(1): Hospital de Apoio de Brasília
(2): Hospital de Apoio de Brasília, Brasília-Distrito Federal, Brasil

Introduction: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common error of metabolism in humans, which can cause hemolytic anemia. An estimated 400 million people worldwide are affected, being most frequently in persons of Africa descent (up to 20%). However, it is common also around the Mediterranean (4% - 30%), and Southeast Asia (0.1%). G6PD deficiency is polymorphic, with more than 400 variants. The prevalence of G6PD deficiency is still unclear in most parts of Brazil, as the diagnostic testing is not mandatory by the Newborn Screening National Program (PNTN). On the other hand, in compliance with the Regional Law 4190/2008, a broadened newborn screening protocol was instituted in the public network of the Federal District (DF), which has enabled the detection and quantification of G6PD deficiency since 2012. Previous studies to 2012 revealed a low frequency of 0.8% of this disorder in DF with high false-positive rate. Herein, we provide the prevalence of G6PD deficiency in our population, as also attempt to assess the diagnostic accuracy during 3 years of PNTN experience in DF. **Materials and methods:** The analyses to determine the enzymatic activity of G6PD were performed using the ND 1000 Neonatal G6PD kit according to the protocol specified by the manufacturer and analyzed by fluorescence reader *Victor* 2 1420 multilabel counter, both from Perkin Elmer. **Results:** During the period between January 2012 and December 2014, 3774 newborn screened by the program in DF were positive for G6PD, as confirmed by a second sample. Our results have revealed a prevalence of 3% in this population when compared to the number of live births in the same public network. Our findings were corroborated by a recent molecular study of 84 children screened by the PNTN in DF, which were positive for G6PD. They were analyzed in January and February 2014. All children presented mutations in the gene *Gd;* 98.8% had the mutation G202A and only one individual had the C563T mutation. **Conclusion:** These data have confirmed the accuracy of the diagnostic test by the Newborn Screening Program of DF and hence, revealed for the first time, the true frequency of the disease in our population.

P086 - Maternal Phenylketonuria: A Preventable Cause of Microcephaly

Fernandes Lorea, C.(1); De Oliveira Poswar, F.(1); Konzen, D.(1); Lopes Carneiro, K.(1); Tonon, T.(1); Refosco, L.(1); Fischinger De Souza, C.(1); Vairo, F.(1); Schwartz, I.(1)

(1): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil

Phenylketonuria (PKU) is an autosomal recessive disorder of the amino acid metabolism. It results from a deficiency of phenylalanine hydroxylase, leading to increased serum levels of phenylalanine. According to the Brazilian Ministry of Health, the prevalence of PKU was 1:23,000 live births. Phenylalanine (Phe) is a well-known teratogen; it affects mainly fetal brain and heart development. Methods: Chart review. Results: We report three cases of affected mothers and their offspring outcomes. Patient 1 presented for first consultation after her two children were born. She had no previous diagnosis, but her

sister was diagnosed with PKU and did not follow the treatment. Both children were microcephalic, small for gestational age (SGA), had intellectual deficiency and normal echocardiograms. Patient 2 had neonatal diagnosis of phenylketonuria and abandoned follow-up. At age 25, she returned pregnant (9+4 weeks) for evaluation, blood Phe was 1185 mmol/L. She had difficulties following recommended diet and was admitted into the hospital twice during pregnancy for control. The baby was male, born at 38 weeks, appropriate for gestational age, occipitofrontal diameter (OFC) at third percentile, no congenital heart defects, normal development. Patient 3 had a late diagnosis of phenylketonuria, mild intellectual deficiency, irregular treatment since diagnosis. The pregnancy was unplanned and she sought treatment at 27+2 weeks, with phenylalanine of 877 mmol/L. Due to previous history of non-adherence to treatment, she was hospitalized until full term. The baby was male, 38 weeks, OFC at third percentile, SGA and normal heart morphology. All three women had unplanned pregnancies, with inadequate control of phenylalanine levels. All four children were microcephalic, three were also SGA and none had heart defects. Conclusions: Due to the large number of unplanned pregnancies in our country patients should be followed at experienced centers during adolescence and through reproductive age. Appropriate counselling should be provided to all patients before reproductive age. We suggest that patients who maintain regular consultations until adulthood are more prone to adhere to treatment before conception during pregnancy, thus ensuring better offspring outcome. The management should be done by a multidisciplinary team at an experienced center.

P087 - Determination of Genotypic and Clinical Characteristics of Colombian Patients With Morquio A Syndrome

Tapiero, S.(1); Acosta, J.(2); Porras, L.(3); Garcia, N.(4); Solano, M.(5); Velasco, H.(1)

(1): Maestría en Genética Humana, Universidad Nacional de Colombia, Bogota, Colombia
(2): Instituto de Investigación en Nutrición, Genética y Metabolismo de la Universidad el Bosque, Bogota, Colombia
(3): Caja de compensación familiar Risaralda, Risaralda, Colombia
(4): Universidad de Caldas, Caldas, Colombia (5): Fundación Cardio infantil, Bogota, Colombia

Introduction: Mucopolysaccharidosis (MPS) type IVA (OMIM # 253000) is an autosomal recessive disease, caused by mutations in the GANLS gene, generating deficiencies in the N- acetylgalactosamine-6-sulfate-sulfatase enzyme, responsible for the degradation of GAGs keratan sulfate and chondroitin 6 sulfate, which accumulate mainly in bone, cartilage, heart and lungs. Since MPS IVA has a high incidence in Colombia (0.68: 100,000), the phenotypic and genotypic description of a population sample was performed. **Materials and methods:** We included 23 patients with Morquio A syndrome; diagnosis was made using clinical criteria and enzymatic activity in patient leukocytes; genotyping was carried out by amplification of the 14 exons of GALNS gene (NC_000016.10) and sanger sequencing, including exon and intron junctions. **Results:** 23 individuals corresponding to 9 men (39.1%) and 14 women (60.8%) were analyzed. The mean age at entry was 14.65 years with an (IC +/- 11 years), the age at diagnosis had an average of 5.78 years (CI +/- 5.7 years) and the mean age at onset of symptoms was 2.31 years (CI +/- 1.56). 4.35% of the population showed an attenuated phenotype while the remaining 95% had a severe phenotype. We found 9 different mutations in this analysis: the p.G301C was the most frequent mutation with 54.3%, p.R386C with 13% and p.S162F with 10.9%. A single nonsense mutation was found in heterozygous state, p.W325X; in this paper we describe a new mutation, in heterozygous state, p. A107S, with bioinformatics analysis by Polyphen 2 and SIFT and reporting pathogenicity. **Discussion and Conclusions:** From the clinical perspective, our patients show similar data in relation with MPS IVA Global Registry. On terms of the genotype phenotype correlation, we believe there is a difficulty to accurately establish the severity / attenuation description, besides it is complex to interpret the interaction of the severity alleles with compounds genotypes for several mutations. Also, significant degree of consanguinity among the study population was found. Genotypic analysis was consequent to the data of mutational characteristics previously described in the literature; current genotypic data showed greater allelic heterogeneity to what was previously reported by Kato et al.

P088 - β-Glucosidase Gene Mutations in Patients With Gaucher Disease in Western Venezuela

Méndez, K.(1); Borjas, L.(1); Pardo, T.(1); Sánchez, Y.(1); Zabala, W.(1); Miranda, L.(1); Gómez, G.(2)

(1): Instituto De Investigaciones Genéticas De La Facultad De Medicina L.U.Z., Maracaibo, Venezuela
(2): Instituto Venezolano De Investigaciones Cientificas, Los Teques, Venezuela

Introduction: Gaucher disease (GD) is the most common lysosomal storage disorders, mainly caused by a defect in the beta-glucosidase enzyme which deficiency determines the accumulation of glucosylceramide in the body causing a heterogeneous, chronic and multisystemic disorder. The GD is caused by mutations in the *GBA* gene (beta glucosidase acid). **Aim:** This research aimed to characterize and determine the prevalence of these mutations in patients with Gaucher disease in western Venezuela, **Materials and Methods:** to do molecular studies 24 unrelated patients were analyzed by combining the techniques of Polymerase Chain Reaction (PCR), Restriction Fragment Length polymorphisms (RFLP) and Sequencing. **Results:** Variants identified in this study were N370S (50%), IVS2 + 1G> A (14.6%), RecNciI (10.4%), L444P (6.25%), 84insG (2.1%) and genotypes mostly found were compound heterozygotes N370S/IVS2+1G> A (29.3%) and N370S /

RecNciI (20.8%). 10.4% of the alleles studied could not be identified; however, a mutation detection rate of 89.6% was achieved. **Conclusions:** The results of this study showed the same trend reported in Caucasian populations (non-Jewish) and Latin America with the difference that in our population a high frequency of IVS2 + G> A mutation was found. Through targeted screening for the detection of mutations N370S, IVS2+1G>A, L444P, RecNciI and 84insG in the *GBA* gene can determine most of the alleles and genotypes present in patients with Gaucher disease in the west of our country.

P089 - Newborn Screening for Congenital Adrenal Hyperplasia (CAH): Improving the Effectiveness of the Neonatal 17OH-Progesterone (N17OHP) and Serum Confirmatory Tests

Hayashi, G.(1); Carvalho, D.(2); Miranda, M.(2); Gomes, L.(2); Madureira, G.(2); Mendonça, B.(2); Bachega, T.(2)

(1): APAE DE SÃO PAULO e Hospital das Clinicas—FMUSP, São Paulo, Brasil
(2): Hospital das Clinicas—FMUSP, São Paulo, Brasil

Introduction: CAH newborn screening (NBS) programs, using N17OHP, present high capacity to detect the salt-wasting (SW) form of CAH. However, the main concerns are high false-positive rate (FPR), low positive predictive value (PPV) of N17OHP levels and the heterogeneity of confirmatory methods. Considering the CAH-NBS implementation in our country, our **objective** is to optimize the best cut-off levels for the first screening and for the confirmatory tests. **Materials and methods:** data from 473,983 newborns were retrospectively evaluated. N17OHP was measured by IFMA assay (*AutoDelfia-PerkinElmer*) and cut-offs (99th percentile) adjusted according to birth-weight (BW1: ≤1500g; BW2:1501-2000g; BW3:2001-2500g; BW4: >2500g), and to age at sample collection (before or after 72h of life). Confirmatory tests consisted in serum 17OHP analysis by RIA and/or mass spectrometry (MS). Entire *CYP21A2* sequencing was performed for newborns with persistently increased serum 17OHP levels. **Results:** the recall rate was 0.05% (n=221) using the P99th of N17OHP levels, and decreased to 0.03% (n=149) using the P99.8th; additionally, PPV increased from 11.4% (P99th) to 16.7% (P99.8th). N17OHP cut-offs in samples collected before 72h were significantly lower than those collected after, which is relevant to our state since most samples are collected earlier. Twenty-six newborns were diagnosed with classical forms (22 SW, 12 males), and confirmed by molecular analysis. N17OHP levels ranged from 53-494 ng/mL (serum equivalence) in SW and from 36.5-52.8 ng/mL in simple virilizing (SV) newborns. Serum confirmatory tests were performed in 149 newborns. In affected newborns, serum 17OHP levels (MS) ranged from 56-668 ng/mL in SW and from 54-117 ng/mL in SV form. FPR persisted in the confirmatory tests in 70% using RIA and in only 13% by MS. Among these cases, molecular analysis identified 2 nonclassical newborns. PPV of MS methodology was significantly higher than RIA (52 *vs.* 27%). **Conclusions:** N17OHP levels adjusted to P99.8th and to sample collection time improve the CAH-NBS by reducing the FPR rate without missing the classical form diagnosis. Although serum 17OHP measurement by RIA is widely used in our country, the MS significantly reduced the FPR in the confirmatory tests. Molecular analysis could be restricted for asymptomatic cases with persistently increased serum 17OHP levels.

P090 - Distribution of 17OH-Progesterone Values by Birth Weight, Gestational Age and Sex in a Population of Mexican Newborns

Herrera Pérez, L.(1); Moreno Graciano, C.(1); Martínez Cruz, P.(1); Arias Vidal, C.(1); Maldonado Solís, F.(1); Maldonado Solís, M.(1); Vela Amieva, M.(2); Ibarra González, I.(3); Chablé Cupil, G.(4)

(1): Tamizaje Plus S.A de C.V, Villahermosa, Tabasco, México
(2): Laboratorio de Errores Innatos del Metabolismo y Tamiz, Instituto Nacional de Pediatría, México, D.F., México
(3): Instituto de Investigaciones Médicas. UNAM, México, D.F., México
(4): Hospital del Niño Rodolfo Nieto Padrón, Villahermosa, Tabasco, México

Introduction: Congenital adrenal hyperplasia (CAH) is characterized by impaired biosynthesis of cortisol and aldosterone, resulting in an increased secretion of 17-hydroxyprogesterone (17OHPg). This last metabolite has been used in newborn screening as a biomarker for this disease. Important variations in 17-OHPg in relation to gestational age and birth weight have been reported. **Objective:** The aim of this study was to determine the effect of birth weight and gestational age on 17OHPg values in a population of Mexican newborns, screened in the first week of life. **Methods:** Analysis of 17OHPg levels stored in the database of the screening laboratory, comprising the period from 2011 to 2014. 17-OHPg was determined by a commercial DELFIA immunoassay in dried blood spot samples on Guthrie cards; only samples taken during the first week of life (0-7 days) were considered for the study. 17OHPg was analyzed in relation to birth weight in the following categories: <1,000 g; 1,000-1,499 g; 1,500-1,999; 2,000-2,499; 2,500-4,999 and >5,000 g; sex and gestational age: preterm (<37 weeks) and full-term (>37 weeks). **Results:** We evaluated data from 41,073 newborns samples, including 21,770 (53%) girls and 19,303 (47%) boys. There were 59 presumptive positive results found and a second sample was required for all of them. Six CAH patients were confirmed (1:6,846 NB) and 53 were false positives (0.14%). As expected, 17OHPg values were higher in newborns with lower birth weight, with a mean concentration of 56.74 ± 54.73 nmol/L in the <1,000g group and 3.7 4±2.3 nmol/L in the >5,000 g group. The mean value in preterm (9.6± 11.76nmol/L) and full-term (4.4±2.93nmol/L) newborns were significant different ($p<0.0001$). The mean value in girls and boys was 5.7±5.3 and

3.85 ± 2.55 respectively, and no significant difference was found. **Conclusions:** Gestational age and birth weight are important factors that must be considered in the proper interpretation of CAH newborn screening. The recall rate found in this study (0.14%) was similar to other previously reported.

P091 - Relation Between Positivity of 17 Hydroxyprogesterone Determination and Non Eutocic Childbirths

González Fernández, R.(1); Arteaga Yera, A.(2); Martínez Ramos, J.(1); Del Río Fabre, L.(1)

(1): Centro de Inmunoensayo, La Habana, Cuba
(2): Centro de Inmunoensayo, La Haban, Cuba

Introduction: The implementation of neonatal screening for Congenital Adrenal Hyperplasia (CAH) is justified. Sometimes false positive results generate economic expenses and anxiety in the families which bring about a debate on its pertinence. The cut-off values have been adjusted to the low birth weight and the gestational age, as the principal factors of this problem. Other situations related to stress also could contribute. This work has the objective to show the existence of a relation between a high positivity of 17-Hydroxyprogesterone determination and non eutocic childbirths. **Materials and Methods:** A descriptive retrospective study of the low-weight births in each province and the special municipality in 2014 (n= 122 649), as well as the different kinds of childbirth, was carried out. Probability and related risk were determined to demonstrate the positive association. **Results:** A 0,3125 conditional probability was obtained, uneven to the 0,2460 marginal probability, proving the existence of some kind of association between the positivity of 17-Hydroxyprogesterone determination and the non eutocic childbirths, stressors on the fetus. The relative risk obtained was 1,9444, which indicates the existence of a positive association. The provinces with the highest partnership relationship were Mayabeque, Matanzas, Sancti Spiritus. **Conclusions:** This study showed the existence of a relation between a high positivity of 17-Hydroxyprogesterone determination and non eutocic childbirth. It is necessary to carry out other studies that further evidence this relation and to propose cut-off levels which take it into account.

P092 - Congenital CLN8 Neuronal Ceroid Lipofuscinosis Disease: A New Phenotype

Pesaola, F.(1); Cismondi, I.(2); Pons, P.(3); Guelbert, N.(4); Becerra, A.(4); Xin, W.(5); Kohan, R.(4); Rautenberg, G.(6); Oller-ramirez, A.(6); Noher De Halac, I.(1)

(1): CEMECO-Hospital de Niños y CONICET, Córdoba, Argentina
(2): CEMECO-Hospital de Niños y Facultad de Odontología, Universidad Nacional de Córdoba, Córdoba, Argentina
(3): Centro de Microscopìa Electrónica, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina
(4): CEMECO-Hospital de Niños, Córdoba, Argentina
(5): Massachusetts General Hospital, Neurology Department, Center for Genetic Research, Boston, MA02334, Estados Unidos
(6): CEMECO-Hospital de Niños, Cordoba, Argentina

Introduction: Neuronal Ceroid Lipofuscinoses are inherited neurodegenerative disorders that may affect individuals of any age, characterized by storage of fluorescent lipofuscin-like pigments in the Central Nervous System, followed by degeneration and death of neurons. Mutations in 14 genes underlie the diseases. Epilepsy Progressive with Mental Retardation (EPMR) prevalent in Scandinavia, and a variant Late Infantile phenotype (vLI) in Italy showed mutations in the CLN8 gene. Congenital phenotypes showed mutations in the CLN10 gene. No congenital CLN8 disease was described before. **Aim:** To assess clinical and morphological features, and the underlying mutations in a girl with variant congenital phenotype. **Methods:** Clinical assessment, electron microscopy, exclusion of PPT1 and TPP1 deficiencies, PCR and Sanger sequencing for DNA-screening; bioinformatics for mutation validation. **Results:** *Clinical assessment:* psychomotor retardation since birth, seizures (3y), myoclonus (6y), cerebellar atrophy (6y); early death (12y), visual failure, not controlled. *Enzyme assays:* PPT1 and TPP1 in the reference interval. *Electron microscopy:* fingerprint and curvilinear profiles in the skin. *Genotype:* Compound heterozygous in the CLN8 gene of E2 c.1A>G, p.Met1Val and E3 c.792C>G, p.Asn264Lys. **Discussion:** The E2 c.1A>G, p.Met1Val mutation was also found in an US individual combined with E2 c.80T>C, p.Leu27Pro (unpublished data of WX) with no data on the phenotype. The Argentinean girl was demented since birth, but seizures began at the age of 3y leading firstly to the suspicion of a vLI NCL disease. In the future, congenital NCL phenotypes with mental and motor retardation since birth should be considered for CLN8 screening.

P093 - Standardization of TPP1 Assays for Testing Neuronal Ceroid Lipofuscinosis LCN2 Disease

Pesaola, F.(1); Gelbert, N.(2); Cismondi, I.(3); Becerra, A.(2); Pons, P.(4); Rautenberg, G.(5); Oller-ramìrez, A.(2); Kohan, R.(5); Noher De Halac, I.(6)

(1): CEMECO-Hospital de Niños y CONICET, Córdoba, Argentina
(2): CEMECO-Hospital de Niños, Córdoba, Argentina
(3): CEMECO-Hospital de Niños y Facultad de Odontología, Universidad Nacional de Córdoba, Córdoba, Argentina
(4): Centro de Micrsocopía Electrónica, Facultad de Ciencias Mèdicas, Universidad Nacional de Córdoba, Córdoba, Argentina
(5): CEMECO-Hospital de Niños, Cordoba, Argentina
(6): CEMECO-Hospital de Niños-CONICET, Córdoba, Argentina

Introduction: Neuronal Ceroid Lipofuscinoses are the most frequent neurodegenerative pathologies in childhood. Among the 14 known genotypes, LCN2 Disease withTPP1 deficiency is prevalent in Argentina with clinical phenotypes late infantile,

juvenile and adult. LCN2 Disease is confirmed by enzymatic, and/or genetic testing. Regarding the emergence of potential enzyme replacement therapies, it is needed to standardize the enzyme activity measurement methodology and set up reference intervals (RI) from healthy control individuals. **Aim:** To standardize TPP1 testing and compare the sensibility of assays in dried blood spots (DBS), saliva and leukocyte pellet. **Methods:** 1) TPP1 activity testing in DBS, saliva and leukocytes of 32 LCN2 Disease affected subjects, their parents (if available), and control individuals (leukocytes: n=100; saliva: n=117; DBS: n=243). 2) Box plot evaluation. **Results:** mean values of TPP1: leukocytes, 4.39 ± 6.03 nmol/h/mg protein (RI: 159.98 ± 64.5); saliva 8.27 ± 9.27 nmol/24 h/mg protein (RI: 215.86 ± 97.5); DBS, 0.08 ± 0.07 nmol/spot (RI: 0.27 ± 0.17). Heterozygous parents showed a tendency to lower results than controls in all kind of samples. **Conclusions:** 1) TPP1 activity testing in leukocytes and saliva showed no false negative results differentiating affected individuals from controls and parents. 2) The DBS assay rendered 32% false negative data making the results not conclusive. 3) Leukocytes and/or saliva need to be tested to confirm DBS results. 4) The TPP1 activity tests allowed no clear discrimination between heterozygotes and control individuals in no one of the assays. 5) International standards are still not available; meanwhile each laboratory may standardize the own RIs for diagnostic purpose testing at least 100 controls samples.

P094 - Identification of Recombinant Alleles in GBA1 Gene in Patients With Neuronopathic and Non-Neuronopathic Gaucher Disease

Basgalupp, S.(1); Siebert, M.(2); Vairo, F.(3); Schwartz, I.(3)

(1): Programa de Pós-Graduação em Medicina: Ciências Médicas, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
(2): Centro de Pesquisa Experimental, Hospital de Cínicas de Porto Alegre, Porto Alegre, Brazil
(3): Serviço de Genética Médica, Hospital de Cínicas de Porto Alegre, Porto Alegre, Brazil

Introduction: Gaucher disease (GD), an autosomal recessive genetic disorder, is caused by deficient activity of the glucocerebrosidase enzyme due to pathogenic mutations in the *GBA1* gene. This gene comprises 11 exons and has a pseudogene (*GBAP*) with 96% of sequence homology. Recombination (Rec) events in the *GBA1* seem to be facilitated by an increased degree of homology and proximity to the *GBAP*, leading to gene conversion, fusion or duplication. The L444P mutation is the second most common pathogenic variant in *GBA1*, and it may occur alone or *in cis* with other mutations. Many protocols of genetic analysis for GD patients include only the investigation of the most frequent mutations, which prevents the differentiation between L444P alleles and those resulting from recombination events. Among the most prevalent complex alleles is the Rec*Nci*I, which includes 3 distinct mutations located at exon 10 (L444P, A456P and V460V) of *GBA1*. The aim of this study was to identify the presence of recombinant alleles in *GBA1* in patients with DG known to be L444P carriers in at least one of their alleles. **Methods:** Twenty-two unrelated GD patients (type I = 17; type II = 3; type III = 2) followed by the GD Reference Center in Rio Grande do Sul, Brazil, were included in our sample group and had their exons 10 and 11 of *GBA1* sequenced. L444P mutation were previously identified in 26 out of 44 alleles (59%). **Results:** Recombinant alleles were present in 14 out of 26 (53.8%) L444P alleles, corresponding to an allele frequency of 31.8% (n=14/44). Twelve (85.7%) out of 14 Rec alleles were Rec*Nci*I. Among those Rec*Nci*I alleles, 7 also had the g.7668G>A variant and 6 out of 7 also had the g.7678T>C alteration, both located in the 3́UTR. The allele frequency of Rec variants was 64.7%, 100% and 0% in GD patients type I, II and III, respectively. **Conclusion:** The present study highlights the importance of sequencing the whole *GBA1* gene, considering that at least half of L444P alleles are complex ones. The identification of recombinant alleles may contribute to a better understanding of genotype-phenotype correlation in GD.

P095 - Diagnosis of Lysosomal Storage Diseases in Cuba: Period 2013-2015

Larrinaga Vicente, L.(1); Acosta Sánchez, T.(1); Menéndez Saínz, M.(2); Martínez Rey, L.(1); Contreras Roura, J.(1); González Reyes, E.(3); Torres, D.(1); De León Ojeda, N.(4); Morales Perralta, E.(1); Tamayo Chang, V.(5); Labaut, K.(6); Zaldívar, T.(2); García, A.(4)

(1): Centro Nacional de Genética Médica, La Habana, Cuba
(2): Instituto de Neurología y Neurocirugía, La Habana, Cuba
(3): Centro de Inmunoensayos, La Habana, Cuba
(4): Hospital William Soler, La Habana, Cuba
(5): Centro Provincial de Genética de Holguín, La Habana, Cuba
(6): Instituto de Hematología e Inmunología, La Habana, Cuba

Introduction: The lysosomal storage diseases (LSD) deposits occur by progressive complex incompletely degraded substrates by three factors: deficiency of lysosomal enzymes, enzyme cofactors or deficit by intra-lysosomal transport defects. This deficiency starts with different pathological processes that result in a multidamage with significant morbidity and mortality. In Cuba, the biochemical confirmation of these diseases takes a place exclusively in the National Center of Medical Genetics. The objective of this work is to characterize the diagnosis of LSD in Cuba during the period 2013-2015, taking into account clinical and biochemical features. **Material and Methods:** We included post-natal studies under clinical suspicion of LSD: 146 patients, 284 parents and 154 healthy controls. Each LSD is confirmed by an analysis of specific enzymatic activity (nmol/mgprotein/h) by spectrophotometric and spectrofluorimetric tests. It was considered as a deficit enzymatic individual when the enzymatic activity relative to healthy control was less than 30%. **Results:** The facial-skeletal, neurological anomalies and hepatosplenomegaly were the most common clinical signs. The 100% of the studies were referred by clinical

geneticists. Samples were received from all country, where 19 patients were confirmed. The Hurler syndrome (n = 6), Pompe disease (n = 3) were the most prevalent. The positive cases of Pompe were confirmed by Genzyme laboratory. **Conclusions:** The LSD in our country as in the rest of the world have low incidence, but our health care system does not absolve the possibility of their diagnosis, constituting a permanent search. From 146 patients studied, 19 were confirmed as LSD patients, representing 13%. MPS I and Pompe were the most common lysosomal diseases diagnosed. The provinces of Havana, Holguin, Santiago de Cuba and Guantanamo reported positive cases three years.

P096 - Differences in Oxidative Stress Parameters Between Mucopolysaccharidoses I and VI

Cé, J.(1); Mello, A.(2); Funchal, C.(3); Dani, C.(3); Coelho, J.(1)

(1): Departamento de Bioquímica do ICBS- UFRGS, Porto Alegre, Brasil
(2): Departamento de Bioquímica do ICBS- UFRGS; Centro Universitário Metodista-IPA, Porto Alegre, Brasil
(3): Centro Universitário Metodista-IPA, Porto Alegre, Brasil

Patients with MUCOPOLYSACCHARIDOSES (MPS) are characterized by biomolecular and tissue damage that results in the accumulation of glycosaminoglycans (GAGs) not degraded in the cells of various organs and systems. High levels of reactive oxygen species (ROS) have been associated with oxidative stress and inflammation being related to cellular changes characteristic, caused by changes in metabolic pathways of individuals with Inborn Errors of Metabolism. The aim of this study was to measure superoxide dismutase (SOD), catalase (CAT) and thiobarbituric acid reactive substances (TBARS) in plasma of MPS I and VI individuals. Three biomarkers of oxidative stress were evaluated in individuals suffering from MPS I (n = 7) and MPS VI (n = 7), deficiency in α -L-iduronidase and Arylsulfatase B enzymes, respectively; apart from healthy controls (HC) [n = 14]. The antioxidant capacity of blood plasma was measured by enzyme superoxide dismutase (SOD) and catalase (CAT), since the damage to lipids (lipid peroxidation) was measured by the presence of thiobarbituric acid reactive substances (TBARS). ANOVA followed by the Tukey Post-Hoc, with Pearson correlation was used to compare results of analysis of plasma with those of both HC and MPS patients. Analysis was performed using statistical software package SPSS 17 (SPSS Inc., Chicago, IL, USA), and level of significance was set at $P < 0.05$. We found a significant increase ($p = 0.02$) in lipid peroxidation (TBARS) in MPS I, but MPS VI no change in any of the parameters studied was observed. Analyzing SOD and CAT, there were no significant differences ($p > 0.05$) among the groups. As the MPS I and MPS VI disease are characterized by rare diseases, the sample size of this study was low. However, with the analysis of the results, there was an increase in damage to lipids in MPS I suggesting that this disease is more vulnerable to oxidative damage that MPS VI.

P097 - Rating Leukocyte Alpha-Glucosidase Using a Natural Substrate for the Diagnostic Approach of Pompe Disease

Uribe Ardila, A.(1); Moreno Silva, P.(2)

(1): Universidad de los Andes, Bogota, Colombia
(2): Universidad de los Andes

Introduction: Pompe disease is an autosomic recessive inherited disorder, resulting from an enzymatic deficiency of the acid alpha-glucosidase also known as acid maltase (acid α-glu; E.C 3.2.1.20/3). The effect of this deficiency is the chronic and systemic accumulation of intra-lysosomal glycogen, affecting primarily the skeletal muscle. The diagnostic confirmation of pathology requires the evaluation of the enzymatic activity. Samples for testing can be obtained from different sources such as fibroblast cultures, muscle biopsy, purified lymphocytes or total leukocytes, which exhibit varying degrees of difficulty. Nevertheless, the use of leukocytes is the simplest procedure but displays more interference with enzymatic isoforms not related to the disease. This interference, can affect the *in vitro* results by degrading the artificial substrate (4MU-alpha-D-glucopyranoside), commonly used in diagnostic assays. **Aim:** Share with the scientific community the experimental processes and preliminary results of the evaluation of activity of the alpha-glucosidase isolated form total leukocyte. We used glycogen as a substrate in the presence or absence of the inhibitor Acarbose in controls and patients with Pompe disease. **Methods:** The evaluation of leukocyte alpha-glucosidase activity was evaluated in a population set 88 individual. The test samples consisted of 75 normal controls (41 Men and 34 Women) in an age range between 3 months to 72 years. And, 13 individuals with Pompe disease (7 Women and 6 Men) in an age range between 6 months to 42 years. The activity was estimated by an endpoint method, modified from the trials presented Reuser et al., 1978 and van Diggelen et al., 2009. Using 75 mg/ml of glycogen as substrate and 10 uM of Acarbose as inhibitor. **Results and conclusion:** The control population showed acid maltase activity in a range of 0.40 to 1.71 mmol/mg protein/hour, in contrast to the population of affected individuals whose range was 0.0 - 0.12 mmol/ mg protein/ hour. The method allowed the establishment of the residual percentage of enzyme activity in affected individuals (0.0 to 14.8%). We highlight, that these findings cannot be determined using the artificial substrate and even more, they can be related to the severity of the disease.

P098 - Biotinidase Deficiency Newborn Screening Experience in México: Epidemiological Overview

Ferrer Arreola, L.(1); Burciaga Torres, M.(1); Delgado González, E.(1); González Guerrero, J.(1); Mendiola Ramírez, K.(1)

(1): Instituto Mexicano del Seguro Social, Coordinación de Atención Integral a la Salud en el Primer Nivel, México D.F., Mexico

Introduction: In July 2005 our institution began screening for biotinidase deficiency (BD), as part of an institutional program for nationwide newborn screening. **Objective:** To report the coverage, index of suspicion, positive predictive value (PPV), cumulative incidence, opportunity of diagnosis and analysis of patients screened in the period from 2005-2014. **Methodology:** The biotinidase activity was determined by colorimetric assay (UMTEST) in dried blood spots on filter paper in newborns. Probable cases were identified with biotinidase activity, without color change. Confirmed cases were detected with quantitative test of biotinidase activity in plasma, with levels lower than 30% of the average for healthy individuals, by ultraviolet/visible light spectrophotometry. All detections were concentrated and registered in the epidemiological surveillance system and were analyzed using a SPSS statistical package to obtain the coverage, positive predictive value (PPV), the cumulative incidence, opportunity of diagnosis and analysis of patients screened in the period from 2012 to 2014. **Results and Discussion:** 4,348,721 detections were realized, coverage was 94.2%. 139 probable cases were identified and 23 cases were confirmed (PPV 16.55%). The cumulated incidence was 1: 200,635 live birth, an opportunity in the diagnosis within 30 days in 10.1%, an average of days to the final diagnosis to 64.94 days. There were confirmed cases in 9 states: Guerrero, Tabasco, Yucatán, Baja California Sur, Jalisco, Federal District, México State, Morelos and Guanajuato. **Conclusions:** The reported incidence of BD is less than international reports; however the real incidence in México is still unknown. We consider maintaining an active surveillance system to improve the opportunity of diagnosis and treatment of these patients.

P099 - Molecular Study of Phenylketonuria in Cuba: 2007-2013

Lopez He Chavarria, K.(1); Pilot Roque, Y.(1); Collazo Mesa, T.(1); Gomez Martinez, M.(1); Reyes Navarro, L.(1); Martínez Rey, L.(1)

(1): Centro Nacional de Genética Médica, La Habana, Cuba

Introduction: Phenylketonuria (PKU) is a disorder of aromatic amino acid metabolism in which phenylalanine cannot be converted to tyrosine. The enzyme responsible for this autosomal recessive disease is the phenylalanine hydroxylase (PAH). PAH gene is located on chromosome 12. Nowadays, more than 500 mutations in this gene have been identified. The most serious manifestation of PKU is mental retardation, thus early treatment is of vital importance. According to the ethnic origin of the Cuban population and previous studies we proposed to detect R261Q, R252W, and IVS10nt I65T mutations in PKU patients in our laboratory. The aim of this work is to identify mutations R261Q, R252W, I65T and IVS10nt and to calculate the allele frequency in Cuban patients with phenylketonuria. **Materials and Methods:** DNA extraction from blood samples from 90 Cuban patients with phenylketonuria was performed. The detection of mutations was performed by a polymerase chain reaction technique, followed by enzymatic digestion and electrophoresis. **Results:** Of the 90 cases analyzed, 12 were heterozygous and one homozygous for the R261Q mutation. We detected 8 heterozygous patients for the R252W mutation and none were homozygous. For the IVS10nt mutation we identified 10 heterozygous patients and one homozygous, whereas for the I65T mutation 2 were homozygous and 6 heterozygous. The allelic frequency of the mutations R261Q, R252W, and I65T IVS10nt were 7.8%, 4.4%, 6.7% and 7.8%, respectively. **Conclusions:** The mutations R261Q, R252W, and IVS10nt I65T are represented in the Cuban phenylketonurics population, and their detection allows prenatal diagnosis in affected families.

P100 - Evaluation of Quality Indicators of a National Newborn Screening Program

Delgado González, E.(1); Burciaga Torres, M.(1); González Guerrero, J.(1)

(1): IMSS Coordinación de Atención Integral a la Salud en el Primer Nivel, México D.F., Mexico

Introduction: The evaluation through indicators of the health-disease process allows measuring or comparing the results obtained in implementing preventive programs and operation of health care services, describing the health status of a population. The neonatal screening program for the detection of congenital metabolic diseases in our country in the last three years is subject to evaluation of each of the processes: from the promotion, epidemiological surveillance of suspected cases, until the control of the confirmed cases. **Objective:** To present the evaluation system of neonatal screening program for congenital hypothyroidism, congenital adrenal hyperplasia, phenylketonuria, galactosemia and biotinidase deficiency through quality indicators in each of the processes, from promotion to definitive diagnosis of the suspected cases of congenital metabolic diseases. **Methodology:** The results for 2014 of the indicators of the different processes in the neonatal screening program, obtained from institutional surveillance system are shown; SPSS was used to obtain frequencies, proportions and means. **Results:** The strategic indicators: detection coverage and opportunity in obtaining screening samples as well as the rate of inadequate samples were within the expected values. However, the opportunity of diagnosis of suspected cases and start treatment of confirmed cases before 30 days of life was 42.2% and 49.4% respectively. Also, we found an opportunity of sending samples to the laboratory within 5 days of 64%, the opportunity in the process of screening laboratory within 5 days: 49.9%, the opportunity in the notice of suspected cases in 24 hours: 51.4%, the opportunity in locating suspected cases within 3 days: 58.4%, the opportunity in pediatric care before 3 days: 53%, and opportunity in obtaining results of diagnostic accuracy within 7 days: 51.3%. **Conclusions:** With the availability of information systems in public health programs, it is possible to obtain results of indicators of coverage, quality and impact to monitor their behavior, allowing decision-making to implement strategies for improvement.

P101 - Long-Term Safety and Efficacy of Taliglucerase Alfa in Pediatric Patients With Gaucher Disease Who Were Treatment-Naive or Previously Treated With Imiglucerase

Gonzalez-rodriguez, D.(1); Zimran, A.(2); Abrahamov, A.(2); Cooper, P.(3); Varughese, S.(3); Giraldo, P.(4); Petakov, M.(5); Tan, E.(6); Brill-almon, E.(7); Chertkoff, R.(7)

(1): Instituto Privado de Hematologia e Investigacion Clinica, Asuncion, Paraguay
(2): Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel
(3): Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa
(4): CIBERER, Instituto Ivestigacion Sanitaria Aragon, Zaragoza, Spain
(5): Clinic of Endocrinology, Diabetes and Metabolic Disease, Belgrade University Medical School, Belgrade, Serbia
(6): Genetics Service, Department of Paediatric Medicine, KK Womens and Childrens Hospital, Singapore, Singapore
(7): Protalix BioTherapeutics, Carmiel, Israel

Introduction: Taliglucerase alfa is an enzyme replacement therapy approved for treatment of patients with Type 1 Gaucher disease and is the first approved plant cell–expressed recombinant therapeutic protein. **Methods:** This extension study of taliglucerase alfa in pediatric patients included those who were either treatment-naïve (n=10) or who were previously switched from imiglucerase (n=5). Patients received taliglucerase alfa 30 U/kg or 60 U/kg (treatment-naïve patients) or at the same dose as previously treated with imiglucerase (switch patients). **Results:** In treatment-naïve patients, taliglucerase alfa 30 and 60 U/kg, respectively, increased mean hemoglobin concentration (+19.7% and +23.3%) and mean platelet count (+23.9% and +156.6%) while also reducing mean spleen volume (−67.8% and −68.9%), liver volume (−37.0% and −34.3%), and chitotriosidase activity (−72.7% and −84.4%) from baseline through 36 total months of treatment. In patients previously treated with imiglucerase, these disease parameters remained stable through 33 total months of treatment with taliglucerase alfa. In both studies, most adverse events were mild/moderate and treatment was well tolerated. **Conclusion:** These long-term results of taliglucerase alfa in pediatric patients with Gaucher disease extend the taliglucerase alfa clinical safety and efficacy data set. **Disclosure:** This study was sponsored by Protalix BioTherapeutics. Pfizer and Protalix entered into an agreement in November 2009 to develop and commercialize taliglucerase alfa.

P102 - Comparison of Taliglucerase Alfa 30 U/kg and 60 U/kg in Treatment-Naive Pediatric Patients With Gaucher Disease

Gonzalez-rodriguez, D.(1); Zimran, A.(2); Abrahamov, A.(2); Cooper, P.(3); Varughese, S.(3); Brill-almon, E.(4); Lewis, D.(5); Wanjrach, M.(6); Chertkoff, R.(4)

(1): Instituto Privado de Hematologia e Investigacion Clinica, Asuncion, Paraguay
(2): Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel
(3): Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa
(4): Protalix BioTherapeutics, Carmiel, Israel
(5): Meridian Medical Technologies, Columbia, United States
(6): Pfizer, New York, United States

Introduction: Taliglucerase alfa is an enzyme replacement therapy approved for treatment of patients with Type 1 Gaucher disease and is the first approved plant cell–expressed recombinant therapeutic protein. **Methods:** Pediatric patients were randomized to receive either 30 (n=6) or 60 (n=5) U/kg of taliglucerase alfa every other week. Due to small patient numbers, there were numerical imbalances in disease parameters between the dose groups at baseline but they were clinically comparable with regard to anemia, risk of bleeding, and organ volumes. Mean percentage changes from baseline were used to compare the response between the dose groups and as a measure of control for numerical imbalances in baseline disease parameters. **Results:** Through 12 months, taliglucerase alfa 30 and 60 U/kg, respectively, increased mean hemoglobin concentration (+13.8% and +15.8%) and mean platelet count (+30.9% and +73.7%), and reduced mean spleen volume (-34.1% and -48.5%), liver volume (-14.5% and -25.0%), chitotriosidase activity (-58.5% and -66.1%), and CCL18 concentration (-50.6% and -52.6%). **Conclusion:** Although statistical analysis was not possible due to small numbers of patients, both treatment groups demonstrated clinically meaningful improvement from baseline in these disease parameters with numerically greater improvement observed in the 60-U/kg dose group. **Disclosure:** This study was sponsored by Protalix BioTherapeutics. Pfizer and Protalix entered into an agreement in November 2009 to develop and commercialize taliglucerase alfa.

P103 - Comparison Analysis of Gene and Exome Sequencing Technology for diagnosis of MPS Complex Disease in a Group of Patients From Southwestern Region of Colombia

Sanchez, A.(1); Satizabal, J.(1); Garcia, F.(1); Jordan, K.(2); Moreno, L.(1); Montoya, J.(1)

(1): Universidad del Valle, Cali, Colombia
(2): University of Georgia Tech, Atlanta, USA

Introduction: We compared gene and exome sequencing technology for the characterization and diagnosis at a group of patients with Mucopolysaccharidosis (MPS) from the Valle del Cauca region of Colombia. The gene sequencing strategy has been the widely used technology for rare Mendelian diseases diagnosis. However, it is well know some discrepancies with results from this strategy. Exome sequencing (ES) holds tremendous promise for the study of Mendelian disease, and steadily

decreasing costs of sequencing will make this approach accessible and widely available in the near future. The ES approach provides substantially increased resolution compared to traditional clinical genetics approaches that rely on the analysis of one or a few genes. **Materials and Methods:** For this study, candidate MPS patients were identified by clinician's experts. Blood samples were taken on whatman paper and sent to lab facilities in Germany and U.S.A. Gene sequencing was performed by standard protocols using an automated sequencing machine. ES sequencing was run in an Illumina platform with coverage of 30X. Gene and Exome sequences were aligned using GRCh37 from HapMap. PolyPhen 2, SIFT and Mutation Taster software were used to associate gene variants with clinical manifestations. **Results:** Using gene sequencing technology we found several SNPs along particular scanned gene correlated with clinical symptoms on MPS patients. Some of them were associated as gene disease causing. From exomic sequencing data an average of 3X104 gene variants were recorded. At least half of all exomic variants were silent. Remaining variants were distributed between missense with a 48 percent of total frequency, nonsense plus insertions and deletions completing the total distribution. With ES we detected gene variants in the cluster gene for lysosomal storage and other gene that control their expression in each patient. **Conclusion:** Exome sequencing technology could be used to look for primary causative mutations for various MPS diseases along with potential modifying mutations localized to additional genes. This expanded approach will allow for a better understanding of the underlying disease etiology and provide for the application of more personalized therapeutic strategies.

P104 - Impact on Pre- and Post-Analytical Factors After Implementation of a Newborn Screening Program

Suldrup, N.(1); Cesari, N.(1); Naretto, A.(1)

(1): Iaca Laboratorios, Bahia Blanca, Argentina

Background: The aim of the Newborn Screening Programs all over the world is to detect and start treatment of affected newborns with minimum delay. Two main factors influencing the response time for the start of treatment are: 1. Quality of the sample and 2. Relay in confirming the results. As a solution to these problems, we have implemented a system of remote assistance and teaching for sampling, whereby drifting refers to an image of the sample sent by analyzing the possible causes of the error and an instructional video on the correct decision sample heel prick for Neonatal Screening. To reduce the delay in the results confirmation whether we obtained a positive result for any of the studied diseases, the required confirmatory determinations were performed as part of the program. **Materials and methods:** We assessed the improvement in the quality factors of samples and confirmation time results after the implementation of the actions outlined by the program. **Results:** Before the program, we received up to 4% of unsatisfactory samples that should be rejected. After the implementation of the program, the amount of unsatisfactory samples fell 0.8%. The average time between the first and confirmatory result was 4.8 days. **Conclusions:** The training provided and the inclusion of confirmatory measurements within the program, made it possible to improve the response times to initiation of treatment. Now the treatment can be started within 10 - 15 days of age.

P105 - External Quality Assurance Program for Neonatal Screening (PEEC-PN): A 15-Year Trajectory

Borrajo, G.(1); Pistaccio, L.(1); Parente, M.(1)

(1): Programa de Evaluación Externa de Calidad. Fundación Bioquímica Argentina, La Plata, Argentina

Introduction: The External Quality Assurance Scheme for Neonatal Screening (PEEC-PN) of Fundacion Bioquimica Argentina began its activity in June/2000 in response to a specific need of the Latin American region. Its general objectives consist in determining the laboratories' performance, detecting errors and establishing their possible causes in order to make a contribution to the analytical harmonization between participants. **Objective:** To present a description of the PEEC-PN highlighting its 15-year trajectory. **Material and Methods:** The analytes evaluated during the first 8 years were Phenylalanine (Phe) and TSH, being expanded to Immunoreactive Trypsinogen (IRT) and Galactose in June/2008. The provided control materials are prepared using human whole blood impregnated on filter paper. The schedule includes 6 surveys per year. In each of them 2 controls for each analyte are provided. The results evaluation is made quantitatively using non-parametric statistics and qualitatively analyzing the results interpretation of each laboratory regarding its own cut-off value. The participation is free of charge and the program scope is limited to Latin American laboratories. **Results:** Since its implementation onwards the number of participants experienced a continuous and sustained growing until 2006 when it started to increase slightly, and since 2010 onwards it resulted stabilized around 180-190 laboratories by survey. In the June/2015 survey, 185 laboratories from 13 countries participated: Argentine: 34, Bolivia: 3, Brazil: 16, Chile: 3, Colombia: 98, Cuba: 1, Ecuador: 1, Mexico: 17, Panama: 2, Paraguay: 3, Peru: 2, Uruguay: 2 and Venezuela: 3, from which 85 were registered for Phe, 180 for TSH, 59 for IRT and 64 for Galactose. **Discussion:** The PEEC-PN has made a very important contribution to the laboratories harmonization and to their analytical performance improvement. Additionally, it has allowed a better knowledge of the newborn screening state in the region. However, the laboratories heterogeneity, the methods diversity, the increased results variability, the trends resulting of the calibration differences between reagents, and the errors caused by inattention or by incorrect results unit expression, determine that the PEEC-PN must face an important challenge which requires the implementation of a continuous education process and an intensive and systematic long-term work.

P106 - Evaluation of the Influence of Collecting Newborn Screening Samples Using Two Different Filter Papers During the Same Time Period

Borrajo, G.(1)

(1): Detección de Errores Congénitos. Fundación Bioquímica Argentina, La Plata, Argentina

Introduction: One consequence observed when a Newborn Screening (NBS) Program decides to change the filter paper (FP) used for sample collection for another one, is their coexistence during a long period, thus determining that samples are collected in some of both FPs. This fact should pass unnoticed if the FPs absorption capacity (AC) are equivalent. However, when AC is very different and the laboratory has only available calibrators prepared in one of them, a shift could be observed in those samples collected in the other one. **Objective:** To present the results corresponding to the comparison of the main statistical parameters that characterize two newborns (NB) populations whose samples were collected using Whatman#903 (W903) or Ahlstrom Grade-226 (AG226) FPs and analyzed during the same working period, in order to verify the potential presence of differences. **Materials and Methods:** Samples collected between 24 h-7th day of life from 33,039 NB and analyzed in a two-month period, were selected. 15,167 samples were collected on W903-Lot W112, and 17,872 on AG226-Lot 103649. Each sample was tested for Phe, Galactose, Biotinidase and Branched Chain Amino Acids (BCAA) using homemade methods and TSH, IRT and 17OHP by AutoDELFIA. All calibrators were impregnated on W903, Lot W112 for homemade methods and W121 for AutoDELFIA. Mean, median, interquartile range and several percentiles were calculated for each group and analytes. **Results and Discussion:** The AC reported by CDC for W903 Lots W112 and W121 were 1.38 and 1.49 ul serum per 1/8" disk respectively, and 1.53 ul for AG226 Lot 103649. Most evaluated parameters did not show significant differences, being observed some expected influence in percentiles corresponding to cut-off values (CO), except for 17OHP and BCAA. In that way, a CO increase for TSH and IRT (calibrators in W903-W121) of 11.1 and 3.2% respectively and a CO decrease for Biotinidase (calibrators in W903-W112) of 8.1%, were observed in AG226 regarding W903 group. Phe and Galactose did not show any differences. BCAA showed a slight CO decrease of 4.7%. 17OHP also showed a CO decrease (14.7%), but it was not considered because variables like gestational age and birth weight were not evaluated in the analysis.

P107 - Wolman Disease ... Not so Wolman

Bay, L.(1); Bindi, V.(2); Andrea, B.(2); Miriam, C.(2); Hernan, E.(2)

(1): Hospital Nacional de Pediatría J.P.Garrahan, CABA, argentina
(2): Idem,

Acid lipase is an hydrolase which acts on cholesterol esters and triglycerides. Íts deficiency cause Wolman disease (W.D.) or cholesterol esters storage disease an autosomal recessive entity in which cholesterol and triglycerides accumulate in various tissues (liver, spleen, lymph nodes, adrenal glands, intestine and macrophages). When it shows symptoms in the first months of life, those are severe(vomiting, diarrhea, malabsorption, malnutrition, liver and spleen enlargement, adrenal calcification) and clinical course is uniform with mortality around one year of age.(W.D.).In children or adults,(storage disease cholesterol esters)have moderate symptoms, but leads to cirrhosis and liver failure, with higher survival. We present the first case of W.D. in literature with different characteristics. **Case:** At 2 months old he showed vomiting, diarrhea, hepatosplenomegaly, low weight with elevated cholesterol TGO and TGP. Acid lipase was measured in leukocytes:0.03 dpm/min/mg protein(controls 0.31-1.1). With diagnosis of W.D. and poor prognosis he returned to his hometown. During follow-up he was hospitalized with repeated episodes of diarrhea and neutropenia. Later he presented exercise intolerance, since 12yo. When we met him for the first time at his 13,65yo, he showed telangiectasias on face and trunk, cyanosis, clubbing. Normal height, emaciated, hepatomegaly and splenomegaly. Quick time 54%.Contrast Echocardiography: hepatopulmonary gradient pathological without pulmonary hypertension. A second enzyme measurement in leukocytes, confirmed the diagnosis. Liver biopsy at 13 years old: Hepatocytes have mild swelling and moderate microvacuolar steatosis greater than 50%. Fibrosis Score 2/6 (Knodell-Ishak). Isolated CD68 positive histiocytes scattered in sinusoids. Liver transplantation was performed, but with persistent hypoxia he died 1 month later. Liver explant showed micronodular appearance. Histologically marked architectural, nodular distortion with wide septa that make hepatocyte nodules. They are full of numerous foamy histiocytes, CD68 positive and a slight level of hepatocyte steatosis microvacuolar about 30%. Micronodular cirrhosis(Fibrosis Score6/6). This course in W.D. was not described before. In previous reports the first symptoms occurred between 0.23-3m, and death 1.45-37.37month old. At the time of diagnosis, treatment was palliative care, but the report on the risk of early death may have changed emotional aspects of child and family. The pathology of the liver explant, provides information on long-term evolution in a very early form of clinical presentation, but very slow evolution.

P108 - Liver Transplant in Niemann Pick B (NPB): Report of 3 Cases

Mabe, P.(1); Acuña, M.(2); Miquel, J.(3); Benitez, C.(4); Jarufe, N.(2); Roa, J.(5); Arrese, M.(2); Martínez, J.(6); Barriga, F.(7); Zanlungo, S.(3)

(1): Hospital de Niños Dr. Exequiel González Cortés, Santiago, Chile
(2): Departamento de Gastroenterología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
(3): Departamento de Gastroenterología, Facultad de Medicina, Pontificia Universidad Católica de Chile. F, Santiago, Chile

(4): 3Departamento de Cirugía Digestiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
(5): Departamento de Anatomía Patológica Pontificia Universidad Católica de Chile, Santiago, Chile
(6): Departamento de Cirugía, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
(7): Departamento de Pediatría, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

NPB is a sphyngolipidosis due to acid sphingomyelinase deficiency. Clinical signs are hepatosplenomegaly, pancytopenia, dyslipidemia, bleeding diathesis, interstitial lung damage, cirrhosis. No specific treatment is available. We report 3 NPB Chilean patients, homozygous for p.Ala359Asp mutation, which underwent successful liver transplant due to liver failure. **Case 1:** Male, 3rd child, non-consanguineous parents. NPB confirmed at age of 2 years. Because antecedent of premature death of a sib due to respiratory failure caused by NPB, a related allogeneic bone marrow transplant at age of 3 years was performed. Normalization of leukocyte sphingomyelinase activity, partial hepatosplenomegaly regression and growth velocity increment were observed. Ten years later portal hypertension was evident, with ascites and large esophageal varices. At age of 16 years and with Child-Pugh score 11 (Child C) the patient was liver transplanted. Follow up after transplant (FUAT) 10 year. **Case 2:** Male, non-consanguineous parents, 2 healthy younger sibs. NPB suspected at age of 22 months due to hepatosplenomegaly, confirmed at age of 12 years. Progressive liver dysfunction noted up age of 15 years. At 22 years he presented a definitive liver decompensation, with ascites and signs of mild encephalopathy. Liver transplantation was performed with Child-Pugh score 11 (Child C). FUAT 4 years. **Case 3:** Female, unique child, first cousin parents. Hepatosplenomegaly at age of 20 months. NPB diagnosed at age of 8 years. She presented frequent epistaxis, which reverted after vitamin K and tranexamic acid therapy. Prothrombin and platelets were approximately 40% and 100.000, respectively. At age of 19 years severe asthenia and impairment of life quality were reported. Epistaxis was more frequent; prothrombin descended to 36% and didn't increase after vitamin K. Liver transplant was performed with Child-Pugh score 11 (Child C), at age of 20 years. FUAT 9 months. None of the patients had graft rejection or severe complications after liver transplant. All present normal hepatic function and good life quality. **Conclusions:** Liver transplant should be considered in patients with liver failure due to NPB. Despite normalization of sphingomyelinase activity after bone marrow transplant, this seems not to avoid progression of cirrhosis in NPB patients.

P109 - Enzymatic Diagnosis of Mucopolysaccharidosis IVA in Chile

Betta, K.(1); Valiente, A.(1); Letelier, M.(1); Fuanzalida, K.(1); Peña, K.(1); Cabello, J.(1)

(1): Laboratorio de Enfermedades Metabólicas (INTA), Santiago, Chile

Introduction: Mucopolysaccharidosis IVA (MPS IVA; Morquio A syndrome) is an autosomal recessive lysosomal storage disorder characterized by a loss of activity of the N-acetylgalactosamine 6-sulfate sulfatase (GALNS) enzyme. In MPS IVA, the degradation of Keratan Sulfate (KS), a type of glycosaminoglycans (GAGs), is defective resulting in a build-up in lysosomes throughout the body. The MPS initial detection method is based on the identification of the KS in the urine of the patient. The definitive diagnosis is established by measuring the enzymatic activity of GALNS in leukocytes or fibroblasts, in which the enzymatic deficiency is proved. In addition to the mentioned tests, the GALNS activity determination in dried blood on filter paper is a practical approach oriented to achieve an initial confirmatory diagnosis. In consideration that our Institute is the National Reference Center for Lysosomal Diseases, we have proposed to perform confirmatory diagnosis of 60 patients with clinical suspicion for MPS IVA by implementing the enzyme activity of GALNS assay on leukocytes and dried blood samples (DBS). **Material and Methods:** DBS and leukocytes from both female and male patients (60) between 1 and 62 years of age with clinic suspicion of diagnosis of MPS IVA were analyzed through the fluorometric and colorimetric method. Peripheral blood samples from patients and controls were collected in order to obtain leukocytes and DBS. To validate the method, we assessed simultaneous GALNS activity assay in leukocytes and DBS. In addition, the enzymatic activity of Beta-galactosidase and Arylsulfatase B were determined in whole patient samples to evaluate sample integrity and to rule out Multiple Sulfatase Deficiency, respectively. **Results:** Twenty-six patients (43%) presented deficit of enzymatic activity of GALNS in both leukocytes and DBS with a significant statistical difference in relation to the control group, that allowing us to confirm the diagnosis of MPS IVA. **Conclusion:** Enzyme assay of GALNS in leukocytes and DBS are suitable and available method to study patients with clinical suspicion of MPS IVA in Chile.

P110 - The Use of Tandem Mass Spectrometry in Newborn Screening

Wiley, V.(1)

(1): The Children's Hospital at Westmead, Westmead, Australia

Electrospray ionisation tandem mass spectrometry (MSMS) has now been incorporated in many dried blood spot newborn screening programs worldwide. There have been many changes in methodology since it was first used to prospectively screen dried blood spot samples from newborns for inborn errors of amino acids, fatty acid oxidation and organic acidurias. However despite many attempts to harmonize its introduction, it remains the responsibility of each programme to determine which disorders are to be screened, what sample to use, and what is acceptable performance. For each analyte tested there is sample, analytical and interpretative considerations. Sample aspects include the optimal time of collection after birth, the effect of feed status and gestational age. Analytical considerations

include the instrumentation, sample preparation, establishing action limits, normal percentiles and expected results for proven positives as well as appropriate quality assurance protocols. The followup algorithms for diagnosis, which may include ratios of analytes or second tier testing on the initial sample as well as additional samples of urine and blood, need to optimize the performance metrics of resample rate, sensitivity, specificity and positive predictive value. Using various MSMS protocols since 1998, we have screened samples collected at 48-72 hours of age from over 1,655,000 babies, requested further samples from 0.15%, and detected a disorder in 1:2691 babies with a sensitivity, specificity and positive predictive value which are currently 99%, 99.9% and 25% respectively. Babies requiring treatment included 198 with phenylketonuria, 153 with other amino acid disorders, 108 with medium chain acyl CoA dehydrogenase deficiency and 212 others with acyl carnitine defects. The use of tandem mass spectrometry in newborn screening is expanding to include many other disorders. The challenge remains how to learn from each other.

P111 - Newborn Screening of Special Cases—Preterm Newborns, Low Birth Weight Infants and Severely Ill Infants: Establishing a National Protocol

Camelo Jr, J.(1); M Carvalho, T.(2); Goldbeck, A.(2); Marchi, A.(2); J Zamaro, P.(2)

(1): Faculdade de Medicina de Ribeirão Preto/USP, Ribeirao Preto, Brasil
(2): Ministerio da Saude, Brasilia, Brasil

Introduction: Brazil has 2.8 million births per year, of which more than 6% include premature (PT) births and low birth weight infants (LBWI), some states reaching more than 9% in referral hospitals. These data show the importance of creating specific protocols for neonatal metabolic screening of preterm, LBWI and critically ill newborns (NB). In spite of the Brazilian Newborn Screening National Program to include the screening of six diseases (phenylketonuria, congenital hypothyroidism, hemoglobinopathies, cystic fibrosis, biotinidase deficiency and congenital adrenal hyperplasia), no special approach is established for the above mentioned conditions. **Methods:** Protocol Workshops were held by the Ministry of Health, with the presence of specialists, when a review of the relevant literature was done, with special attention to the CLSI's recommendations (CLSI-Clinical and Laboratory Standards Institute) on their "Approved Guidelines – Newborn Screening for Preterm, Low Birth and Sick Newborns". **Results:** It is recommended that first sample of the dried blood spot should be obtained by venipuncture on the first day or sooner to the child's admission to the neonatal unit, if there is a need to submit the NB to transfusion of blood products and/or early intensive treatment using steroids, vasoactive amines, antibiotics, etc. Second sample should be obtained on the third day (72 hours) of life of the NB which remains hospitalized. Third sample should be obtained on the 28 days old baby held in hospital or NB with less than 34 weeks gestational age or weighing less than 2,000g at birth, regardless of discharge. Special situations related to the interpretation should be considered when analyzing the results of the samples such as: 1) Maternal conditions affecting the newborn screening in NB; 2) Conditions affecting the newborn screening on retained NB; 3) treatments that affect the newborn screening of retained NB and 4) factors that may influence the outcome of neonatal screening in NB and situations potentially causing false-positive and false-negative. **Conclusions:** Interpretation should be comprehensive, predicting future inclusions in newborn screening such as galactosemia, aminoacidopathies, organic acidemias and fatty acids beta-oxidation defects, made by tandem mass spectrometry. The review of the Brazilian Protocol for special collections makes it appropriate to approach premature babies, LBWI, retained on hospital admissions and transfused with blood products.

P112 - Stability of Creatine Kinase in Dried Blood Spots

Hall, E.(1); De Jesus, V.(1)

(1): US Centers for Disease Control and Prevention, Atlanta, USA

Introduction: Duchenne Muscular Dystrophy (DMD) is an X-linked, muscle-wasting disease affecting about 1 in every 3500 boys. Early screening for DMD tests for high levels of the muscle enzyme creatine kinase (CK) in dried blood spots (DBS). We investigated the stability of CK activity in DBS stored under different temperature and humidity conditions for up to one year. **Material and Methods:** We produced DBS specimens using human blood enriched with purified CK from rabbit muscle. Identical sets of CK-enriched DBS specimens were exposed to high, low, and ambient humidity environments for one month at both room temperature and 37°C. Other identical sets of CK-enriched DBS specimens were stored with desiccants and stored at -20°C, 4°C, room temperature, and 37°C for periods of one month, three months, six months, and one year. All specimens were then assayed for CK enzymatic activity using an artificial substrate with fluorometric detection. **Results:** In DBS stored at 37°C for one month, those stored at high humidity lost >95% CK activity by day 14 while those stored at low humidity maintained >55% activity over the full month. When stored at room temperature, DBS exposed to high humidity lost 47% CK activity by month's end while those stored with desiccants lost <20%. In DBS stored with desiccants, >90% of CK enzymatic activity was maintained over the course of a year when the samples were stored at -20°C. When stored at 37°C, even desiccated specimens lost >75% activity in three months and 95% activity by six months. **Conclusions:** CK's enzymatic activity was far more susceptible to degradation in high humidity than in low humidity and declined rapidly at higher temperatures. Our data suggest that, whenever CK activity is of interest, DBS specimens should be stored with desiccants and at low temperatures.

P113 - Anesthesia for MRI and Diagnostic Tests in Mucopolysaccharidosis Patients

Moraes Ferreira, M.(1); Dalla-corte, A.(2); Fischinger M. De Souza, C.(1); Giugliani, R.(2)

(1): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
(2): Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Introduction: The mucopolysaccharidoses (MPS) are a group of inheritable, clinically heterogeneous lysosomal storage disorders characterized by the progressive accumulation of glycosaminoglycans (GAGs) in different organs and tissues. Among the clinical manifestations, airway changes are very significant in the anesthetic management of these patients. The presence of macroglossia, tonsillar hypertrophy and swelling of tissues in laryngopharyngeal challenge the airway management. The anesthesiologist must be prepared to deal with inability to ventilate or intubate and also with sudden airway obstruction during anesthesia. On average 3 anesthetic-surgical procedures will be performed in every MPS patient throughout his life. Thus, it is essential the use of appropriate anesthetic techniques especially in diagnostic tests performed outside the operating room. **Material and Methods:** All patients underwent a brain CSF and flow study MRI followed by a standard lumbar puncture with the CSF opening pressure assessment in the radiology unit. Patients were assessed before the procedure and the anesthetic technique was individualized for each case due to complexity and rarity of the condition. The difficult airway risk factors were evaluated and an ENT might be called in cases of difficult ventilation and intubation. **Results:** A total of 12 patients aged 4-34 years old were anesthetized by the same anesthesiologist. In 8 cases it was decided to carry out sedation while in the other 4 cases there was need for general anesthesia. The airway management in cases of general anesthesia was performed with the use of laryngeal mask and tracheal intubation was not necessary. The inducing drugs used included ketamine and propofol, and anesthesia was maintained with sevoflurane. In cases of sedation we choosed the use of diazepam and dexmedetomidine. Only one patient had an episode of transient desaturation. No complications were observed in the other cases. **Conclusions:** MRI and diagnostic tests in MPS patients can be properly performed under sedation. In cases where general anesthesia becomes necessary, the laryngeal mask is a suitable alternative. The choice of anesthetic technique and the anesthesiologist's experience in the management of these patients are critical to the success of the procedure.

P114 - Description of 11 Cases of Neuronalceroid Lipofuscinosis

Witting, S.(1); Troncoso, M.(1); Ortega, P.(1); Troncoso, L.(1); Santander, P.(1); Barrios, A.(1); Guzmán, G.(1); Fariña, G.(1)

(1): Servicio de Neurología infantil, Hospital San Borja Arriaran, Santiago, Chile

Introduction: Neuronal ceroid lipofuscinosis (NCL) is a neurodegenerative disease, autosomal recessive, characterized by cognitive decline, ataxia, epilepsy and vision loss. Diagnosis is based on clinical, imaging, microscopic, enzymatic and genetic findings. **Aim:** To describe clinical manifestations, exams and genetic study of patients with diagnosis of NCL. **Method:** Medical records of 11 patients with NCL were analyzed. **Results:** 6 females, 5 males. Age of onset: between 1,5 and 9 years. Nine patients debuted with seizures, two with cerebellar syndrome. Myoclonic (8), generalized tonic-clonic (5) and focal complex (7) seizures were the most common. All patients presented developmental regression, cerebellar symptoms and pyramidal syndrome afterwards, followed by gait and language loss. Eight patients presented optic atrophy. Cerebral MRI: 10 with cortical and cerebellar atrophy, 3 with hyperintensive periventricular white matter, one with ventriculomegaly. EEG was abnormal in 11/11. Low frequency photo stimulation was positive in two patients. Skin biopsy: 6 with curvilinear inclusion bodies, 2 fingerprints, 3 normal. Enzymatic study: Six presented TTP-1 enzyme deficit, characteristic of NCL2. Of these, 3 presented normal skin biopsy. Genetic study showed mutations of NCL2 gene in three patients, with positive skin biopsy in all of them, but one had normal enzymatic study. **Conclusions:** In our series of patients the most common form was late infantile lipofuscinosis. Clinical manifestations, electrophysiological study and neuroimaging were distinctive. It is important to confirm diagnosis with skin biopsy, enzymatic and genetic study, because in some cases they can be negative, even though findings are distinctive.

P115 - Identification of the Genetic Mutations of a Group of Chilean Patients With Mucopolysaccharidosis Type II Diagnostics

Troncoso, M.(1); Márquez Félix, E.(2); Rozenfeld, P.(3)

(1): Servicio de Neuropsiquiatría Infantil Hospital Clínico San Borja Arriarán. Facultad de Medicina, Campus Centro, Universidad de Chile, Santiago, Chile
(2): ervicio de Neuropsiquiatría Infantil Hospital Clínico San Borja Arriarán. Facultad de Medicina, Camp, Santiago, Chile
(3): Laboratorio DIEL. Facultad de Ciencias Exactas de la Universidad Nacional de la Plata—CONICET, Buenos Aires, Argentina

Introduction: Mucopolysaccharidosis type II (MPS II) is an X-linked recessive genetic disorder, caused by deficiency of iduronate-2-sulfatase enzyme (IDS), required for the degradation of glycosaminoglycans (GAG) generating progressive accumulation of substrates causing intralysosomal clinical manifestations. 20% of patients with MPS II have large gene alterations, including deletions, rearrangements and total IDS gene, while the remaining 80% have small genetic alterations. **Methods**: A descriptive study of 8 patients with clinical diagnosis of urinary GAG levels and enzymatic activity of I2S compatible with MPS II and determination of genetic mutations by PCR amplification technique of the 9 exons of IDS. **Results:** All

patients, 7 men and 1 woman, had neuronopathy phenotype with intellectual disabilities from mild to profound, age at diagnosis between 15-60 months. The first symptom of suspicion at 38% were dysmorphic syndrome, followed by recurrent obstructive airway syndrome and psychomotor retardation (RDSM). All showed macrocephaly, varying degrees of scoliosis, hepatosplenomegaly and 50% developed heart disease. 3 mutations reported in the literature were detected, which affected exons 9,7 and 8 respectively; three brothers presented the c.1421A> C mutation not previously reported. The c.1000G> T mutation, exon 7 corresponded to a patient who had cardiac disease, attenuated phenotype. Mutational rearrangement c.1033T> C was detected in a patient with classic phenotype. The only woman in the study had gene-pseudogene recombination in heterozygous state, is typically related to the later age at diagnosis, 60 months. **Conclusions:** Our patients have classic phenotypic features of systemic involvement, all with some degree of cognitive impairment; both new and previously reported mutations have a characteristic of MPS II but no specific phenotype, which makes the possibility of a genotype phenotype correlation based on the large allelic variability present.

P116 - Prevalence of Sickle Cell Trait and Sickle Cell Anemia From the Neonatal Screening Program in the Pará State, Brazil in 2014

Leitão, A.(1); Nascimento, E.(1); Trindade, E.(2); Silva, O.(1)

(1): Universidade Federal do Pará, Belem, Brasil
(2): Universidade Estadual do Pará, Belem, Brasil

Introduction: Sickle cell disease (SCD) is one of the genetic diseases of greatest epidemiological importance in Brazil and worldwide. Due to the high incidence in Brazil, SCD has come to represent a major public health problem. **Objective:** To determine the prevalence of trait and sickle cell anemia in newborn infants who underwent screening for hemoglobinopathies in the public health system in the state of Para in 2014. **Method:** A descriptive cross-sectional study based on exploratory analysis of newborn data who underwent screening tests for hemoglobinopathies in 2014. **Results:** In this study, we performed a screening for hemoglobinopathies in 105,854 newborns treated in the neonatal screening program in the public health system in the state of Para in the period from January to December 2014. We identified 102,390 (96.7%) children with normal pattern of Hb, 3,426 (3.2%) with sickle cell trait and 38 (0.04%) children with sickle cell anemia confirmed by HPLC technique. The prevalence of sickle cell anemia was 35.9 / 100,000, which means that for every 10,000 children born in the state of Para, approximately 4 presented the disease. **Conclusion:** The data showed the importance of investigation of abnormal hemoglobins in order to take preventive measures through newborn screening. Additionally, genetic counseling was enabled and necessary for family planning purposes.

P117 - Quality Guarantee of Neonatal Screening Assays

González Quintero, A.(1); López Brauet, L.(1); Turró Grau, G.(1); Sabina Cebreiros, M.(1); Lefrán Gómez, M.(1)

(1): Centro de InmunoEnsayo, Habana, Cuba

Introduction: The Immunoassay Center (CIE) has implemented a Quality Management System (QMS) based on the Good Manufacturing Practices of Diagnostic Assays (BOPD), which guarantees the quality of products used in neonatal screening providing confidence in results. **Materials and Methods:** Our QMS includes Assurance and Quality Control, which verifies the conformity of each batch produced. The analytical control of the tests in conjunction with the inspection of the packaging, complemented fitness batch, which is checked in the process of final liberation, the CIE also participates in programs of external evaluation organized by the CDC and the ABF. Meanwhile assurance involves performing internal audits to verify compliance with GMPD. **Results:** QMS implementation has allowed the release of 544 lots in the past five years, all intended for neonatal screening assays with a 100% compliance with quality specifications. The evaluation of the precision yielded CVs between 5 and 10% and for accuracy, percentage difference $\leq$ 10%, quantified using international standards reference materials. The detection and quantification limit of the assays showed 100% concordance with specifications. Participation in various programs of External Quality Assessment (EQA) International has demonstrated comparable results with other laboratories with a correspondence over 90% compared to the consensus value, demonstrating the satisfactory performance of our products at the stage of post-marketing. Major nonconformities detected in audits have been related to the noncompliance of procedures, the lack of updated documentation and detection of deviations not notified promptly, each of which has helped the process of continuous improvement of our QMS. **Conclusions:** The implementation of a QMS including diagnosticians CIE has helped maintain and contribute to the improvement of our products and has guaranteed the reliability of results, meeting the regulatory requirements and encouraging our customers to be provided with a sustainable product of proven quality in time.

P118 - Perception That Medical Students Have About Neonatal Screening Tests for Inborn Metabolic Diseases in Four Hospitals

Dussan, A.(1); Yasno, D.(1); Ramirez Rey, A.(1); Beltran, O.(1)

(1): Facultad De Medicina Universidad Militar Nueva Granada, Bogota, Colombia

Introduction: Inborn Metabolic Diseases (IMD) belong to a group of entities known for their low prevalence and

chronicity, associated with low life expectancy in children. In April of 2013, the Colombian Ministry of Health introduced the guidelines for clinical practice that determine the protocol of screening tests (ST) for seven IMD in neonates. **Methods:** A virtual survey of three questions (used for the score of the subject corresponding to pediatrics) was designed to evaluate the grade of knowledge for the ST used in IMD and the subjective perception about this topic. It was applied in a group of 73 students in fourth year of medical school, who were performing pediatric practice in four academic hospitals. Qualitative and descriptive analyses of the answers were performed in November 2014. **Results:** 63 answered the survey. Of these, 1 was excluded, leaving 62 for the analysis. The whole population studied showed an accurate theoretical knowledge about the ST for IMD. The quality of the answers was subjectively categorized as: 'poor', 'normal' and 'detailed'; 12.9% was 'poor', 40.32% 'normal' and 46.77% 'detailed'. 96.77% commented that in their practice they didn't witness the performance of ST for 6 IMD recommended in the guideline, that the ST was only run for congenital hypothyroidism. However, it was reported that the detection of this disease was done by the umbilical cord thyroid-stimulating hormone (TSH) levels, instead of doing it by the heel prick sample (between 2nd and 3rd day of life) as it is recommended in the guideline. It was generally commented by the students in the survey that they didn't have previous knowledge of the existence of these national guidelines, and that it is important to introduce them in the pediatric services of hospitals. **Conclusions:** this study shows the influence of the academic environment to encourage these activities that shows the understanding of an academic population about the health policies used in countries. This motivates studies to find the cause of the poor implementation of the clinical guidelines in some hospitals, and the academic investigation around these topics.

P119 - Molecular Characterization of Patients With Mucopolysaccharidosis IVA in south Western Colombia

Pachajoa, H.(1); Posso, J.(1); Rámirez, A.(1); Ruíz, F.(1)

(1): Universidad Icesi, Cali, Colombia

Morquio syndrome A, (Mucopolysaccharidosis IV A, MPS IVA) is a lysosomal storage disease caused by the deficiency of N-acetylgalactosamine-6-sulfatase (GALNS). Molecular studies in Colombian patients with MPS IVA, and especially in south western Colombia, are very scarce. The purpose of this study was to mutations on the GALNS gene on patients with MPS IVA from south western Colombia by amplifying and sequencing the exons and the adjacent intronic regions of this gene in seven unrelated families. The result of this was the identification of 14 mutant alleles containing six different mutations. Three novel mutations were found (c.998G>A p.G333D, c.214T>A p.Phe72Ile, c.425A>T p.His142Leu), and three mutations previously identified mutations were found as well (c.901G>T p.Gly301Cys, c.280C>T p.R94C, c.1156C>T p.Arg386Cys). Furthermore, it was found that the most frequent mutation in south western Colombia in patients with MPS IVA is c.901G>T p.Gly301Cys, since this mutation was found as homozygous affecting three families, and as heterozygous in two families. The conclusion of this was that the GALNS gene mutation spectrum in south western Colombia patients with MPS IVA is broad; however, there is a high prevalence of the c.901G>T p.Gly301Cys mutation.

P120 - Neuroclinical and Neuroradiological Aspects of Mucopolysaccharidosis Type II Patients Following at Centro De Referencia Em Erros Inatos do Metabolismo (CREIM) of Universidade Federal De Sao Paulo (UNIFESP)

Mendes, C.(1); Curiati, M.(1); Rand, M.(1); Martins, A.(1)

(1): CREIM—UNIFESP, Sao Paulo, Brasil

Introduction: Mucopolysaccharidosis II (MPS II) is an X-linked lysosomal storage disease caused by a deficiency of the enzyme iduronate-2 sulfatase, leading to the accumulation of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate in lysosomes. Storage of these GAGs causes several clinical manifestations. Neurological abnormalities include Intellectual disability, behavioral disturbance, epilepsy, communicating hydrocephalus and compressive myelopathy. Intellectual disability may not occur and is used as a landmark to determine the severity of the phenotype. There is a need to review and re-evaluate the neuroclinical and neurorradiological spectrum of the disease. **Objective:** To describe the neuroclinical and neurorradiological aspects in MPS II patients being followed at CREIM, UNIFESP. **Methods:** Retrospective analysis of clinical and radiological findings using neurological evaluation and brain MRI in eleven MPS II patients. **Results:** The patients' age at first neurological evaluation ranged between 3 months and 28,5y. the physical examination showed: macrocrania in 11/1 (9%); behavioral disturbances in 3/11 (27,3%); apendicular spasticity in 5/11 (45,4%); Babinski in 1/11 (9%); language disability in 1/11 (9%), neurodevelopment delay in 4/11 (36,4%). From the total of patients, we considered 4 to be severe phenotype and 7 to be mild phenotype. Brain MRI was performed in 6 patients, being 5 of them a severe phenotype and 1 mild phenotype. Brain MRI findings were: high signal T2 and FLAIR in periventricular white matter in 6/6 (100%), supratentorial ventricular dilation with no signs of intracranial high pressure in 5/6 (83,3%), virchow-robin perivascular spaces 4/6 (66,6%), cortical atrophy in 2/6 (33,3%). **Conclusion:** Most of our patients presented a mild neurological phenotype. In the severe phenotype patients, no epilepsy was reported. The most frequent clinical

finding was spasticity and the most frequent neuroradiological finding was periventricular white matter lesion.

P121 - A New Mutation in the Intron of the IDS Gene in an Adult Patient with Mucopolysaccharidosis Type II

Pachajoa, H.(1); Posso, J.(1)

(1): Universidad Icesi, Cali, Colombia

Mucopolysaccharidosis type II (Hunter syndrome) is a rare X-linked lysosomal storage disorder. It is caused by mutations in the gene that produces the lysosomal enzyme Iduronate sulphatase (IDS), resulting in incomplete degradation of heparan and dermatan sulphate in the lysosomes. Main symptoms include skeletal dysplasia, vision impairment, heart and valve disfunction, among others. In the present work we present the case of a 33 year old patient with a new mutation in the intron 1 of the IDS gene (c.103+2T>A).

P122 - The Role of the Laboratory in the Early Diagnosis of Cystic Fibrosis

Cánepa, P.(1); López, M.(2); Alonso, P.(3)

(1): Pesquisa Neonatal-Laboratorio Central de Salúd Pública del Chaco, Resistencia, Argentina
(2): Laboratoriio de Genética Molecular e Histocompatibilidad. Gran Hospital Dr. Julio C. Perrando, Resistencia, Argentina
(3): Laboratorio Área Química clínica del Hospital Pediátrico Dr. Avelino castelán, Resistencia, Argentina

Introduction: The diagnosis of Cystic Fibrosis (CF) is based on clinical and biochemical markers of dysfunction on CFTR protein (CF transmembrane conductance regulator) and detection of mutations in the CFTR gene. In our province, there is a CF Center composed of doctors and specialized professionals, in coordination with laboratories. Since the neonatal screening and genetic diagnosis for CF were implemented in 2010, 13 new cases were detected, referred to the CF Center and confirmed by genetic and sweat test. **Material and methods:** The neonatal screening algorithm follows the IRT/IRT (immunoreactive trypsinogen) strategy. We evaluated dried blood spot samples on filter paper from infants between 36 hours and 30 days of life by ELISA (MP) method. Samples were considered positive for IRT values $\geq$ 140 ng/mL for the first sample and $\geq$ 120 ng/mL for the second. Genetic analysis was performed on blood by allele-specific PCR to detect frequent mutations: F508del, G542X, N1303K, and a commercial panel of 29 mutations (Elucigene CF29). The sweat test is performed by Macroduct Sweat Collection / Sweat Check, and pathological values were determined as > 80 mmol/L. Results: From 2010 to May 2015, 82589 newborns were screened and 13 CF cases were detected. The IRT values were between 160 and 700 ng/mL in the first sample and between 140 and 800 ng/mL in the second. The sweat test was performed in 8 of 13 cases, being pathological in all of them, with values between 98 and 127 mmol/L (mean 110 mmol/L). The genetic study found 8 cases of F508del homozygotes, a case of F508del / N1303K compound heterozygous, and F508del/———— in 4 cases. At diagnosis the patients were between 12 and 126 days (mean 51 days). **Conclusions:** The coordinated participation of newborn screening, genetic and sweat test laboratories allowed the CF confirmation and diagnosis in an average of 50 days. Early diagnosis is essential to ensure a better nutritional status and growth, potentially associated with better respiratory function, prognosis and quality of life. The coordinated work between laboratories and the medical team allowed us to validate results professionally, add experiences and consolidate as a working team for the benefit of patients.

P123 - Cystic Fibrosis: Diagnosis on Newborn Screening in Espirito Santo State, Brazil

Bravin, C.(1); Motta Correia, S.(1); Fardin, S.(1); Sarquis Cintra, T.(1); Passamani, E.(1); Goulart, S.(1)

(1): Apae Vitória Es Brasil, Vitória, Brazil

Introduction: Cystic Fibrosis (CF), originally described by Andersen in 1938 as cystic fibrosis of the pancreas, was virtually fatal during the first years of life. Newborn screening (NBS) has contributed to the diagnostic criteria during the asymptomatic phases of the disease, supporting early therapeutic approach. APAE Vitoria, Espirito Santo State's NBS Reference Service, started Cystic Fibrosis screening in June 2009. **Materials and Methods:** We describe the epidemiologic data of the Cystic Fibrosis in Espirito Santo State (ES) since we started CF screening in our program. Immunoreactive trypsinogen (IRT) was assayed using an immunofluorometric method. The blood samples were collected on filter paper. Children with IRT 70 ng/ml and over in two different samples not longer than 30 days of life were tested for the Sweat Chloride Test on the Gibson & Cooke method to confirm a CF diagnosis. **Results:** 35 patients were diagnosed with CF during the period of 2009, June – 2015, May; 15 were male (43%) and 20 were female (57%). The average age on diagnosis was 41 days of life. The molecular analysis of 21 patients has shown that 81% of them had the ΔF508 mutation at least in one allele. The incidence in ES was 1:7507. **Conclusion:** NBS for Cystic Fibrosis supports the early diagnosis in asymptomatic patients as well as the immediate multidisciplinary approach, improving the preventive actions and the follow up in specialized services yielding more knowledge of the natural history of the disease and treatment. The genetic predictive approach on the relatives provides more information and better understanding of the disease, supporting more commitment to the treatment and less impact on the mortality and morbidity.

P124 - Neonatal Screening for Hemoglobinopathies in Mexico: An Analysis of 277,760 Newborns

Martinez Cruz, P.(1); Herrera Pérez, L.(1); Moreno Graciano, C.(1); Maldonado Solís, F.(2); Maldonado Solís, M.(2); Sanchez Zebadua, R.(3); Salazar Escalante, R.(4); Díaz Gallardo, J.(5); Trigo Madrid, M.(5); De La Torre García, O.(5); Madrigal Mendoza, L.(6); Arias Vidal, C.(1)

(1): Tamizaje Plus S. A de C. V, Villahermosa, México
(2): Químicos Maldonado S.A de C.V, Villahermosa, México
(3): TamizMas de Químicos Maldonado Unidad Chiapas, Tuxtla Gutierrez, Chiapas
(4): TamizMas de Químicos Maldonado Unidad Yucatán, Mérida, Yucatán
(5): Secretaria de Marina Armada de México, Distrito Federal, México
(6): Secretaria de la Defensa Nacional, Distrito Federal, México

Introduction: The benefits of early diagnosis of hemoglobinopathies are widely known, and have led to the implementation of neonatal screening programs, in order to reduce the morbidity and mortality associated with these disorders. In Mexico, routine newborn screening for these diseases has been only performed in the southeast of Mexico (Tabasco, Chiapas and Yucatán), but recently, the Mexican Navy (SEMAR) and the Mexican Army (SEDENA) newborn population have begun performing it. The objective of this work was to analyze the results of newborn screening programs for hemoglobinopathies in Mexico. **Material and methods:** Review of the results of newborn screening programs from the Ministry of Health of Tabasco, Yucatán, Chiapas and of the Mexican Navy (SEMAR) and Mexican Army (SEDENA), from September 2007 to July 2015. The screening was performed in dry blood samples on Guthrie cards, obtained by heel prick. Samples were analyzed by isoelectric focusing and/or HPLC. **Results:** 28/32 states that constitute the Mexican Republic participate in the study. From 277,760 NB analyzed, 4071 hemoglobin variants (1.47%, 1:68 NB) were detected and 34 patients were confirmed: 21 with sickle cell disease, 10 with Hb S/β-Thalassemia, 2 with β-Thalassemia minor, and 1 with α-Thalassemia minor. HbS is the most frequent (84.4%) of all the abnormal hemoglobins found by our study, followed by Hb C (2.33%), the rest account for 4.32%. The birth prevalence of sickle cell disease in the studied population is 13.2:1,000 NB, and the birth prevalence of all the hemoglobinopathies is 14.7:1,000 NB. **Conclusion:** Our results showed that 1:8,169 NB in Mexico have a hemoglobinopathy, and 1:68 NB is carrier of an abnormal hemoglobin variant. It is necessary to implement routine neonatal screening for hemoglobinopathies in the entire country, in addition to a national program that includes genetic counseling and medical attention of patients and carriers.

P125 - Response to Compassionate Use of Triheptanoin in Infants With Cardiomyopathy Due To Long Chain Fatty Acid Oxidation Defects (LC-FAODS)

Sampaio Filho (Jr), Claudio(1)

(1): INTERCIENTIFICA, S.J.Campos, Brasil

Introduction: The most severe LC-FAOD phenotype may present in the newborn period or early infancy, when energy demands are higher, especially in the heart. Symptoms may include cardiomyopathy, arrhythmia, hypoglycemia and hepatic dysfunction. Morbidity and mortality are high despite early detection by newborn screening, where available, and early intervention with standard treatment, including supplementation with even medium chain triglycerides (MCT). Triheptanoin (UX007) is an investigational 7-carbon odd medium chain triglyceride, shown in animal studies to be both ketogenic and gluconeogenic, by providing anaplerotic substrate for the depleted TCA cycle. **Methods:** Triheptanoin was provided on an emergency compassionate use basis to 6 infants with severe cardiomyopathy due to LC-FAODs. All had been previously treated with MCT before starting on triheptanoin between ages 3-11 months. In order to evaluate the response, we reviewed data provided by the treating physicians. **Results:** Six patients with LC-FAODs (TFP, VLCAD [2], CACT, LCHAD [2]), presented with moderate (1/6) or severe, life-threatening (5/6) cardiomyopathy in infancy, despite maximal treatment with MCT and cardiac support (ventilation/ECMO, pressors). All patients were detected by newborn screening, with further confirmation. Five were treated with triheptanoin (4g/kg) on emergency protocols (FDA eINDs), and one was enrolled in an existing compassionate use study. Rapid improvement occurred within 48 hours in 2 patients near death, (CACT, VLCAD), or within 2-3 weeks (LCHAD, TFP) of starting treatment. One patient (VLCAD) had a more gradual rate of improvement. Representative 2D-echo ejection fractions were 21, 22, N/A, 39, 44, 37% pre-treatment and 71, 33, 71, 69, 53, 38% post- treatment, respectively. Four severe patients were successfully weaned from support and remain stable; the moderately severe TFP patient did not require acute ventilator support, but had declining EF. One (LCHAD) developed pericardial effusion and bradycardia, and died from cardiac arrest after treatment for almost 4 weeks. Adverse events were GI distress, including loose stools; 4 patients remain clinically well continuing on treatment; 1 patient withdrew from treatment due to GI distress. **Conclusion:** These data demonstrate the potential therapeutic benefit of triheptanoin treatment in infants with cardiomyopathy due to LC-FAODs. Further studies are warranted to confirm these initial promising findings.

P126 - When Two Conditions With Similar Features Meet: A Case of Erdheim Chester Disease in a Patient With a Common Genetic Disorder

Estrada-veras, J.(1); Obrien, K.(1); Gahl, W.(1)

(1): National Institutes of Health—National Human Genome Research Institute, Bethesda, MD, United States

Introduction: Primary Hemochromatosis is the most common genetic disease in Caucasians causing iron overload. About 1:10 Caucasians carry one copy of C282Y in the *HFE* gene. Clinical manifestations such as fatigue, joint pain, weight loss, hypogonadism, diabetes insipidus, arrhythmia and liver disease may not manifest until age 50. Hemochromatosis has overlapping features with Erdheim-Chester Diseases (ECD), an ultrarare form of Non Langerhans cell histiocytosis caused by somatic mutations in genes such as *BRAF, NRAS* and *MAPK1*, which can also manifest at age 50 with fatigue, hypogonadism, diabetes insipidus among other manifestations. Here we present a case of ECD that remained undiagnosed for 5 years since the initial manifestation was diabetes insipidus thought to be secondary to the patient's known diagnosis of hemochromatosis. **Materials and Methods:** A 53 year old Caucasian male with diagnosis of hemochromatosis and ECD was evaluated at the NIH Clinical Center as part of ECD Natural History study. Clinical evaluations and images such as brain/pituitary/orbital/abdominal/pelvic MRI, CT scan of the heart and chest, FDG-PET and T-99 bone scans were performed. Results and Conclusions: Skin biopsy and imaging findings confirmed ECD. Molecular testing detected the *BRAF* V600E mutation. Excess iron was seen on brain MRI, but no other complications associated with hemochromatosis were seen. Presence of ECD was seen in bones, kidneys, heart, skin and pituitary stalk. Mild cerebral atrophy was reported. Endocrine abnormalities included hypogonadism and diabetes insipidus. Patient was treated with interferon (IFN) alpha, but because of side effects, therapy was modified to Anakinra. Today he is on BRAF – MEK inhibitors therapy. Having a common and a rare disorder that share clinical manifestations can also be rare, but not impossible. Having a diagnosis does not make one immune to other common or rare diagnoses. When manifestations sound similar, but there is something that doesn't add up, keep looking and keep looking. New treatments are becoming available for rare diseases so it is important not to miss now treatable conditions.

P127 - Methylmalonic Acidemia

Herrera Gana, M.(1); Muñoz, M.(1); Rojas C, A.(1)

(1): Hospital Clinico Universidad de Chile, Santiago, Chile

Methylmalonic academia is a methylmalonic metabolic disease caused by the deficiency or absence of methylmalonyl-CoA mutase enzyme involved in the metabolism of the amino acids methionine, threonine, valine and isoleucine. There forms that may be due to failure of the Cobalamin. The accumulation of Methylmalonic acid in the blood causes according to the type of alteration, symptoms such as food refusal, vomiting, impaired consciousness and neonatal-onset seizures or variant forms that arise from slightest way at later ages. A case is presented, in which an infant, with a history of being newborn term without perinatal pathology, daughter of consanguineous parents, that at 4 months post pentavalent vaccine box in left-sided clonic seizures associated with flicker. At this time it is interpreted as a 2nd vaccination. Two EEG Videos are taken and reported as normal. Computed axial tomography informed to be normal. Nuclear Magnetic Resonance regular shows hyperintensity of pale nuclei, bulbar pyramid and signs of decreased brain volume predominantly front-temporal that may correspond to degenerative inherited metabolic disease (AGT1). Admitted to our hospital with history of one week of decreased stool consistency, coryza, decay. To this a seizure is added with limb movement and blink about 20 min duration. She comes to the emergency service, where is noted that she is feverish, at that time after overall evaluation she is discharged with paracetamol every 6 hrs, however sub-fever persisted with respiratory symptoms and watery stools. The patient decided to consult again and on the way it presents blink and lower limb movements. It is hospitalized for study and management. **Initial examinations:** Normal blood count, standard biochemical profile, gases, ammonia and normal serum electrolytes .Presents nutritional risk at admission (P / T -1). For treating the seizures she was charged with phenobarbital iv and then through oral of maintenance. After initially leaving her with regimen at 0, she is fed with breast milk and start supplementation with L-carnitine 300 mg / kg / day and gets zinc. The result of metabolic screening in her urine: marked increase in methylmalonic acid also methyl citric acid excretion is detected. Homocysteine levels in the normal range and acylcarnitines. B12 levels below the normal range. (Mild) dg probably methylmalonic aciduria variant form so breastfeeding is maintained and special formula (Propinex) and 10 mg vitamin B12 starts. The patient didn't tolerate well the special formula by mouth. A month later presented convulsive status with exams of Gases, plasma electrolytes, Ammonia and Lactic normal. Infectious regular screening is normal. It is added to the Levetiracetam therapy and breastfeeding is suspended .It starts solid food snack lunch and dessert, and left with 4 bottles of 200 ml Propinex 1 with regulating tolerance. The neurological point of view now has a slight delay psychomotor development and has continued to submit partial seizures that are short blink about 3 per day, presents regular oral tolerance and steady weight so she poses in performing gastrostomy. **Conclusions:** methylmalonic aciduria is a metabolic disease with relative low frequency 1: 50,000, which is necessary to suspect against infant with delayed psychomotor development and seizures, existing variant forms that are harder to detect. The research emphasizes the importance of the neonatal metabolic screening tests so as to have early treatment and monitoring that allow to give these children a better survival and quality of life.

P128 - Galactosemia Due to Galactokinase Deficiency: Report of a New Mutation in a Mexican Patient

Torres Sepúlveda, M.(1); Martínez Garza, L.(1); Díaz Alvarado, L.(1); López Uriarte, G.(1); Sánchez Peña, A.(1); Villarreal Pérez, J.(2); Ranieri, E.(3)

(1): Departamento de Genética UANL, Monterrey Nuevo León, México
(2): Servicios de Salud de Nuevo León, Monterrey Nuevo León, México
(3): Women's and Children's Hospital, Adelaide, Australia

Introduction: Since the year 2000, an expanded neonatal screening for more than 30 metabolic disorders, included Galactosemia, has been conducted in Nuevo Leon, Mexico. Here we present a case of Galactosemia due to GALK deficiency and the molecular diagnosis. **Presentation of case:** A blood sample was obtained at 24 hours birth, from a male neonate born at term from non-consanguineous parents. Total galactose (Perkin Elmer Neonatal Kit) was reported elevated in first and second samples (22 and 21 mg/dl, respectively. Normal <10). GALT Enzyme activity was reported slightly below normal reference values (29%). Allele specific PCR was performed for Q188R and Duarte variants as well as a bi-directional sequence of the GALT gene finding no mutations. The sequence of the gene GALK (Sanger, ABI Prism 3130 XL Generic Analyzer), showed two mutant alleles, p.Arg256Trp (c.766 C>T) and p.gly373Ala fs*61 (c.1118delG), the last didn't reported previously. **Discussion:** The frequency of Galactosemia due to GALK deficiency reported in the literature is 1:40,000 alive newborns while in our population was 1: 100,000. The diagnosis was made by three weeks of age, given the chance to treat the baby opportunely. After three years of follow up the baby is asymptomatic and motor and neurologic development is normal. He is under a supervised diet supplemented with calcium and vitamin D. **Conclusion:** It is important that neonatal screening programs have confirmatory test even for the non common causes of IEM. We here reported a new pathologic mutation of *GALK* gene.

P129 - Hyperornithinemia: Diagnostics and Nutritional Food Handling on the First Case Reported in Cuba

Zayas Torriente, G.(1); Carrillo Estrada, U.(2); Torriente Valle, J.(3); Robaina, Z.(4); Abreu Soto, D.(1)

(1): Instituto Nacional de Higiene, Epidemiología y Microbiología, La Habana, Cuba
(2): Hospital pediátrico marfan-borrás, La habana, Cuba
(3): Instituto Nacional de Higiene, Epidemiología y microbiolofgía, La habana, Cuba
(4): Centro Nacional de Genética Médica, La habana, Cuba

Introduction: The Hyperornithynemia is a disorder of the metabolism of amino acids considered fairly rare, with a recessive autosomal inheritance. World literature reported 100 cases. This disease was initially described by Jacobson in 1888. In 1896 Fuchs gave it the name which has been maintained until today. It is due to a lack of the enzyme ornithine Aminotransferase (OAT), dependent on phosphate pyridoxine which is reduced in about 50% of patients producing increased ornithine levels in plasma (6-10 times more than normal), blood, aqueous humour and urine. Clinical manifestations generally appear in the school, as a result of the visual deficit observed in fundus atrophy of choroid and retina gyrate. **Aim:** To describe the case for a female patient of 7 years of apparently healthy. Early childhood psychomotor development was normal. At the beginning of the school presents difficulties for the vision progressively causing learning disabilities. **Methodology:** Ophthalmological (eye and refractive Fund) and electromyography tests; biochemical genetic study (quantification of ornithine in serum by HPLC); nutritional evaluation by means of weight, size; rates (weight/age; Size/age; Weight/height; Body Mass Index); psychometric test. After the diagnosis indicated dietetic and nutritional treatment. By calculating the energy and nutrients using the nutritional recommendations for the Cuban population, taking into account the control of proteins of animal origin, indicating diet consistent en1851 Kcal; Protein: 56 g; Fat: 47 grams; Carbohydrates: 301 grams; and vitamin B6 supplementation. **Results:** Fundus: atrophy, gyrate from the retina, papillae of defined borders, attenuation of vascular caliber, pigments in bone spicules in periphery media; sometimes Exstrophy 15°. Refraction: Eye right: 6.00 - 100 x 180°; Left eye: 6.50 - 100 x 20°. Normal electromyography. Quantification of ornithine in serum: 975 umo/l (high). Nutritional evaluation: weight/age percentile 90-97; Size/age 50-75th percentile; weight/height >percentile 97; Body Mass Index: percentile 90-97, Classification: obesity. Test psychometric: intelligence quotient = 69 (cognitive ability. Slight Mental retardation). **Conclusions:** Regular food, and ophthalmologic monitoring are necessary for metabolic and ocular disorders and learning improvement.

P130 - Can the Same Platform of Tandem Mass Spectrometry on Newborn Screening of Amino Acid and acylcarnitine be Used for Investigation of Symptomatic Patients? A 4-Year Experience

Piazzon, F.(1); Garcia, L.(1); Arita, D.(1); Martins, H.(1); Silva, E.(1); Kok, F.(2); Bueno, C.(2); Hadachi, S.(1)

(1): Associação de Pais e Amigos dos Excepcionais de São Paulo, São Paulo, Brazil
(2): Universidade de São Paulo, São Paulo, Brazil

Introduction and methods: Amino acid (AA) and acylcarnitine (AC) profile by tandem mass spectrometry (TMS) is a well-established technology for newborn screening (NBS), but its usefulness in diagnosing symptomatic patients beyond neonatal period in not well determined. APAE-SP, a non-profit

institution pioneer in NBS in Brazil, offers AA and AC profile by TMS for patients with suspicion of IEM around the country, by filling in a clinical form on your website. **Results:** In the last 4 years, we have screened 2,178 symptomatic individuals and we were able to diagnose 18 cases of IEM (0.8%), later confirmed by other means, including molecular analysis. Confirmed IEM is at least 16 times more frequent in this population than in NBS. AA disorders were detected in 7 patients (PKU in 1, UCD in 4, MSUD in 1 and NKH in 1), organic acidemias in 7 (MMA in 3, GA1 in 3, and HMGCL deficiency in 1), and fatty acid oxidation disorders in 4 individuals (CUD in 2 and MADD in 2). **Conclusions:** Even knowing that AA and AC profile by TMS using paper filter is not the gold standard for investigation of IEM in symptomatic patients, in countries like Brazil, with severe access constrains to more specialized biochemical tests, it can be a fast and reliable alternative.

P131 - Three Cases of Niemann Pick Type C: Clinical, Biochemical and Molecular Aspects

Lemes, A.(1); Zabala, C.(1); Cerisola, A.(2); Cabrera, A.(1); Castro, M.(1); Fernandez, L.(1)

(1): Instituto de Seguridad Social-BPS, Montevideo, Uruguay
(2): Facultad de Medicina-Cátedra de Neuropediatria, Montevideo, Uruguay

Introduction: Niemann-Pick C disease (NP-C) is a rare progressive neurovisceral lysosomal lipid storage disorder with an estimated incidence of 1/120 000 live births. It has a broad clinical spectrum. The neurological involvement defines the disease severity but is typically preceded by systemic signs like splenomegaly. The most characteristic sign is vertical supranuclear gaze palsy. Is transmitted in an autosomal recessive manner and is caused by mutations of either the NPC1 (95% of families) or the NPC2 genes. The exact functions of the NPC1 and NPC2 proteins are still unclear. NP-C is described as a cellular cholesterol trafficking defect but in the brain, the prominently stored lipids are gangliosides. Symptomatic treatment of patients is crucial. A first product, Miglustat, has been approved in some countries for specific treatment of the neurological manifestations. The prognosis largely correlates with the age at onset of the neurological manifestations. **Aim:** To present clinical, biochemical and molecular aspects of three unrelated cases of NPC. **Clinical cases:** our cases first clinical manifestation was splenomegaly detected at age: 6 months, 10 months, and 14 years of age. Sex: a female and two males. In all cases: bone marrow showed storage cells, plasma oxysterols were elevated. All but one have slight elevation of chitotriosidase, Pathogenic NPC1 gene mutations were detected in all cases. Neurological function is monitored periodically. One case installed vertical supranuclear gaze palsy and specific treatment was started. Positron emission tomography was performed in two cases; it showed abnormalities before vertical supranuclear gaze palsy, in one. **Conclusion:** with this presentation, we highlight 1) the importance to search for NPC in case of a child or adolescent with isolated splenomegaly; and 2) the importance of monitoring neurological function because it allows to start immediately the specific treatment which has shown stabilization or reduced rate of disease progression.

P132 - Renal Failure in Propionic Acidemia, Not Such an Infrequent Complication: Report of 2 Cases

Arias Pefaur, C.(1); Campo, K.(1); Bravo, P.(1); Cabello, J.(1); Manterola, C.(2); Castro, G.(1); Hamilton, V.(1); Cornejo, V.(1); Valiente, A.(1)

(1): Instituto de Nutrición y Tecnología de los alimentos, Santiago, Chile
(2): Hospital Luis Calvo Mackenna, Santiago, Chile

Introduction: Propionic acidemia (PA) is a metabolic disease of propionate metabolism caused by enzymatic deficiency of propionyl-Coa Carboxylase (PCC). Renal failure has been mainly reported in adult patients as a long term and unusual complication. **Objective:** report and describe two cases with propionic acidemia and renal failure, one of them starting in childhood. **Methods:** Review of clinical records and the prospective follow up that has been made at the metabolic clinic of Institute of nutrition and food technology (INTA), University of Chile). **Description:** Case 1: full-term newborn, female, consanguineous parents, with normal pregnancy and delivery. History of two relatives who died in the newborn period. Patient was diagnosed at 5 months old because of developmental delay, axial hypotonia, cyclic vomiting and metabolic acidosis. Metabolic workup showed elevation of ammonium and propionylcarnitine (C3) in Tandem Mass Spectrometry; also, organic acids profile shows high excretion 3-hydroxypropionic acid, tiglylglycine and propionylglycine consistent with the diagnosis of propionic acidemia. Poor adhesion to nutritional treatment and bad metabolic control resulted in later obesity, hypertension, insulin resistance and intellectual disability. At 19 years of age, patient presents a metabolic decompensation with hallucinations, encephalopathy and bleeding; laboratory results show acute renal failure that evolved into a chronic renal failure with current need of periodic dialysis. Case 2: brother of patient 1; diagnosed in the newborn period with normal pregnancy and delivery. His evolution was similar with bad compliance to metabolic management. At the age of nine years routine laboratory tests suggested chronic renal failure because of high serum creatinine and reduced glomerular filtration rate. Currently, patient remains clinically asymptomatic. **Discussion:** In the past years, more reported cases of renal failure in propionic acidemia has been described, generally as a longterm follow-up complication, with a pathophysiology that remains unknown, however the lack of adequate metabolic control in these cases may have contributed to kidney damage. **Conclusion:** With the increase of survival in patients with PA, complications such as kidney failure may occur, so the metabolic team follow-up must be aware of this complication.

P133 - Diagnosis, Management and Follow Up of Patients With Maple Syrup Urine Disease: Report of a Case

Martínez Rey, L.(1); Contreras Roura, J.(1); Camayd Viera, I.(1); Nogueras Rodríguez, L.(1); Padrón Díaz, A.(1); Busto Aguiar, R.(2); Zayas Torriente, G.(3); Falcón Rodríguez, D.(4); Rodríguez Hernández, E.(2); González Reyes, E.(5)

(1): Centro Nacional de Genética Médica, La Habana, Cuba
(2): Hospital Pediátrico Matanzas, Matanzas, Cuba
(3): Instituto de Nutrición e Higiene de los Alimentos, La Habana, Cuba
(4): Centro Provincial de Genética de Matanzas, Matanzas, Cuba
(5): Centro de Inmunoensayo, La Habana, Cuba

Introduction: Maple syrup urine disease (MSUD) is an autosomal recessive inherited metabolic disease that affects the body's ability to metabolize the essential branched chain amino acids (BCAA). There are five clinical forms where classical neonatal variant is the most severe. The diagnosis is made by determining of high levels of BCAA and ketoacids in blood and urine. The aim of this study is to describe clinical and biochemical features, who's made the diagnosis of MSUD, and to propose a protocol for management and monitoring biochemical of these patients. **Materials and Methods:** The diagnosis was made by qualitative chemical tests in urine and Thin Layer Chromatography (TLC) for the determination of amino acids in urine and serum. Gas Chromatography/ Mass Spectrometry and High Performance Liquid Chromatography (HPLC) were used for confirmation and biochemical monitoring after starting treatment. **Results:** The test of 2,4 dinitrophenylhydrazine for ketoacids was positive. High levels of BCAA were detected by TLC and HPLC. Organic acids profile showed elevated excretion of ketoacids in urine. So we suggested a classical neonatal form of MSUD for the clinical manifestations of the patient, the age of onset of symptoms and the reversal of neurological symptoms. Finally we implemented a protocol for the biochemical diagnosis, management and monitoring of MSUD in our country. **Conclusions:** The proposed protocol allowed to revert the most several neurological symptoms of MSUD. The acquired experience in this case consolidated the Cuban algorithm for the diagnosis's MSUD and introduced this protocol for the follow up of these patients in our country.

P134 - Atypical Nonketotic Hyperglycinemia by Dysfunction of T Protein of Glycine Cleavage System

Salgado, P.(1); Galvis, J.(2); Vargas, C.(2); Ramírez, A.(1); Beltrán, O.(3); Guio, L.(2); Marquez, W.(2)

(1): Facultad de Medicina. Universidad Militar Nueva Granada, Bogota, Colombia
(2): Fundación HOMI Hospital de la Misericordia, Bogota, Colombia
(3): Facultad de Medicina. Universidad Militar Nueva Granada. Fundación HOMI Hospital de la Misericordia, Bogota, Colombia

Introduction: Atypical nonketotic hyperglycinemia (NKH) is a heterogeneous disease with variable expression consistent at three clinical forms: *neonatal, infantile*, and *late onset.* Etiology caused by mutations in three genes in the mitochondrial glycine cleavage system (GCS). **Materials and methods:** Description of a female infant of 14 months old with intractable seizures and developmental delay by dysfunction of T protein of glycine cleavage system at childreńs hospital in Colombia. **Case Report:** Third pregnancy without complications of consanguineous parents, vaginal delivery at term, weight 2990g, height 50cm, breast feeding at 10 minutes of life. At 4 days-old enters to emergency room coursing with apnea, respiratory distress and cardiac arrest, which requires ventilatory support. Additionally, presents seizures treated with phenobarbital, without amelioration therefore is added to her treatment oxcarbazepine and levetiracetam. Despite the polypharmacy management continues with abnormal movements, so she was treated with topiramate, clonazepam, and phenytoin; finally by the improvement in the frequency of episodes, left a definitive pharmacological management has been phenobarbital, oxcarbazepine and levetiracetam. Also presents developmental delay and swallowing difficulties, so actually uses gastrostomy tube. Auditory evoked potential test shows bilateral hypoacusia and a brain nuclear magnetic resonance with spectroscopy reveals neuronal and membranes loss with mildly retarded myelination for age. It was not possible the cerebral spinal fluid/ plasma glycine ratio analysis. Nonetheless, cytogenetic genomic comparative array coupled with single nucleotide polymorphism identify homozygotic loci in 2,5% of the genome, and in the complete sequencing of AMT gene (encodes T protein) reports biallelic mutation c.959G>A, with an aminoacid change p.Arg320His. Allowing a confirmed diagnosis by which to the management was added dextromethorphan. **Conclusion:** In atypical NKH the presentation in the neonatal form is similar to the classical one but with a subsequent better outcome. The metabolic defect in neonatal and infantile forms is usually an abnormality in the P-protein or less commonly in the T-protein of GCS. The specific mutation founded in the patient was previously reported that causes the NKH in a classical form, but in our case it develops in atypical way in the clinical presentation and its correlation to the genetic studies.

P135 - Pregnancy in a Patient With Mucopolysaccharidosis Type I (MPS I) Treated With Enzyme Replacement Therapy—Case Report

Silva, A.(1); Souza, C.(1); Sanseverino, M.(1); Magalhães, J.(1); Vairo, F.(1); Fagondes, S.(1); Manica, D.(1); Barrios, P.(1); Dalla-corte, A.(1); Giugliani, R.(1)

(1): Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

Introduction: Mucopolysaccharidosis type I (MPS I) is a progressive lysosomal storage disease that results from the deficiency of α-l-iduronidase (IDUA). There are different phenotypes of the disease according to the degree of clinical severity, the mild form (Scheie) and severe form (Hurler). The main manifestations include facial, skeletal and upper airway abnormalities, corneal opacity, organomegaly and valvular heart disease. Enzyme replacement therapy (ERT) with laronidase is the only specific treatment for the disease. The objective of this report is to describe the case of a MPS I patient in her first pregnancy, treated with laronidase, every other week, in double dose. **Methods:** Chart review and description of gestational and postnatal follow-up data. **Results:** The mother is a 28-year-old with Sheie MPS I (genotype R89Q/W402X), no consanguineous couple. The patient remained in ERT every other week and monitored by a multidisciplinary team throughout pregnancy (including obstetrician, pulmonologist, cardiologist, otorhinolaryngologist, neurosurgeon, geneticist, fetal medicine group and nutritionist). On physical examination, the patient had height = 136cm. Echocardiogram shows mild to moderate valve insufficiency and spirometry suggest moderate restrictive respiratory disorder. Morphological ultrasound and fetal echocardiogram were normal. A healthy 1,7kg female was delivered by cesarean section at 31 weeks. There are no complications or congenital malformations. No adverse event related to ERT was reported. The IDUA enzymatic dosage of the baby was normal. **Conclusions:** There are still few reports of pregnancies in patients with MPS. No teratogenic effects are expected of ERT. Reports of pregnancies treated with ERT available for other lysosomal diseases also showed pregnancies without adverse events to the fetus. The strict monitoring of patients for possible complications is important and multidisciplinary management was critical to the successful outcome of this case.

P136 - Hyperphenylalaninemia and BH4 Deficiency: Two Case Reports

Bravin, C.(1); Sarquis Cintra, T.(1); Passamani, E.(1); Correa Motta, S.(1); Fardin, S.(1); Goulart, S.(1)

(1): Apae Vitória Es Brasil, Vitória, Brazil

Introduction: Tetrahydrobiopterin (BH4) deficiency can manifest as hyperphenylalaninemia persistency even after conventional dietetic therapy. The BH4 is the cofactor on many pathways: on the hydroxylation conversion of the phenylalanine to tyrosine; on the conversion of tyrosine to L-Dopa and to Dopamine; and on the hydroxylation conversion of tryptophan to 5-hidroxitriptophan, which is essential to the serotonin synthesis. Consequently, the BH4 deficiency can compromise the neurotransmitters synthesis. **Design:** Research of bh4 deficiency on blood test samples of two case reports diagnosed on newborn screening after unsuccessful dietetic therapeutic, showing neurological and psychomotor delay. **Results and Conclusion:** One patient showed PTTS deficiency (6-piruvoil tetrahydrobipterin synthesis) and the other, DHPR deficiency (dihidropterin reductase). Although the main reason for hyperphenylalaninemias concerns to the phenylalanine hydroxylase deficiency (98% of the cases), the BH4 synthesis and repair defect (2% of the cases) should also be investigated on the differential diagnosis as long as they may not respond to the dietetic restriction trial and neurological function deterioration could appear. The early diagnosis and adequate treatment yield on the patient prognosis as well as could offer proper genetic prediction advice to the relatives.

P137 - An Unusual Sight of the Epilepsy: ATP1A3 Mutations

Fiesco Roa, M.(1); Kleinert Altamirano, A.(1); Brockmann, K.(2)

(1): Crit Chiapas, Tuxtla Gutiérrez, Chiapas, México
(2): Faculty of Medicine, University of Göttingen, Göttingen, Germany

Introduction: Alternating hemiplegia of childhood (AHC) an autosomal dominant disorder, arises from mutations in *ATP1A3* gene, which encode the neuron-specific Na+/K+-ATPase α3 subunit and is predominantly expressed in the neurons of basal ganglia, hippocampus, and cerebellum. It is characterized by transient episodes of hemiplegia combined with paroxysmal symptoms (dystonia, nystagmus, autonomic disturbances, seizures, and permanent neurological deficit) before age 18 months and often is precipitated by specific triggers. **Material and methods:** We report the diagnostic approach of 2 unrelated patients. The first one is a 6-year-old girl and the other one is a 4-year-old boy, both of them are the first child of healthy Mexican parents, there was no family history, after an uneventful pregnancy were born at term without complications. Their early motor development was normal, until 5 and 3 months, respectively, when the girl begun with recurrent episodes of transient alternating hemiplegia and seizures, while the boy with irritability and seizures. At the onset of symptoms, both patients were misdiagnosed as cerebral palsy. **Results:** Diagnostic approach included cerebral MRI and several metabolic evaluations, all of which were normal. Sanger and whole genome sequencing of coding exons 1-23 of *ATP1A3* gene revealed a heterozygous missense mutation, c.2401G>A (exon 17, p.Asp801Asn) in the first patient, and c.2327A>T (exon 17, p.Glu776Val) in the other one, neither mutations being found neither in the parents nor in 100 controls. **Conclusions:** Both patients presented a heterozygous de novo *ATP1A3* gene mutation, one of them not previously reported, and in the case of our patient, associated with an early onset and worst presentation. AHC represents significant challenge in diagnosis, management, and treatment. Early clinical suspicion of AHC is important in patients with refractory childhood epilepsy associated with dyskinesias, hypotonia or severe developmental disability. Early diagnosis can prevent invasive diagnostic procedures or triggers attacks, and choose the best therapy to improve prognosis and quality of life of

patients and their families. It is important to keep in mind the wide variability of onset and presentation of the symptoms. Nowadays, both patients still have seizures even with combined therapy. No reports in Mexican patients.

P138 - Experience in Management of a Patient With Ethylmalonic Encephalopathy

Morales Acosta, M.(1); Dueñas Roque, M.(1); Prötzel Pinedo, A.(1)

(1): Hospital Nacional Edgardo Rebagliati Martins, Lima, Perú

Introduction: Ethylmalonic encephalopathy (EE) is a rare autosomal recessive metabolic disorder, which affects the brain, gastrointestinal tract and peripheral vessels. Patients with EE have been treated more or less successfully with L-carnitine, riboflavin and/or Q10 supplements, as well as other vitamin therapies, which may improve energy metabolism and alleviate oxidative stress. The prognosis is generally poor: although milder chronic cases are known, most patients die before the age of ten years. **Material and Methods:** We report a two-year-old peruvian boy with ethylmalonic encephalopathy. **Results:** He was born from healthy and non-consanguineous parents, at 35 weeks of gestational age; his born weight was 2100 g. He had an older sister who died when she was 2 years old with ''Leigh Disease''. He presented at the age of sixth months old with mucous chronic diarrhea, developmental delay and myoclonic seizures. He was found to have petechiae, central hypotonia, and weight and head circumference below the third percentile. He was admitted several times at the emergency room because of recurrent pneumonia, wheezing and refractory epilepsy. Plasma lactate was mildly elevated. Visual and auditory evoked potentials reported signs of bilateral dysfunction. EEG was abnormal with multifocal epileptiform activity. Cerebral MRI showed basal ganglia and white matter changes probably related to secondary ischemic lesions. Urine organic acids results was consistent with the diagnosis of ethylmalonic encephalopathy. Seizures were partially controlled with levetiracetam and vigabatrin. Nutritional management has included a fat-restricted diet, Q10 coenzyme, riboflavin (B2) and L-carnitine. Later, acetylcysteine was added to medical treatment. Currently, the respiratory symptoms and diarrhea have improved, and the seizures are partially controlled. The patient has remained stable for 11 months without new emergency admissions. **Conclusion:** Ethylmalonic encephalopathy is a devastating metabolic disease with a difficult clinical management especially because of the refractory epilepsy and the respiratory symptoms who cause frequent emergency admissions. We report our experience managing a case of EE with evidenced clinical improvement.

P139 - Nutritional Treatment for Maple Syrup Urine Disease (MSUD): A Case Report

Sanchez Peña, M.(1); Serrato Sanchez, K.(2); Bazaldua Ledesma, V.(2); Leyva Mendez, P.(2)

(1): Departamento De Genética Facultad De Medicina Universidad Autonoma De Nuevo Leon, Monterrey Nuevo Leon, Mexico
(2): Facultad De Salud Pública Y Nutrición Universidad Autonoma De Nuevo Leon, Monterrey Nuevo Leon, Mexico

Introduction: Maple Syrup Urine Disease (MSUD) is an autosomal recessive disorder caused by branched-chain α- ketoacid dehydrogenase (BCKAD) complex deficiency resulting in the accumulation of the branched-chain amino acids (BCAA) (leucine. isoleucine, and valine) and their corresponding α-ketoacids (BCKA) and alloisoleucine (ALLO) in blood, urine and cerebrospinal fluid. **Materials and methods:** Patient from 1 month old female with a weight of 2.9 kg and length of 49 cm (-2SD) diagnosed with MSUD by newborn screening test with elevated valine 1066 μmol/L (Normal 66-299 μmol/L), isoleucine 619 μmol/L (Normal 20-96 μmol/L), leucine 3323 μmol/L (Normal 29-151 μmol/L) and alloisoleucine 234 μmol/L (Normal 0-2 μmol/L). With diaper rash, we started the treatment with diet limited in branched amino acids, 120 kcal/kg and 3 g of proteins/kg, using free formula branched amino acids (BCAD-MJ®) and 3 Oz a day of Similac®; ablactation was started at 5 months of age. **Results:** After 15 days of treatment the patient showed clinical improvement and a month later laboratory parameters they indicated levels of valine 28 μmol/L (Normal 84-354 μmol/L), isoleucine 71 μmol/L (Normal 10-109 μmol/L), leucine 85 μmol/L (Normal 43-181 μmol/L). The nutrition treatment has been carried by the parents with adherence, her current weight is 6.8 kg (-1SD) and length 69 cm (+3SD). **Conclusion:** Early diagnosis and adequate treatment allows a better nutritional prognosis.

P140 - Lysinuric Protein Intolerance (LPI), Report of 2 New Cases

Durand, C.(1); Szlago, M.(2); Marchione, M.(1); Salina, M.(1); Weil, K.(1); Carabajal, R.(1); Schenone, A.(1)

(1): FESEN-Laboratorio de Neuroquímica "Dr. N.A. Chamoles", Buenos Aires, Argentina (2): Enfermedades Metabólicas, Servicio de Genética. Hospital de Niños "Ricardo Gutierrez", Buenos Aires, Argentina

Introduction: LPI is an autosomal recessive inborn error of metabolism (IEM). The disease typically appears in infancy with gastrointestinal symptoms and clinical manifestations consistent with hyperammonemia (emesis, lethargy, coma). Nonspecific laboratory manifestations include microcytic anemia/pancytopenia, increased ferritin, zinc and LDH. Hemophagocytic lymphohistiocytosis and alveolar proteinosis are known severe complications. The disease is due to a defect in the

transport of dibasic aminoacids (ornithine, lysine and arginine), leading to their chronic loss through GI tract and kidney. The overall depletion of those aminoacids leads to malfunctioning of the urea cycle(UC), hyperammonemia and orotic aciduria. The diagnosis requires careful evaluation of intermediate metabolism. Treatment with low protein diet, citrulline and lysine can avoid episodes of hyperammoneia and decrease the severity/frequency of the complications. **Aim:** To report our experience in the diagnosis of a very rare disease that, because of the biochemical profile, could be misdiagnosed as an UC disease. **Material and Methods:** Review of medical records of patients diagnosed with LPI in a reference center for the diagnosis of IEM. **Results:** Patient 1: At 3 month presents with refusal to eat and respiratory distress with torpid evolution that requires tracheostomy and mechanical ventilation. Bibasal ground glass opacities in images and alveolar proteinosis in biopsy were seen. At 2 years old presents hypertonic crises and loss of awareness with normal EEG. MRI shows abnormal images in basal gangli. Metabolic studies show hyperammonemia, elevated orotic acid and results in urinary aminoacids that resembles those found in LPI. Medical and nutritional treatment is started and evolution is good. Patient 2: Presents at 8 months with drowsiness, hypotonia and refusal to eat that recede spontaneously. Hepatosplenomegaly, leukopenia, thrombocytopenia, elevated transaminases and metabolic acidosis. At 2 and 3 years presents similar episodes that yields with food intake cessation. The initial presumptive diagnosis was OTC deficiency but as there was no response to treatment, a citrulline test was performed and LPI confirmed. Outcome is good till 8 years old follow up. **Conclusion:** LPI is a rare disorder that has to be suspected in patients with hyperammonemia and orotic aciduria when criteria are not met for urea cycle disorders.

P141 - A 3-Month-Old Boy Presenting With Fulminant Hepatic Failure and Mitochondrial Depletion Syndrome With a Homozygous Missense Variant in the POLG2 Gene

Iglesias, A.(1); Wou, K.(2); Naini, A.(2); Hirano, M.(2)

(1): Columbia University Medical Center, Hastings on Hudson, USA
(2): Columbia University Medical Center

Introduction: Mitochondrial DNA (mtDNA) depletion syndromes are autosomal recessive disorders characterized by significant mtDNA depletion with progressive impaired energy production. Myopathic, encephalomyopathic, hepatocerebral or neurogastrointestinal are known. Mutations in nuclear genes for mitochondrial nucleotide synthesis or mtDNA replication have been described. One of them, *POLG*, encodes for mtDNA polymerase gamma. Mutations in *POLG* cause early-onset liver failure and encephalopathy with refractory seizures. *POLG* encodes the catalytic subunit and *POLG2* encodes the accessory subunit of the POLG enzyme, required for replication of mtDNA. **Aim:** We are reporting a 3-month-old boy with a novel homozygous missense variant in *POLG2*. **Results:** Pregnancy and newborn period were uneventful. Family history was negative. He was healthy until 3 months when he was diagnosed with lactic acidosis and liver failure. He was admitted for fulminant hepatic failure, stabilized and metabolically compensated. Exam was positive for an upturned nose, jaundice, fisting and hepatomegaly. Whole exome sequencing (WES) and mitochondrial studies on blood, muscle and liver were done. Sequencing and deletion/duplication of mtDNA were negative in all tissues. Quantitative PCR for mtDNA level normalized to a nuclear DNA gene showed partial mtDNA depletion in blood leukocytes (53% of control mean) and severe depletion in liver (75%) and muscle (81%). SNP-array showed an 877kb interstitial deletion associated with 16p13.11 syndrome; but unrelated to mitochondrial depletion. On WES a homozygous missense variant in *POLG2* (Chr17:62492543G>A, NM_007215.3, NP009146.2:p.182R>W) was found. This is a novel variant and in silico analysis predicts to be deleterious. MR spectroscopy showed small lactate peaks, indicating mitochondrial dysfunction. Accordingly, supportive/palliative care was given including CoQ10, riboflavin and L-carnitine. Heterozygous mutations in *POLG2* have been associated with progressive external ophthalmoplegia. However, a homozygous missense variant in *POLG2* has not previously been identified. Encoding for the accessory subunit of POLG enzyme, the only DNA polymerase in the mitochondria, makes likely that the homozygous variant caused the mtDNA depletion in our patient. **Conclusion:** Multiplex quantitative PCR for both mitochondrial DNA and nuclear DNA and WES provided diagnostic evidence allowing appropriate counseling and coherent follow-up. Moreover, it allowed us to diagnose a new patient with an extremely rare form of mtDNA depletion syndrome. Mitochondrial DNA (mtDNA) depletion syndromes are autosomal recessive disorders characterized by significant mtDNA depletion with progressive impaired energy production. Myopathic, encephalomyopathic, hepatocerebral or neurogastrointestinal are known. Mutations in nuclear genes for mitochondrial nucleotide synthesis or mtDNA replication have been described. One of them, *POLG,* encodes for mtDNA polymerase gamma. Mutations in *POLG* cause early-onset liver failure and encephalopathy with refractory seizures. *POLG* encodes the catalytic subunit and *POLG2* encodes the accessory subunit of the POLG enzyme, required for replication of mtDNA. We are reporting a 3-month-old boy with a novel homozygous missense variant in *POLG2*. Pregnancy and newborn period were uneventful. Family history was negative. He was healthy until 3 months when he was diagnosed with lactic acidosis and liver failure. He was admitted for fulminant hepatic failure, stabilized and metabolically compensated. Exam was positive for an upturned nose, jaundice, fisting and hepatomegaly. Whole exome sequencing (WES) and mitochondrial studies on blood, muscle and liver were done. Sequencing and deletion/duplication of mtDNA were negative in all tissues. Quantitative PCR for mtDNA level normalized to a nuclear DNA gene showed partial mtDNA depletion in blood leukocytes (53% of control mean) and severe depletion in liver (75%) and muscle (81%). SNP-array showed an 877kb interstitial deletion associated with 16p13.11 syndrome; but unrelated to mitochondrial depletion. On WES a homozygous missense variant in *POLG2* (Chr17:62492543G>A, NM_007215.3,

NP009146.2:p.182R>W) was found. This is a novel variant and in silico analysis predicts to be deleterious. MR spectroscopy showed small lactate peaks, indicating mitochondrial dysfunction. Accordingly, supportive/palliative care was given including CoQ10, riboflavin and L-carnitine. Heterozygous mutations in *POLG2* have been associated with progressive external ophthalmoplegia. However, a homozygous missense variant in *POLG2* has not previously been identified. Encoding for the accessory subunit of POLG enzyme, the only DNA polymerase in the mitochondria, makes likely that the homozygous variant caused the mtDNA depletion in our patient. Multiplex quantitative PCR for both mitochondrial DNA and nuclear DNA and WES provided diagnostic evidence allowing appropriate counseling and coherent follow-up. Moreover, it allowed us to diagnose a new patient with an extremely rare form of mtDNA depletion syndrome.

P142 - Pelizaeus Merzbacher: A Rapidly Fatal Leukodystrophy

Salgado Riaño, P.(1); Castillo Brito, J.(1); Beltrán Casas, O.(2)

(1): Facultad de Medicina, Universidad Militar Nueva Granada., Bogotá, Colombia
(2): Facultad de Medicina, Universidad Militar Nueva Granada. Fundación HOMI Hospital de la Misericordia, Bogotá, Colombia

Introduction: Pelizaeus Merzbacher disease (PMD) is an entity of X-linked inheritance, produced by mutation of PLP1 gene, which encodes the proteolipid protein 1 also called lipophilin, which constitutes 50% of the structure of myelin in the central nervous system. **Methods:** Description of a 13 month old child with PMD in a pediatric referral hospital in Bogotá, Colombia. **Case description:** 4 months old male infant that course with psychomotor delay, generalized hypotonia, no head control, head hesitation, lateral nystagmus, dysphagia to semisolid food with poor weight gain. In the background are: consanguineous union product, controlled pregnancy and vaginal delivery at term without complications, birth weight of 3350g, height and head circumference of 52cm to 35cm each. He is assessed neurophysiology department at 5 months of age with abnormal visual evoked potentials study with impaired bilateral axonomyelinic retinocortical path. Brain MRI performed at 11 months showing alteration in the white matter signal including U and cerebellum fibers, characterized by hyperintensity on T2 and FLAIR sequences. At 13 months old weighing 7.2 kg (-2 SD to -3DS), height of 72cm lateral nystagmus, axial hypotonia, in addition to widespread distal hypotrophy and hypertonia. Gastrostomy was indicated but the parents do not accept. 30 days later, he requires hospitalization for broncho-obstructive episode with neurological impairment given by hypoactivity, hyperreflexia of lower limbs with bilateral clonus and urinary retention. He evolves with rapidly progressive deterioration and loss of consciousness, finally died. **Conclusion:** The analysis of the natural history of symptoms, the rapidly deterioration and radiological findings are indicative of PMD, guiding the differential diagnosis with respect to other leukodystrophies. In general, manifest in the infant with characteristic symptoms such as hypotonia, lateral nystagmus and severe psychomotor retardation may progress to spasticity and ataxia. The PMD is a type of demyelinating leukodystrophy with two clinical presentations: first the connatal form has very rapid progression and it is lethal around the first year, and a classic form which is progressive and with life expectancy at 5 years. Our case is consistent with PMD in a transient form of both phenotypes.

P143 - Optic Nerve Enlargement in a Case of Krabbe Disease

Araya, G.(1); Oliva, B.(1); Cabello, J.(1); Andrade, L.(2); Campodonico, P.(1); Vega, S.(1); Arriagada, P.(1); Zambrano, K.(1)

(1): Universidad de Valparaíso, Valparaíso, Chile
(2): Hospital Carlos Van Buren, Valparaíso, Chile

Introduction: Krabbe Disease(KD) is a neurodegenerative lysosomal storage disorder, which involves the central and peripheral nervous system. The optic nerve enlargement(ONE) is rarely reported in the literature **Case presentation:** Term newborn without perinatal disease. No consanguinity. Family history of neurofibromatosis type 1(NF1). At 4 months developed generalized hypotonia, hyperreflexia with normal gross motor development(PD) at that point. At 6 months old the patient was admitted and macrocephaly, persistent thumbs and developmental delay was noted. Brain magnetic resonance imaging(MRI) evidence prechiasmatic ONE and perisylvian atrophy. Acylcarnitines and aminoacids profile and ophthalmic evaluation were normal. Electroencephalogram shows moderate slow generalized rhythm. At 9 months old she presented severe swallowing disorder, development regression, persistent irritability, disconnection with the environment, wandering eye, opisthotonus posture, generalized hyperreflexia and progressive stiffness of limbs. She presented with focal epileptic status several times. Brain and spinal MRI shows progression of brain atrophy, ONE, T2 signal increased at the semioval center; pons, cerebellar, cortical spinal tract and olives commitment, respecting U fibers, consistent with leukodystrophy. Nerve conduction velocity shows motor demyelinating polyneuropathy. Galactocerebrosidase enzymatic activity was 0.2 uM/hr (normal> 0.5). KD diagnosis was made, because clinical, image and enzyme activity. The patient died at 13 months of age because respiratory failure. **Discussion and conclusions:** Leukodystrophies are a diagnostic challenge, considering the large list of conditions to be considered. Additional findings should be screened to have a clinical approach before to order a large number of enzymatic or molecular tests. ONE in association with KD has been previously reported, and in the present case it was an important clinical feature to reach the diagnosis.

P144 - Magnetic Resonance Patterns in Children With Adrenoleukodystrophy

Araya, S.(1); Troncoso, M.(1); Araya, S.(1); Santander, P.(1); Troncoso, L.(1); López, F.(1); Barrios, A.(1); Muñoz, D.(1); Guzman, G.(1)

(1): Servicio Neuropsiquiatría Infantil Hospital Clínico San Borja Arriaran, Facultad de Medicina, Campus Centro, Universidad de Chile, Santiago, Chile

Introduction: X-linked adrenoleukodystrophy (X-ALD) is a progressive disease associated with the accumulation of fatty acids of very long chain, involving brain, adrenal glands and testes. It has different forms of presentation, ranging from the cerebral form, with presentation in childhood adrenal isolation, combined adrenal and brain involvement, and adrenomyeloneuropathy. The brain magnetic resonance images (MRI) often show symmetrical hyperintense lesions parietal occipital periventricular white matter on T2-weighted sequences, with involvement of the corpus callosum and peripheral uptake of contrast. **Objective:** To describe the images characteristics in 16 children with a confirmed diagnosis of X-ALD. **Materials and methods:** Retrospective analysis of clinical and MRI of children diagnosed in our hospital with X-ALD. **Results:** 16 men, aged 6-19 years, all with confirmed diagnosis of X-ALD. 14/16 have child cerebral form. 10/14 have the classic RM alterations characterized by symmetrical lesions parietal occipital periventricular white matter, hypointense on T1 and hyperintense on T2 with commitment corpus callosum and peripheral contrast enhancement Intravenous. 2/14 presented asymmetrical occipital biparieto lateralized lesions with a great commitment to a hemisphere. All had injuries corticospinal tracts. 2/14 have symmetrical lesions bifrontal previous commitment corpus callosum. Only two patients had adrenal pure form, without injuries RMC. **Conclusions:** In our series, predominate patients with cerebral form. The symmetrical bilateral parietal occipital classic lesions were the most frequent in the RM, followed by asymmetric. The presence of children with previous injuries that can lead to diagnostic confusion.

P145 - Methylmalonic Acid (MMA), One Metabolite-Several Diseases

Spécola, N.(1); Núñez, M.(1); Salerno, M.(1); Muschietti, L.(1); Fuertes, A.(2); Schenone, A.(2)

(1): Hospital de Niños de La Plata, La Plata, Argentina
(2): FESEN CABA, Buenos Aires, Argentina

Introduction: MMA accumulation in body fluids is due to inability to convert methylmalonyl-CoA to succinyl-CoA in the propionate catabolic pathway. Acquire or genetic conditions as nutritional, absorption, transport or intracellular metabolism of vitamin B12 deficiency and defects of methylmalonyl-CoA mutase can cause increased MMA, most of which are treatable. **Objective:** Observational study that present the diverse clinical, biochemical and genetic features of a group of patients with elevated MMA, emphasized the diagnostic approach. **Material and methods:** Five patients with increase in propionylcarnitine (C3) in neonatal screening (NS) or MMA in symptomatic screening were selected. We revised clinical presentation and outcome. Biochemical features (urine and blood MMA, acylcarnitines, carnitine, total homocystein, vitamin B12) and mutation analyzed were presented. Hydroxocobalamin (OHCbl) test was considered positive after a reduction higher than 50% in urine MMA after IM 1mg/d by 3 days. **Results:** Patient 1. Increased C3 in NS. Elevated MMA with low B12 in newborn of vegan mother. Patient 2. Increased C3 in NS. Elevated MMA, normal homocystein and B12. Positive response to OHCbl test. Methylmalonyl-CoA mutase deficit (mut-). Patient 3. Metabolic acidosis with coma and hypotonia in a newborn. High C3 and MMA. No response to OHCbl test. Genotype MUTo. Psychomotor delay. Patient 4. Metabolic acidosis, lethargy in a newborn. Increased C3 and MMA. Normal homocystein and B12. No response to OHCbl test. Genotype CblB. Patient 5. Low weight newborn with respiratory distress, feeding refusal without metabolic acidosis. Seizures and hydrocephalia during the first months. Mild elevation of C3, MMA, homocystein with normal B12. Partial response to OHCbl at higher doses. Genotype CblC. Developed severe psychomotor delay and pigmentary retinopathy. **Conclusions:** Emphasized the need of careful biochemical evaluation that cover all the metabolic compounds related with MMA increased. Standardized the OHCbl test. Remarked that early diagnosis and intensive treatment, even in severe diseases, improve the prognosis.

P146 - Parenting Styles and Coping Strategies in Congenital Hypothyroid Children

Pardo Campos, M.(1); Musso, M.(2); Keselman, A.(3); Bergadá, I.(4); Gruñeiro -papendieck, L.(3); Chiesa, A.(3)

(1): Fundacion de Endocrinologia Infantil. Universidad Catolica Argentina, CABA, Argentina
(2): CIPME (Conicet)-UADE, CABA, Argentina
(3): CEDIE-CONICET-FEI-División de Endocrinología, Hospital de Niños R. Gutiérrez, CABA, Argentina
(4): CEDIE-CONICET-FEI- División de Endocrinología, Hospital de Niños R. Gutiérrez, CABA, Argentina

Introduction: Congenital hypothyroidism detected early and treated properly does not lead to mental impairment, but requires prolonged treatment, care, and control. As a chronic disease it requires lifelong treatment and this may influence the bonding between parents and child. This link also influences on the resources of the child to deal with conflictive situations. **Objectives:** To describe predominant perceived parenting styles in congenital hypothyroid children from the perception of the child (son) and to identify their coping strategies. **Patients and methods:** An intentional sample of 60 congenital hypothyroid children, detected through neonatal screening and adequately treated since the first month of life, aged 9 to 10 years, was selected among patients of the Endocrinology Division of the

Buenos Aires Children's Hospital R Gutierrez. 60 healthy children of the same age were recruited as a control group. Inclusion criteria were: absence of other concurrent diseases, half day school, parents with a complete high school educational level. 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. MANOVAs were carried out as statistical analysis, with a significance level of $p < 0.002$. **Results:** Congenital hypothyroid children perceived the relationship with their mother as democratic based on tight control while the perception of the relationship with their father was based on acceptation. Regarding to coping strategies the CH children showed a tendency to seek greater support and a tendency to stop facing problems. **Conclusion:** The tendency to seek greater support and to stop facing conflictive situations could be linked to the greater maternal control. This could be expressed as a psychological and behavioral trait of greater dependence and paralysis that must be taken into account in the monitoring of the CH children's development.

P147 - Investigation of Inborn Errors of Metabolism (IEM) in Cartagena de Indias, Colombia: Experience of 13 Years

Alvear, C.(1); Barboza, M.(1); Moneriz, C.(1); Suárez, A.(1); Ocampo, J.(1)

(1): Universidad de Cartagena, Cartagena, Colombia

Introduction: The Inborn Errors of Metabolism (IEM) have been some very interesting models of genetic disease, and although individually rare, collectively are numerous and their number increases every year continuously and quickly. **Material and methods:** From September 2002 to June 2015 they were studied in 2413 patients based on clinical impression of the doctor and the tests requested. Laboratory tests were realized for amino acids, organic acids, carbohydrates, lipids, mucopolysaccharides, enzymes, hemoglobin and molecular biology for PKU in the CEDEM of the Autonomous University of Madrid. Also was with the help of IEIM and Pregen of the Pontifical University Javeriana and the CIBI of the University of the Andes in Bogotá-Colombia, FESEN of Buenos Aires-Argentina and laboratory Genzyme. **Results:** They were diagnosed 117 hemoglobinopathies, 13 mucopolysaccharidosis (MPS), 7 glycogenosis, one phenylketonuria (PKU), one tyrosinosis, one homocystinuria, one hyperphenylalaninemia, one albinism and one Niemann-Pick C (NPC). The patient of PKU has a severe mutation (S349P) and a soft mutation (L348V), while the mother presented the S349P mutation. **Conclusions:** The estimated prevalence of EIM in the city of Cartagena de Indias, is 6.1%, which demonstrates the importance of establishing a neonatal screening program and the consolidation of strategic alliances to optimize resources. According to partial results presented here, efforts should be directed toward the diseases that have been shown to be more prevalent in our environment, that is, the glycogen storage diseases, the mucopolysaccharidoses and the hemoglobinopathies. However, we must draw attention to the likely sub-diagnosis other diseases, promoting their search with interdisciplinary work. Regarding the hemoglobinopathies, is intended to alert our health systems about the implementation of a program of mass screening, model for control of one of the chronic diseases of childhood in a population with large afrocolombian component.

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P148 - Membrane Protein Carbonylation Patterns of Human Erythrocytes in G6PD-Deficient And HBS Patients

Quinto, A.(1); Contreras, N.(1); Alvear, C.(1); Rodríguez, E.(1); Moneriz, C.(1); Fanco, O.(2); Méndez, D.(1)

(1): Universidad de Cartagena, Cartagena, Colombia
(2): Universidade Católica, Brasilia, Brasil

Introduction: G6PD deficiency is a common X-linked erythroenzymopathy, while the sickle cell trait is one of the most frequent severe monogenic disorders in the world. Both have reached polymorphic frequencies in various parts of the world, because of the relative protection they confer against malaria infection. RBC membrane protein plays a central role in the molecular protective mechanism proposed until now. These proteins are susceptible to oxidative damage that resides in erythrocytes with reduce activity of G6PD or HbS presence. Here, protein carbonylation profiles were used to identify oxidative damage in order to explore their potential protective role in malaria. **Material and methods:** Peripheral whole blood from 300 human donors, who provided informed consent was analyzed. 18 HbS carriers were identified by isoelectric focusing technique, while 17 were identified as G6PD deficient using the Beultler spot test and enzyme kinetic assay. Next, RBC membrane proteins were obtained by osmotic lysis, quantified by Bradford method and labelled with 2,4-DNPH probes. 3 μg of protein derivatized were electrophoresed in 12% SDS-PAGE, transferred in semidry to PVDF membrane and incubated with polyclonal anti-DNP antibodies. Carbonylated protein bands were detected using an transilluminator chemidoc by quimioluminiscence reaction. Oxyblots showing carbonylation patterns were analyzed by densitometric analysis using Imagelab software. From duplicate Coomassie stained gel, proteins bands were excised, trypsin digested and analyzed in a Maldi-TOF-TOF spectrometer. **Results:** Protein carbonylated bands were divide into six zones according Rf values. At Rf range of 0.2 to 0.25 (80-100 KDa) oxidized bands from 13 of 17 G6PD deficient samples, 6 of 18 HbS carriers and 3 of 18 controls were observed. While Rf range of 0.32 to 0.37 (40-60 KDa) oxidized bands of 12 G6PD deficient, 11 HbS carriers and 2 controls were observed. From Coomassie stained gel, the glucose transporter Glut-1 was identified in all samples; while protein Band-3 only was identified in samples of patients. **Conclusions:** G6PD deficient and HbS carriers erythrocites sharing carbonylated protein bands. Protein band 3

is the most important anion exchange ion transport in the RBC and was identified as oxidized in both polymorphism.

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P149 - Real-World Experience in the Diagnosis of Neuronal Ceroid Lipofuscinosis Type 2 (CLN2): Report From an International Collaboration of Experts

Noher De Halac, I.(1); Miller, N.(2); Mole, S.(3); L. Cohen-pfeffer, J.(2); Crystal, R.(4); De Los Reyes, E.(5); Eto, Y.(6); Fietz, M.(7); Héron, B.(8); Izzo, E.(2); Kohlschütter, A.(9); Marques Lourenço, C.(10); A. Pearce, D.(11); Socorro Pérez-poyato, M.(12); Simonati, A.(13); Schulz, A.(9);

(1): Universidad Nacional de Córdoba, Facultad de Ciencias Médicas, Cordoba, Argentina, Cordoba, Argentina
(2): BioMarin Pharmaceutical Inc., Novato, CA, USA, Novato, USA
(3): MRC Laboratory for Molecular Cell Biology, University College London, London, UK, London, UK
(4): Department of Genetic Medicine, Weill Cornell Medical College, New York, NY, USA, New York, USA
(5): Department of Pediatric Neurology, Nationwide Children's Hospital, The Ohio State University, Columbus, USA
(6): Advanced Clinical Research Center, Southern Tohoku Brain Research Center, Kawasaki, Japan, Kawasaki, Japan
(7): SA Pathology, North Adelaide, South Australia, Australia, North Adelaide, South Australia, Australia
(8): Department of Pediatric Neurology, Trousseau Hospital, CHU Paris Est, Paris, France, Paris, France
(9): Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, Hamburg, Germany
(10): Department of Medical Genetics, School of Medicine of Ribeirao Preto, University of São Paulo, São P, São Paulo, Brazil
(11): Sanford Children's Health Research Center, Sioux Falls, South Dakota, USA, South Dakota, USA
(12): Pediatric Neurology, Hospital Universitario Marqués de Valdecilla, Cantabria, Spain, Cantabria, Spain
(13): Department of Neurological and Movement Sciences-Neurology, University of Verona, Verona, Italy, Verona, Italy

Background: CLN2 disease is a lysosomal storage disorder resulting from TPP1 enzyme deficiency that causes progressive neurological degeneration and early mortality. CLN2 disease is rare and often unsuspected, leading to delay in the diagnosis. **Methods:** In late 2014, 18 international CLN2 experts (clinicians, academic researchers, and laboratory directors) answered a comprehensive survey on CLN2 disease and a subset met to discuss experiences, current practices and shortcomings in diagnosis of CLN2. **Results:** 70% of laboratory experts considered the standard for CLN2 diagnosis the demonstration of decrease in TPP1 enzyme activity, with the remaining experts favoring molecular detection of pathogenic *CLN2/TPP1* mutations. Delay in the diagnosis of CLN2 were identified as a crucial concern: 82% of the group responded that patient referral to a specialist can typically take longer than one year. Laboratory experts identified the challenge in reaching a suspicious patient with CLN2 (50%) and lack of awareness of available tests (83%) as common reasons for delay. **Discussion:** Experts agreed that reliable techniques exist for CLN2 diagnosis and identified timely referral is a key challenge. An upcoming CLN2 expert meeting will define laboratory-based screening and diagnostic guidelines in order to establish best practices for use of biochemical and genetic testing for CLN2 diagnosis.

P150 - Gastrostomy Improves Chronic–Acute Malnutrition in Patients With Inborn Errors of Metabolism

Guillén López, S.(1); Vela-amieva, M.(2); Juárez-cruz, M.(3); González Zamora, J.(2); Monroy-santoyo, S.(2); Belmont-martínez, L.(2)

(1): Instituto Nacional de Pediatría, D.F., México
(2): Instituto Nacional de Pediatría, D.F., México
(3): Instituto Politécnico Nacional, D.F., México

Introduction: Inborn errors of intermediary metabolism (IEIM) generate an accumulation of toxic metabolites that cause damage to different organs and systems. IEIM often results in gastrointestinal symptoms such as anorexia, gastroesophageal reflux and vomiting, that could be related to the disease itself or be secondary to medical treatments, as a consequence these may hinder oral feeding, compromising nutritional status and complicating progression of the disease. In some cases gastrostomy has proven to be an alternative to improve or maintain feeding and treatment, but its use is controversial in relation to costs, patient's morbidity and mortality, emotional factors in parents and patients and also its effect on the nutritional status of IEIM patients has been little studied. **Objective:** To compare the nutritional diagnosis of a group of IEIM patients with chronic-acute malnutrition before and after gastrostomy. **Material and Methods:** Records of 7 patients with IEIM and chronic-acute malnutrition were analyzed; patients were subjected to gastrostomy for having feeding difficulties. Standardized dietitians performed the measurements of height and weight. Before and after gastrostomy tube placement, calculation of percentage of the actual weight and height in relation to the 50th percentile of weight for age in children under one year was performed, weight for height (W/H) and height for age in children older than 12 months was obtained from WHO growth charts. Waterlow and Gomez criteria was used to distinguished the degree of malnutrition that range from stage 0 to stage 3: normal, mild, moderate and severe. The time between nutritional measurements was the same before and after gastrostomy procedure. **Results and Discussion:** Before gastrostomy, 71% of patients had chronic-acute

malnutrition stage 1 (mild) according to W/H parameter and 29% had chronic-acute malnutrition stage 2 (moderate) given also by W/H; after gastrostomy tube feeding procedure, anthropometric measurements resulted in 57% of patients with an adequate height and weight nutritional status, 29% with chronic-acute mild malnutrition heightened for W/ H and 14% with chronic malnutrition and W/H in stage 0. **Conclusions:** The findings in these IEIM patients analyzed was that gastrostomy improved nutritional status in 85% of the patients, leading 4 of 7 patients (57%) to eutrophic classification.

P151 - Experiences for More Than 20 Years in the Nutritional Management of Patients Diagnosed With Galactosemia

Carrillo Estrada, U.(1); Zayas Torriente, G.(2); Torriente Valle, J.(3); Abreu Soto, D.(3); Henriquez, L.(1)

(1): Hospital Docente Marfan-Borrás, La Habana, Cuba
(2): Instituto Nacional de Higiene, Epidemiologia y Microbiología, La Habana, Cuba
(3): Instituto Nacional de Higiene, Epidemiología, La Habana, Cuba

Introduction: Galactosemia included among inborn errors of metabolism affects 1/40 000 live births in the world; in children whose diagnosis is not performed early in life can be severe, sometimes fatal. **Objective:** To characterize by anthropometric assessment; clinical and biochemical nutritional status at attracting disease patients; after 1 month of establishing dieto therapeutic treatment and up to 19 years. **Methods:** An observational study was conducted; age, sex, weight, height and arm circumference, compared with the values of the Cuban stage to determine their status: a retrospective 13 patients diagnosed and followed in the period from March 1988 to March 2014 were analyzed indicators Nutritional diagnosis and evolutionarily and the most important clinical manifestations in which age at onset of symptoms was specified; biochemists at the beginning of the disease and developmental indicators, including the therapeutic regimen to follow dieto after diagnosis. **Results:** Predominant female 61.5%. The most frequent clinical manifestations were 61.5% diarrhea, lethargy and crises of hypoglycemia 15.4%, 7.7% hepatic cholestasis..; Falls 15.4%. Most 69.2% had compromised their nutritional status diagnosis default. Dieto therapeutic regime to impose a significant improvement in their clinical appreciated 100%; anthropometric and biochemical 84.6% 100%. **Conclusions:** With early and appropriate nutritional management satisfactory evolution of the disease is achieved.

P152 - Systematic Review of Liver Cancer Differential Expression Analysis Using Oncomine: Genes Causing Hepatic Glycogenosis and its Implication in Hepatocarcinogenesis

Vallejo Ardila, D.(1); Doederlein Schwartz, I.(2)

(1): Universidade Federal do Rio Grande do Sul (UFRGS)—Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brasil
(2): Universidade Federal do Rio Grande do Su (UFRGS)I—Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brasil

Glycogen storage is emerging as a metabolic survival pathway of cancer cells. The glycogen synthesis is enhanced in non-cancer and cancer cells when exposed to hypoxia, resulting in a large increase in glycogen storage. The objective of this study was to use Oncomine to identify individual expression patterns of genes causing Hepatic Glycogenosis and their possible implication in hepatocarcinogenesis. The target genes with respect to each type of Hepatic Glycogenosis for the systematic review were: G6PC (Ia), AGL (III), GBE1 (IV), PYGL (VI), PHKA2 (IXa), PHKB (IXb) and PHKG2 (IXc). We chose to perform differential expression analysis using two separate categories: Normal vs. Cancer and Cancer vs. Cancer. Oncomine processes and normalizes each dataset used in these analyses independently. For the differential expression analysis, they use t-statistics with false discovery rates as a corrected measure of significance. We sorted the results based on each class of analysis, noted the significant studies produced, and then created a boxplot with the results of this analysis. The results across several studies revealed that G6PC was over-expressed in Cancer vs. Cancer; it was under-expressed in Hepatocellular Carcinoma vs. Normal. AGL was underexpressed in Hepatocellular Carcinoma vs. Normal. GBE1 was overexpressed in Cancer vs. Cancer; it was under-expressed in Hepatocellular Carcinoma vs. Normal. PYGL was over-expressed in Cancer vs. Cancer; it was under-expressed in Hepatocellular Carcinoma vs. Normal. PHKA2 was over-expressed in Cancer vs. Cancer; it was under-expressed in Focal Nodular Hyperplasia vs. Normal. PHKB was over-expressed in Cancer vs. Cancer; it was under-expressed in Focal Nodular Hyperplasia vs. Normal. PHKG2 was over-expressed in Cancer vs. Cancer; it was under-expressed in Hepatocellular Carcinoma vs. Normal. This analysis provided substantial preliminary evidence as to the significance of our target genes in hepatocarcinogenesis. Point mutations in those genes causing loss of enzymatic function are recognized as the cause of Hepatic Glycogenosis. What still remains unknown is the level of connectivity up-stream or regulation pattern in both sporadic and hereditary liver cancer. In a future study, we are intending to identify genes as significantly co-expressed in a meta-analysis on Myc, ChREBP, and HIF1.

P153 - Homocystinuric Patients With Cystathionine Beta-Synthase (CBS) Deficiency. Study of Genotype-Phenotype Correlation: 15 Years' Experience in Cemeco, Argentina

Grosso, C.(1); Urreizti, R.(2); Balcell, S.(2); Grinberg, D.(2); Dodelson De Kremer, R.(1)

(1): Centro de Estudio de las Metabolopatías Congénitas, CEMECO, Hospital de Niños, Fac. Cs. Médicas, UNC, Córdoba, Argentina

(2): Departament de Genética, Universitat de Barcelona, Barcelona, Spain

Classical homocystinuria is the most commonly inherited disorder of sulfur metabolism, caused by the genetic alterations in cystathionine beta-synthase, *CBS* gene, and is characterized by multiple connective tissue disturbances, mental retardation and mainly, thromboembolic complications. The expression of all clinical signs is extremely variable. The first choice of therapy consists of administration of mega doses of pyridoxine (B6). The response to this treatment establishes two phenotypic variants: B6-responsive homocystinuria and B6-nonresponsive. Excluding some CBS mutations, detailed genotype-phenotype correlation for different CBS mutations has not been established in literature. The aim of the present report is communicate clinical, biochemical and molecular findings in eight non-related patients with CBS deficiency, in order to assess the correlation between genotype and phenotype, in these patients. Lens ectopia was the common diagnostic symptom (n=8, 100% ocular presentation); followed by a variable CNS involvement (n=6, 75%), as a main neurological presentation; marfanoid features (n=3, 37,5% connective tissue presentation) and, thromboembolic events (n=2, 25% vascular presentation). Three patients were B6-responsive (37,5%) and the remaining 62,5%, result B6-nonresponsive to the treatment with pyridoxine. All 16 alleles were identified; five of which had already been reported, and six are novel (p.A446S, p.429delI, p.D321V, c.689delT, c.677-14-7del8 and c.69_70+8del10). In addition, the thrombophilic nucleotide change MTHFR c.677 C>T was investigated to assess their contributions to the clinical spectrum. Seven of them were heterozygous for this condition; it suggest that the effect of this polymorphism on clinical phenotype of CBS is not very clear since the distribution of thrombophilic change does not differ among our patients. This study extends the molecular findings in eight Argentinian probands with Classical homocystinuria, and discusses the clinical presentations and putative effects of the CBS mutations.

P154 - Undescribed Altered Biotinidase Activity in Metabolic Pathologies Unrelated to defects in the Cycle of Biotin

Angaroni, C.(1); Hill, L.(1); Giner-ayala, A.(1); Oller-ramirez, A.(1); Bezard, M.(1); Dodelson De Kremer, R.(1)

(1): CEMECO. Hospital de Niños de la Santísima Trinidad. Facultad de Ciencias Médicas, UNC, Córdoba, Argentina

Introduction: An increased biotinidase (BTD) activity was described in liver glycogen storage diseases (GSD) with high sensitivity for GSD Type Ia. In a previous work, we demonstrated oscillating enzymatic values in GSD-Ia, GSD-III and GSD-IX patients. On the other hand, a decreased BTD activity was recognized in acute and chronic liver diseases. In all these cases the enzyme BTD is proposed as a biomarker with varying degrees of sensitivity. The objective of this work is to broaden the spectrum of metabolic diseases exhibiting altered biotinidase activity. **Materials and methods:** Eight patients with defined metabolic disorder (unrelated to defects in the cycle of biotin) were included: I-Cell disease (2), Sandhoff Disease (2),Tyrosinemia type I (1), 3-hydroxy-3-methyl-glutaric aciduria (2) and 3-methylcrotonyl glycine aciduria (1). All these probands with an exact nosological definition were diagnosed by clinical, biochemical and/or molecular studies. BTD activity was assayed by measuring the hydrolysis of n-biotinyl-p-amino benzoate according to Pettit-Wolf. The reported normal range values (4.6-13.6 nmol/min/ml) represent the mean $\pm$ 2SD (9.1 $\pm$ 4.5). **Results:** A) Patients with increased BTD activity detected in one determination: I-Cell disease (1/2 patient (P); 16.1 nmol/min/ml); tyrosinemia type I (1/1 P; 14.4 nmol/min/ml). B) Patients with persistently increased BTD activities: Sandhoff disease (1/2 (P); 17.9-13.8 nmol/min/ml). C) Patients with oscillating BTD activities (from normal to elevated): I-Cell disease (1/2 P; 5.5-18.8 nmol/min/ml); Sandhoff disease (1/2 P; 11-17.9 nmol/min/ml). D) Patients with persistently decreased BTD activities: 3-hydroxy-3-methyl-glutaric aciduria (1/2 P; 0.04-0.07 nmol/min/ml). E) Patients with oscillating BTD activities (from normal to decrease): 3-hydroxy-3-methyl-glutaric aciduria (1/2 P; 2.2-9.5 nmol/min/ml) and 3-methylcrotonyl glycine aciduria (1/1 P, 2.7-10.6 nmol/min/ml). **Conclusion:** This study revealed that the increased BTD activity is not exclusive for liver GSD. Including, now, I-Cell disease, Sandhoff Disease and Tyrosinemia type I. In addition, before a result of a decreased BTD activity, other metabolic diseases will have to be considered. Additional studies will be necessary to evaluate the role of the BTD as a marker in these disorders. Meanwhile, an altered result of BTD activity should be interpreted with cautious.

P155 - Cerebellar Hypometabolism and Cognitive Deficits in Erdheim Chester Disease: Just Accumulation of Histiocytes or Secondary Metabolic/Endocrine Deficits?

Estrada-veras, J.(1); Obrien, K.(1); Toro, C.(1); Gahl, W.(1)

(1): National Institutes of Health—National Human Genome Research Institute, Bethesda, MD, USA

Introduction: Erdheim-Chester Diseases (ECD) is a rare non-Langerhans cell histiocytosis with up to 50% of cases having the *BRAF* V600E mutation in affected tissues. Its clinical characteristics range from asymptomatic to multisystemic. If left untreated, the disease progresses causing fatal outcomes. Diagnosis of ECD relies upon imaging studies and pathological findings. There is no standard treatment for ECD, but BRAF inhibitors are under study. Central nervous system (CNS) involvement is a predictor for increased morbidity and mortality. Neurological deficits are usually attributed to histiocytic accumulation in the pons, midbrain and cerebellum causing cerebellar syndrome and other CNS deficits. A subset of patients present with typical cerebellar-midbrain findings on exam and no evidence of disease on MRI. **Material and Methods:** A 61 year old female with *BRAF* V600E positive

ECD on interferon alpha was evaluated at the NIH Clinical Center during a follow up visit secondary to worsening cerebellar syndrome. Brain/cerebellar/orbital/pituitary MRI, FDG-PET scans, metabolic testing, CSF studies and endocrine testing were performed. **Results and Conclusions:** T2 - Flair hyperintense signal abnormalities involving the pyramidal tracts, deep cerebellar and pontine white matters in a symmetric configuration were seen on MRI. PET showed cerebellar hypometabolism. Vitamin B12 was 286pg/ml, TSH was 0.16 mcIU/ml and ADH < 0.5pg/ml. Urine organic acids showed elevations in 3- methylglutaconic and 3-methylglutaric acids. CSF revealed oligoclonal bands pattern 3 and cerebral folate deficiency. Endocrine testing confirmed central hypothyroidism. Here we see evidence that other factors play a role in CNS disease presenting with similar findings as seen in pure ECD cases. Neurodegeneration can also be present. Further evaluations in patients that show CNS deterioration are indicated since some findings can be treated by supplementation improving the patient's quality of life. Here, thyroid, cyanocobalamin and folinic acid supplementations were recommended. BRAF and MEK inhibitors therapy was also started.

P156 - Is Alfa 1 Antitrypsin Heterozygosity A Phenotype Modifier for Glycogen Storage Disorders?

Besen, A.(1); Vairo, F.(1); Souza, C.(1); Nalin, T.(1); Leistner-segal, S.(1); D. Schwartz, I.(1)

(1): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Introduction: Glycogen storage diseases (GSD) are inherited metabolic disorders of glycogen metabolism which may affect many tissues, especially muscle and liver. Alfa 1 antitrypsin deficiency (AAT) is one of the most common inherited metabolic disorders and the most common genetic cause of liver disease in children. There is no consensus if the heterozygous state for AAT could increase severity of other liver diseases. **Objectives:** To compare clinical, laboratory and ultrasound findings among GSD patients who carrier the alleles PiS and PiZ of AAT with non-carrier GSD patients. **Methods:** Twenty two GSD patients (eleven type Ia, four type Ib, five type III, two type IX) from Hospital de Clínicas de Porto Alegre, Brazil were included. The alleles PiS and PiZ of AAT gene were analyzed by Real time PCR. **Results:** For two patients the analysis for PiS was not performed; 2/ 20 patients (10%) were heterozygous for PiS (both GSD patients type Ib) and 1 /22 (4%) was heterozygous for PiZ (GSD type Ia). No patient had both PiS and PiZ alleles. The patient who is heterozygous for PiZ have normal liver enzymes. The patients who are heterozygous for PiS presented hyperechoic liver at ultrasound, without nodular lesion, with normal liver enzymes. **Conclusion:** The prevalence of the heterozygosity of PiS and PiZ alleles in our sample was similar of that described in general population including the proportion between PiZ/PiS carriers. Our data suggest there is no clinical differences between GSD patients who are carriers or non-carriers of PiS or PiZ. More studies are necessary to clarify this question.

P157 - Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency: Acylcarnitine (AC) Profile in Two Different Situations: Newborn Screening Versus Metabolic Decompensation

Schenone, A.(1); Fuertes, A.(1); Velasquez Rivas, D.(1); Maccarone, M.(1); Fernández, J.(1); Guinle, A.(1); Massari, M.(1); Marchione, M.(1); Sokn, S.(1)

(1): FESEN-Laboratorio de Neuroquimica "Dr. N. A. Chamoles", Buenos Aires, Argentina

Introduction: VLACD is an autosomal recessive inborn error of metabolism due to mutations in ACADVL gene. It is a disorder of fatty acids beta oxidation and could be detected by expanded newborn screening. Clinical manifestations are heterogeneous, and the presentation could be from early to late onset. The primary biomarker is C14:1 AC which elevation could be detected during the DBS analysis using tandem mass spectrometry. Many publications mentioned the possibility of pitfalls in the diagnosis of this disease during asymptomatic periods or in neonatal screening. **Aim:** To show, from a patient detected in our center, how different could the AC profile in VLACAD deficiency according to clinical and nutritional situation. **Material and method:** We were able to get the newborn screening card from a patient diagnosed in our center with VLACAD at 4 month of life by DBS AC analysis and urine organic acids. DBS samples were prepared as butylester and analyzed on a Quatro Ultima PT. **Results:** AC analysis revealed: NBS card: C14:1: 11.38 μM (NV<0.75), C14:0: 6.28 μM (NV<0.74), C14:2: 0.42 μM (NV<0.17) and Free Carnitnine: 76.21(NV: 18.4- 232.0). The values obtained at the diagnosis were: C14:1: 0.75 μM (NV<0.24), C14:0: 0.48 (NV<0.35), C14:2: 0.10 (NV<0.19) and Free Carnitine 6.61 (NV: 41.6-218.0). **Conclusions:** The elevation of the characteristic AC biomarkers of VLCAD is more significant in the NBS card than in the sample obtained at the diagnosis. During metabolic decompensation it is frequent to find very low free carnitine level which determinates AC to remain low, leading to a misdiagnosis. On the other hand, it has been reported in the literature pitfalls in the detection of this disorder during anabolic conditions. Considering that VLCAD could be detected in the pre-symptomatic period avoiding the irreversible damage in the patient, it is important to establish the first 48 hs of life as the critical time to obtain the NBS sample in which the C14:1 exhibit the highest level.

P158 - Nutritional Status by Anthropometry in Children Diagnosed With Inborn Errors of Metabolism

Sanchez Peña, M.(1); Serrato Sanchez, K.(2); Lopez Uriarte, G.(2); Torres Sepulveda, M.(2); Arredondo Vazquez, P.(3); Torres, M.(3); Villarreal Perez, J.(3); Martinez Garza De Villarreal, L.(2)

(1): Universidad Autonoma de Nuevo Leon, Guadalupe Nuevo Leon, Mexico
(2): Departamento de Genética, Facultad de Medicina, Universidad Autonoma de Nuevo Leon, Monterrey Nuevo Leon, Mexico
(3): Servicios de Salud de Nuevo Leon, Monterrey Nuevo Leon, Mexico

Introduction: Inborn errors of metabolism (IEM) are monogenic, autosomal recessive disorders. The affected gene produces an enzymatic deficiency in a metabolic pathway leading to biochemical abnormalities, manifesting in childhood. **Materials and methods:** Descriptive, transversal, comparative study. In 27 children diagnosed with IEM for expanded newborn screening, performing nutritional assessment and intervention. The data of weight and height were measured in each of the interventions at the nutrition. Determining the indexes weight/age (W/A), weight/height (W/H), body mass index (BMI) (WHO, 2007); comparing the first and third intervention, using nutritional diagnostics by Gomez and Waterlow, data analysis was performed by T student for related samples with SPSS 15.0 statistical package for Windows. **Results:** Of 27 individuals diagnosed with IEM 51.9% were male and 48.1% female, with an age range of 0.54 months with an average of 6 months. According to diagnosed diseases branched-chain amino acids and medium chain fatty acids were most prevalent while galactosemia were the less. There was a statistical significance ($p=0.035$), between the first and the third intervention for W/A using the Gomez nutritional diagnostic and for W/H with Waterlow and BIM were $p=0.001$ and $p=0.000$ respectively. **Conclusion:** To maintain and adequate status with a special diet is a critical component to prevent acute complications, such as metabolic decompensation, and/or to long-term complications.

P159 - Groups of Health Education in Ceaps: An Accession Strategy to Youth Treatment With Phenylketonuria

Isabel Spínola Castro, I.(1); Raíssa Hilda, R.(2); Elisabelle Letícia, E.(2); Josiane Cecília Alves, J.(2); Adriana Temponi, A.(2)

(1): Universidade Federal de Minas Gerais/Faculdade de Medicina, Belo Horizonte, Brasil
(2): Universidade Federal de Minas Gerais/Faculdade de Medicina, Belo Horizonte, Brasil

Introduction: The Education and Social Support Centre (CEAPS), created in 2006, is responsible for developing training activities and special educational projects for professionals and community and to guide and welcome patients and families treated by the Newborn Screening Program of Minas Gerais. The work with groups is a necessary education strategy on public health to stimulate engagement and adherence of the family to treatment, through the appropriation of knowledge and exchange of experiences. **Objective:** To describe the health education group performed in CEAPS, for youth (10 to 20 years) with phenylketonuria. **Methodology:** The groups held twice a year. A theme is defined by the multidisciplinary team for discussion(ex.: drugs, sexuality, updates, professionalization, among others). A dynamic designed to introduce the subject followed by a time of discussion, with a maximum of 2.5 hours in total is held. **Results and Discussion:** We conducted 10 health education groups, serving 100 patients with phenylketonuria. Each participant contributed his experience, result of distinct historical and social boundaries marked by diversity, which form the juvenile condition of this group of young people. It can be seen that by sharing their experiences and intertwining their experiences with others, emerge possible solutions built collectively presented to the demand. Opens space for dialogue and critical reflection of the individual and the group, thus enabling young people to take an active stance on the issue presented that day and that they can make changes in their daily lives for a better quality of life of patients. **Conclusion:** The health education groups are extremely important for the advancement of youth cultures and adherence to treatment, causing the patient to empower care, experiences, rights, duties and origins.

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P160 - Epilepsy Associated to Inborn Errors of Metabolism, Study, and Evolution of 68 Patients

Witting, S.(1); Troncoso, M.(1); Canales, P.(1); Santander, P.(1); Guzmán, G.(1); Rojas, C.(1); Troncoso, L.(1); Barrios, A.(1); Hernández, A.(1)

(1): Servicio Neurología Infantil Hospital San Borja Arriarán, Campus Centro Universidad de Chile, Santiago, Chile

Introduction: Seizures are a common symptom in a great number of metabolic diseases. They occur as an occasional event secondary to metabolic decompensation or as a known epileptic condition. Epilepsy in these cases can be classified depending on physiopathology, age of onset and type of crisis. The objective of this study is to determine the main metabolic disorders associated to epileptic seizures, age of onset, clinical presentation and treatment response. **Materials and Method:** Retrospective study of 130 patients with metabolic diseases controlled in our service. Review of clinical history. **Results:** 23 metabolic diseases were evaluated, with a total of 130 patients, 68 (52%) presented epileptic seizures. Seizures appeared between the first hours of life and 21 years of age

(mean 60 months). Focal seizures predominated in 74%, followed by generalized seizures in 26%. Epilepsy was found in 100% of patients with: non ketosic hyperglycemia, gangliosidosis, lipofuscinosis, peroxisomal disorders of neonatal onset, sulfite oxidase deficiency, MELAS, MERRF and GLUT 1 deficiency. The most used antiepileptic drugs were phenobarbital, followed by carbamazepine and valproic acid. 22% of patients evolved with pharmacological refractoriness. **Conclusion:** In our series, more than half of patients (52%) presented epileptic seizures. The main metabolic diseases associated to seizures were the ones described. Age of onset was more frequently during the first five years of life. Focal epileptic seizures with secondary generalization predominated and 22% of refractoriness was observed. The identification of epilepsy secondary to metabolic disorders is of great importance to establish an early and appropriate treatment.

P161 - Metal Inborn Errors of Metabolism (MIEM): Clinical, Laboratory, and Radiological Features

Saez, V.(1); Troncoso, M.(2); Gittermann, K.(2); Hidalgo, M.(2); Muñoz, D.(2); Santander, P.(2); Troncoso, L.(2); Retamales, A.(3); Barrios, A.(2); Witting, S.(2); Guzman, G.(2); Fariña, G.(2); Rivera, G.(3)

(1): Hospital San Borja Arriaran, Santiago, Chile
(2): Hospital San Borja Arriaran, Santiago, Chile
(3): Hospital Regional Temuco, Temuco, Chile

Introduction: Metals are essential in embryogenesis, CNS myelination, enzymatic activity, electron transport and neurotransmission. Defects in metals metabolism are associated with progressive neurodegeneration, especially basal ganglia deposit. **Objective:** To describe clinical, laboratory and radiological features of patients with Metal Inborn Errors of Metabolism disorders. **Methods:** Descriptive-retrospective and prospective follow-up study of genetically confirmed Metal Metabolism Disorders patients controlled in our center from 2005 to 2014. **Results:** Total 22 patients, (I) 14/22 Neurodegeneration with brain iron accumulation (NBIA): a) 13/14 (NBIA1) PANK1 mutation, all of them associated with MRI image "tiger eye", 4/13 with early onset phenotype: developmental delay, severe generalized dystonia, spasticity, 9/13 with late onset phenotype: bucolingual manifestations, dystonia; b) 1/14 (NBIA2, PLAN) associated with PLA2G6 mutation, average age of onset 6 months, presented with developmental detention, generalized dystonia, MRI with iron deposit in globus pallidus, substantia nigra, cerebellar atrophy. (II) 8/22 diagnosed with copper metabolism disorders: a) 5/8 Menkes disease, diagnosis average age 4.7 months, presented developmental delay, refractory epilepsy, pili-torti, low levels of cupremia and ceruloplasmin, images with cerebral atrophy, subdural collections. One of them received Cu-histidine, 4/5 died (average age 11.9 months) b) 3/8 Wilson disease, presentation average age 9.6 years, 1/3 presented initially hepatic dysfunction, 2/3 behavioral disorders, all developed generalized dystonia, Kayser-Fleischer ring, characteristic laboratory and neuroimaging with basal ganglia involvement. All of them were treated with penicillamine. **Conclusion:** In our patients, the most frequent Metal Metabolism Disorders was Iron Metabolism Defects. All patients with MIEM presented progressive symptoms, especially extrapyramidal signs. Only patients with copper EIMM received specific therapy, Wilson's disease presented the best prognosis

P162 - Glycogen Storage Disease Type III (GSDIII): Clinical Characterization of a Group of Chilean Patients

Mabe, P.(1); Sfeir, C.(1); Giadach, C.(1)

(1): Hospital de Niños Dr. Exequiel González Cortés, Santiago, Chile

GSDIII is a recessive hereditary disorder due to deficiency of glycogen debranching enzyme. Clinical manifestations are of variable severity and are secondary to glycogen storage in the liver, heart, and skeletal muscle. The patients present with hepatomegaly, hypoglycemia, hyperlipidemia, myopathy and growth retardation. The therapy is based on a rich carbohydrate and protein diet. No specific treatment is available. **Objective:** To describe clinical and laboratory characteristics of a group of GSDIII Chilean patients. **Methods:** Retrospective analysis of 6 GSDIII patients. **Results:** Gender: male (2), female (4). Parents consanguinity 1/6. Current age range: 1 year 11 months - 17 years. The age at onset of symptoms was 6 months to 7 years (average 23.2 months). The age at diagnosis was 8 months to 11 years (average 40.8 months). The reasons for referral were: abdominal distension (2), hepatomegaly (2), hepatomegaly and hypoglycemia (1) and hypotonia (1). At diagnosis all patients presented with moderate to severe hepatomegaly and mild septal myocardic hypertrophy was described in 3/6 patients. The mean of lower glycaemia value at diagnosis was 29 mg/dl (26 -51 mg/dl). Myopathy is present in 2/6 patients, starting at the age of 26 months and 7 years respectively. All patients present elevated transaminases in variable range. Four patients have mixed dyslipidemia. In 4/6 patients creatine phosphokinase was increased 2-4 fold the normal range. During follow up (6 months to 9 years) all the patients maintained normal cognitive level. As dietary treatment, all received raw cornstarch in average 2 gr/kg and protein in average 3.5 gr/kg. Average hours of tolerated night fasting: 7 hours (range 4-9 hours). One patient received glycoside, a new amylopectin maize starch, increasing tolerated night fasting from 5 to 8 hours. During follow up (6 months to 6 years) all the patients reduced significantly the frequency and severity of the hypoglycemia events and the hepatomegaly magnitude. **Conclusion:** The more relevant manifestation of GSDIII are hepatomegaly and hypoglycemia, but it can manifest also as a myopathy. Adequate therapy of GSDIII allows a good metabolic control of hypoglycemia. Glycosade can increase tolerance to night fasting.

P163 - Child Mortality in Brazil: An Epidemiological Study on Inborn Metabolic Disorders of Intermediary Metabolism

Hendges De Bitencourt, F.(1); Sales Vianna, F.(2); Doederlein Schwartz, I.(2)

(1): Universidade Federal Do Rio Grande Do Sul—Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil
(2): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil

Introduction: Disorders of intermediary metabolism are inborn errors of metabolism (IEM) that cause symptoms of an acute or progressive intoxication or deficiency in energy production or utilization, which can lead to episodes of hypoglycemia and metabolic attacks, and in some cases, to sudden death. According to international studies, IEM appear to be associated with 3% of cases of sudden death. **Objectives:** To assess and characterize, by region of Brazil, the infantile mortality rate related to disorders of intermediary metabolism. **Methodology:** A cross-sectional study based on database review. The survey was conducted in the Brazilian National Mortality Information System (Sistema de Informação sobre Mortalidade - SIM) and was directed to identify all infantile death records in the country, occurred from 2002 to 2011, and whose cause of death was associated with ICD10 E70 (*classic phenylketonuria, hyperphenylalaninemias, tyrosinemia),* E71 (maple syrup urine disease, organic acidemias, adrenoleukodystrophy), E72 (Disorders of amino acid transport, of sulfur-containing amino acids, of urea cycle metabolism, of lysine and hydroxylysine metabolism, of ornithine metabolism, and of glycine metabolism), E74 (glycogen storage diseases, disorders of fructose and galactose metabolism, disorders of pyruvate metabolism and gluconeogenesis), and E80 (disorders of porphyrin and bilirubin metabolism). **Results:** During the study period, there were records of 160 deaths of children under one year old caused by IEM of intermediary metabolism (ICD10 E-70=31; E-71=22; E-72=34; E-74=61 and E80=12 deaths). Out of the them, 11 occurred in the North, 45 in the Northeast, 63 in the Southeast, 32 in the South and 9 in the Midwest region of Brazil. **Conclusions:** This is the first Brazilian study to evaluate the child mortality caused by IEM of intermediary metabolism. The small number of death registration due to IEM in the country could not represent the rarity of the disorders, but their underdiagnosis. The highest number of deaths in the Northeast, Southeast and South is probably due to the fact that these regions are the most populous in Brazil. On the other hand, South and Southern regions present a greater number of specialized centers in Genetics.

(P-3) Poster Session With Authors III

P164 - Incidence of Cystic Fibrosis: A Decreasing Trend Throughout the Years

Borrajo, G.(1); Procopio, D(1); D Alessandro, V.(2); Diez, G.(2);

(1): Detección de Errores Congénitos. Fundación Bioquímica Argentina, La Plata, Argentina
(2): Servicio de Neumonología. Hospital de Niños "Sor María Ludovica", La Plata, Argentina

Introduction: Newborn Screening (NBS) for Cystic Fibrosis (CF) was implemented by Fundacion Bioquimica Argentina with the support of Children's Hospital ''Sor Maria Ludovica'' in July/1995. During the first 15 years, NBS was made by request and without an organized program. However, in July/2010 it was implemented systematically as part of the ''Diagnostic and Treatment of Congenital Diseases Program'' (Prodytec) of the Ministry of Health of Buenos Aires Province (BAP). **Objective:** To present the variation experienced by the CF incidence in the period 1995-2014, highlighting its trend to decrease throughout the years. **Material and Methods:** The newborn (NB) population screened belonged mainly to BAP and in a lesser percentage to other provinces. The IRT measure was made using DELFIA and AutoDELFIA methods (cut-off value: 70 ng/ml). **Results:** The number of NB annually screened increased progressively during the period evaluated, reaching on average 198,000 NB/year in 2010-2014, meanwhile the other provinces contribution decreased since 2005 onwards representing 12.6% in the period 2010-2014. The total population screened was 1,762,342 NB, in which 212 CF children were diagnosed (14 false negatives, 8 presenting meconium ileus), thus determining a global incidence of 1:8,314 live births. The analysis of the CF incidence allows to divide the population in two groups: The first one represented by 636,134 NB screened between 1995-2007, showing a stable incidence around 1:5,500; and the second one, represented by 1,126,508 NB screened between 2008-2014, showing a progressive decrease in the global incidence, with a specific incidence for this period of 1:11,858 live births. **Discussion:** Until 2007, CF incidence keeps stable but lower than the expected. However, from then on, it shows a noticeable and unexplained decreasing trend, having been discarded the possibility of unreported lost cases. The only variable that changed significantly in this period was the origin of the population studied, because the passing a BAP law -which defined NBS for CF as mandatory-, gave place to its inclusion in the Prodytec in 2010, thus determining the access of all NB born in BAP public hospitals, probably introducing a change in the characteristics of the studied population.

P165 - Monitoring of Congenital Hypothyroidism in Tucuman, Argentina's Neonatal Screening Program

Luna Claraso, A.(1); Chahla, R.(2); Graiff, O.(3); Elias, A.(4); Alvarez Sollazi, C.(5); Albarracin, M.(5); Granito, S.(5); Bazan, C.(6)

(1): Instituto de Maternidad Ntra. Sra. de las Mercedes, San Miguel de Tucumán, Argentina

(2): Inst. de Maternidad Ntra. Sra. de las Mercedes. Fac. de Medicina. Universidad Nacional de Tucumán
(3): Inst. de Maternidad Ntra. Sra. de las Mercedes
(4): Inst. de Maternidad Ntra. Sra. de las Mercedes. Fac. de Bqca, Qca y Fcia. UNT
(5): Hospital del Niño Jesús
(6): Hospital del Niño Jesús. Fac. de Medicina. Universidad Nacional de Tucumán

Introduction: The Neonatal Screening Program of the Province of Tucuman, Argentina, is headquartered in the Neonatal Screening Laboratory of the Institute of Maternity and Gynecology Ntra. Sra. de las Mercedes. It receives and processes dried blood spot filter paper samples for all the newborns (NB) in 13 hospitals of the 17 departments in the province. Congenital hypothyroidism (CH) is one of six congenital diseases screened for (CH, Congenital Adrenal Hyperplasia, Phenylketonuria, Cystic Fibrosis, Galactosemia and Biotinidase Deficiency). **Objectives:** To assess the prevalence of CH, and to evaluate comorbidities and sonographic features of thyroid glands in children; To assess a child's development through its height. **Patients and Methods:** A descriptive epidemiological study. Population Accessible included 139775 newborns whose samples were analyzed at the Neonatal Screening Laboratory in the period 2006-2014. The newborns with suspected CH were referred to Hospital of Niño Jesús for confirmation, treatment and monitoring. The clinical monitoring was conducted on a monthly during the first semester, every two months during of the second semester, and then every 3 months until to 6 years of life. From 7 years of life they received semiannual controls. Laboratory control was performed every two months during the first year of life. The growth control was made considering the SAP curves (Lejarraga et al). **Results:** Prevalence = 76/139775= 5/10000. Concomitant diseases: Down Syndrome 5/76, 20/76 with jaundice. Sonographic features of thyroid gland: 7% (increased), 18% (Hypoplastic), 24% (not displayed) and 7% (structural alteration). Height: 6 children with height value below the 3rd percentile. **Conclusion**: Early diagnosis and proper treatment allowed bone maturation and growth according to chronological age in the most of patients.

P166 - 22 Years of Experience in Newborn Screening for Congenital Hypothyroidism

Borrajo, G.(1); Dietz, M.(1); Castillo, P.(1); Doña, V.(1); González, V.(2); Tournier, A.(3)

(1): Detección de Errores Congénitos. Fundación Bioquímica Argentina, La Plata, Argentina
(2): Sala de Endocrinología. Hospital de Niños "Sor María Ludovica", La Plata, Argentina
(3): Laboratorio Central. Hospital de Niños "Sor María Ludovica", La Plata, Argentina

Introduction: Newborn Screening (NBS) for Congenital Hypothyroidism (CH) was implemented by Fundacion Bioquimica Argentina (FBA) together with Children's Hospital "Sor María Ludovica" (HSML), in July/1992. Initially, NBS was carried out by request and without a structured program until the "Diagnostic and Treatment of Congenital Diseases Program" (Prodytec) was implemented by the Ministry of Health of Buenos Aires Province (BAP), on April/1995. **Objective:** To present the results of 22 years of experience working in NBS for CH. **Materials and Methods:** The functional organization of Prodytec includes: screening testing at FBA NBS Laboratory, and confirmation, diagnostic, treatment and follow-up at the HSML. Coverage is provided free of charge to all newborns (NB) born in public hospitals of BAP since July/2010. The screened NB population mainly belonged to BAP and in a lesser percentage to other provinces, but only those on the first group were attended and treated in the HSML. Sample collection was recommended between 24 h to 5th day of life, and TSH was measured using AutoDELFIA Neonatal hTSH method (cut-off: 11.0 uU/mL). **Results and Discussion:** Until December/2013, 3,404,852 NB were screened, 85.6% belonging to BAP and 14.4% to other provinces, with a recall-rate of 0.14%. Diagnostic was confirmed in 1,567 children, thus determining a global incidence of 1:2,173 live births and showing a higher incidence in BAP regarding other provinces group (1:2,103 vs 1:2,708). Median (interquartile range) of age at sample collection and at screening result were 3 (2-6) and 12 (8-16) days for BAP group, and 5 (3-13) and 15 (10-24) days for other provinces group; while the age at diagnosis for BAP group was 18 (14-26) days. Reevaluation at 3 years of age was made at the HSML in 675 NB, being confirmed 644 (95.4%) as Permanent CH and 31 (4.6%) as transient forms. Etiologies of Permanent forms were: athyreosis 25.0%, ectopic disgenetic gland 57.1%, eutopic disgenetic gland 2.2% and eutopic thyroid gland 15.7%. About coverage, during 2013 Prodytec screened around 130.000 NB from public hospitals of BAP reaching a rate in this group > 97%. Until 2013, no one false negative result was reported.

P167 - Relationship Between Anthropometric Development and Metabolic Control of Children With Diagnosis of Maple Syrup Urine Disease (MSUD) Monitored in a Reference Service in Newborn Screening (RSNS)

Santos Calmon, L.(1); Da Anunciação Do Espírito Santo, D.(1); Efigenia De Queiroz Leite, M.(1); Cristian Amaral Boa Sorte, N.(2); Kraychete Costa, B.(2); Amorim, T.(2)

(1): APAE/UFBA, Salvador, Brasil
(2): APAE/UNEB, Salvador, Brasil

Introduction: MSUD is caused by deficient activity of the enzymes responsible for metabolism of amino acids leucine, isoleucine and valine. Neonatal screening allows diagnosis and early treatment of patients. Treatment aims to reduce serum concentrations of leucine, valine and isoleucine in order to enable normal development and growth. **Objective:** To relate

the anthropometric development and metabolic control of children with MSUD followed at RSNS-Salvador/Bahia/Brazil. **Methods:** Retrospective study which evaluated patients diagnosed until July 2015. Data obtained from medical reports. Anthropometric status assessment used the indicators height/age (H/A), weight/age (W/A) and weight/height (W/H), for those under 05 years old, using value of z-score as a point cutting according to WHO classification, 2006. Metabolic control tests were performed using the NeoLISA®MSUD kit and high-performance liquid chromatography (HPLC). Data were analyzed using EpiData software (v3.1). **Results:** Among nine patients, five (55.6%) were female. They had mean(SD) age of 39(34.8) months, ranging from 4 to 120. Six had classical form of disease, two had intermediate form and one was not determined. Mean(SD) age of diagnosis was 23.4(19.4) days, with average(SD) age of onset of symptoms of 7.0(4.1) days. There was inverse correlation weak to moderate between the laboratory values serum of leucine, isoleucine and valine and W/H in the first three years of life, respectively, -0.275; -0448 and -0228. **Conclusions:** There was not a definite trend of association between laboratory values and anthropometric indicators W/H and H/A in the first five years, although an inverse relationship between these variables. This suggests a worse anthropometric development in presence of metabolic decompensation.

P168 - Outcome in Patients With Phenylketonuria (PKU): What Should be Improved?

Fain, H.(1); Cabrera, A.(1); Gatti, M.(1); Campbell, C.(1); Blanco, V.(1); Buiras, V.(1); Bonetto, V.(1)

(1): Hospital de NIños V. J. Vilela, Rosario, Argentina

Objective: To link adherence, neurological development and nutritional status of patients with phenylketonuria treated at a public hospital, identifying factors associated with poor outcome. **Materials and methods:** All patients with PKU treated at the Nutrition Department were included. They were classified, according to the value of phenylalanine achieved with usual diet, in severe, moderate, light PKU and persistent benign hyperphenylalaninemia. A patient was considered adherent to treatment if during the 1st year of life had 1 monthly control.4 controls were considered appropriated in 1 to 10 patents and over 10, 3 controls were appropriated. We also took into account the average value of plasmatic phenylalanine to consider adherent to treatment: less than 360 for those under 13 and less than 600 for older children. The neurological development was evaluated considering school performance or neurologic evaluation for assistant physician. Nutritional status was determined by anthropometric control. Town of origin of the patient, and distance to specialized care center was recorded. **Results:** 20 patients were included, 5 with severe, 3 patients with moderate, 9 with light PKU and 3 persistent benign phenylketonuria. Considering all age groups 70% were adherents. 16 children had proper neurological development (80%) . 4 were considered neurologically compromised, 3 of them had severe PKU and were not adherent to treatment. However 2 of the severe PKU, adherent to treatment patients, had neurological development according to age. All patients had adequate nutritional status. All patients with poor adherence lived near de reference hospital and Just one patient live with only one parent. **Conclusion:** The nutritional status was adequate in all patients. Malnutrition didn't cause worse outcome. The distance between home and control center and living with only one parent didn't affected treatment adherence or outcome. Neurological development is compromised to a greater extent in patients with poor adherence, in accordance with the literature, and influenced by the type of PKU. Severe PKU have a higher incidence of neurological impairment. However 40% of patients with severe PKU have normal neurological exams. So the efforts of the medical and support team should focus on the monitoring of these patients especially, working with families, reevaluating strategies to improve adherence.

P169 - The Role of the Psychologist as a facilitator of Mourning From Preparation Helping Improve Adherence to Treatment of Phenylketonuria

Isabel Spínola Castro, I.(1); Claudia Do Couto, C.(2); Jonantan De Oliveira, J.(2); Josiane Cecília Alves, J.(2); Luís Canto, L.(2)

(1): Universidade Federal de Minas Gerais, Belo Horizonte, Brasil (2): Universidade Federal de Minas Gerais/Faculdade de Medicina, Belo Horizonte, Brasil

Introduction: During life, and more intensely during pregnancy, expectant parents build an idealized image of a perfect son. The relationship between parents and children starts from that ideal. It is the relationship with the imaginary child who prepares the psyche of the country to establish ties with the real child who is to be born. The Neonatal Screening Program of Minas Gerais -PTN-MG, collects samples of blood on filter paper taken from the heel of newborns to diagnose genetic and metabolic diseases, including the Phenylketonuria (PKU). Grief has the function of preparing and psychic assimilation of the loss. In the case of a diagnosis of PKU, the child conceived no longer exists. Now there is a child with a chronic illness, full of limitations and differences, not the idealized love object. **Objectives:** To present the performance of the psychology team in supporting parents in the preparation of mourning the loss of the idealized son and his importance in the acceptance and compliance. **Methodology:** Through the methods of care, guidance and counseling conducted by Nupad - a reference center in neonatal screening Gerais- Gerais seeks to ease the grief process. We were met 22 families in the last 12 months, with an average of 05 calls per family. The sessions were weekly and made the psychology team. **Results:** Parents had great difficulties to get diagnosed. In that first moment the real baby is denied. Guilt, fear, anger, anxiety, anguish are

some elements observed initially. The weekly survey allows evaluate parental grieving process as well as their preparation. It is through this monitoring that identifies the construction of a new bond and consequently a better acceptance to treatment adherence. **Conclusion:** The grieving process experienced by parents can lead to poor adherence to treatment of the baby, which, especially in the early stages of the disease can lead to irreversible consequences. The psychological treatment ratify the importance of creating a new link with the real baby which allows parents not only adherence to treatment.

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P170 - The Feasibility of Using an MSMS Based Method With Perkin Elmer Lysosomal Storage Disease (LSD) Reagents to Implement a Newborn Screening Test for Six LSD

Ranieri, E.(1); Stark, S.(2); Gelb, M.(3)

(1): Biochemical Genetics, Directorate of Genetics & Molecualr Pathology, SAPathology at the Women's & Children's Hospital, Adelaide, Australia
(2): Biochemical Genetics, Directorate of Genetics & Molecualr Pathology, SAPathology at the Women's & Ch, Adelaide, Australia
(3): Department of Chemistry, University of Washington WA, Washington, USA

A study was undertaken to determine the feasibility of an Mass Spectrometry based method with PerkinElmer (PE) tandem mass spectrometry (MSMS) lysosomal storage disease (LSD) reagents to determine the activity of six LSD enzymes in dried blood spots (DBS): galactocerebroside β-galactosidase (Krabbe disease), acid α-galactosidase A (Fabry disease), acid sphingomyelinase (Niemann Pick A/B disease), acid α-glucosidase (Pompe disease), α-L-iduronidase (mucopolysaccharidosis type I) and acid β-glucocerebrosidase (Gaucher disease). De-identified DBS were sourced from the South Australian newborn population (n=1,000) and confirmed positive LSD cases (n=75) from the National Referral Laboratory (NRL). The PE LSD reagents make use of optimized substrates and unique stable isotopes for each of the 6 enzyme reactions. All 6 assays are performed in a single incubation reaction buffer from one 3mm DBS in a microtitre plate format. The activity of each enzyme is determined by stable isotope dilution MSMS using flow injection analysis. Following the enzyme reaction, a single organic solvent extraction and reconstitution in acetonitrile/water carrier buffer is performed, followed by flow-injection into an API5000 MSMS. Each multiple reaction mode (MRM) pair for the 6 LSD substrates/products was optimized on the API5000 MSMS using the following parameters: IS voltage 5000, DP 95, CE 55 and CXP 15, at a flow rate of 80 µl/min using an Agilent 1200 HPLC and autosampler, Reference ranges for each enzyme were determined from the analysis of 1,000 DBS from a normal newborn population. In addition, enzyme activities in DBS from patients affected by Krabbe disease, Fabry disease, Niemann Pick disease A/B, MPS I, Pompe disease or Gaucher disease were used to develop action limits for each respective LSD. The linearity and sensitivity of each of the 6 LSD assays was determined using leukocyte preparations from normal and affected LSD cases. Analysis of the 6 relevant enzyme activities was also compared between the PE LSD reagents and the current fluorometric substrates used by the NRL for the diagnosis of LSD. The results of this study will be presented indicating the feasibility of using the PE LSD MSMS reagents.

P171 - Lysosomal Acid Lipase in Dried Blood Spots (DBS) in Argentinean Population

Frabasil, J.(1); Gaggioli, D.(1); Carozza, P.(1); Sokn, S.(1); Durand, C.(1); Schenone, A.(1);

(1): FESEN-Laboratorio de Neuroquimica, Buenos Aires, Argentina

Introduction: Lysosomal acid lipase (LAL) deficiency is an autosomal recessive disorder due to mutation in the LIPA gene. It may present as a severe form of early onset, Wolman Disease (WD), or as a less severe form of juvenile or adult onset: cholesteryl esters storage disease (CESD). WD is progressive, starts in the first month of life, and is characterized by hepatosplenomegaly, abdominal distension, severe malabsorption and calcification of the adrenal glands, leading to death within the first year of life. CESD has a less progressive course, with a wide clinical presentation, with hypercholesterolemia and hepatomegaly, followed by premature cardiovascular disease, eventually leading to liver fibrosis and cirrhosis. The development of a technique to measure LAL activity in DBS is allowing the study and diagnosis of a larger number of patients. **Aim:** To validate the method to measure the activity of LAL in DBS in a reference center and set the cutoff target ranges for the Argentinean population. **Materials and Methods:** The activity of LAL (punch 3.2mm) was evaluated using the method reported by Hamilton et al. The cutoff target range of the activity was established

studying 312 controls from healthy volunteers. The population was divided in 3 categories according to age: newborns (0-1 month, n = 84) infants (1 month to 18 years; n = 104) and adults (18-74 years, n = 126). Seven true positive samples were also included in the study. **Results:** The activities obtained were: newborn population: 43.0 - 272.3 umol/h/l (mean: 106.0, SD: 57.5); pediatric population: 57,2- 379.4 umol/h/l (mean: 179.7, SD: 71.9); adult population: 55.0 -394, 7 umol/h/l (mean: 170.1, SD: 68.4). The pathological samples were between: 0.0 - 15.5 umol/h/l (mean: 6.5, SD: 5.12). **Conclusions:** Since there are no significant differences between the LAL activity measured in pediatric and adult populations ($p>0.05$), it was decided to unify them in one group. The neonatal population showed significant differences with the other age groups ($p<0.01$). On this basis the cutoffs set were: newborn $\geq$ 43.0; infants and adult $\geq$ 55.0 and pathological $\leq$15.5 (umol/h/l).

P172 - Evaluation of Long-Term Stability of Lysosomal Enzyme Activities in Dried Blood Spots in Different Storage Conditions

Frabasil, J.(1); Gaggioli, D.(2); Carozza, P.(3); Sokn, S.(2); Schenone, A.(3)

(1): FESEN-Laboratorio de Neuroquimica "DR. N. A. Chamoles", Buenos Aires, Argentina
(2): FESEN-Laboratorio de Neuroquimica "Dr. N. A. Chamoles", Buenos Aires, Argentina
(3): FESEN-Laboratorio de Neuroquímica "Dr. N.A. Chamoles", Buenos Aires, Argentina

Introduction: Lysosomal storage disorders are a group of inborn errors of metabolism due to the deficiency of one or more lysosomal enzyme activities (LEA). During the last years a number of specific therapies for some of these disorders have been introduced. Early diagnosis is a real need in all of them. The analysis of the LEA in dried blood spot on filter paper (DBS) is a powerful instrument to detect patients with these pathologies, overall in countries like Brazil or Argentina where large extension and logistic troubles may help to delay the diagnosis. **Aim:** To evaluate the stability of two LEA: Acid Lipase(LAL) and Beta-Galactosidase (BGAL), in three different storage conditions through time to determine the integrity of the samples at the moment they arrived to the laboratory. **Materials and Methods:** LAL and BGAL DBS activities, of three normal controls were measured by fluorometric methods at 0, 7, 14, 30, 45, 60, 90, 120, 150 and180 days in three different storage conditions: room temperature, 4 °C and -20 °C. All samples were stored double-bagged with desiccants. **Results:** A gradual decrease in enzyme activities of the two enzymes was observed over time in the three storage conditions. The highest percentage of residual activity was obtained in the samples stored at -20°C. The LAL activity after 90 days fall to: at room temperature 50.3% (SD=3,91), at 4°C: 28% (SD=2,95) and at -20°C: 21.6% (SD=2,76). The BGAL activity after 90 days fell to: at room temperature 62.2% (SD=4,62), at 4°C: 20.5% (SD=5,05) and at - 20°C: 15.1% (SD=2,40). The protocol will be finished in two months. **Conclusions:** DBS for LEA should be stored at 4°C if they are not going to be sent to the lab immediately after collection. The results showed similar stability between BGAL and LAL, allowing the use of BGAL as sample quality control. Analyzing the time that the sample may be delayed to arrive to the lab, in a large Latin American country, we suggest sending a control sample from a healthy volunteer to analyze in parallel with the suspected sample.

P173 - Panorama of the Last Year of Operation of MSUD Network

Romariz Ferreira, F.(1); Tonon, T.(1); Hendges De Bitencourt, F.(1); Teixeira, A.(2); Sitta, A.(2); De Moura Coelho, D.(2); Batista, C.(2); Fischinger Moura De Souza,, C.(2); Vanessa Doederlein Schwartz, I.(1)

(1): Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
(2): Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

Introduction: Maple Syrup Urine Disease (MSUD) is an inborn error of metabolism that is growing interest in Brazilian society, since the early diagnosis and treatment can prevent mental retardation and early death of patients. The MSUD is autosomal recessive disease and its worldwide incidence is estimated at 1:185,000 births. In Brazil there is no data in the literature about its prevalence. Regarding treatment, there are two types: dietary treatment, which is for lifetime, and more recently, liver transplantation. The MSUD Network was designed in 2010 and is in full operation since June 2014. This study sought to present an overview of the first year of operation of the MSUD Network, coordinated by the Medical Genetics Service of HCPA (SGM-HCPA), Brazil. **Methodology:** This is a retrospective cross-sectional study based on information in the Network database (June, 2014-April, 2015. Although the network has been created in 2014 some patients were automatically include in the network by already being in compliance with the previous period to that date. **Results:** Currently, the network has its own website (www.redexaropedobordo.com.br), where it can be found not only relevant information about the project objectives and the disease, but information about centers that provide patient care, new researches in the area and the participating centers of the network, thus constituting up an important channel of communication and support for doctors, relatives and patients. In addition, the network has different channels of "contact us" (toll free, e-mail, e-form) to answer questions and provide information. Of the 117 patients registered at MSUD Network, all from five Brazilian regions, 10 died. From June 2014 to April 2015 there were 11 patients who were suspected of having MSUD. Ten of which were confirmed. In the analyzed period, three patients received a liver transplant and no deaths have been registered. **Conclusion:** This is the first MSUD service research network, and it allows the diagnosis and monitoring of patients. The data to be downloaded over the network will be an important tool for epidemiological surveys in Brazil, something that is lacking in the literature, and will help to improve clinical outcomes nationwide.

P174 - Chitotriosidase: A Biomarker for the Diagnostic Approach of Lysosomal Storage Disorders

Uribe Ardila, A.(1); Pacheco, N.(2)

(1): Universidad de los Andes, Bogota, Colombia
(2): Universidad de los Andes

Introduction: Lysosomal storage disorders (LSDs) are a group of pathologies that enclose an enzymatic damage and its pathological consequences due to the accumulation of substrate in the lysosomes. In Colombia, these entities are misdiagnosed because many of them are not widely known. A biomarker is defined as a molecule that works as an indicator of disease, being a useful tool for the diagnostic approach. Chitotriosidase (Cht) is a chitin hydrolyzing enzyme that cleaves the 1,4-β linkage of chitin. In human, its function has not been entirely elucidated, but its increase has been associated with inflammation, fungal/parasitic infection or LSDs. **Objective:** Here we propose chitotriosidase as a reliable biomarker for the diagnostic approach to LSDs in Colombia. **Methods:** We took dried blood Spots on filter paper samples from 270 patients with Pompe, Fabry, Metachromatic Leucodystrophy, Mucopolysaccharidosis, Mucolipidosis, Gaucher, Niemann Pick, Gangliosidosis GM1 or Sialidosis, previously diagnosed by enzymatic assays in leukocytes. Additionally, 55 patients with symptoms suggestive of an LSD and 450 control subjects were analyzed. The activity was estimated by an endpoint method, modified from Chamoles et al., 2001. Which uses 4-methylumelliferyl-β-D-N,N',N'' triacetylchitotrioside as substrate. **Results and conclusion:** While most patients with LSDs showed an increase in ChT (Ranging between 0,0 – 3118,0 nmol/ml/h), Morquio A patients showed no increase (n=50, range: 4,0-78,1 nmol/ml/h) in relation to the reference value (<94 nmol/ml/h). Although ChT is not an specific biomarker, we believe it can be used for an LSD diagnosis approach as long as the clinical symptoms strongly suggest it.

P175 - Spontaneous Subdural Hematoma in Mucopolysaccharidosis: Report of Five Cases and Literature Review

Dalla-corte, A.(1); Anjos Da Silva, A.(2); Fischinger M. De Souza, C.(2); Vanessa D. Schwartz, I.(1); Dain G. Horovitz, D.(3); Barth, A.(3); Giugliani, R.(1)

(1): Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
(2): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
(3): Instituto Fernandes Figueira—FIOCRUZ, Rio de Janeiro, Brazil

Introduction: The mucopolysaccharidoses (MPS) represent a group of inheritable, clinically heterogeneous lysosomal storage disorders, in which progressive accumulation of glycosaminoglycans (GAGs) can affect organs and tissues all over the body, including blood vessels. Spontaneous subdural hematoma (SDH) is a very rare complication seen in all types of MPS and may also develop after a ventriculoperitoneal shunt (VPS) placement. Although not used in diagnosis of MPS, neuroimaging of brain and spine are critical for evaluating the complications of MPS and the need for neurosurgical treatment. **Material and Methods:** This is a case series study which included five MPS patients with spontaneous SDH: MPS type I in 1 patient and MPS type II in 4 patients. The age range was 2 to 10 years, 4 males and 1 female. All the MPS II patients presented inversion or complex rearrangement in IDS gene. In three patients the SDH was followed by a VPS placement. Four patients presented massive SDH and two patients required surgical drainage. Three patients were in enzyme replacement therapy. Three patients experienced own complications of natural history of MPS and two of them died. **Discussion:** Because only three other cases have been reported, this is the largest series of cases already described. One explanation would be the high GAGs concentration having a "heparin-like" effect, decreasing blood viscosity and enhancing bleeding tendencies. In the other hand, some authors hypothesized that the more vessels vulnerability in MPS characterized by smooth muscle hyperplasia and degenerative changes in the intima and media were responsible for the vasculopathy and central hemorrhages. Due the occurrence of SDH after VPS placement in three of our patients, abnormal cerebral blood vessel architecture secondary to the ventricular enlargement leading to rupture could be considered. SDH may also occur after a VPS insertion due to the siphoning effect and overdrainage of cerebrospinal fluid, producing negative pressure inside the skull and causing rupture of veins in subdural space. **Conclusions:** The pathophysiology of the SDH in MPS patients is not clear established. Because the spontaneous SDH are usually found without clinical manifestations, neuroimaging should become part of the routine assessment.

P176 - Neurocognition in Early Detected and Treated Congenital Hypothyroid Children

Pardo Campos, M.(1); Musso, M.(2); Keselman, A.(3); Bergadá, I.(4); Gruñeiro -papendieck, L.(3); Chiesa, A.(3)

(1): Fundacion de Endocrinologia Infantil. Universidad Catolica Argentina, CABA, Argentina
(2): CIPME (Conicet)-UADE, CABA, Argentina
(3): CEDIE-CONICET-FEI-División de Endocrinología, Hospital de Niños R. Gutiérrez, CABA, Argentina
(4): CEDIE-CONICET-FEI- División de Endocrinología, Hospital de Niños R. Gutiérrez, CABA, Argentina

Introduction: It has been reported that children with congenital hypothyroidism (CH) detected through neonatal screening and adequately treated might present mild cognitive deficits possibly related to the underlying disease. **Objectives:** To characterize the cognitive profiles of children with CH, and to assess specific deficits and their relationship with variables of severity, duration and treatment of the disease. **Patients and methods:** One hundred and twenty children aged 9 to 10 years were selected. Sixty had CH, had been detected through

neonatal screening and were adequately treated within the first month of age. Sixty healthy children without CH were used as control group. Inclusion criteria were: Absence of other concurrent diseases, half day school and parents that had achieved complete high school educational level. The association of cognitive profile was related to: 1) LT4 initial dose (10-12 vs. 12-16 ug/kg/day), 2) Initial serum T4 level: (≤2ug/dl vs.>2,1ug/dl), 3) Etiology: athyreotic vs. ectopic, 4) Age at starting treatment (≤ 20 vs.21-30 days) y 5) Epiphyseal Knee surface (≥5mm2 vs.<5mm2). The following tests were administered: WISC III, Rey-Osterrieth Complex Figure Test, Woodcock Muñoz–R, Continuous Performance Test (CPT II), ITPA (Illinois test of psycholinguistic abilities), Verbal Fluency Test, Test Knox Cubes, Trail Making Test, Faces Test, 5 digits Test. Student T test for independent samples, Bonferroni's adjustment ($p<0.002$) were carried out. **Results:** CH patients showed normal average IQ without significant differences from controls. Scholar level was always the one expected for chronological age. CH patients had lower performance in processing speed, reaction time, attention, cognitive flexibility, visuoconstruction abilities and long term memory. Athyreotic children (with more severe disease) showed lower processing speed. The other evaluated variables were not statistically associated with cognitive impairments. **Conclusion:** Our findings confirm the importance of thyroid hormone during fetal development and the utility of early detection and treatment. Although CH children do not have mental impairment, they show mild cognitive disorders, more pronounced in those with severe etiology to consider in their follow up.

P177 - Analysis of Foxe1 Gene in a Sample of Mexican Patients With Primary Congenital Hypothyroidism Due to Thyroid Dysgenesis

Alcántara-ortigoza, M.(1); Sánchez-verdiguel, I.(2); Martínez-cruz, V.(1); Sánchez-pérez, M.(3); González-del Angel, A.(1)

(1): I Laboratorio de Biología Molecular, Departamento de Genética Humana, Instituto Nacional de Pediatria, México, Distrito Federal, México

(2): Consulta Externa de Pediatría, Instituto Nacional de Pediatria, México, Distrito Federal, México

(3): Laboratorio de Seguimiento del Neurodesarrollo, Instituto Nacional de Pediatria, México, Distrito Federal, México

Introduction: Mexico has one of the highest worldwide incidences (1: 1,000 births) of primary congenital hypothyroidism (CH) due to thyroid dysgenesis (TD), whose etiology suggests the involvement of environmental and / or genetic factors. FOXE1 (9q22) is a CH candidate gene which encodes an essential transcription factor for thyroid development and has a polymorphic tract of polyalanines (TPolyA) associated as a risk factor to CH; however its participation in TD in Mexican population is still unknown. **Objective:** To determine whether pathogenic and / or polymorphic FOXE1 variants contribute to TD in Mexican CH patients. **Material and methods:** Sequencing of the coding exon of FOXE1 gene was performed in 131 unrelated Mexican CH patients whose diagnosis and TD classification relied on serum TSH/T3/T4 profile and thyroid scintigraphy/ultrasonography: ectopy (n=60), athyrosis (n=54) and hypoplasia (n=17). Undescribed FOXE1 variants and TPolyA alleles were directly searched in 111 ethnically matched healthy controls. The TPolyA genotypes were compared between cases and controls using Fisher's exact test ($p<0.05$). **Results:** No FOXE1 pathogenic variants were identified in the 131 CH cases analyzed, although 5 polymorphic variants (rs3021523, rs201181824, rs3021524, rs3021526 and rs373427403) and 4 not yet published (p.Pro243 =, p.Gly124Arg, p.Ala335Gly and p.Pro203Arg) were documented. The p.Pro203Arg was considered a benign variant due to an allelic frequency of 0.017 in controls; searching of p.Gly124Arg and p.Ala335Gly in controls is ongoing. Six TPolyA alleles (10,12,13,14,16&17 alanines) were identified. The 14/14 genotype was the most prevalent both in cases (75.57%) as controls (81.08%), but allelic frequencies for TPolyA <14 were greater in cases vs. controls (7.63% vs. 0.90%). When comparing both groups, the 14 TPolyA allele vs. TPolyA <14 has an OR = 8.68 (IC95 1.10-68.44, p = 0.014), whereas that homozygous genotype 14/14 vs. ≤14 / ≤14, has an OR = 8.18 (IC95 1.017-65.08, p = 0.018). **Conclusions:** If any pathogenic effect is corroborated to p.Ala335Gly and p.Gly124Arg, it suggests that pathogenic FOXE1 variants are also an infrequent etiological factor for CH (<2%) in our population. Statistical analyses indicate that alleles TPolyA <14 in homozygous or heterozygous state could be a genetic risk factor for developing CH in Mexican population.

P178) Variability of Thyroid Stimulating Hormone (TSH) Values in Newborn Dry Blood Samples According to Birth Weight and Maternal Body Mass Index in a Mexican Population

De La Torre García, O.(1); Trigo Madrid, M.(1); Ibarra Gonzalez, I.(2); Herrera Pérez, L.(3); Vela Amieva, M.(4)

(1): Secretaría de Marina Armada de México, Mexico D.F., México

(2): Instituto de Investigaciones Biomédicas, UNAM, Mexico D.F., México

(3): Laboratorio TamizMas de Químicos Maldonado, Villahermosa, Tabasco, México

(4): Laboratorio de Errores del Metabolismo y Tamiz del Instituto Nacional de Pediatría, México D.F., México

Introduction: Macrosomia is a term used to describe newborns with an abnormally high birth weight. Although there is no absolute consensus in the definition of this disorder, most of the published studies consider birth weights >4,000 g, the 90th percentile or 2 standard deviations for gestational age. The proportion of macrosomic NB varies between different populations (5-20%), but an increase in macrosomic births, especially related with maternal obesity and diabetes has been reported.

Macrosomic products have higher morbidity and mortality. The variability of TSH values according to gestational age and low birth weight are well known, but the effect of high birth weight on TSH values are not always recognized. **Objective:** To analyze TSH concentrations according to birth weight, with emphasis on macrosomic newborns (> 4,000 g) in dry blood samples on filter paper. **Material and Methods:** Analysis of the TSH values in the expanded newborn screening program database. The NB data were divided in 2 categories: normal birth weight (<4,000 g) and macrosomic products (≥4,000 g). TSH was measured in dried blood spots on Guthrie cards by AutoDELFIA kit. Only samples taken between 3-5 days of life were considered for study. Maternal body mass index (BMI) ≥ 25.0 kg/m2 was also considered. **Results:** A total of 2,807 samples were analyzed (48.1% girls and 51.9% boys); 2,648 NB had normal birth weight (94.34%) and 159 NB (5.66%) were macrosomic, 62 girls (39%) and 97 boys (61%). TSH mean concentrations were significant different (p=0.009) between groups, being higher in macrosomic NB than in normal birth weight NB (1.47 vs.1.26 mIU/L, respectively). Maternal BMI was significantly higher in the macrosomic NB group (p=2.16x10e-11). **Conclusions:** In the studied population the proportion of macrosomic NB (5.6%) was similar to the reported for other developing countries; TSH concentrations and maternal BMI (≥ 25.0 kg/m2), are slightly higher in NB with birth weight ≥4,000 g.

P179 - Mucopolysaccharidosis and Their Enzyme-Replacement Therapies. Long-Term Considerations

Guelbert, N.(1); Becerra, A.(1); Giner-ayala, A.(1); Peralta, L.(1); Guelbert, G.(1)

(1): Hospital de Niños de Cordoba, Cordoba, Argentina

Introduction: Mucopolysaccharidosis (MPS) are lysosomal storage diseases with severe multisystem involvement. The deficiency of any of the 11 specific lysosomal enzymes, capable of degrading the 5 different glycosaminoglycans (GAGs), is responsible for any of the seven known mucopolysaccharidosis. Since May 2003 when the FDA approves Aldurazyme as Enzyme-Replacement Therapies (ERT) for MPS-I, the natural history of the MPS begins to change. In May 2005, Galsulfase for MPS-VI was approved, in July 2006 Elaprase for MPS-II, in February 2014 Elosulfase for MPS-IV and currently ERT for MPS-IIIA, MPS- IIIB and MPS-VII is being investigated. **Objectives:** 1. Evaluate the response to long-term ERT in different MPS (Benefits and adverse events). 2. Show our clinical and biochemical experience in patients management. **Materials and methods:** 26 patients (9 women and 17 men) with different types of MPS receiving specific ERT, were evaluated since 2006 up to the present: 4 patients with Hurler; 8 patients with Hurler-Scheie; 6 patients with Hunter syndrome; 1 patient with Maroteaux-Lamy and 7 Morquio A syndrome. Their clinical evolution was evaluated with Six-Minute Walk Test and Three-Minute Stairs Climb test, radiological, cardiological and neumonological studies, and urinary GAGs levels. **Results:** In MPS-IH, 3 patients received successfully ERT combined with bone marrow transplantation. (BMT) and their enzyme values are normal today. All patients reduced their visceromegaly and normalized their urinary GAGs with ERT. MPS-IHS patients lead a normal active life although they didńt show skeletal or corneal commitment improvement. All the MPS-II patients started late ERT, and some of them died due to respiratory complications. We didǹt observe improvement in their cognitive impairment. The MPS-VI patient died from cardiovascular complications at 17 years, after five years of ERT.MPS-IVA adult patients with ERT shows a significant improvement in short time, evidenced by effort test and skeletal pain decrease. **Conclusions:** ERT was beneficial in all cases treated, improving the quality of life of patients and their families. In most cases the onset was delayed. We observed significant improvement in symptoms and signs when the patients were treated early.

P180 - Plasma Oxysterol Analysis for Niemann-Pick Type C Disease Diagnosis and Pre-Analytical Conditions

Giugliani, R.(1); Deon, M.(1); Mescka, C.(1); Ribas, G.(1); Souza, H.(1); Pereira, M.(1); Gus Kessler, R.(1); Timm Souza, F.(1); Freitas, T.(1); Pinto Vairo, F.(1); F M Souza, C.(1); R Vargas, C.(1)

(1): SGM/HCPA, Porto Alegre, Brazil

Introduction: Niemann-Pick type C (NPC) disease is a rare neurodegenerative lipid storage disorder caused by mutations in either the NPC1 or the NPC2 gene. The diagnosis of NPC disease is currently done by a set of consecutive tests, none of them being simultaneously simple and specific. The analysis of oxysterol, specially cholestan-3β,5α,6β-triol (triol), has recently been proposed as a potential method to identify NPC patients. Since our group coordinates a large network of Brazilian services that investigate patients at risk of presenting NPC, pre-analytical precautions about the triol stability are necessary for samples' shipment. **Material and Methods:** Plasma from 21 high-risk patients investigated by Filipin test were also submitted to the tandem mass spectrometry assay of plasma triol. We investigated the effect of anticoagulants, heparin and EDTA, on triol levels as well as sample stability at 4°C and 25°C (24 and 48 hours) in order to evaluate the adequate shipment condition. **Results and conclusions:** In 21 high-risk patients investigated, we found that all 3 cases with positive Filipin test had also increased plasmatic triol and the diagnosis was confirmed by molecular analysis. In 9 patients in whom Filipin test resulted inconclusive, 1 had increased triol levels, being potentially a variant NPC case (molecular analysis for NPC is in progress). In 9 cases with negative Filipin test, triol was normal in all, excepted one (later diagnosed NPC type A). We did not observe statically difference among the

anticoagulants for plasma triol levels. At 4°C, triol plasmatic concentration was stable for 24 hours, but not for 48hours. On the other hand, triol plasmatic levels were not stable at 25°C. Our results indicate that the choice of anticoagulants, EDTA and heparin did not affect oxysterol measurement and that the shipment of plasma samples should be done in 24 hours using cooling devices on dry ice. In these conditions, oxysterol measurement plays an important role in the diagnosis of NPC disease.

P181 - Investigation of Lysosomal Acid Lipase Deficiency: Experience of a Reference Center

Giugliani, R.(1); Scholz Magalhães, A.(2); De Mari, J.(2); Civallero, G.(2); Barbosa Trapp, F.(2); Michelin-tirelli, K.(2); Graeff Burin, M.(2)

(1): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil
(2): Hospital de Clínicas de Porto Alegre

Introduction: The cholesteryl ester storage disease is a rare lysosomal storage disorder (LSD) caused by the deficiency of lysosomal acid lipase (LAL). In Wolman disease, the rarest and most severe form of lysosomal acid lipase deficiency (LAL-D), the beginning of symptoms can occur in the first weeks and can be lethal in the first year of life. The early diagnosis is very important due the disease severity and the possibility of treatment, recently developed. **Material and Methods:** Review of the number of patients, samples analyzed and diagnosis obtained, signs and symptoms, biochemical results, age at the diagnosis and cases requiring a second sample. **Results:** We analyzed samples from 787 patients with clinical suspicion of LAL-D. The diagnosis was achieved in 9 patients. Six had the specific clinical suspicion of LAL-D, while 3 had the initial suspicion of Niemann-Pick C. The high activity of chitotriosidase was seen in these 3 patients. In affected patients, LAL activity in DBS ranged from undetectable to 3.8 nmol/h/mL (RR 36 -283), and in leukocytes ranged from undetectable to 37 nmol/h/mg protein (RR 131 - 744). The age at the diagnosis ranged from 2 months to 32 years. When the first sample was DBS it was needed to repeat the collection in 19% of cases. In 11% the new sample was requested due to low activity in both LAL and the reference enzyme. From the 18 cases that required a new sample, 4 diagnoses were confirmed. **Conclusion:** The high activity of chitotriosidase observed in three patients with LAL-D, shows again the importance of this biomarker for LSD diagnosis. The diagnosis process can start by the analysis of LAL in DBS, because it allows a simpler sample collection and transportation. However, our results made clear the importance of the diagnosis confirmation by leukocytes analysis, once there is the possibility of false positive results using DBS. We suggest that in severe cases both samples (DBS and heparinized blood for leukocytes) should be sent simultaneously to allow a faster diagnosis and an earlier initiation of treatment.

P182 - Epidemiological Behavior of the Screened Diseases in Costa Rica by the National Newborn Screening Program (NSP) 1990-2014

Chaves Guzmán, I.(1); Obando Rodríguez, S.(1); Jiménez Hérnandez, M.(2); Saborío Rocafort, M.(2)

(1): Asociación Costarricense para el Tamizaje (ASTA), San José, Costa Rica
(2): Programa Nacional de Tamizaje Neonatal, San José, Costa Rica

Introduction: The National Screening Program (NSP) has been for 25 years responsible to implement the screening test for inborn errors of metabolism in newborn population. This program is categorized as one of the best in Latin America. Since its establishment, the program has screened 1.5 million children and approximately a thousand newborns have been diagnosed with congenital or genetic disorders, alteration or diseases. **Methods:** The target population of this study is newborns screened by NSP since 1990. An observational descriptive study was conducted to characterize the trends and frequencies of diseases and analyzing epidemiological events among them. **Results:** NSP has a nationwide organized structure which includes: sampling, processing, laboratory confirmation and comprehensive monitoring of diagnosed patients. Its central panel contemplates 29 diseases; however, it has the capacity to diagnose 52 inborn errors of metabolism. Epidemiologically speaking, the temporal analyses evidence a seasonal trend up to 2014 being endocrine defects such as congenital hyperthyroidism (HC) (mostly diagnosed with 484 cases and a prevalence of 1: 3.300), and congenital adrenal hyperplasia (CAH - 1: 6.900) more common. Both have similar prevalence worldwise. Contrary, diseases such as PKU have significantly lower prevalence in comparison to international statistics. **Conclusion:** The NSP 25th anniversary has brought successful implementation in the newborn population screening processes and a good acceptance of all the involved parties. The knowledge gained about the behavior and disease epidemiology not only quantifies the magnitude of the problem, but also has specific surveillance systems for IEM. Besides analyzing the impact of these programs in the defined population, the gathered data also allows to estimate specific individual risks of suffering from some EIM. Therefore, it is the challenge of the National Screening Program to keep the reached standards as well as to enhance some other processes which involve quality management.

P183 - First Year After Congenital Adrenal Hyperplasia Neonatal Screening in a Public Health Program in Southern Brazil

Castro, S.(1); Prado, M.(2); Beltrão, L.(3); Chapper, M.(3); Vargas, P.(3); Dornelles, C.(4); Kopacek, C.(5)

(1): Serviço Referência Triagem Neonatal RS/UFRGS, Porto Alegre, Brasil

(2): Centro de Desenvolvimento Científico e Tecnológico (CDCT)—FEPPS/UFRGS, Porto Alegre, Brasil
(3): Serviço de Referência em Triagem Neonatal do Rio Grande do Sul, Porto Alegre, Brasil (4): Centro de Desenvolvimento Científico e Tecnológico (CDCT)—FEPPS, Porto Alegre, Brasil
(5): Serviço de Referência em Triagem Neonatal RS/UFRGS, Porto Alegre, Brasil

Introduction: Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disease with impaired adrenal steroidogenesis that leads to excess androgen and glucocorticoid deficiency with or without mineralocorticoid deficiency. It is caused in about 95% of the cases by 21-hydroxylase deficiency. Screening for the disease in the neonatal period is part of the Brazilian National Neonatal Screening Program and aims at early diagnosis, especially of the salt-wasting form (CAH-SW), which is potentially lethal. **Objectives:** To evaluate the results of the first year of public neonatal screening for CAH in the state of Rio Grande do Sul (RS). **Materials and Methods:** Retrospective analysis of screening results, false positives and deaths in the period from May 2014 to April 2015. We used the cutoffs of 17OH progesterone (17OHP) in ng/mL stratified by weight of newborns. **Results:** In this period, 109,030 newborns were screened and 8 cases were detected, with an incidence of 1:13,628. Of these, 6 were CAH-SW and 2 simple virilizing form (CAH-SV). The degree of virilization (Prader scale) ranged from I to III, 2 of them with markedly ambiguous genitalia. One of the cases was associated with multiple malformations. The median and interquartile range of age at the time of collecting in cases of the first and the second samples was 6.5 (3.5 - 10) and 19.5 (17 – 20) days respectively. The mean value of 17-OHP in the first sample was 268.5 (57.6 – 476.8) and 25.8 (18.0 – 42.0) in the second sample was 359.0 (180.5 – 580.5) and 8.2 (5.8 – 12.0), among cases and newborns that did not have the disease, respectively ($P < 0,001$). **Conclusions:** Screening for CAH in RS during the study period showed frequency similar to other national studies. The effectiveness of early detection of CAH was demonstrated in the flow of care strategy and in the cutoff point of 17 OHP used.

P184 - Extended Neonatal Screening In Indigenous Population of Mexico

Pérez Reyes, P.(1); Olvera Alvarez, J.(1); Ortíz Garcia, F.(1); Munguía Ramirez, M.(1)

(1): Mexican Institute of Social Security, IMSS PROSPERA Unit, México, D.F., Mexico

Introduction: IMSS PROSPERA, provides health care to indigenous populations. It carries out neonatal screening for congenital hypothyroidism (CH) since the year 2000, phenylketonuria (PKU), Congenital Adrenal Hyperplasia (CAH) and Biotinidase Deficiency (BD) since 2007 and for Classic Galactosemia (CG) since 2012. **Objective:** To measure the frequency of CH, PKU, CAH, BD and CG in infants. **Methodology:** Cross-sectional and descriptive study. Screening: blood samples were collected and placed on filter paper; samples for CH were obtained from cord blood (at birth) or heel (third to fifth day of extrauterine life). For PKU, CAH, CG and BD, samples were obtained from heel, and all samples were processed by inmmuno-enzymatic assay (UMELISA). Diagnostic confirmation was performed by thyroid profile (CH); 17-hydroxyprogesterone, cortisol and testosterone by radioimmunoassay (CAH), quantification of biotinidase activity by UV/VIS spectrophotometry, and organic acids by gas chromatography/mass spectrometry. **Results:** IMSS PROSPERA evaluates annually around 124,000 infants; 1,866,936 children were screened from 2000 to 2014; confirmed 443 cases of CH (frequency 1: 4,214). From 2007 to 2014, screening for PKU, CAH, BD and CG was carried in 1,054,066 infants; 40 were confirmed with CAH (frequency 1,350), and three with BD (frequency 1:351,335). No confirmed cases of PKU or CG. **Conclusions:** IMSS PROSPERA performs extended neonatal screening since 2000 in rural areas with a predominantly indigenous population. Bringing this service to this population has been a great achievement for public health in Mexico, detecting, diagnosing and providing treatment to affected children.

P185 - MPS Brazil Network: Over a Decade Improving Diagnosis of MPS

Federhen, A.(1); Burin, M.(1); Leistner-segal, S.(1); Matte, U.(1); Batista, C.(1); Rafaelli, C.(1); Giugliani, R.(1)

(1): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil

Introduction: MPS BRAZIL-NETWORK (MBN) was created to improve diagnosis and management of MPS diseases in Brazil. Since then, physicians from all Brazilian regions have requested support for the investigation of patients with suspected MPS. **Methods:** The contact with MBN has been performed through website (www.mps.ufrgs.br), email (mps@ufrgs.br) or a toll-free helpline (0800-510-2030, only in Brazil). Informative materials and instructions for sample collection and shipment, as well as educational material about MPS can be downloaded in the website. An annual meeting with MPS patients and their families, as well as with health professionals, is organized to provide the latest update about the MPS disease. The families come from Brazil and from some Latin America countries as well. Services from all Brazilian regions and from Latin America countries sent biological samples to MBN headquarters, located at the Medical Genetics Service of HCPA, where the laboratory investigation for MPS is performed free of charge. **Results:** From April/2004 to December/2014, 1192 patients with MPS were identified, being 645 new diagnoses (average 5.0/month, almost the double of the previous average). Most frequent type of MPS diagnosed was MPS II, confirmed in 390/1192 (32.7%) of MPS patients, followed by MPS VI (19.3%), MPS I (16.5%) and MPS IVA (9.6%). Most MPS I patients came from South or Southeast regions (49.6%), while most MPS VI patients came from Northeast region (49.5%). MPS III-B and IV-A are also

frequent in South with 42% and 31.5% of patients, respectively coming from this region. Diagnosis of MPS was confirmed in 218 foreign patients, being 150/218 (68%) from other Latin American countries. **Conclusion:** Around 12.5% of the foreign patients diagnosed with MPS by the MBN came from Latin America countries, suggesting that easy access to information and to diagnostic tests provided by MBN helped to identify many patients not only in Brazil, but also in other Latin American countries, transforming MBN in a template to develop similar initiatives for other rare diseases.

P186 - Analysis of Signaling Pathways Associated With Liver Damage Using In-Vitro and In-Vivo Models of Niemann-Pick Disease

Oyarzún, J.(1); Acuña, M.(1); Castro, J.(1); Arrese, M.(1); Zanlungo, S.(1)

(1): Pontificia Universidad Católica de Chile, Santiago, Chile

Introduction: Niemann-Pick diseases (NPDs) are a group of genetic diseases, which have altered lysosomal storage. Three forms of NPDs are described depending on the phenotype or cause of the disease; type A and B (NPDA/B), caused by acid sphingomyelinase (ASM) deficiency and type C (NPDC), caused by mutations in genes involved in cholesterol efflux from lysosomes (Npc1 or Npc2 genes). Nonetheless, NPDs share symptoms and combine common alterations in traffic and lipid metabolism, and we propose that common pathogenic mechanisms leading to cell death and liver damage are involved in these diseases. **Material and Methods:** We used ASM deficient mice (ASMKO) at 3, 4 and 5 months-old and Npc1 deficient mice (Npc1KO) at different ages for analyze liver damage. We evaluated damage (Cathepsin B and D), fibrosis (Collagen I) and inflammation (NLRP3 inflammasome) markers in liver by protein and mRNA expression. As cellular models hepatocyte cell lines were stably transfected with shRNA for ASM or Npc1 (work in progress). **Results:** We found an increase in mRNA and protein expression on cathepsin D, NLRP3 inflammasome and collagen I in the livers of the murine models of NPDs. **Conclusions:** The different NPDs animal models show increase in cathepsin B and inflammasome NLRP3 signaling pathways. It would be interesting to study and modulate these pathways to understand the present mechanisms of liver damage in NPDs to find common therapeutic targets that could give rise to novel therapeutic approaches for these diseases.

P187 - Vitamin B12 Deficit in Infant of a Vegetarian Mother: Application of Tandem Mass Spectrometry and Gas Chromatography

Cesari, N.(1); Suldrup, N.(1); Naretto, A.(1)

(1): IACA Laboratorios, Bahia Blanca, Argentina

Background: The vegetarian diet is being adopted by an increasing percentage of the population. A strict vegetarian diet can have a negative impact, especially during periods fast growth on pregnancy, affecting physical and psychomotor development. Tandem Mass Spectrometry and Gas Chromatography allows us to analyze children with vitamin B12 deficiency of vegetarian mothers, quickly and efficiently in the laboratory. **Objective:** Report a case about vitamin B12 deficiency in a boy of vegetarian mother. **Case Report:** A 5-month old infant, son of a longtime vegetarian woman, who presented neurological compromise to vitamin B12 deficiency, is diagnosed in laboratory by determination of organic acids in urine, acylcarnitines in dried blood spots on filter paper and homocysteine. He had an elevation of metilmalonic acid, propionylcarnitine and homocysteine. After a short period of administration of cyanocobalamin, the patient evolved with clinical and laboratory improvement, although he still had residual development delay. **Conclusions:** Laboratory technology allows us to perform a set of measurements for the diagnosis of this condition and prevent the neurological and hematological damage generated by vitamin B12 deficiency in newborn of vegetarian mothers. Vitamin B12 deficiency is often not suspected by the obstetrician in healthy pregnant woman. An anamnesis and nutritional monitoring of pregnant women should be incorporated into obstetric routine.

P188 - Implementation of the Newborn Screening Program at the Nicaraguan Social Security Institute: First Year Results

Del Río Fabre, L.(1); Álvarez Abreu, M.(2); Sequeira Gudiel, B.(3); Delgado Pérez, R.(3); Barrios Rocha, L.(3); Salazar Ortiz, Y.(2)

(1): Centro de Inmunoensayo, La Habana, Cuba
(2): Centro de Inmunoensayo, La Habana, Cuba
(3): Servicios Médicos Especializados (SERMESA), Managua

Introduction: On March 2014, the Nicaraguan Social Security Institute (NSSI) started a newborn screening program (NSP) to detect congenital hypothyroidism, phenylketonuria, galactosemia, congenital adrenal hyperplasia and biotinidase deficiency. The aim of this work is to present the strategies used for the implementation of the NSP and the results obtained in the period March/2014-May/2015, as well as to evaluate the program's efficiency. **Materials and Methods:** First, the stage of implementation consisted in establishing the newborn screening laboratory and visiting NSSI's health institutions where coordination meetings and lectures about general aspects of newborn screening were developed. Finally, the program flowchart was established and the staff involved in the different phases of NSP was trained. Reagents and equipment from SUMA Technology were used for newborn screening. The program efficiency was evaluated using defined quality indicators such as coverage rate, percent of unsatisfactory dried blood spot specimens and time elapsed in the different phases of the NSP. **Results:** At this first stage, five hospitals from NSSI have been incorporated in the

NSP, where samples are collected and sent to central laboratory in less than 48 hours. In the period, 4 301 newborns were screened with an average age at collection of seven days. Sample analysis were carried out within 48 hours and the results are reported by e-mail in less than 11 days. The coverage rate was 84.8% and the percent of unsatisfactory dried blood spot specimens was 3%. Two cases of hypothyroidism and one of congenital adrenal hyperplasia have been confirmed and the average elapsed time from birth to starting treatment was 22.5 days. **Conclusion:** The establishment of the NSP by NSSI has guaranteed, during the last year, the early detection of five metabolic diseases. The study of performance indicators shows that times for pre-analytical and analytical phases are within acceptable ranges, although evidences the necessity of designing other strategies to improve the efficiency of the NSP as for sample quality, coverage rate and follow up of elevated cases.

P189 - Newborn Screening for Cystic Fibrosis in Nuevo León, México

Torres Sepúlveda, M.(1); Martínez Garza, L.(1); Peña Cabrera, A.(1); López Uriarte, G.(1); Bustamante Saénz, A.(2); Villarreal Pérez, J.(3)

(1): Departamento de Genética UANL, Monterrey Nuevo León, México
(2): Centro de Prevención y Rehabilitación de Enfermedades Pulmonares CEPREP, Hospital Univesitario, México
(3): Servicios de Salud, Monterrey Nuevo León, México

Introduction: Cystic fibrosis (CF) is an autosomal recessive hereditary disorder, characterized by pancreatic insufficiency and progressive damage to the respiratory system which leads to failure to thrive. Early diagnosis and prompt intervention limits the disease progression. In September 2011, CF was included in the expanded neonatal screening (NS) program in Nuevo León México. **Objective:** To determine the CF incidence in the Northeastern Mexico population and to provide timely multidisciplinary management. **Methods:** Quantification of immunoreactive trypsinogen (IRT) in dried blood spot samples was made by immunofluorometric assay (PerkinElmer Neonatal Kit). Results above the cut off value in the first sample were repeated, and if found to be again high, a second sample was requested **Results:** From September 2011 to April 2015 a total of 105,500 babies were screened; 214 (0.2%) were abnormal and only 176 (82.2%) second samples were recovered, from which, 159 (90.3%) were normal and 17 (9.7%) continued above normal levels. The latter were referred to the CF clinic for a sweat electrolytes test (SET). We diagnosed 12 cases with abnormal SET and referred to molecular test for *CFTR* mutations. **Conclusion:** The incidence of CF was found to be 1:10000 live births, similar to the one reported in a Caucasian population. Early detection allowed babies to receive timely specialized evaluation in the CF clinic with a positive impact on morbidity and mortality, avoiding interventions that would delay treatment. This is the second NS program for CF in Mexicans and can be used as a reference for incidence at least in the Northeast population.

P190 - High Birth Prevalence of Congenital Hypothyroidism and Geographical Variations of the Disease in the Mexican State of Tabasco

Herrera Pérez, L.(1); Moreno Graciano, C.(1); Martínez Cruz, P.(1); Arias Vidal, C.(1); Maldonado Solís, F.(1); Maldonado Solís, M.(1); Vela Amieva, M.(2); Ibarra González, I.(3); Chablé Cupil, G.(4)

(1): Tamizaje Plus S.A de C.V, Villahermosa, Tabasco, México
(2): Laboratorio de Errores Innatos del Metabolismo y Tamiz, Instituto Nacional de Pediatría, México, D.F., México
(3): Instituto de Investigaciones Médicas. UNAM, México, D.F., México
(4): Hospital del Niño Rodolfo Nieto Padrón, Villahermosa, Tabasco, México

Introduction: The birth prevalence of congenital hypothyroidism (CH) has been increasing in Western countries and there are variations depending on ethnicity, being the Asian and Hispanic populations the most affected ones. Nowadays, there is no satisfactory explanation of these occurrences, but genetic susceptibility or differences in environmental exposures (e.g., environmental contaminants as endocrine disruptors) have been involved. In the medical units of the Ministry of Health of Tabasco, Mexico, newborn screening for CH has been routinely performed since 2007 with a coverage close to 99%. **Objective:** To describe de geographic distribution of CH cases in the State of Tabasco, Mexico. **Methods:** Population-based retrospective study; data were extracted from the newborn screening laboratory database. Thyroid stimulating hormone (TSH) was quantified by time-resolved fluoroimmunoassay (DELFIA® Perkin-Elmer), following the manufacturer's instructions. All samples with TSH above 10 uIU/mL serum were considered as suspect, requiring immediate contact with the NB's family. CH cases were defined as those suspected cases with abnormal confirmatory tests. Birth prevalence was calculated as the number of confirmed cases per 10,000 newborn screened in the period. The habitual maternal place of residence was analyzed with the following regional categories: Chontalpa, Centro, Pantanos, Ríos and Sierra. **Results:** Between July 2014 and May 2015, 31,855 NB were screened; 54 suspected cases were found and 33 CH cases were confirmed (8.79:10,000 NB), with a female predominance of 64,81%. The birth prevalence rate found by region was: 4.3:10,000 NB in Ríos; 4.7:10,000 in Sierra; 8.6: 10,000 NB in Pantanos; 9.2:10,000 NB in Centro and 12.31:10,000 NB in Chontalpa. **Conclusion:** CH birth prevalence in the Mexican State of Tabasco showed important variations by geographic region, being the Chontalpa region the most affected (1:812 NB); in contrast, Ríos region showed the lowest CH rate (1: 2,318 NB). High CH prevalence and geographical variations found in our study must be explained and further research into underlying causes should be done.

P191 - Biochemical Findings of Beta-Ketothiolase T2-Deficiency in a Patient With Severe Neurological Involvement

Gomez Castro, J.(1); Echeverri Peña, O.(2); Ardila Gomez, Y.(3); Pulido Ochoa, N.(3); Guevara Morales, J.(2); Barrera Avellaneda, L.(4)

(1): Unidad Materno Infantil Fundacion Valle del Lili—Universidad ICESI—Universidad CES, Cali, Colombia
(2): Pontificia Universidad Javeriana—IEIM, Bogotá, Colombia
(3): Hospital Universitario San Ignacio—IEIM, Bogotá, Colombia
(4): Pontificia Universidad Javeriana- Hospital Universitario San Ignacio—IEIM, Bogotá, Colombia

Introduction: Ketone bodies are produced normally in response to fasting, they are metabolized using two enzymes: a transferase and a thiolase, if one of them fails there will be metabolic decompensation characterized by Ketoacidosis and hypoglycemia. Decompensation is caused by minor illness or prolonged fasting; in the basal state patients remain asymptomatic. T2-deficiency is characterized by increased excretion of 2-methylacetoacetic and 2-methyl-3-hydroxybutyric acids in urine. The definitive diagnosis requires enzymatic and molecular studies. **Case Presentation:** Female 80 days old; without complications at birth. Few minutes after she presented apnea, seizure with upper limbs tonic posture, was sleepy, hypoactive, with poor or absent primary responses, dolichocephalism, generalized hypotonia, restricted limb mobility, broad epicanthus, low-set ears, hypertelorism, and micrognathia were observed. Phenobarbital was initiated; without improvement of encephalopathy. **Results:** Cerebral CT showed posterior ventricular dilatation and hypodensity of grey/white substances in right frontoparietal region; MRI revealed bilateral hippocampal dysplastic configuration and changes in the ventricular floor, cerebellar hypoplasia and multiple cortical turns, polymicrogyric aspect in some parietooccipitalis areas predominantly in the right side. Hyperintensity and diffusion restriction in cortico-subcortical region of the right frontoparietal region were observed. AO test showed marked increase of 2-methyl-3-hydroxybutyric, 2-methylacetoacetic acids and tiglylglycine; the amino-acid test in plasma showed increase in Ser-Tre-Glu-Orn-Lis-Arg suggestive of T2-deficiency. A second test under nutritional restriction was normal. A third sample on free diet gave results suggestive of T2-deficiency. **Conclusions:** Nowadays the patient receives anticonvulsant and carnitine supplementation. Although the biochemical findings are highly suggestive of T2-deficiency, the patient manifestations do not correspond to the mild intermittent presentation reported in literature, where brain and facial dysmorphisms have not been reported. Analysis of ACAT1 genes is recommended, since T2-deficiciency is susceptible of nutritional management with good prognosis. She must avoid fasting or excessive lipids intake. This case illustrates the difficulty of evaluating patients with heterogeneous symptomatology.

P192 - Mucopolysaccharidosis Type VI, a Family Event Presentation

Miño Arango, M.(1); Forero Delgadillo, J.(1); Mondragón Gaviria, M.(1); Maya, J.(1)

(1): Universidad del Cauca, Popayan, Colombia

Introduction: Mucopolysaccharidosis Type VI (MPS), is an autosomal recessive disorder and is part of the diseases caused by inborn errors of metabolism of glycosaminoglycans, it is due to deficiency of the enzyme arylsulfatase B (ASB). The incidence is estimated at 1: 43.261 to 1: 1.505.160 million live births. However, its true prevalence is unknown. The clinical manifestations are considerable and include involvement of skeletal system, respiratory, heart, eye, skin, gastrointestinal and particular phenotypic characteristics. For diagnosis in addition to clinical suspicion and imaging studies analysis of glycosaminoglycans in urine and molecular studies (ASB analysis) is performed. **Methods:** A family case of indigenous origin is presented with involvement of the two sons; the 8 year old son presents clinical debut with hydrocephalus and intracranial hypertension adding to the phenotypic characteristics (macrocephaly, prominent forehead, corneal opacity, pavilion with low implantation, depressed nasal bridge, claw hands, short stature, short neck and trunk) made metabolically suspected disease which MPS VI is confirmed. The son under 6 is asymptomatic but with similar phenotypic characteristics by family history extension studies were performed establishing the diagnosis of the disease. Results. Two cases of MPS VI in our population with phenotypic initial suspicion were identified and confirmed by radiological findings and molecular type tests. **Conclusions.** MPS VI is a rare disease presentation with higher prevalence in indigenous population probably by inbreeding and inbreeding among parents. A family event with early involvement of the central nervous system characterized by hydrocephalus and intracranial hypertension in children as one of the atypical manifestation and another in which there are only involvement in physical traits as typical is presented. A case of familial recurrence is exposed without genetic counseling and late diagnosis but stability of the disease progression by starting enzyme replacement therapy once the diagnosis is made. it does not reverse damage so that an early diagnosis of the disease with genetic counseling is necessary to prevent recurrence in familial cases.

P193 - Inborn Errors of Metabolism and Pregnancy

Campo, K.(1); Castro, G.(1); Hamilton, V.(1); Bravo, P.(1); Arias, C.(1); Cabello, J.(1); Peredo, P.(1); Cornejo, V.(1)

(1): INTA, Universidad de Chile, Santiago, Chile

Introduction: Inborn Errors of Metabolism (IEM) are genetic conditions that can compromise in different ways to a patient during pregnancy, also have effects on the fetus. EIM as phenylketonuria can produce teratogenic effects in children of

mothers with this disease. In other conditions such as Tyrosinemia Type I they have been reported anecdotally with favorable results of the pregnancy, probably because of the recent emergence of specific therapies that manage to modify the phenotype of these conditions, prolonging the life to women of childbearing age affected. **Objectives:** To present the experience in the nutritional management of one pregnant PKU patient and one with tyrosinemia type I. **Methods:** Medical, nutritional and biochemical monitoring (phenylalanine [FA] and tyrosine [TIR]) during pregnancy. **Results:** Case PKU: Inadequate pre-pregnancy metabolic control (6.3 ± 3.5 mg / dl FA) initiates treatment. The diet provides: 598 ± 218 mg / day FA (Recommendation 200 - 1200 mg / day), 1.9 g / kg / day ± 0.3 Protein (84% special formula). Daily intake 74 ± 34 g / day (Recommendation> 75 g / day); 1897 ± 345 kcal / day. (Recommendation 1400-2500 Kcal / day) and 8.8 ± 1.4 g / day Tyrosine (Recommendation 4.5 to 7.5 g / day). During pregnancy it has excellent metabolic control (2.7 ± 1.9 mg / dl FA) and Tyrosine (1.1 ± 0.6 mg / dl). The delivery occurs at 37 weeks. Healthy newborn Weight: 2450 gr, Height 46 cm, head circumference 33cm. Now five months old with normal growth and development. Tyrosinemia Type I: Patient monitored and treated with nitisinone from 8 months old, poor metabolic control. It becomes pregnant at age 17 (tyrosine 838 ± 106 pmol / L). **Complications:** Urinary tract infection and anemia which is controlled postpartum. Nitisinone maintained during pregnancy. Weight gain 9.7 kg, 613 ± 106 Tyrosine levels 613 ± 106 umol / L, FA 40.2 ± 8 umol / L. Succinylacetone 0.38 mmol / mol creatinine, α-Fetoprotein two sampled values of 11.8 and 142 ug / L, respectively. Normal delivery at 40 weeks without complications. Healthy newborn with weight: 3150, height 48 cm, head circumference: 32 cm. Currently has 13 months with normal growth and development. **Conclusion:** It is particularly important the care of patients with EIM that occur with pregnancy. It requires a physician and nutrition specialist team and the design of monitoring protocols.

P194 - Mitochondrial DNA Depletion Syndrome Due to Thymidine Kinase 2 Mutation in Two Argentinian Patients

Loos, M.(1); Monges, S.(2); Lubieniecki, F.(2); Ruggieri, V.(2); Taratuto, A.(3); Hirano, M.(4); Arroyo, H.(5)

(1): Hospital de pediatría Prof Dr J P Garrahan, Buenos Aires, Argentina
(2): Hospital de Pediatria Prof Dr JP Garrahan, Buenos Aires, Argentina
(3): Instituto de investigaciones neurológicas FLENI, Buenos Aires, Argentina
(4): Houston Merritt Neuromuscular Research center. Columbia University., Nueva York, Estados Unidos de America
(5): Hospital de Pediatria Prof Dr JP Garrahan, Buenos Aires, Argentina

Introduction: Mitochondrial DNA depletion syndrome is an autosomal recessive disorder characterized by decreased mitochondrial DNA copy numbers in affected tissues. Mutations in thymidine kinase 2 (TK2) have been responsible for the myopathic form that typically cause fatal infantile mitochondrial DNA depletion syndrome, however the progression of weakness may vary even manifesting in adulthood. **Objective:** To describe the clinical variability in two pediatric patients with mitochondrial DNA depletion syndrome due to TK2 mutation. **Methods:** Histochemical and biochemical studies of respiratory chain complexes were performed in muscle biopsy specimens. Mitochondrial DNA was quantified using real-time PCR. The whole coding region of the TK2 gene was sequenced. **Results:** Case 1: A 16-year-old boy born to consanguineous parents. At the age of six years he presented with gradually progressive generalized muscle weakness and diffuse muscle wasting. Cognitive level was normal. Currently 16 years old he walks independently but shows pronounced lumbar lordosis and positive Gowers sign. Muscle biopsy showed a mosaic pattern of ragged-red and COX-negative fibers. Quantitative analysis of mtDNA content in skeletal showed a marked reduction. Sequence analysis of the TK2 gene revealed a homozygous c.323C.T, (p.T108M) mutation. Case 2: A boy who presented motor developmental delay since born, starting to walk at 18 months. At the age of 2 years there was a regression in acquired motor skills. He could no longer hold objects or sit, and he lost head control. He developed severe generalized muscle weakness and respiratory insufficiency and died at 3 years old. The muscle biopsy disclosed increased mitochondrial proliferation and numerous cox deficient fibers. Mitochondrial DNA content was severe reduced in muscle. Two known heterozygous missense mutation on TK2 gene were revealed c.547C>T, (p.Arg183Trp) and c.416C>T (p.Ala139Val). **Conclusion:** Mitochondrial myopathy due to mitochondrial DNA depletion syndrome is a rare condition. The clinical spectrum has expanded from severe infantile myopathy and early death to a milder adult form. Tk2 gene analysis should be included in the differential diagnosis of unexplained progressive myopathies with mitochondrial DNA depletion.

P195 - Retrospective Diagnosis of Lysosomal Acid Lipase Deficiency

Pacheco, M.(1); Filtrín, R.(1); Dlugoszewski, C.(1); Campos, E.(1); Rozenfeld, P.(2)

(1): Hospital Público Materno Infantil de Salta, Salta, Argentina
(2): DIEL/LISIN Universidad de La Plata, La Plata, Argentina

Introduction: In Wolman's disease there is a deficit of the enzyme known as lysosomal acid lipase. Symptoms appear within the first few days or weeks of life, such as vomiting, diarrhea and the rapid progress of cachexia with hepatosplenomegaly and anemia. It is characterized by hypercholesterolemia, hypertriglyceridemia, HDL deficiency and abnormal lipid deposits in the organs. Most patients die within the first 6 months of life. **Material and methods:** Observational, descriptive and retrospective study. Digitized clinical history.

Results: Case l: Gestation: 2 Births: Abortion: 1 Couple not inbred. Male; weight 1300 g; Gestational age: 35 weeks Clinical decompensation after 8 days: neonatal sepsis and suspected necrotizing enterocolitis with poor outcome; liver and kidney failure. Candida is found in the urine and is treated with antibiotics and antifungals. Lab test results find hypertriglyceridemia, cholestasis and anemia. Severe malnutrition, dies at 44 days of life. Case II: Gestation: 4, caesarean at 39 weeks Male; weight 1240 g; vigorous at birth; brother of previous clinical case; in neonatal unit for 43 days due to intrauterine growth restriction. On day 11 develops Klebsiella pneumoniae sepsis. Gastroesophageal reflux. Neonatal screening normal. OEA absent in both ears. 2nd hospital admission at 3 months due to convulsions and microcephaly. CT scan normal. Begins treatment with anticonvulsants with good results. 3rd hospital admission at five months due to second degree dehydration caused by vomiting. Chronic malnutrition, severe RGE and Global developmental delay. Epilepsy; Anemia; Suspected Adrenal Insufficiency; Sepsis; Metabolic disorders: hyponatremia (129 mg/dl), hypertriglyceridemia from 270 mg/dl to 2263 mg/dl, GOT 117, GPT 210, GGT 507, low HDL (21 mg/dl), and hyperglycemia (301 mg/dl). Quik 71%. Hemoglobin of 9 mg/dl. Physical showed hepatosplenomegaly. Abdominal echo: hepatic steatosis. Patient is referred to a more complex hospital where he died 4 days later. Acid lipase deficiency is suspected post mortem and is later confirmed. **Conclusions:** This rare form of acid lipase deficiency should be suspected in newborns with IUGR with poor progress and gastrointestinal involvement with hepatomegaly, intestinal malabsorption, ascites, with or without calcification of the adrenal glands, growth disorders and dyslipidemia.

P196 - Hepatic Failure Associated With Type I Citrullinemia

Oliva, B.(1); Cabello, J.(1); Arriagada, P.(1); Zambrano, K.(1); Fierro, L.(1); Araya, G.(1); Novoa, F.(1)

(1): Universidad de Valparaiso, Viña Del Mar, Chile

Introduction: Type 1 citrullinemia is a disorder of the urea cycle (DUC) typically presents in the neonatal period or in infancy with severe hyperammonemia and encephalopathy. The discovery of (DUC) presented with severe liver failure is rare and has been reported more frequently in ornithine transcarbamylase deficiency. We report the case of a patient of 6 year old with type 1 citrullinemia who developed fulminant hepatic failure. **Materials and methods:** Clinical case of male patient, 6 years old, diagnosed with type 1 citrullinemia of neonatal presentation, undergoing treatment since. In June this year he was admitted to Hospital Carlos Van Buren for vomiting, watery stools and abdominal pain. In laboratory tests he has 8.1 ammonium evolving without encephalopathy but maintained hyperammonemia is found. In liver function tests highlighted increased transaminases (glutamic pyruvic transaminase GPT: 4113, glutamic oxaloacetic transaminase GOT: 338, and prothrombin time TP: 19.1%). It was decided to operate in intensive care unit with a diagnosis of fulminant hepatic failure, the treatment was lactulose and vitamin K. Study was done: Serology for hepatitis A, B and C negative, negative ceruloplasmin, anti-smooth muscle antibodies and anti LKM1 negatives. Abdominal ultrasound liver with structure and normal size. Considering negative study of possible causes autoimmune hepatitis is suspected and steroid treatment was started with good clinical and laboratory parameters response. **Conclusions:** In this case, it could not establish relationship between citrullinemia and liver failure. It could correspond to two concomitant phenomena, however, the previous report of association between DUC and liver failure may relate both events. It is important to consider the diagnosis of acute liver failure in patients with type 1 and citrullinemia if we consider that your suspicion and early treatment can be key to ensuring a better outcome.

P197 - The Use of Percentiles for Determination of Cut-Off Values in Newborn Screening Using Totally Automated System and Multiplex Assays

Sampaio Filho (jr), C.(1); Frias, F.(1); Veturiano, R.(1); Silva, V.(1); Bernardes, F.(1); Boalento, J.(1); Massi, A.(1); Lira, J.(1)

(1): INTERCIENTIFICA, S.J. Campos, Brasil

Introduction: High numbers of false positives and identification of false negatives suggests adjustment of cut-off values is needed. Many studies about Cystic Fibrosis (CF) and Congenital Adrenal Hyperplasia (CAH) have been published recommending the use of percentiles to correctly classify negative and positives samples, mainly for CF when quantification of immunoreactive trypsinogen (IRT) is used. The use of percentiles has demonstrated benefits for the screening of CAH instead fixed cut-off point. For both diseases, other factors such as weight, sample collection date, and transportation conditions must be controlled to determine the correct classification of the samples, even using percentiles. INTERCIENTIFICA has developed a totally automated system for newborn screening for CH, CAH and CF in multiplex format that offers additionally the classification of the samples using percentiles per routine. **Material and Methods:** Positive confirmed samples were obtained from different labs in Brazil, plus external quality control materials, including internal controls with 3 different concentrations for each analyte (T4, TSH, IRT and 17OHP). The Nimbus NeoMAP associated to NeoMAP 4plex was used, with the software calculating and identifying samples using percentiles. The appropriate cut-off for each analyte is shown in the table with the sample results for each marker, against the classification using the fixed cut-off. **Results:** All the samples were corrected classified using the percentiles. The table shows the differences obtained between the use of fixed cut-off and cut-off determined by the percentile. The percentiles can be

adjusted by the supervisor anytime and can directly affect the number of classified samples (positive/negative). **Conclusion:** The use of percentiles is offered as alternative method to the usual fixed cut-off for each marker and demonstrated advantages with reduction of false positives and false negatives in newborn screening. The use of a totally automated system, with multiplex format and automatic classification of the samples for each analyte, using percentiles per routine, is considered the most advanced and revolutionary solution for newborn screening programs.

P198 - A Totally Automated System for Newborn Screening of PKU, GAL, and MSUD Using 384 Well Microplates

Sampaio Filho (jr), C.(1); Frias, F.(1); Veturiano, R.(1); Silva, V.(1); Bernardes, F.(1); Boalento, J.(1); Massi, A.(1); Lira, J.(1)

(1): INTERCIENTIFICA, S.J.Campos, Brasil

Introduction: The search for lab innovation in newborn screening is a constant process. The implementation of new markers, the necessity to obtain a robust process, cost effectiveness while minimizing steps, reduce infrastructure adjustments, reduce investments in human resources, keep or improve quality in the results are considered essential points. The Brazilian industry, with the objective to offer better solutions for newborn screening labs has developed a new solution for quantification of Phenylalanine, Total Galactose and Leucine using a totally automated system and microplates with 384 wells. **Materials and Methods:** An automatic puncher was configured for the use of 384 wells, spots of 3mm in diameter, associated to a totally automated equipment (Nimbus NeoLISA 384) and the kits NeoLISA PKU 384, NeoLISA GAL 384 and NeoLISA MSUD 384 to run in one batch/routine 1940 samples. A run with 1940 samples takes 7 hours. For the same number of samples using the 96 well in automated system the same process takes 12 hours. Samples from different concentrations of each analyte, external quality control material and internal controls have been used for comparison analysis and reproducibility. The results are directly compared to the 96 well format in a totally automated system. A demonstrative graphics and tables are used to present the data. **Results:** Excellent reproducibility was observed between 384 well analysis and 96 well analysis. While a routine workflow with 1940 samples is rare, since most labs run 500-1000 samples a day, demonstrating the capacity of the equipment, the reduction of time process and the possibility to run simultaneously the 3 products in the same run is important. **Conclusion:** The use of 384 wells associated with a totally automated equipment, Nimbus NeoLISA 384 and kits NeoLISA PKU, GAL and MSUD 384 are considered an innovation for newborn screening labs in the quantification of Phenylalanine, Total Galactose and Leucine.

P199 - Congenital Hypothyroidism in a Provincial Newborn Screening Program

Albrekt, A.(1); Czubarko, L.(1); Klein, P.(1)

(1): Programa Provincial de Pesquisa Neonatal Misiones, Posadas, Argentina

Introduction: Congenital hypothyroidism (CH) is one of the most common congenital diseases in newborns (NB). It is due to the partial or complete absence of the thyroid gland or alteration in the function, synthesis and metabolism of thyroid hormone and it is the leading cause of preventable mental retardation. Establishing a neonatal screening (NS) program accessible to the entire population is, therefore, a priority for preventive medicine. CH screening began in our province in January 2006, in the form of a comprehensive program that includes detection, confirmation, treatment and monitoring of newborns diagnosed and intended primarily to public health subsector, but open to on-demand testing. Our aim is to evaluate the program for the detection of CH. **Materials and Methods:** A descriptive and retrospective study of the program data. **Results:** From its start date to June 30, 2015, 122,200 blood samples from NB's heel were tested, corresponding to an average coverage of 85.7% of all births (142516); it was increased from 28.4% in 2006 to over 95% since 2010. In this period 59 suspected cases were detected; 57 were confirmed with CH, and two patients could not be located, one of them resident in the province and another one in Paraguay. The average age at diagnosis and start of treatment was 19 days, ranging from 39 (2006) to 12 (2015) days; this figure is strongly influenced by place of residence of the patient. The calculated frequency of CH is 1: 2144. Etiology was established only in one patient (athyreosis). **Conclusions:** The evaluation of the results after nine years of experience reaffirms the importance of the NS and indicates the need to strengthen the mechanisms to improve the timely diagnosis and location of patients for confirmation and monitoring of patients.

P200 - Correlation Genotype/Phenotype in Hunter Syndrome in Two Unrelated Boys

Forero, L.(1); Beltran, O.(2); Ladino, Y.(3)

(1): Facultad de Medicina. Universidad Militar Nueva Granada, Bogota, Colombia
(2): Facultad de Medicina. Universidad Militar Nueva Granada. Fundación HOMI Hospital de la Misericordia, Bogota, Colombia
(3): Fundación HOMI Hospital de la Misericordia, Bogota, Colombia

Introduction: Hunter syndrome is classified in mild and severe forms and it depends on its severity, onset and progression. Caused by IDS gene mutations, it consists of 9 exons encoding a protein of 550 aminoacids. Located in Xq28, IDS is responsible for the catabolism of dermatan sulfate and heparan sulfate, its deficiency causes an accumulation of these glycosaminoglycans in different organs. **Materials and methods:** Identify phenotypic and genotypic difference between two unrelated boys with

Hunter syndrome: 9 years old (Patient 1, P1) with mild form and 7 years old (Patient 2, P2) with severe form. Clinically both present coarse facial features, skeletal abnormalities, stiff joints, hepatosplenomegaly, cardiovascular and respiratory disorders, and developmental delay. P1 has been normal mental function. In contrast, P2 had ventricular dilatation, subarachnoid space asymmetry, active hydrocephalus requiring ventriculoperitoneal shunt, arachnoid cysts and ectopic posterior pituitary gland and mental retardation. P1 has hemizygous mutation in exon 2 (c.212G>A p.S71N) and P2 has hemizygous mutation in exon 3 (c.369deIC p.F123Lfs*7). Mothers of both patients are carriers. **Discussion:** Missense mutation found in P1 has been reported as a recurrent mutation in mild phenotype, and has shown that changing the residue at position 71 is far from the catalytic core. P2 has a type frame shift mutation in exon 3 that reduce protein to fifth part of its normal length. This mutation has not been previously described, but deleterious effects on enzyme function are severe, when translated in a truncated protein with an altered function. The enzyme replacement therapy that began three years ago has allowed has fewer episodes of respiratory disease and improve their academic performance. Also improvement of joint mobility and behavior have been in P2. **Conclusion:** Hunter syndrome is a multisystemic disease with severe or mild commitment clinical presentation in a variable range. Early diagnosis is imperative to perform simple techniques such as detection of urinary glycosaminoglycans and establish a comprehensive management associated with the enzyme substitution to prevent the disease from progressing and generate irreversible changes. It is also important to identify mutations and assess family healthy carriers for genetic counseling.

P201 - Evidences of Lipid Metabolism Regulation by Sulfur Amino Acids in Classical Homocystinuria

Poloni, S.(1); Spritzer, P.(1); Hack Mendes, R.(1); Dalmeida, V.(2); Castro, K.(1); Sperb-ludwig, F.(1); Tucci, S.(3); Blom, H.(3); Doederlein Schwartz, I.(1)

(1): Universidade Federal do Rio Grande do Sul- UFRGS, Porto Alegre, Brazil

(2): Universidade Federal de São Paulo – UNIFESP, Porto Alegre, Brazil

(3): University Medical Center, Freiburg, Freiburg, Germany

Background: Classical homocystinuria (HCU; CβS deficiency) is an IEM characterized by high levels of homocysteine and methionine and deficiency of cysteine in plasma. Growing evidence suggests that sulfur amino acids (SAA) affect fat mass deposition and lipid metabolism. CβS deficient mice present a 50% reduction in fat mass, associated with a marked suppression of the enzyme SCD-1 in liver. SCD-1 is a key enzyme for the synthesis of monounsaturated fatty acids. **Objective:** To investigate alterations in body composition, lipid metabolism, and SCD-1 activity in treated patients with HCU. **Design:** In this cross-sectional study, 10 patients with HCU, who received homocysteine lowering therapy, and 16 healthy controls were included. Body composition was assessed by DXA. Lipoproteins, free fatty acids, acylcarnitines, Met, tHcys, Cys AdoHcy, AdoMet, leptin, adiponectin, glucose and insulin were measured in plasma. HOMA-IR index was used to determine insulin resistance. SCD-16 and SCD-18 indices were calculated to estimate liver SCD-1 activity. **Results:** No significant changes in body composition, adiponectin, acylcarnitines or HOMA-IR were found. LDL-cholesterol, leptin, C16:1 percentage and the SCD-16 index were significantly reduced among patients ($p<0.05$). Total fat mass (%) was positively associated with cysteine, lipoproteins and leptin levels, while methionine showed a negative association ($p<0.05$). **Conclusions:** These results are in agreement with previous findings in animal models that suggest that SAA modulate lipid metabolism, probably mediated by leptin and SCD-1 expression in liver. The lack of difference in body composition between groups might be due to the small sample size or the effect of treatment.

P202 - Smith-Lemli-Opitz. Clinical Spectrum

Zabala, C.(1); Cabrera, A.(1); Castro, M.(1); Fernandez, L.(1); Bonaglia, R.(1); Lemes, A.(1);

(1): Instituto de Seguridad Social-BPS, Montevideo, Uruguay

Introduction: Smith-Lemli-Opitz syndrome (SLOS) is a congenital multiple anomaly syndrome caused by an abnormality in cholesterol metabolism resulting from deficiency of the enzyme 7-dehydrocholesterol reductase. It is characterized by prenatal and postnatal growth retardation, microcephaly, moderate to severe intellectual disability, and multiple major and minor malformations. The malformations include distinctive facial features, cleft palate, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly, and 2-3 syndactyly of the toes. The clinical spectrum is wide and individuals have been described with normal development and only minor malformations. The diagnosis of SLOS relies on clinical suspicion and detection of elevated serum concentration of 7-DHC. Although serum concentration of cholesterol is usually low, it may be in the normal range in approximately 10% of affected individuals, making it an unreliable test for screening and diagnosis. While no dietary studies on cholesterol supplementation have been conducted in a randomized fashion, cholesterol supplementation may result in clinical improvement. **Aim:** To present clinical and biochemical aspects of three unrelated cases of SLOS. **Clinical cases: Case 1:** First pregnancy, unrelated couple, female, characteristic facies features, microcephaly, syndactyly, ptosis, unilateral postaxial polydactyly, structural heart disease. By age one year SLO was diagnosed. He attends a special school, good social integration. Case 2: First pregnancy, unrelated couple, male, multiple malformations, characteristic facies features, microcephaly, syndactyly, ptosis, postaxial polydactyly, ambiguous genitalia. At 3 months of age, SLO diagnosed was performed. Failure to thrive, irritability, stereotyped behaviors. Case 3: First pregnancy, unrelated couple, male, characteristic facies features, microcephaly, syndactyly, severe

chronic nutritional failure, severe cognitive impairment, spasticity of 4 members, self-injurious behavior, autism spectrum behavior. **Conclusion:** With this presentation we highlight the importance of the clinical suspicion of a metabolic defect in a multiple malformations syndrome like SLO and show it wide clinical spectrum.

P203 - Neonatal Screening Program Experience in the Public Health Laboratory Department of Magdalena, Colombia

Donado Barros, M.(1)

(1): Secretaria de Salud de Magdalena, Santa Marta, Colombia

Introduction: The Health Department Laboratory of Magdalena, Colombia, started screening for congenital hypothyroidism (CH) in 2004, and since the decentralization of screening activities in 2009, its regulatory powers are to continue running the screening tests for the population of uninsured or poor people not affiliated with the health system, represented mostly by residents of more scattered, rural and remote areas of the department of Magdalena. **Methods:** 1536 dried blood spots from the umbilical cord, collected on filter paper, during the period January 2009 to December 2012, in infants born institutionally, and forwarded by the Magdalena laboratory network were used. TSH was measured by the method NEONATAL TSH UMELISA of Tecnosuma with a cutoff level of 15 mIU/L; suspected cases were referred to the INS for confirmation. They set quality parameters to evaluate analytical and clinical efficacy of the program, internal control and external laboratory quality (SAC software and evaluation by the INS), activated later time and diagnostic time. **Results:** The laboratory screening identified 13 suspected samples (0.85%) and 2 were confirmed hypothyroid, for a frequency of 1: 767. The performance indicators were always very good in the external control that is submitted by the National Reference Laboratory and the External Evaluation Indirect International with headquarters Tecnosuma International, the average time of activated later was 12 days and the average age of diagnosis was 21 days. **Conclusions:** The results show that the incidence of CH in the department of Magdalena is higher than the national average of 1: 2,500 to 3,000 live births which is located very near the epidemiologic indicators of incidence worldwide. The need to maintain an active surveillance program for neonatal screening in the active search for support in the Colombian population CH cases is founded, and to include other markers for neonatal screening in the country.

P204 - Congenital Hypothyroidism Neonatal Screening Program: Ten-Year Experience in Guatemala

Lemus Arias, G.(1); Velasco, R.(1)

(1): Hospital Roosevelt, Guatemala, Guatemala

Introduction: Congenital hypothyroidism (CH) is a common and preventable cause of mental disability if early diagnosis is performed and the appropriate treatment is provided. Only two public institutions provide CH screening in Guatemala, which only covers a small portion of the population. Over a 10 year period, 97.328 blood samples were collected by heel prick and spotted onto filter paper to create dried blood spots (DBS). **Methods:** Retrospective analysis from 2004 to 2014 from data from routine surveillance of neonatal CH. Samples were collected from heel prick within the firsts 24 hours after birth, collected using Whatman 903 filter paper and thyroid stimulating hormone (TSH) quantified by Delfia Neonatal hTSH Kit (PelkinElmer) fluoroimmunoassay. The cutoff was established as TSH levels 20.0 microIU/mL or higher. Confirmation was performed by chemiluminescent magnetic microparticle immunoassay with a sample drawn at 7 days of birth. Statistical analysis was performed using OpenEpi; yearly and accumulated incidence were calculated. **Results:** 97,328 newborns were screened during that period, with coverage of 75% of the total births in one hospital. A global incidence of 7.1 cases of CH for each 10,000 children screened (1: 1769), with a peak of incidence in the year 2010 with 15.9 cases per 10,000 children. During this time we reported 55 cases of CH in children born in the hospital and 14 cases in children referred from other centers. **Conclusions:** Congenital Hypothyroidism is a major problem in the country, with an incidence rate higher than other countries in America. It was possible to maintain the coverage of the program during these 10 years. Based on our experience it is necessary to expand the coverage in all public and private institutions in the country to achieve early and timely detection.

P205 - Fifteen Years of Continuous Monitoring of the Turnaround Times in Newborn Screening for Congenital Hypothyroidism

Maccallini, G.(1); Oneto, A.(1); Castillo, C.(1); Micenmacher, V.(1); Dure, A.(1); Hunt, M.(1); Stivel, M.(1); Fernandez Menteberry, V.(1); Chiesa, A.(1); Glikman, P.(1); Dratler, G.(1); Ropelato, G.(1); Muntaasbki, P.(1); Aranda, C.(1)

(1): Programa de Pesquisa Neonatal Gobierno de la Ciudad de Buenos Aires, Buenos Aires, Argentina

Introduction: The use of quality indicators is an effective way of monitoring and reviewing the processes for the decision making. Actions are implemented in order to achieve continuous improvement over the years in every step of the processes. **Objective:** To evaluate the evolution of different turnaround times (TAT) covering pre-analytical, 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. Three TAT were used: TAT1 days of life at sampling, TAT2 days between sampling and confirmatory results and TAT3 days at start of treatment. The data of each TAT include

information of 3 years, starting in 2001 and finishing at June 2015. For each TAT, data of mean and 90th percentile were registered. **Results:** 221 congenital hypothyroidism newborns between 2001 and June 2015 were included. The number of patients in each time and the TAT are shown in the table:

Time	TAT 1 (days) Mean 90th Perc	TAT 2 (days) Mean 90th Perc.	TAT 3 (days) Mean 90th Perc.
2001-2003 (36)	6.3 16.8	11.8 21.6	20.4 33
2004-2006 (50)	4.6 12.6	9.7 18.0	14.8 23.8
2007-2009 (33)	3.3 4.6	8.1 11.6	12.1 16.2
2010-2012 (52)	3.8 6.0	8.0 12.9	11.9 16.0
2013-June 2015 (50)	3.3 4.4	7.2 12.0	10.6 16.0

Conclusion: There were improvements in all the TAT over the years. Effective strategies at all levels were introduced in order to improve, achieve and keep acceptable turnaround times over time.

P206 - Biotinidase Deficiency in Brazil: A Clinical, Biochemical and Genetic Study

Borsatto, T.(1); Sperb-ludwig, F.(2); Lima, S.(3); Leistner-segal, S.(4); Pinto, L.(5); De Luca, G.(5); Carvalho, F.(5); De Medeiros, P.(6); Camelo, J.(7); De Souza, C.(4); Lourenço, C.(7); Ribeiro, E.(8); Felix, T.(4); Bittar, C.(4); Bernardi, P.(9); Silva, R.(10); Filho, R.(11); Neto, E.(12); Schwartz, I.(13)

(1): Brain laboratory-HCPA, PPGBM-Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
(2): Brain laboratory-HCPA, PPGCM-Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
(3): Brain laboratory-HCPA, Centro Universitário Ritter dos Reis, Porto Alegre, Brazil
(4): Medical Genetics Service-Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
(5): Hospital Infantil Joana de Gusmão, Florianópolis, Brazil
(6): Universidade Federal de Campina Grande, Campina Grande, Brazil
(7): Hospital das Clínicas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, Brazil
(8): Hospital Infantil Albert Sabin, Fortaleza, Brazil
(9): Hospital Universitário-Universidade Federal de Santa Catarina, Florianópolis, Brazil
(10): Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil
(11): Universidade Estadual de Ciências da Saúde de Alagoas, Maceió, Brazil
(12): CTN Diagnósticos, Porto Alegre, Brazil
(13): Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Introduction: Patients with reduced biotinidase activity may have total or partial deficiency (BD), or are heterozygous for pathogenic variants in the *BTD* gene. Due to the lability of this enzyme, genetic evaluation can be helpful in defining the associated phenotype. **Objectives:** To describe genetic and biochemical profile of Brazilian patients with reduced activity of biotinidase. **Methods:** Cross-sectional multicenter study, with convenience sampling. Clinical data and DNA samples were obtained from 67 unrelated individuals with reduced activity of biotinidase (37 male; 4 cases of consanguineous parents; age: 1 month-18 years) from South (39), Southeast (15) and Northeast (13) of Brazil; most were diagnosed by neonatal screening and are asymptomatic (62/67). The promoter, 5'UTR and exons 1-4 of the *BTD* gene were sequenced. **Results:** Twenty-eight different variants were detected: five novel variants, eighteen known pathogenic variants, two synonymous mutations and three variants in promoter region. The novel variants were not found in one hundred controls and the missense ones were considered pathogenic by *in silico* evaluation. According to the enzyme activity in plasma (available for 53/67 patients), 3.8% patients were classified as having profound BD, 30.2% as partial BD, 52.8% as heterozygous, 11.3% as borderline and 1.8% (one patient) had normal result after enrollment in the research. The expected classification according to genotype could be determined for 58/67 patients: 6.9% patients were classified as having profound BD, 31% as partial BD, 25.9% as similar to heterozygous (homozygous for p.D444H), 12% as heterozygous, 12% as similar to normal (heterozygous for p.D444H) and 12% as normal. The expected biochemical phenotype matched the biochemical phenotype in 68.2% cases (comparison available for 44/67 patients). The frequency of c.1330G>C (or p.D444H, associated with the partial BD) in the South, Southeast and Northeast of the country was 51.3%, 40% and 33.3%, respectively, which is in accordance with the highest frequency of partial BD in the Southern region in relation to the others (40% vs. 17.4%, respectively). **Conclusions:** The data shows that partial BD is the most common form of BD in Brazil, and that it is more common in the South than in the Southeast/Northeast regions. The variants found in promoter region are polymorphic according to ''The 1000 Genomes Project'', and further *in silico* analysis might inform about their effect. **Financial support:** FIPE/HCPA, CNPq.

P207 - Advances in IEM Diagnosis During the Last 7 Years: Overview From a Biochemical Diagnosis Reference Center

Guevara Morales, J.(1); Echeverri Peña, O.(2); Pulido Ochoa, N.(3); Ardila Gomez, Y.(3); Espinosa, E.(4); Barrera Avellaneda, L.(5)

(1): Pontificia Universidad Javeriana—IEIM, Bogotá, Colombia
(2): Pontificia Universidad Javeriana, Bogotá, Colombia
(3): Hospital Universitario San Ignacio—IEIM, Bogotá, Colombia
(4): Instituto de ortopedia Infantil Roosevelt, Bogotá, Colombia
(5): Pontificia Universidad Javeriana- Hospital Universitario San Ignacio—IEIM, Bogotá, Colombia

Introduction: Our institution is a reference laboratory for IEM diagnosis. Nowadays our laboratory receives near 4500 samples/year for analysis of Amino acids (TLC/HPLC), Organic Acids (GC-MS), Glycosaminoglycans, Lactic/Pyruvic acids quantification, Lysosomal enzyme activities, glucose-6-fosfate-dehidrogenase activity, and VLCFAs. During the last 5 years, interest in IEM has improved as a result of increased knowledge about these diseases among clinicians, availability of confirmatory tests, progress in legislation and importation and distribution of drugs, among other reasons. In order to approach the real impact of these aspects in IEM diagnosis, here we present a snapshot of the situation of IEM diagnosis in our country from our experience, contrasting data of the last 2 years with the reported 6 years ago in SLEIMPN congress. **Methods:** Retrospective analysis of performed tests between 2013 and 2014 in our institution. **Results:** Between 2013 and 2014; 8553 samples were analyzed. We confirmed 43 IEM including organic acidurias-(OA) (42%), aminoacidopathies-(AP) (21%), peroxisomal diseases-(PD) (19%), lysosomal diseases-(LSD) (14%), and G6PDH-deficiency (5%). In addition 305 cases presented increased lactate levels or abnormal GAG excretion that requires further study. Sample submission increased four times compared to 2007-2008 period. Currently the percentage of OA and AP changed from 2007-2008 when each. groups represented 40% PD increased almost four times (4% in 2007-2008). Most frequent entities were glutaric-aciduria type I (8 cases) Phenylketonuria (5 cases) and X-ALD (6 affected males and 1 carrier) respectively. LSD showed no change representing around 15% of the IEM diagnosed. **Conclusion:** In our country there is no national screening for IEM, in most of the cases, diagnosis is made after clinical onset. The data reflect an improvement in clinical suspicion of IEM, leading to increased number of patients diagnosed and identified entities. However, for some entities like mitochondrial diseases there are still several pitfalls in diagnosis that need to be overcome.

P208 - Congenital Metabolism Diseases of Neurotransmitters in Pediatric Neurology: Clinical Description and Neurological Tracing of a Group of Patients

Troncoso, M.(1); Santander, P.(1); Micolich Espejo, V.(1); Rojas, C.(1); Guzmán, G.(1); Wicki, A.(1); Leon, D.(1); Troncoso, L.(1)

(1): Servicio Neurología Infantil Hospital San Borja Arriarán, Universidad de Chile Campus centro, Santiago, Chile

Introduction: The neurological manifestations of congenital metabolism diseases of aminergic neurotransmitters (NT) are diverse. The autosomal dominant Dopa-responsive dystonia (DRD), with deficiency of GTP cyclohydrolase1 (GTPCH1), is the most common type, with a satisfactory response to treatment. We describe clinical features, response to treatment and outcome of patients diagnosed with inborn errors of aminergic neurotransmitters in our center. **Materials and methods:** A retrospective descriptive study and a prospective follow-up of 17 patients. Review of clinical records. **Results:** 17 patients. 16/17 exhibit DRD. 12/16 women. On 9/16 the average was 5 years age at onset and 9.5 years at diagnosis. In all patients the initial symptom was gait disturbance with diurnal fluctuation, lower limb (8/9) and upper limb (8/9) dystonia, trunk dystonia (3/9), tremor (3/9). Adult relatives (7/16) begin symptoms between 20 and 40 years: focal dystonia, parkinsonism. The mode of inheritance was autosomal dominant. The phenylalanine test was guiding. Diagnosis is confirmed with measurement of CSF levels of NT: low concentrations of neopterins, biopterins and 5HIAA HVA suggest deficiency of GTPCH1. Positive genetic study in 2 families. The response to levodopa treatment was satisfactory. One patient (1/17) shows a deficit of L-Dopa decarboxylase with severe global psychomotor retardation, fever, hypotonia, epilepsy, dystonia, and fatal outcome. **Conclusions:** In our series predominates DRD, with clinical features and response to treatment classically described. Early diagnosis allows prompt treatment with improvement of symptoms and favorable course.

P209 - Lower TSH Cutoff Level for Congenital Hypothyroidism Neonatal Screening: Pilot Experience in the Buenos Aires City Neonatal Screening Program (PPN)

Vieites, A.(1); Enacan, R.(1); Gotta, G.(1); Ropelato, G.(1); Junco, M.(1); Maccallini, G.(1); Dratler, G.(1); Rodriguez, E.(1); Glikman, P.(1); Onetto, A.(1); Odriozola, A.(1); Marino, S.(1); Micenmacher, V.(1); Dure, A.(1); Muntaabski, P.(1); Aranda, C.(1); Chiesa, A.(2)

(1): Rograma de Pesquisa Neonatal Gobierno de la Ciudad de Buenos Aires, CABA, Argentina

(2): Programa de Pesquisa Neonatal Gobierno de la Ciudad de Buenos Aires, CABA, Argentina

Introduction: A lower TSH cutoff level in the neonatal screening for congenital hypothyroidism (CH) would increase both detection and recall. **Objective:** We report recall changes and characteristics of detection in the pilot experience carried out by our Neonatal Screening Program for CH lowering TSH cutoff level from 10 to 8 mUI/l blood. **Population and methods:** From 1/6/13 to 31/5/15, CH screening was performed measuring TSH (IFMA-DELFIA) in dried blood spots. Children with TSH between 8 and 10 mUI/l blood were recalled and evaluated by a pediatric endocrinologist. Serum TSH,T4,FT4,T3, thyroglobulin and antithyroid antibodies were determined. All of them were followed until confirming or eliminating the diagnostic suspicion. **Results:** 59.887 newborn were screened, 218 recalled with TSH >10 mUI/l blood and 52 CH were detected. Recall rate (RR):0,36%. With the new cutoff 55 extra newborns were recalled (24 girls, 52 at term, 11 exposed to iodide), RR: 0.45%. Six (10%) came between 45 and 101 days of life with normal thyroid profile. The remaining 49 were seen at a median

age of 12 days(Range:6-25). 46/49 (93%) had TSH and thyroid hormones in the normal reference range for age before the first month of life (36 with a single evaluation) and did not require treatment. Three babies had persistent elevated TSH. Diagnoses of stable hyperthyrotropinemia was achieved in two patients (TSH: 10 and 12 mUI/l with normal thyroid hormones and eutopic gland in TC99 scan). The third presented transient hypothyroidism with goiter (TSH:25.7mUI/I, T4:10.8ug/dl,F4L:1.51ng/ml, negative antibodies). Treatment was started for 3 months and accidentally withdrawn, finding complete recovery of thyroid function (followed up for 9 months). No relationship was found between diagnosis, gestational age, exposure to iodide or autoimmunity. **Conclusion:** With the new cutoff, RR is still acceptable for a neonatal screening program. 95% of the recalled babies reached a normal thyroid profile within the first month of life. This strategy allowed the identification of newborns with either functional and/or transient thyroid disorders not related to prematurity, iodide or autoimmunity that represent a mild variant of the CH spectrum. This experience has to continue to draw out definitive conclusions about objectives and strategies for CH detection in our program.

P210 - Incidence of Congenital Hypothyroidism Remains Constant in Chile

Grob, F.(1); Carrillo, D.(1); Viviani, P.(1); Torres, C.(2); Lobo, G.(3); Opazo, M.(2); Bruggendieck, B.(3); Vega, R.(2); Valdebenito, S.(3); Concha, C.(2)

(1): Pontificia Universidad Católica de Chile, Santiago, Chile
(2): Hospital Guillermo Grant Benavente, Concepción, Chile
(3): Hospital San Juan de Dios, Santiago, Chile

Introduction: Congenital hypothyroidism (CH) is the main cause of preventable cognitive disability in the world. Its incidence is increasing worldwide. In Chile, a newborn screening program was started in 1992, becoming nationwide in 1998. There is no updated data about the incidence of CH in the country. The objective of this study is to report the incidence of CH in Chile since the start of the program and to describe its variation by region. **Methods:** A retrospective population-based study was designed. The Database of the Chilean national newborn screening program was used to identify the incidence of CH between 1999 and 2013. Screening was performed with thyrotropin (TSH) as the primary marker. A TSH level greater than 20 uIU/mL by RIA until 2008, and then, greater than 15 uIU/mL by DELFIA is considered a positive screen for CH. TSH >10 uIU/mL and T4 <10 ug/dL in serum confirms the diagnosis of CH, while TSH >10 uIU/mL with a T4 > 10 ug/dL is defined as Hyperthyrotropinemia (HTT). For data analysis, we divided the country into four regions. **Results:** Out of 3.623.226 newborns screened between 1999 and 2013, 943 cases of CH were diagnosed. Incidence of CH during this period was 2.60 per 10000 births (1:3842), with 2.59 cases per 10000 births between 1999-2006, and 2.62 cases between 2007 and 2013. The incidence rate remained constant over time with an increase of 1% between those periods. The incidence of Hyperthyrotropinemia increased from 0.84 to 0.96 per 10000 births (1:1114). Incidence varied markedly among the regions of the country. Considering both diagnoses, the Southern area presented the highest incidence (5.85 per 10000 births) while the Central area presented the lowest (2.62 per 10000 births). **Conclusion:** The incidence of CH has remained constant in Chile but Hyperthyrotropinemia is increasing. The highest incidence in the Southern area is due to the elevated rate of Hyperthyrotropinemia. Possible explanations might be the increased rate of premature births between the two periods analyzed and the highest proportion of Amerindian population in some regions of the Southern area.

P211 - Twelve Years of Neonatal Screening Program for Congenital Hypothyroidism

Zumaeta Beramendi, R.(1); Davila Aliaga, C.(1); Lujan Lujan, C.(1); Santiago, G.(1); Palomino Ochoa, C.(1); Larrabure Torrealva, G.(1)

(1): Instituto Nacional Materno Perinatal, Lima, Peru

Introduction: Congenital hypothyroidism (CH) causes mental retardation if not detected and treated early, and the incidence is estimated at 1:2300 newborns. Since 2003, the Instituto Nacional Materno Perinatal (INMP) runs the Newborn Screening Program. **Objective:** To determine the incidence of congenital hypothyroidism in the INMP, and to determine the clinical characteristics of patients with congenital hypothyroidism. **Material and Methods:** Retrospective and descriptive study for the period 2003-2014. 172.317 Dried blood spots samples on filter paper were analyzed by ELISA with a cutoff level of TSH $\geq$ 10 uIU / mL. CH diagnosis was confirmed by measuring the levels of TSH, T3, and free T4 in serum. **Results:** 172 317 Newborns were screened. Of those, 81 cases were diagnosed, for an incidence of 1:2127 live births. Average TSH level in blood was 69.0 uIU/ml. TSH serum was greater 50.0 uIU/ ml (95%); free T4 less than 1 ng / ml (100%). Gestational age: 39.2 $\pm$ 1.6 weeks (34-42). Gender: Male: 27.2% (22), Female: 72.8% (59). Weight: 3406.4 g $\pm$ 528 (1430-4500). Size: 49.8 $\pm$ 2.8 cm. Head circumference: 34.8 $\pm$ 2.6 cm. Thoracic perimeter: 34.5 $\pm$ (24-39). Apgar 1 ': 8.3 $\pm$ 0.7 (6-9). Apgar 5 ': 8.9 $\pm$ 0.2 (8-9). At birth, 95% were asymptomatic and 5% had some clinical signs (prematurity, posterior fontanelle persistent, omphalocele, hypoglycemia). At the moment of treatment initiation (10 to 30 days), the following clinical signs were observed: jaundice: 49.4% (40), Umbilical hernia: 46.9% (38). Dry skin: 25.9%. Wide fontanelle: 21% (17). Macroglossia: 17.3% (14). Hypotonia 18.5% (15), hoarse cry 5% (4), tremor 4.9% (4), abdominal distension 3.7% (3), irritability 6.2% (5), hypertonia 3.7% (3), strabismus 2% (2). The physical growth is within 10-90 percentile for 94% of cases. 100% had thyroid ultrasound. Neurological monitoring 85%, psychological 58%, cardiological 100% finding congenital heart disease 7%. Otoacoustic emissions to 65%, thyroid scintigraphy were performed on 47%. **Conclusions:** The incidence of CH was found to be 1:2127

(81 cases). In this period, neonatal screening for CH reached a coverage of 92%. Most patients are asymptomatic. A multidisciplinary evaluation was made for 70% of cases.

P212 - Extrapyramidal Symptoms in Patients With Inborn Errors of Metabolism

Hidalgo, M.(1); Muñoz Chesta, D.(1); Cardenas Galli, J.(2); Troncoso, M.(1); Santander, P.(1); Fariña, G.(1); Lara, S.(1); Peña, C.(1)

(1): Hospital San Borja Arriaran, Santiago, Chile
(2): Hospital San Borja Arriaran, Santiago, Chile

Introduction: Neurological symptoms are relevant in the onset and evolution of inborn errors of metabolism (IEM), constituting a key element in the diagnosis. **Objective:** The aim of this study was to describe the extrapyramidal symptoms among patients with IEM and to characterize its frequency, type, relationship with the course of the disease and relevance in the diagnosis. **Methods:** Medical records were investigated through a retrospective and descriptive analysis to identify extrapyramidal symptoms among patients with IEM. **Results:** 180 patients were analyzed: 47% male; 23% debuted with extrapyramidal symptoms, being the most common dystonia; 48% of all patients had abnormal movements at some point in the evolution, being the most common dystonia 87% (66/88) of which 80% were generalized. Other symptoms found were Corea 9%, Tremors 3% and Myoclonus 8%. Average age of onset of extrapyramidal symptoms was 1.7 years since the beginning of the disease (0 days to 5 years). Abnormal movements as group:neurotransmitters diseases 100% (14/14) of which 85% had a focal onset; inborn errors of purine and pyrimidine metabolism 100% (10/10), heavy metal storage diseases 61% (13/17), aminoacidopathies / organic acidurias 64% (18/28), mitochondrial diseases 60% (24/40), lysosomal diseases 22% (8/36), peroxisomal diseases 5% (1/19), others (0/6). **Conclusions:** The presence of abnormal movements/extrapyramidal symptoms in IEM patients is common, both at the beginning as well as during the course of the disease, and are keys in the suspicion of these pathologies. The highest rate occurs in neurotransmitters diseases, inborn errors of purine and pyrimidine metabolism and heavy metal storage diseases, followed by aminoacidopathies/organic acidurias and mitochondrial diseases, being dystonia the main symptom.

P213 - White Matter Disorders in a Serie of 150 Patients With Metabolic Disease

Santander, P.(1); Troncoso, M.(1); Mendoza, A.(1); Jaque, C.(1); Witting, S.(1); Troncoso, L.(1); Rojas, C.(1); Lopez, C.(1); Barrios, A.(1); Guzman, G.(1); Faroña, G.(1); Zamora, J.(1); Guerra, P.(1); Díaz, C.(1)

(1): Servicio Neurología Infantil, Hospital San Borja Arriaran—Fac.Medicina Campus Centro U. Chile, Santiago, Chile

Introduction: The secondary disturbances of the white matter (WM) are caused by various diseases, like the metabolic disorders, causing myelin detention or destruction. **Objectives:** Identify the presence of WM disturbances and describe the neurorradiologic alterations in patients with metabolic diseases diagnosed in our center. **Materials and Methods:** Descriptive and retrospective study. Review of clinical records and neuroimaging (magnetic resonance and computed tomography) of 150 patients. **Results:** 150 patients were studied. 88 with WM disturbances. 4/6 PKU patients with periventricular hypomyelination. 3/3 maple syrup urine disease with posterior fossa swelling. 15/150 with organic acidemia, 11/11 Glutaric Acidemia type I with extensive involvement of WM, basal ganglia and frontotemporal atrophy. 49/150 with Lysosomal storage disorders; 11/49 ceroid lipofuscinosis with slight periventricular WM hyperintensity and cerebellar atrophy; 22/49 with mucopolysaccharidosis, 8/11 type II with periventricular WM involvement, increase in perivascular spaces and diffuse atrophy. 8/49 with gangliosidosis; 3/3 type 1 showed slight periventricular WM involvement and 5/5 type 2 with marked symmetrical WM involvement and caudate, lenticular and thalamus hypointensity; 4/49 metachromatic leukodystrophy showed confluent symmetrical WM involvement with U fibers respect ("tigroid aspect"). Also presented corpus callosum, internal capsule and cerebellar involvement; 4/49 with Krabbe disease, 4/4 symmetrical and bilateral WM, corpus callosum, posterior limb of internal capsule, pyramidal tracts and cerebellar involvement. 32/150 with mitochondrial diseases; 9/9 MELAS disease with stroke-like WM involvement, 1/8 Leigh showed diffuse WM involvement. 21/150 with peroxisomal storage disease; 4 neonatal ALD and Zelweger showed hypomyelination; 16/17 X linked ADL with parieto occipital WM and splenium involvement, 1/17 showed anterior pattern. 2 patients with molybdenum cofactor deficiency showed multicystic encephalomalacia and diffuse WM involvement. 62/150 without WM involvement, including 13 PANK, 4 Menkes, 3 Wilson disease, 1 SCAD, 1 mDNA depletion, 2 PDH deficit, 7/8 Leigh, 8 LHON, 3 MERFF, 2 GLUT1, 1 with 3-metylglutaconic acidemia and isovalérica, 2 MPS II and 8 with MPS IV. **Conclusion:** In our serie, more than half of patients showed WM involvement, with characteristics and counselors pattern for each disease, which reflects the susceptibility of WM metabolic changes, independent of the metabolic pathway affected.

P214 - Mitochondrial DNA Disease: Clinical Spectrum From the Genotype to the Phenotype

Santander, P.(1); Troncoso, M.(1); Mateluna, C.(1); Barrios, A.(1); Guerra, P.(1); Flandes, A.(1); Díaz, R.(1); Troncoso, L.(1); Millan, F.(1)

(1): Servicio Neuropsiquiatría Infantil Hospital Clínico San Borja Arriarán, Santiago, Chile

Introduction: Mitochondrial diseases are a group of maternally inherited disorders, clinically heterogeneous produced

by mitochondrial DNA mutations. Clinical features related to a specific mutation are usually variable and multisystemic. The objective was to evaluate clinical manifestations, genogram, testing and evolution of patients diagnosed in our center with mitochondrial diseases and their phenotypic characteristics in relation to the genotype with different point mutations of mitochondrial DNA (A3243G, G11778A, A8344G). **Methods:** Retrospective descriptive and monitoring of all patients with mitochondrial DNA mutations confirmed. Review of clinical records. **Results:** 45 patients were studied,9 present A3243G mutation, 33 G11778A mutation and 3 A8344G mutation. In patients with A3243G mutation, average age of symptoms onset was nine years: headache (5/9), stunting (9/9), sensorineural deafness (8/9), cardiac disorders (2/9). They present stroke-like episodes (9/9) between 6 to 21 years, generalized tonic-clonic seizures (9/9). Study:elevated lactic acid plasma-CSF relation (9/9), ragged-red fibers (RRF) (7/9), CT/MRI: basal ganglia calcification (8/9), areas of infarction (strokelike) temporo-occipital (9/9). Evolution: progressive, 3 died. Their relatives were affected by deafness, diabetes, heart disease. 33 patients with G11778A mutation, 12 symptomatic. Presentation mean age 16 years, visual impairment (9/12), optic atrophy (7/12), impaired gait (4/12), dystonia (3/12). CT/MRI: putamens necrosis (4/12). Evolution: stable (5/12), slowly progressive (7/12). 3 brothers with A8344G mutation, average age presentation 10.6 years: all with myoclonic epilepsy, neuropathy, ataxia and FRR(+). Evolution: progressive. **Conclusions:** In our series, A3243G mutation was related to mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) phenotype, G11778A mutation with Leber's optic neuropathy (LHON) phenotype and mutation A8344G with myoclonus epilepsy with ragged red fibers (MERRF) phenotype. Clinical manifestations, tests and maternally inherited form were the classically described for these phenotypes.

P215 - 15 Years of Experience of Neonatal Screening Program in Mendoza-Argentina

Villarías, N.(1); Guercio, A.(1); Lobato, V.(1); Castro, B.(1); Bassino, S.(1); Carminati, N.(1); Ayub, E.(1); Verdaguer, L.(1); Pereyra, M.(2); Valle, S.(1)

(1): Programa Pesquisa Neonatal-CEPEII. Hospital Pediátrico Dr. Humberto Notti, Mendoza, Argentina
(2): Crecimiento y Desarrollo.Hospital Pediátrico Dr. Humberto Notti, Mendoza, Argentina

Introduction: Early detection and diagnosis of presymptomatic congenital disorders, treatment and follow up of the affected children with systematic and continuous evaluation are the pillars of a Neonatal Screening (NS) Program. We aim to present the results and quality indicators of our NS Program. **Methods:** 1999-2009: neonatal samples were processed to determine TSH and phenylalanine (Phe) using Perkin Elmer (PE) reagents. Since 2010, two stages were followed: ·1st: samples were processed to determine TSH, Phe, 17-OHProgesterone, Total Galactose and Biotinidase activity using SUMA reagents. ·2nd: samples with ''uncertain or positive'' results on the previous stage were processed using the PE reagents. Immunoreactive trypsinogen (IRT) to screen for Cystic Fibrosis was determined only by PE reagent. NS data and indicators were analyzed using specially designed software. **Results:** 1999-2009: 200004 newborns. 2010-2014: 113532 newborns. Indicators: -Child's age (CA) when collecting the dried blood spot samples: 3 days. -Transit time trail: 3 days. -CA at screening result report: 8 days. -CA at results delivery: 10 days. -Diagnostic confirmation and treatment initiation: 14 days. -Samples with incomplete data: 1%. -Rejected samples: 0,1%. -Recall rate: 1,61%. -Recalled newborns: 98% were located. -Coverage: 98% from public hospitals. -NS Program, 15 years: 154 children with congenital hypothyroidism, 5 phenylketonuria, 15 persistent hyperphenylalaninemia, 11 congenital adrenal hyperplasia and 12 cystic fibrosis. **Conclusion:** Prevention of disability and other consequences of diseases is possible with strong interdisciplinary work and optimizing NS Program indicators.

P216 - Implementation of Screening Program to Detect Endocrine and Metabolic Diseases in the Province of Salta, Argentina

Pacheco, M.(1); Pasteris, E.(1); Gómez, M.(1); Morales, M.(1); Morales, A.(1); Del Carril, A.(1); Nader, J.(1); Filtrin, R.(1)

(1): Hospital Público Materno Infantil de Salta, Salta, Argentina

Introduction: In 2006, the Department of Public Health's Program for Neonatal Screening, which was created in accordance with Law 26279, was implemented in public hospitals throughout the Province of Salta. **Material and Methods:** Observational, descriptive and retrospective studies. Use of Neonatal Screening Computer Program and the review of digitalized medical histories. **Results:** From October 2006 until April 2015 we studied 159,973 newborns in public hospitals. Through neonatal screening we detected the following cases: 120 with congenital hypothyroidism, 7 with classic phenylketonuria, 7 with biotinidase deficiency (2 total deficit and 5 partial), 4 with nonclassical galactosemia, 5 with congenital adrenal hyperplasia, and 1 with cystic fibrosis in the pancreas. The congenital errors that were not included in the newborn screening were: 2 with methylmalonic acidemia, 1 with glutaric acidemia type I, 1 with isovaleric acidemia, 2 with defective cetolisis, 2 with congenital hyperinsulinism, 1 with urea cycle disorder, 2 with acid lipase deficiency, 1 with Pompe disease, 2 with mucopolysaccharidosis (MPS) I, 1 with MPS II,5 with MPS III, 2 with MPS VI, 1 with MPS IV, 3 with Gaucher disease, 1 with Niemann-Pick disease, 2 with glycogen storage disease type III, 2 with intestinal glucose-galactose deficit, 1 with adrenoleukodystrophy, 1 with congenital lactic acidosis, 3

with apolipoprotein C-II deficiency, and 1 with gangliosidosis type II. **Conclusions:** The implementation of the program made the diagnosis and treatment of children accessible in public hospitals throughout the province. An entire area and circuit was created with trained professionals for the detection and study of inborn errors of metabolism. These are rare and uncommon illnesses, with a high demand of attention as they are chronic and highly evolutionary pathologies that need multidisciplinary teams for its treatment. This requires the development of reference centers in order to provide better quality of care.

P217 - Strategy for the Implementation of a Neonatal Screening Program in a Municipality of Bolivia With S.U.M.A. Technology

Hidalgo Ugarte, L.(1)

(1): Ministerio de Salud, La Paz, Bolivia

Introduction: A neonatal screening program includes education, research, monitoring, diagnosis and evaluation. This paper describes the strategies for the implementation of a neonatal screening program for inborn errors of metabolism with ULTRA MICRO ANALYTIC SYSTEM (acronyms in Spanish: SUMA) Technology in the municipality El Alto – La Paz through Medical Service ''Mi Salud'' and first level of attention centers. **Materials and Methods:** The first strategy included meetings with social organizations and health institutions. There were coordination meetings and lectures about general aspects of neonatal screening and the application of SUMA technology in the population of this municipality. In the second stage, clinic staff was trained, as well as health centers of first level of attention level, according to their participation in the care of newborns and the quality indicators used to evaluate the efficiency of the program. **Results.** 150 doctors of ''Mi Salud'' (first phase) participated in the period from November 2014 to June 2015. In the second stage we trained 1 biochemist and 2 laboratory technicians in the collection, handling and transfer of dried blood spot samples. These professionals were trained in techniques for the diagnosis of congenital hypothyroidism, phenylketonuria, galactosemia, congenital adrenal hyperplasia and biotinidase deficiency. The first results show the importance of neonatal screening. We diagnosed 14 cases of congenital adrenal hyperplasia, which represent 9% out of a total of 154 neonates studied, and identified the need to devise new strategies to achieve better performance of the program in terms of coverage, tracking and confirmation. **Conclusions:** These strategies helped start a neonatal screening in the municipality of El Alto - La Paz, Bolivia. In a short time, we began the early diagnosis of five diseases that can cause different disabilities, both physiological and bio-psychological, with great benefit to the person, the family and society.

P218 - Diet Therapy and Perception of Parent/Caregiver of Individuals With Phenylketonuria, With and Without Autism, Accompanied the Reference Service in Newborn Screening

Regina Gomes De Queiroz, I.(1); Santos Calmon, L.(2); Efigenia De Queiroz Leite, M.(2); Pereira Pondé, M.(3); Da Anunciação Do Espírito Santo, D.(2);

(1): APAE/EBMSP, Salvador, Brasil
(2): APAE/UFBA, Salvador, Brasil
(3): EBMSP, Salvador, Brasil

Introduction: Lack of treatment in PKU can lead to: intellectual disability, irritability and autism. In childhood, chronic illness favors changes in psychic structure and instrumental acquisitions, in real and imaginary plans. **Objective:** To describe family functioning and perception of parents / caregivers about treatment of phenylketonuria in patients with this diagnosis, with and without autism. **Methods:** A qualitative study, starting from the review of psychological records of siblings with PKU, with and without autism, in the Reference Service for Neonatal Screening (SRTN). From the thematic content analysis, four thematic trees were structured - two of them addressed in this article: Family functioning; Perception of parents and / or caregivers on the treatment of phenylketonuria. Research approved by the Ethics and Research Committee of EBMSP, no. 518.464. **Discussion:** Suffering, also the loss of the idealized son, was present in the studied cases. Disintegration and family psychic illness aggravated patients' symptoms. The disarticulation of parental functions contributed to transgressions and handicapped dietary control of their children. **Conclusions:** The involvement of chronic disease, such as phenylketonuria, requires an ethic of care that includes the subjective dimension, aiming the true prevention, notably in childhood phase of psychic structure.

P219 - 10 Years of Neonatal Screening Experience for Congenital Hypothyroidism Using the Suma Technology in Arauca, Colombia

Robinson Hidalgo, A.(1)

(1): Unidad Administrativa Especial de Salud de Arauca, Arauca, Colombia

Introduction: In Colombia as a public health policy it is mandatory to perform neonatal screening for all newborns for early diagnosis of congenital hypothyroidism, to avoid sequelae such as mental retardation and cretinism. The objective of this paper is to present the experience of 10 years (2004-2013) of neonatal screening in the department of Arauca (Colombia). **Materials and methods:** A total of 20.593 samples of cord blood collected on filter paper were processed, and the

TSH hormone was quantified using the technique UMELISA NEONATAL TSH, with a cutoff of 15 mIU / L. The samples were collected at the hospitals of the 7 municipalities in the department of Arauca and processed in the Departmental Laboratory of Health of Arauca. The cases that had elevated TSH were notified immediately to the local health institutions for the identification, confirmation, and timely handling of the suspected cases. The Laboratory's quality is assured by a SAC (Quality Assurance System) software, provided by the Center for Immunoassay and External Performance Evaluation by the National Institute of Health. **Results:** During the years 2004 to 2013, a total of 20.593 newborns were screened. Of all infants studied, 56 had elevated TSH, confirming 8 as hypothyroid (0.038%), with an incidence of 1: 2574. The average recall time was 5 days and the average age of early diagnosis was 15 days old. External Control results reflected a suitable analytical performance. **Conclusions:** The diagnosis of confirmed cases for congenital hypothyroidism was performed to children before the age of 1 month old. All children with CH are provided early treatment and follow-up, avoiding mental retardation. The Public Health Laboratory of Arauca has 10 years of experience, with excellent results in quality control programs. To contribute to the reduction of morbidity and mortality and childhood disability, it is recommended to include further tests or markers of expanded newborn screening for all newborns.

P220 - Newborn Screening for Pompe Disease: Trying to Reach an Earlier Diagnosis

Sokn, S.(1); Frabasil, J.(2); Durand, C.(2); Bambara, C.(2); Naymark, L.(2); Gaggiolli, D.(2); Carozza, P.(2); Schenone, A.(2)

(1): FESEN-Laboratorio de Neuroquimica, Buenos Aires, Argentina
(2): FESEN-Laboratorio de Neuroquimica

Introduction: Pompe disease (PD) is an autosomal recessive inborn error of metabolism due to the deficiency of acid alfa-glucosidase. The storage of glycogen in the cells is the direct consequence of the enzyme deficiency. PD has a wide clinical spectrum, from the classic infantile form to the late-onset in adulthood. Without treatment, infants rarely survive more than the first year of age. Several methods for the detection of PD in dried blood spots (DBS) are available to be applied in newborn screening programs (NBS), because of the severity of this disease and the availability of the treatment, some states of USA and Taiwan included PD in the newborn screening panel. **Objective:** The aim of this work is to introduce a new element to improve the diagnosis of PD in newborns with low alfa-glucosidase activity detected by NBS methods. **Methods:** Peripheral blood films, DBS and leukocytes were collected from 40 healthy newborn and 4 patients suspected of PD. All of them were evaluated for the presence of periodic acid –Schiff (PAS) positive lymphocytes (PPL). The quantitation was expressed as percentage of PPL per 100, counted with light microscopy. Alfa-glucosidase activity was measure in DBS with a fluorometric method. The pathologic results were confirmed in leukocytes. **Results:** Healthy newborns showed PPL between 1 and 10% with DBS enzyme activity within the normal range. The classical infantile PD patients showed PPL between 46 to 56%, all of them have DBS and leukocytes enzyme activity in the pathological range. **Conclusion:** The algorithm of the American College of Medical Genetics for positive NBS for PD includes a blood-based method to evaluate the enzyme activity and the mutation analysis of the GAA gene. These assays are time-consuming and may delay the identification of patients as early as possible to initiate the treatment. We consider that blood films evaluation for PPL could be considered as another step in the algorithm to diagnose PD. Blood film staining with Pas reagent is a quick, easy and inexpensive method to support the diagnosis of PD.

(O-2.1) Oral Communications II—NBS

O09 - Obtention of Low Phenylalanine Whole Blood for Preparation of Reference Materials and Calibrators for Newborn Screening Using Phenylalanine Ammonia Lyase

Borrajo, G.(1); Castañeda, M.(2); Hours, R.(2)

(1): Detección de Errores Congénitos. Fundación Bioquímica Argentina, La Plata, Argentina
(2): CINDEFI. Facultad de Ciencias Exactas. Universidad Nacional de La Plata, La Plata, Argentina

Introduction: One of the main limitations regarding the preparation of Phenylalanine (Phe) reference materials and calibrators in dried blood spots (DBS) is the unavailability of human blood free of Phe. Consequently, the basal level of Phe in the blood used for the preparation must be analytically determined, thus introducing an extra variable: the error of the measurement method. **Objective:** To develop a procedure for the preparation of low Phe whole blood using Phenylalanine Ammonia Lyase (PAL) in order to obtain reference materials and calibrators for newborn screening. **Materials and Methods:** The procedure consists in two independent steps. In the first one, a normal serum pool is incubated during 6 h at 37°C with PAL from *Rhodosporidium toruloides* (EC 4.3.1.25) immobilized on calcium alginate beads. PAL catalyzes the non-oxidative deamination of L-Phe producing *trans*-cinnamic acid. After this treatment, the serum is recovered unaltered and without addition of exogenous substances. In the second step, red blood cells collected with EDTA are deprived of Phe by successive washing with sodium chloride 9.0 g/L. Then, red blood cells are rinsed with the serum previously treated with PAL in order to eliminate the saline solution. Finally, both fractions are properly combined to obtain whole blood with hematocrit adjusted to 50%. Phe concentration in treated serum and in DBS was determined by Tandem Mass

Spectrometry. **Results:** The low Phe whole blood obtained was evaluated for its potential use in the preparation of Phe reference materials and calibrators in DBS. Preliminary experiments following the procedure described above resulted in Phe concentrations of 3.1 and 5.9 umol/L in treated serum and in DBS, respectively. **Conclusions:** From the above results it can be concluded that this is an appropriate material for the intended purpose. Nevertheless, optimization in the PAL treatment procedure is in progress in order to minimize the final Phe levels. The developed technique is reproducible, inexpensive and operatively easy to carry out, offering a new alternative in order to achieve the harmonization in the assignment of Phe values to reference material and calibrators provided for commercial reagent kits.

O10 - Initial Experience of Newborn Screening for Medium Chain Acyl Co-A Dehydrogenase Deficiency (MCADD)

Maccallini, G.(1); Castillo, C.(1); Junco, M.(1); Hunt, M.(1); Oneto, A.(1); Smithuis, F.(1); Eiroa, H.(1); Chiesa, A.(1); Muntaabski, P.(1); Aranda, C.(1)

(1): Programa de Pesquisa Neonatal Gobierno de la Ciudad de Buenos Aires, Buenos Aires, Argentina

Introduction: Newborn screening for MCADD was added to our programme after the set up of mass spectrometry (LC-MS/MS) technology. It is the seventh disease that is screened in our programme. **Objective:** To describe the initial results of the MCADD newborn screening at 18 months of its implementation. **Materials and methods:** Beginning in January 2014, MCADD screening was implemented in every newborn of our programme. Blood samples were collected on filter paper Whatman 903 within 2-5 days of life. Non derivatized reagent from PerkinElmer was used on API 3200 LC-MS/MS instrument from ABSciex. Primary marker used was octanoylcarnitine (C8), cut off value of 0.28 uM (99.9th percentile). Since July 2014, the informative ratio C8/C10 was added with a cut off value of 1.0. Since that moment, babies with C8 and C8/C10 ratio above cut-off values were recalled. Confirmatory studies included acylcarnitines profile, urine organic acids and molecular studies. **Results:** The total number of newborns tested until June 2015 was 39,346. Five newborns were recalled, 4 with the first criterion and one with the second one. Global recall rate was 0.012% One patient was confirmed with MCADD. It was a three-day old full term newborn at screening. The results at screening were C8 16.8 uM and C8/C10 20.9. The baby arrived to the confirmatory visit at day 5 of life. Confirmatory results in plasma acylcarnitines: C0 6.5, C2 11.2, C8 3.16 and C10 0.17 uM. Hexanoylglycine in diluted urine was absent. Molecular studies: q338x mutation was detected in heterozygosis besides, variant c.1012 c>t in also exon 11. In follow-up, the patient had no complications and was in good conditions at the last control at 5 months of life. **Conclusion:** The set up of mass spectrometry technology made it possible to study medium chain acyl coA dehydrogenase deficiency disease in all of the newborns of our programme. Recall rate was acceptable. The implemented work flow allowed the timely identification of our first patient in our programme.

O11 - Benefits of Second-Tier Confirmation of Newborn Metabolic Screening Using Targeted Next Generation Sequencing in Latin America

Naylor, E.(1); Sololsky, T.(2); Rousseau, R.(2); Maldonado, F.(3); Vela-amieva, M.(4); Cabello, J.(5); Bhattacharjee, F.(2)

(1): Medial University of South Carolina, Charleston, USA
(2): Parabase Genomics, Inc., Boston, USA
(3): Quimicos Maldonado, Villa Hermosa, Mexico
(4): Instituto Nacional de Pediatría, Mexico
(5): INTA Universidad de Chile, Santiago, Chile

Second-tier DNA molecular analysis has become routine for confirmation of newborn screening results in some programs for sickle cell disease, MCAD deficiency, and cystic fibrosis by identification of common mutations in the original dried blood specimen (DBS). We have developed a targeted Next Generation Sequencing (tNGS) second-tier newborn metabolic screening panel consisting of 126 genes corresponding to the metabolic disorders currently recommended for inclusion in population based screening programs. The method starts with DBS used in screening and DNA extracted from the DBS which is subjected sequencing of regions representing entire coding exons, intron boundaries, and non-exonic mutation containing regions using Ilumina Hi-Seq 2500 instrument. For targeting, am enrichment technology is used in which tens of thousands of probes were utilize to hybridize and capture genomic DNA regions of interest. tNGS using a focused set of 126 genes has advantages over whole genome or whole exon sequencing including lower cost, greater accuracy, shorter turnaround time, and less complex data interpretation and fewer incidental findings. The reliability of this approach is illustrated using sample from patients, including patients from Mexico and Chile, with a variety of such disorders illustrating the benefits of tNGS. The newborn samples were isovaleric academia patients from Mexico City; a maple syrup urine disease patient and a suspected cystic fibrosis patient from Villahermosa, Mexico; and a patient with suspected VLCAD deficiency from Chile. These patients illustrate the clear benefits of the second-tier tNGS panel by resolving potential incorrect diagnoses and providing information on the patient's prognosis. This approach also has the potential to improve the sensitivity and specificity of existing newborn metabolic screening programs. A single tNGS test is relatively simple and straight forward while traditional Sanger sequencing may require running various protocols. It also lays the foundation for future primary DNA based molecular newborn screening for metabolic disorders.

O12 - Molecular Characterization of Galt Gene in Argentinean Patients With Decreased Galactose-1-Phosphate Uridyltransferase Activity

Crespo, C.(1); Eiroa, H.(1); Otegui, M.(1); Chertkoff, L.(1); Gravina, L.(1)

(1): Hospital de Pediatría "Prof. Dr. Juan P. Garrahan," Ciudad Autónoma de Buenos Aires, Argentina

Introduction: Classical galactosemia is an autosomal recessive inherited metabolic disorder caused by mutations in the galactose-1-phosphate uridyltransferase (*GALT*) gene. GALT enzyme deficiency leads to the accumulation of galactose-1-phosphate in various organs, causing hepatic, renal and cerebral impairment. Over 180 disease-causing mutations have been reported in the *GALT* gene. Diagnosis of galactosemia through analysis of total galactose and/or activity of GALT enzyme is effective, but environmental factors and the high frequency of the Duarte D2 mutation, which causes partial deficiency of enzyme activity, lead to false positive results. **Objective:** To describe molecular characterization of *GALT* gene in Argentinean patients with decreased GALT activity, and to correlate molecular results with the enzyme activity. **Patients and Methods:** 20 patients with enzyme activity below 9 μmol/h/g Hb (50% of normal value) were included. DNA was extracted from peripheral blood. Q188R mutation was studied by PCR-RFLP. Samples negative or heterozygous for Q188R were sequenced by analysis of the 11 exons and the exon-intron boundaries of the *GALT* gene. **Results:** 10 different sequence variations were identified, including two novel mutations (p.M1Tand p.S222R). The three most common disease-causing mutations were p. Q188R, p.K285N and IVS8-13A>G. They accounted for 12, 9 and 3 of the 40 alleles respectively. N314D Duarte 2 variant appeared in 9 of the 40 alleles. *GALT* genotype correlated with enzyme activity in 90% of patients. **Conclusion:** This is the first report of mutations in the *GALT* gene in Argentinean patients with decreased GALT activity. Molecular analysis is useful to reduce false positive results, differentiate D/G mixed heterozygotes from classical galactosemia. This study supports that galactosemia is a heterogeneous disorder at the molecular level, such as described in other populations.

O13 - 25 Years of Experience on Newborn Screening for Phenylketonuria in Costa Rica: Identification of the Most Common Mutations in the Phenylalanine Hydroxylase (PAH) Gene

Camacho, N.(1); Reuben, A.(1); Alvarado, D.(1); Arroyo, J.(1); Jiménez, M.(1); Saborío, M.(2)

(1): Laboratorio Nacional de Tamizaje Neonatal y Alto Riesgo, San José, Costa Rica

(2): Servicio de Genética Médica y Metabolismo, Hospital Nacional de Niños, San José, Costa Rica

Introduction: Phenylketonuria (PKU) is an autosomal recessive inborn error of the metabolism, caused by the deficiency of phenylalanine hydroxylase (PAH). Newborn screening (NBS) for PKU has been done for 25 years in Costa Rica. During this time we screened 1.612.734 samples, and we identified 27 affected individuals, for an estimated prevalence of 1:59,731. **Materials and Methods:** 23 patients, of the 27 cases detected through NBS, are described. For NBS we used a bacterial inhibition test (Guthrie) from 1990 to 2004. In 2005 the method was changed to tandem mass spectrometry. Confirmatory tests included plasma amino acids quantification by high performance liquid chromatography (HPLC) and molecular analysis of the *PAH* gene using Sanger sequencing. BIOPKU database (http://www.biopku.org) was consulted for information about probable associated phenotypes and responsiveness to tetrahydrobiopterin (BH4). For all patients detected starting in 2005, the concentration of Phenylalanine and Phenylalanine/Tyrosine ratio on dried blood spots (DBS) was established, as well as the concentration of plasma Phenylalanine. We also describe the genotype, the frequency of the mutations encountered, and the expected BH4 responsiveness. **Results:** The mean concentration of Phenylalanine (Phe) in the first sample was 447 μmol/L in DBS and 12.3 mg/dL in plasma. The most frequent mutation was p.L48S located in exon 2, with a relative allele frequency of 41%. Genotype p.L48S/IVS7+3G>C was found in 4 patients, followed by p.L48S/p.R241H, p.L48S/p.V388M, p.L48S/IVS1+5G>T and p.L48S/p.L48S with 2 patients each. According to the BIOPKU database, 4 genotypes are associated with classic PKU phenotype, 6 with mild PKU, 3 with hyperphenylalaninemia and the others haven't been recorded. Additionally, based on the same database, 9 of the 23 patients would respond effectively to BH4. **Conclusions:** In our sample, the most frequent genotype was p.L48S/IVS7+3G>C which is associated with mild PKU phenotype. Treatment with BH4 is not yet available in our country; however, this study shows that a significant number of our patients could benefit from it, suggesting that BH4 therapy should be evaluated for an eventual inclusion in our social health system.

O14 - Development of First and Second Tier Newborn Screening Assays for Spinal Muscular Atrophy

Taylor, J.(1); Lee, F.(2); Yazdanpanah, G.(2); Staropoli, J.(3); Liu, M.(3); Caruilli, J.(3); Sun, C.(3); Hannon, H.(4); Vogt, R.(2)

(1): RTI International, Research Triangle Park, United States

(2): CDC, Atlanta, United States

(3): Biogen Idec, Boston, United States
(4): CDC Foundation, Atlanta, United States

Introduction: Spinal muscular atrophy (SMA) is one of the most common fatal genetic disorders in infancy and a major contributor to disability in childhood. The birth prevalence of SMA is 1:6000-10,000, with a carrier rate of 1:40. This disease is caused by a homozygous deletion or mutation in the survival motor neuron 1 (*SMN1*) gene and the severity of the disease is strongly influenced by the number of copies of survival motor neuron 2 (*SMN2*) genes. Recent developments in therapeutic intervention have resulted in promising treatments for SMA. Because of the pathogenesis of this disease, therapy should start soon after birth and before symptoms develop, which would require newborn screening. **Methods and Materials:** The two major considerations in developing an SMA screening test were to use an assay platform established in many newborn screening laboratories and could be multiplexed within an existing assay. This would lower the capital and the labor costs and ensure adequate throughput. The implementation of screening for severe combined immunodeficiency (SCID) has been growing rapidly among the newborn screening programs use a T-cell receptor excision circle (TREC) assay based on real-time PCR. We have incorporated the SMN1 target into our current TREC assay for SCID. By using a SMN1 Taqman probe based on locked nucleic acid (LNA) technology, which has eliminated cross-reactivity to the SMN2 gene. We have also developed a confirmatory test using droplet digital PCR (ddPCR), a method that can confirm the absence of SMN1 and determine the SMN2 copy number. **Results and Conclusion:** We have incorporated the SMN1 target into a multiplex real-time PCR assay for newborn screening that can detect SMA or SCID in dried blood spots (DBS) by only adding cents to the current TREC assay. Results demonstrated excellent specificity for SMA. The clinical validity was provided by a double blind test of 26 donor samples, which correctly differentiated all 11 patients from the 15 parental carriers, with the TREC results appropriate for the ages of individual donors. The SMN2 copy number was also determined from these samples using ddPCR and showed concordance in two independent laboratories.

O-2.2 - Oral Communications II—EIM

O15 - Classical Homocystinuria: A Comprehensive Study in Brazil

Poloni, S.(1); Borsatto, T.(1); Weber, G.(1); Doriqui, M.(2); Lourenço, C.(3); Kim, C.(4); Souza, C.(5); Rocha, H.(6); Ribeiro, M.(6); Fonseca, G.(6); Valladares, E.(7); Bernardi, P.(8); Artigalas, O.(1); Carvalho, G.(9); Steiner, C.(10); Moreno, C.(10); Wanderley, H.(11); Boa Sorte, N.(12); Kyosen, S.(13); Martins, A.(13); Dalmeida, V.(13); Blom, H.(14); Giugliani, R.(1); Doederlein Schwartz, I.(15);

(1): Genetics Department, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
(2): Complexo Hospitalar Materno-Infantil do Maranhão, São Luiz, Brazil
(3): Hospital das Clínicas de Ribeirão Preto, Ribeirão Preto, Brazil
(4): Universidade de São Paulo, São Paulo, Brazil
(5): Genetics Department, Federal University of Rio Grande do Sul, Brazil, Porto Alegre, Brasil
(6): Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
(7): Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
(8): Universidade Federal de Santa Catarina, Florianópolis, Brazil
(9): Hospital de Apoio de Brasília, Brasilia, Brazil
(10): Universidade Estadual de Campinas, Campinas, Brazil
(11): Hospital Infantil Nossa Senhora da Glória, Vitoria, Brazil
(12): Universidade do Estado da Bahia, Salvador, Brazil
(13): Universidade Federal de São Paulo, São Paulo, Brazil
(14): University of Freiburg, Freiburg, Germany
(15): Genetics Department, Federal University of Rio Grande do Sul, de do Sul, BrazilPorto Alegre, Brazil

Introduction: Brazil is a large country with 200 million inhabitants, and presents a heterogeneous genetic and cultural background. Screening for Classical Homocystinuria (HCU) is not included in the Brazilian Neonatal Screening Program, and no specific treatment for this disorder is covered by the public health system. In this study we aimed to describe the clinical and molecular profile of HCU in Brazil. **Methodology:** Since 2010, we have been collecting data about HCU in Brazil, through multiple ways: review of literature; review of the cases diagnosed by Brazilian inborn errors of metabolism networks and laboratories; contact with physicians around the country; and contact with patients' organizations. Besides that, we are providing, in a research basis, analysis of the *CBS* gene for affected families. **Results:** No epidemiological study about HCU in Brazil was found in the literature. According to the patients' organizations, only sixty HCU patients are currently alive in the country. We were able to obtain clinical data from 49 patients (40 families). The patients were followed in 13 Hospitals located in the Southeast (n=7), South (n=3), Northeast (n=2) and Middle-West (n=1) regions of Brazil. Parental consanguinity was reported in 44% of the families. The median age at inclusion was 19 years; at diagnosis, 10 years; and at beginning of symptoms, 4 years. The most common reason leading to investigation of HCU was *ectopia lentis,* in 65% of the patients; followed by mental retardation (25%). Regarding pyridoxine responsiveness, 68% of the patients were classified as nonresponsive, 19% fully responsive and 12% partially responsive. DNA samples were received from 32 nonrelated patients. *CBS* gene was completely sequenced for 26 patients, and the remaining are currently under analysis. The most frequent mutations were c.833T>C (10 alleles); c.572C> T (6 alleles); and c.828+1G>A (6 alleles). Eight novel mutations were found. **Conclusions:** HCU appears to be underdiagnosed and

identified late in Brazil. In addition, the care of patients is decentralized, which can negatively affect the development of medical expertise. We are developing several actions in order to change this scenario, including publication of booklets in Portuguese and promoting the draft of national guidelines for the diagnosis and management of the disease.

O16 - Ethylmalonic Encephalopathy (EE). Clinical, Biochemical and Imaging Data in Six Patients and the Importance of Urine Thiosulfates in the Diagnosis

Durand, C.(1); Velasquez Rivas, D.(1); Maccarone, M.(1); Sokn, S.(1); Tommasi, F.(1); Fuertes, A.(1); Marchione, M.(1); Szlago, M.(2); Abdenur, J.(3); Schenone, A.(1)

(1): FESEN-Laboratorio de Neuroquimica, Buenos Aires, Argentina
(2): Enf. Metabólicas. Servicio de Genética-Hospital de Niños Ricardo Gutierrez., Buenos Aires, Argentina
(3): CHOC Childreńs, Orange, USA

Introduction: EE is a rare autosomal recessive disorder due to mutations in ETHE1 gene that encodes a mitochondrial dioxygenase. The defect leads to accumulation of hydrogen sulfide (H2S) that affect the brain and the microvasculature. Biochemical alterations reflect the toxic effect of H2S in several pathways, including the fatty acid oxidation, leading to persistent elevations of ethylmalonic acid (EMA). However, elevation in EMA is not specific, and other abnormalities in acylcarnitines or acylglycines can be intermittent, making the diagnosis difficult. Urine thiosulfates have been reported as additional biomarker **Aim:** To present the clinical, imaging and biochemical information of six patients with EE, and highlight the importance of thiosulfates in the diagnosis. **Material and Methods:** From 1992 to 2014 six cases of EE were identified based on clinical presentation and consistent urine organic acid profile. Detailed chart review was performed in all cases and urine thiosulfates were measured in all available samples, with a colorimetric method. **Results:** Clinical presentation included, failure to thrive, developmental delay, regression, acrocyanosis, petechiae, diarrhea. Three patients had a positive family history of a sibling who died with similar "undiagnosed disease". Urine organic acids (OA) showed abnormal ethylmalonic acid, 2- methylsuccinate and isovalerylglycine (n= 6). Acylcarnitines showed increased C4 and C5 acylcarnitines (n=3) . Of note, retrospective analysis of the NBS card in one patient showed elevated C4 with normal C5 levels. Thiosulfates were markedly elevated in all available urine samples (n=4). Media age at diagnosis was 19 moths (R 12-23) Imaging data (n=5), demonstrated bilateral basal ganglia abnormalities. Three patients were confirmed molecularly and the most recently diagnosed patient is on treatment with metronidazole and N-acetylcysteine, resulting in arrest of disease progression. **Conclusion:** EE is a very rare, likely underdiagnosed disorder. Expanded NBS allows for early detection. However AC and OA may not always show typical abnormalities. Thiosulfates are a very sensitive marker that can expedite the diagnosis, which is particularly important due to the availability of new treatment modalities.

O17 - In Vitro Uptake and Kinetic Characterization of Recombinant Human Beta-Hexosaminidases

Espejo Mojica, A.(1); Ramírez, A.(2); Beltrán, L.(1); Rodríguez López, A.(1); Díaz, D.(1); Mosquera, A.(1); Alméciga Díaz, C.(1); Barrera, L.(1)

(1): Insituto de Errores Innatos del Metabolismo; Pontificia Universidad Javeriana, Bogota, Colombia
(2): Insituto de Errores Innatos del Metabolismo; Pontificia Universidad JaverianaInsituto de Errores Inn, Bogota, Colombia

Introduction: Enzyme Replacement Therapy (ERT) for lysosomal storage diseases is based on the capacity of the heterologous lysosomal enzymes to be taken up and targeted to the lysosome, where they can degrade the accumulated substrate. Recombinant beta-hexosaminidases produced in different hosts with or without post-production enzymatic treatments, have been proved to be taken up via cation independent manner. In this work, recombinant beta-hexosaminidases rhHex-A, rhHex-B, and rhHex-S were produced in the yeast *P. pastoris* and tested for kinetic profile, and cellular uptake by HEK293 cells, normal fibroblasts, and Sandhoff's patient fibroblasts. The effect of temperature in the endocytic pathway and the use of mannose 6 phosphate (M6P) to block the membrane receptors were also evaluated. **Material and methods:** Recombinant proteins were produced in *Pichia pastoris* and purified by ion exchange chromatography. Kinetic assays were done evaluating different concentrations of both substrate and each enzyme. Cells were cultured in Dulbecco's modified medium and purified enzymes were independently added to a final concentration of 10 and 50 nM. After 5 hours of incubation, the culture medium was removed, cells were washed with PBS 1X, and lysed with 1% sodium deoxycholate. Cell uptake assay was carried out at 37 and 4°C. To evaluate if proteins were entering through mannose 6-phosphate receptors, cell uptake assay was carried out in presence of 10mM Mannose 6-Phosphate (M6P). **Results and Conclusions:** The Km and Vmax for rhHex-A, rhHex-B, and rhHex-S were similar to those of beta-hexosaminidases obtained from human tissues. Intracellular enzyme activity was increased after exposure to the purified recombinant enzymes. These results suggest that recombinant hexosaminidases can be taken up by culture cells At 4°C higher enzyme activity was mainly detected in the culture medium than at 37°C, suggesting that the cellular capture of the enzymes was partially mediated by an endocytic pathway. Nevertheless, internalization was not completely inhibited at 4°C, suggesting that an alternative mechanism may be used for cellular capture of these recombinant enzymes.

O18 - Intracranial Hypertension in Mucopolysaccharidosis Patients: What Should we Take Into Account?

Dalla-corte, A.(1); Fischinger M. De Souza, C.(2); Vairo, F.(2); Anés, M.(2); Modesti Vedolin, L.(2); Moraes Ferreira, M.(2); Graciana P. Perrone, S.(2); Di S. D'andréa, L.(2); Giugliani, R.(1)

(1): Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
(2): Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Introduction: Very little is known about the incidence and prevalence of hydrocephalus with increased intracranial pressure in mucopolysaccharidosis (MPS) patients. Because venous hypertension is a known cause of hydrocephalus, one hypothesis could be the reduced venous outflow through bone dysostosis of the skull base. Cerebrospinal fluid (CSF) flow study is a noninvasive imaging technique that is useful for the evaluation of patients with hydrocephalus. Lumbar subarachnoid pressure higher than 20 cm H2O can be considered indicative of hydrocephalus. **Methods:** We performed a CSF flow study by phase-contrast MRI followed by a standard lumbar puncture with the CSF opening pressure assessment in 27 patients: MPS type I in 5 patients, MPS type II in 12 patients, MPS type III in 3 patients, MPS type IV A in 6 patients and MPS type VI in 1 patient. The age range was 1 to 30 years, 18 males and 9 females. **Results:** Neurological findings included pyramidal signs in 5 patients and macrocephaly in 7 patients. Eight patients had no cognitive impairment. The most frequent MRI findings were white matter changes in 18 patients, dilated perivascular spaces in 17 patients, craniovertebral junction stenosis in 15 patients and ventricle enlargement in 8 patients. Of the 8 patients with radiological signs of hydrocephalus, hyperdynamic aqueductal CSF flow was obtained in 2 of them, 4 patients showed CSF lumbar pressure values above 200 mm H2O and 6 presented left cerebral venous drainage. On the other hand, in 12 patients with no typical ventriculomegaly elevated CSF pressure values were obtained and 10 of them had craniovertebral junction stenosis. **Conclusion:** Aqueductal CSF flow measurement seems to be little specific for helping diagnosis and therapy planning of hydrocephalus and high intracranial pressure in MPS patients. CSF opening pressure showed better correlation with typical findings of hydrocephalus and with CSF flow restriction across the craniocervical junction. Variations in sinuses of the posterior cranial fossa may be associated. Although this is the first description using these parameters to diagnose high intracranial pressure in MPS patients larger studies must be done to best determine which patients will respond positively to shunting.

O19 - Neurocognitive Functioning in Patients Tyrosinemia Type I Under NTBC and Nutritional Management

Arias, C.(1); Garcia, M.(1); De La Parra, A.(1); Hamilton, V.(1); Campo, K.(1); Castro, G.(1); Bravo, P.(1); Cabello, J.(1); Peredo, P.(1); Raimann, E.(1); Valiente, A.(1); Fuenzalida, K.(1); Cornejo, V.(1)

(1): Instituto de Nutrición y Tecnología de los alimentos, Santiago, Chile

Introduction: Hereditary Tyrosinemia Type 1 (HT1) is an autosomal recessive disorder due to fumarylacetoacetate hydroxylase enzyme deficiency. Nitisinone (NTBC) treatment has dramatically improved survival, but induces high plasmatic levels of tyrosine. Cognitive impairment in patients with elevated plasma tyrosine concentrations has been reported. **Objective:** Report cognitive function in HT1 patients under NTBC and phenylalanine - Tyrosine restricted diet and find an association with tyrosine plasmatic levels. **Methods:** A sample of 15 children diagnosed with HT1 was included. The age at diagnosis was x=17 months and NTBC treatment was initiated at x=27 months. Psychomotor development was assessed with Bayley-II at 18 and 30 months, and cognitive performance at preschool and school age with Wechsler Scale. Mean plasmatic Tyrosine levels during fist four years of life and complete treatment period were analyzed. **Results:** Mental developmental index (MDI) and psychomotor developmental index (PDI) in evaluated infants was x=80 (sd=17) and x=74 (sd=15) respectively at 18 month and x=76 (sd=19) and x=85 (sd=20) at 30 months. At preschool age, Global IQ (IQ) was x=85 (sd=18). 6/10 assessed children were in normal range (82-114), and two children showed mental retardation. No significant correlation was found between this scores and plasma tyrosine levels during first 4 years of life x=368umol/lt (sd=198). At school age IQ was x=82 (sd=17). 3/9 children performed within normal range (89-118) and two showed mental retardation. No significant association was found between IQ and mean life tyrosine levels x= 417umol/lt (sd=196). **Discussion:** Many factors have been implicated in cognitive impairment in Ty1 patients like high levels of tyrosine and low phenylalanine plasmatic levels. The lack of correlation between IQ and tyrosine levels in our population may be related to limited sample size or delay in diagnosis and start of treatment, since newborn screening for this condition is not available in Chile at the present time. **Conclusion:** Patients with HT1 treated with NTBC might still be at risk for impaired cognitive function despite nutritional management, then routine cognitive assessment is recommended during monitoring. Larger sample of patients and additional data is needed to establish a correlation between cognitive functions and tyrosine levels.

O20 - Urea Cycle Disorders: Previous and Novel Genetic Findings in Argentine Patients

Silvera-ruiz, S.(1); Angaroni, C.(1); Arranz, J.(2); Häberle, J.(3); Dodelson De Kremer, R.(1); Laróvere, L.(1)

(1): CEMECO, Hospital de Niños de Córdoba, Clínica Pediátrica, Fac. Cs. Médicas, UNC, Córdoba, Argentina
(2): Unitat Metab, Hospital Vall dHebron, Barcelona, Spain

(3): University Children's Hospital and Children's Research Center, Zurich, Switzerland

Urea cycle disorders (UCD) are inborn errors of ammonia detoxification/arginine synthesis due to defects of five core enzymes, one activating enzyme and one mitochondrial ornithine/citrulline antiporter. The onset and severity of UCD is highly variable; this depends on the specific mutation involved and correlates with the amount of urea cycle enzyme function. These disorders are transmitted as autosomal recessive genes, except ornithine transcarbamylase deficiency (OTC), which is transmitted as an X-linked trait. In some cases OTC disorders occur as a result of spontaneous mutation in a developing fetus. **Objective:** To characterize the genetic defect in Argentine patients with UCD. **Methods:** We studied DNA samples from Argentine patients (n=31) with the biochemical diagnosis of different UCD. The genetic analysis included PCR, restriction assays, sequencing, MLPA and computational methods for mutation effect prediction. **Results:** i) OTC deficiency: 11 families, 13 patients; 3 males with neonatal onset (OTC mutations: delE2-10, c.533C>T, c.697delG), 4 males with late onset (c.216+1G>A, c.386G>A, c.622G>A, c.829C>T), 6 females (delE2-10, c.533C>T, c.452T>G, c.540+1G>A, dupE1-9/delE10). ii) Argininosuccinate synthetase deficiency (ASS), Citrullinemia type I (CTLN1), 17 patients from 10 unrelated families. Fifteen patients belong from the same geographic area, all showed the same ASS1 genotype: c.1168G>A/c.1168G>A and died during neonatal period. This change was studied in their relatives and 172 healthy volunteers. The calculated carrier frequency in that population was 4.1%, suggesting the incidence of CTLN1 to be 1:2,427. The other two patients presented symptoms during the first year of life; the genotype were c.79T>C/c.970G>A and c.79T>C/c.847G>A. iii) Argininosuccinate lyase, 1 patient, he died in the neonatal period; his genotype was c.857A>G/ c.857A>G. **Conclusions:** This study reports 15 mutations, of which 5 have not been previously reported. In OTC gene, we found a complex chromosomal rearrangement (dupE1-9/delE10), delE2-10, c.697de3G and c.540+1G>A. In ASS1 gene, we described c.79T>C in two not related patients. The mutations were validated with bioinformatic tools that allowed elucidate the correlation of each genotype with the phenotype data. 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.

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