NEUROGENETICS

P338

CLINICAL AND RADIOLOGICAL FINDINGS IN MALFORMATIONS OF CORTICAL DEVELOPMENT: CLUES FOR GENETIC TESTING

M. Paulina Carullo, Mercedes Villanueva, Rita Valdez, Gabriel Vazquez, Lucas Bongiorni, Cecilia Perandones, Paulina Yañez, Soma Das, Mario Massaro, Angeles Schteinschnaider. FLENI, Raúl Carrea Instituto de Investigaciones Neurológicas, Argentina

Genetically inherited disorders of neuronal migration are being increasingly implicated in the etiology of common childhood neurologic problems. The diagnoses is based in genetic studies as karyotyping; FISH studies for regions 17p13.3 and 22q11.2; and specific tests for monogenic entities (for example : LIS1 , DCX , ARX)

METHODS: Description of the elements of the physical examination and neuroimaging pattern that motivated the specific molecular testing in 4 patients with cortical malformations.

RESULTS:

Patient 1: 3y.o. male with microcephaly, hypotonia, epileptic encephalopathy, no other dysmorphic features. Brain MRI: posterior greater than anterior lissencephaly gradient, subcortical band heterotopia. Novel LIS1 mutation c.1233A>AC (missense). Normal parental testing.

Patient 2: 7y.o. male with microcephaly, spastic quadriparesis, epileptic encephalopathy, no other dysmorphic features. Brain MRI: anterior greater than posterior lissencephaly gradient. DCX mutation c.907C>T (stop codon). Normal parental testing.

Patient 3: 5y.o. female with spastic quadriparesis, refractory epilepsy, dysmorphic features. Brain MRI: agyria-pachygyria complex. 22q11.2 microdeletion. Normal parental testing.

Patient 4: 3y.o. male with spastic quadriparesis and neonatal epileptic encephalopathy, hypothalamic dysfunction with defective temperature regulation, chronic diarrhea and ambiguous genitalia. . Brain MRI: lissencephaly with absent corpus callosum, severe bilateral hippocampal hypoplasia. Novel ARX mutation c.1034G>C (missense). Mother: carrier of same mutation.

CONCLUSION:

The sensitivity of genetic studies in cortical malformations is high when requested according to the characteristics of neuroimaging and associated anomalies. Using this knowledge the clinician can provide accurate diagnosis and counselling, avoiding unnecessary testing.

P339

HOTFOOT MUTANT IN HUMAN CHARACTERIZED BY CEREBELLAR ATAXIA AND EARLY-ONSET RETINAL DYSTROPHY CAUSED BY HOMOZYGOUS GRID2 DELETION

Nicolas Deconinck[1], Kristof Van Schil[2], Francois Meire[3], Miriam Bauwens[2], Hannah Verdin[2], Frauke Coppieters[2], Elfride De Baere[2]. [1]Department of Neurology. Hôpital Universitaire des Enfants Reine Fabiola (HUDERF). Av JJ Crocq [15]; [1020] Brussels, Belgium; [2]Center for Medical Genetics, Ghent University and Ghent University Hospital, Ghent, Belgium; [3]Department of Paediatric Ophthalmology, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium

Introduction: We aimed to identify the underlying genetic cause of a cerebellar ataxia and early-onset retinal dystrophy (EORD) phenotype in a child of consanguineous origin.

Results: The child had hypotonia from the age of 3 months and developmental delay mainly in gross motor skills with a rather static neurological course. Neurological examination demonstrated multidirectional nystagmus, truncal hypotonia and ataxia. Fundoscopy showed pigmentary abnormalities, electroretinography (ERG) demonstrated reduced scotopic and photopic amplitudes and brain MRI showed cerebellar atrophy.

Homozygosity mapping revealed a homozygous deletion of exon 2 of the **GRID2** gene in the proband, leading to an in-frame deletion (p.Gly30_Glu81del). This deletion is the human counterpart of the natural mouse hotfoot mutant ho15J, disrupting exon 2 of **Grid2.** We demonstrated **GRID2** mRNA expression in human cerebellum, and retina and GRID2 protein expression in both murine and human retina. Whole exome sequencing (WES) did not reveal disease-causing mutations in known RD or other genes, supporting the neurological and retinal phenotype as a single clinical entity.

Conclusions: Human **GRID2** deletions have only recently been described in recessive cerebellar ataxia1. Hotfoot mice are characterized by cerebellar ataxia and are caused by different **Grid2**deletions. We identified (mRNA and protein expression studies) for the first time, **GRID2** as an underlying disease gene in cerebellar ataxia and EORD. Interestingly, a CRX-bound **cis**-regulatory element (retina-specific transcription factor Crx) of **GRID2** was removed by the deletion in our patient. Our study expands the expression domain of GRID2 and the clinical spectrum of **GRID2** hotfoot deletion mutants in human.

P340

TREATMENT OF FACIAL MYOTONIA WITH BOTULINUM TOXIN TYPE A (BTX-A) IN THE SCHWARTZ-JAMPEL SYNDROME (SJS): REPORT OF TWO CASES

Igor Dórea Bandeira, João Gabriel Jagersbacher Passos Oliveira, Camilo Vieira Santos, Fernanda Costa de Queirós, Rita de Cássia Saldanha de Lucena. Federal University of Bahia, Brazil

Introduction: The individuals with the Schwartz-Jampel syndrome usually presents a face feature with low-set ears, prominent eyebrows, micrognathia, facial muscles hypertrophy, pursed mouth, and lips. The objective of the study was to evaluate the use of BTX-A in the treatment of facial myotonia related to SJS.

Methods: We offered explanations about the disease and the use of BTX-A in perioral muscles to two patients with this condition that attended our ambulatory care clinic.

Case report:

Case 01: JSN, female, age 36, was diagnosed at the first year of life with blepharophimosis, reduced mouth opening, and lips' protrusion.

Case 02: JSS, 18, female, was diagnosed at the first year of life with "shrinking chin", puckering of mouth, blepharophimosis, and valgus genu.

Results: Patients were reassessed two weeks after application. The myotonia was no longer detected, facial appearance was better, and mouth opening had increased.

Conclusion/discussion: Botulinum toxin should be considered as an alternative treatment when facial myotomy interferes with self-esteem and functionality (impairing eating and communication). Lack of major adverse events and the relative ease of application indicate that this strategy can be widely used.

P341

THE CHROMOSOME 14Q TERMINAL DELETION SYNDROME: CASE REPORT WITH EMPHASIS ON NEUROLOGICAL ASPECTS

Clay Brites[1], Sylvia Maria Ciasca[1], Salmo Raskin[2]. [1]UNICAMP, Brazil; [2]Pontificia Universidade Católica do Paraná (PUC-PR)

Scarce descriptions concerning the phenotype of children with chromosome 14 terminal deletion show the fewness of this genetic pathology. The clinic, neuropsychological and genetic profiles accomplished and described in this case report bring new information and phenotypic dimensions for this syndrome. This article also makes a brief literature review and compares it to the phenotype of this patient contributing for a better diagnostic and therapeutic propaedeutic in order to contribute in the elucidation of new cases.

P342

BROWN-VIALETTO-VAN LAERE SYNDROME: A CASE REPORT

Aline Cupertino Lemos, Igor Dórea Bandeira, João Gabriel Jagersbacher Passos Oliveira, Fernanda Costa de Queirós, Rita de Cássia Saldanha de Lucena. Federal University of Bahia, Brazil

Introduction: Brown-Vialetto-van Laere syndrome is a rare genetic neurological disease whose onset of symptoms varies from infancy to the third decade of life. It is common the existence of consanguinity between parents. Usually, there is motor neuron lesion and involvement of cranial motor nerves. The symptoms most commonly reported in the literature are generalized muscle weakness, hypotonia, progressive hearing loss, respiratory failure, hampered swallowing and dysarthrophonia.

Case description: RCB, 24-years-old male, child of non-consanguineous parents, reported dyspnoea, tachycardia, weakness and hearing loss since age 12. He has bilateral sensorineural hearing loss of retrocochlear type, tremor in the upper limbs and loss of muscle strength. He has a sister with hearing loss, the father reported hypertension and diabetes mellitus, the mother is deceased (unknown cause). No similar cases have been identified in the family.

Results: Clinical examination revealed the presence of fasciculations, muscle weakness, hyporeflexia, hipomimics, absence of gag reflex, flaccid dysarthrophonia, and breathing difficulties. EMG/evoked potential showed signs of chronic denervation in distal muscles. Genetic testing confirmed the diagnosis.

Conclusion/discussion: Despite having very peculiar characteristics, to define the diagnosis of this syndrome, it is necessary to perform differential diagnosis with other neurological disorders in which there is involvement of cranial nerves, or where there is evidence of lower motor neuron lesion.

P343

GM2 SYNTHASE DEFICIENCY: A NEW INBORN ERROR OF METABOLISM PRESENTING AS HEREDITARY SPASTIC PARAPLEGIA WITH INFANTILE ONSET

Charles Marques Lourenco[1], Giovanni Stevanin[2], Stephan Zuchner[3], Wilson Marques Junior[4]. [1]University of Sao Paulo, Brazil; [2]Université Pierre-et-Marie-Curie, Universite Paris VI, Centre de Recherche de l'Institut du Cerveau et de la Moelle epiniere, EPHE, and Centre national de la recherche scientifique , Unité mixte de recherche [7225], Groupe Hospitalier Pitie-Salpêtriere, Paris; [3]John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami,FL., USA; [4]Department of Neuroscience and Behaviour Sciences, School of Medicine of Ribeirão Preto, University of Sao Paulo, Brazil

Majority of cases of Hereditary spastic paraplegias (HSPs) are due to genes involved in axonal growth or vesicular trafficking, there is an overlooked group of HSPs that can be caused by inborn errors of metabolism (IEMs). Adrenomyeloneuropathy, late-onset biotinidase deficiency, cerebrotendineous xanthomatosis are among relatively known metabolic causes of HSPs.

Objective: To report a new hereditary metabolic cause of HSP in a Brazilian family caused by enzyme deficiency of beta-1, 4-N-acetyl-galactosaminyl transferase 1 (B4GALNT1), involved in ganglioside biosynthesis.

Methodology: After excluding the traditional IEMs associated with HSPs and molecular analysis of SPG11 and SPG15 genes, whole exome sequencing (WES) effort was performed. All sequencing results were imported and analyzed by the GEnomes Management Application (GEM.app).

Results: Mutations in the B4GALNT1 gene (in the SPG26 locus) were identified in all affected patients in the family; parents were heterozygous carriers of the mutation. Patients affected by this disease have early onset spastic paresis, mild intellectual disability, cerebellar ataxia, strabismus and some can develop psychiatric disturbance. Male hypogonadism was also noticed. Brain MRI showed nonspecific white matter changes in older patients.

Conclusions: Although there are many IEMs involved in ganglioside catabolism presenting as neurodegenerative disorders, this enzyme deficiency is the second human disorder identified in the pathway of ganglioside biosynthesis, suggesting that other human diseases can be caused by metabolic errors in this biochemical pathway.

P344

LISDEXANFETAMINE AS A TREATMENT OPTION FOR NARCOLEPSY

Fernanda Guedes Morgado, Stella Pinto dos Santos, Roseane Beker, Marcella Vieira, Heloisa Pereira. ABENEPI SOPERJ, Brazil

Narcolepsy is a chronic disorder. Excessive daytime somnolence, cataplexia (the hallmark of the disease is present in 70% of the cases), hypnopompic hallucinations, sleep paralysis and short latency of REM sleep are often present. The impact of narcolepsy on quality of life justifies efforts for early diagnosis and treatment.

Case report: TFA, 14 years old, presented with excessive sleep since the first months of life. History included precocious puberty at age five and ADHD inattentive subtype treated with methylphenidate with a partial response. Polysmonography with multiple latencies test results disclosed improper sleep onset in Three out of four opportunities, with a mean latency of 5, 1 minute and three REM sleep cycles.

Her medication was progressively escalated to a combination of modafinil, methylphenidate and amitriptyline and the response was described as initially good but worsening afterwards. She slept during one hour of the first consult, and it was impossible to keep her awake. The EEG, MRI and blood workout were normal.

The medications were changed for Lisdexanfetamine 50 mg/Day and the patient presented very good response in sleep symptoms, return to social life. Depression was diagnosed in subsequent consultations and fluoxetine 20 mg/ Day was added with good response.

Discussion: Lisdexanfetamine is indicated as a treatment option to ADHD but, in this case, it was prescribed as a central nervous system stimulant in order to control the symptoms of narcolepsy and we obtained a very good response. It seems reasonable to include the drug as a treatment option for narcolepsy.

P345

PROTEIN C DEFICIENCY IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL ANEMIA POST-STROKE

João Gabriel Jagersbacher Passos Oliveira, Igor Dórea Bandeira, Camilo Vieira Santos, Fernanda Costa de Queirós, Rita de Cássia Saldanha de Lucena. Federal University of Bahia, Brazil

Introduction: Stroke is an uncommon event in the pediatric population. However, in patients with sickle cell anemia its occurrence is extremely high, with an incidence of 0.61/100 patients/year. Protein C deficiency, by itself, is a thrombogenic factor that increases the risk of stroke in population without sickle cell anemia. The association of sickle cell anemia and protein C deficiency may be related to a higher chance of recurrent stroke.

Methods: A descriptive study involving 24 pediatric patients with sickle cell anemia and stroke was conducted in a specialized unit of a Teaching Hospital. Deficiency was considered from below 70% of expected values.

Results: Twelve Patients (50%) were female, mean age 11.2 years (4-17). The average age of the first occurrence of stroke was 6.2 years (3-12) and 45% of patients had more than one episode of stroke (mean 1.7 episode/patient). Protein C deficiency was present in 5 (20.8 %) patients. There was significant difference ($p < 0.05$) in the presence of protein C deficiency among individuals with a stroke episode (7.7%) and patients with two or more episodes (36.4%).

Conclusion/discussion: The presence of protein C deficiency in children and adolescents with sickle cell anemia may be related to a higher chance of recurrent stroke. The dosage of protein C in this population may be a useful prevention tool.

P346

INFANTILE POMPE'S DISEASE: A CASE REPORT

Juliana de Castro Naves Peixoto[1], Avessandra Costa Cardoso Oliveira[1], Cristina Nogueira Marques Alencar[1], Paulo Roberto Alves Seixas[1], Janaína Monteiro Chaves[1], Renata Brasileiro Reis Pereira[1], Cristiane Sales Low[1], Marisa Vale Cavalcante[1], Maria Angélica Cavalcante Barbosa Viana[1], Christian Muller[1], Gerson da Silva Carvalho[1], Maria Teresinha de Oliveira Cardoso[1], Cristina Touguinha Neves Medina[2]. [1]Hospital de Base do Distrito Federal Hospital da Criança de Brasília, Brazil; [2]Hospital de Base do Distrito Federal, Hospital da Criança de Brasília, Brazil

Pompe's disease is a rare, progressive and often fatal glycogen storage disorder. The pathology is caused by deficiency of acid alpha-glucosidase (AAG) enzyme activity, that hydrolyses lysosomal glycogen. The glycogen is primarily accumulated in the lysosomes, which later breakdown and occur cytoplasmic accumulation causing muscle fibers disruption and contractile dysfunction. There is a range of phenotypes resulting from AAG deficiency, which the most severe presentation is infantile-onset Pompe's disease. The prevalence is estimated in 1 for 146.000 live births. In this case report the patient is female, 7 months old, with non blood-related parents, with history of severe hypotony observed since she was 2 months old. She was hospitalized three times for pneumonia and dehydration treatment, two of those being in the Intensive Care Unit. During the hospitalization, was observed hypertrophic cardiomyopathy, hepatomegaly, and macroglossia. There was a suspicion for PompeXCHARXs disease and the material for investigation was collected.. The procedure diagnostic was perfomed and AAG enzyme was deficient with 0,3 µmol/L/h level (reference > or = 3,9 µmol/L/h).

The gene sequence of AAG enzyme demonstrated two heterozygous mutations (c.1657C>T p.Q553* and deletion encompassing exon 18). The pacient begun the enzymatic replacing therapy and the proposal treatment it will be once every two weeks. Since the infantile form of PompeXCHARXs disease is rare, the importance of this case is to call attention to hypotonia differential diagnosis and remember that despite rarity, PompeXCHARXs disease must be considered, avoiding the waste of time in introducing treatment.

P347

TORSION DYSTONIA (DYT 1) CAUSED BY MUTATION IN TOR 1A PRESENTING WITH MYOCLONIC DYSTONIA

André Luiz Santos Pessoa[1], Danielle Pessoa Lima[1], Alexandre Bastos Lima[1], Fernando Kok[2]. [1]Universidade de Fortaleza- Unifor, Brazil; [2]Universidade de São Paulo - USP, Brazil

A 12-year-old with appropriate development male was healthy until the age of 10. At that age he began to have difficulty to write and had dystonia at supination of the right wrist associated with myoclonus. His Brain MRI was normal and eletroneuromiography exam, confirmed the dystonic pattern with myoclonic components. There was no response to treatment with levodopa and benserazide even with titration of the dosage. He was stable for a year then presented dystonia during gait in lower limbs with a tendency to foot inversion. A Molecular study was performed to mutations the epsilon - sarcoglycano gene (SGCE) responsible for Myoclonic Dystonia (DYT 11) no changes were found. Exome sequencing identified the variant c. 907_909del GAG (p.Glu303del) in TOR1A gene that variant leads to a deletion of the amino acid glutamate at codon 303.

Discussion: The torsion dystonia is a neurogenetic disorder with autosomal dominant inheritance caused by mutations in the gene TOR1A locus 9q34.11 with incomplete penetrance. The onset of symptoms occurs in the second half of the first decade of life. The symptoms begin in the limbs and evolve to a global dystonia. This case presents important presence of myoclonus since the onset of dystonia and it also has symptoms initially in the arms. It was initially thought to be a myoclonus dystonia (DYT 11). There are no reports of other affected family members which mean that the dystonia is secondary to a de novo mutation or even the result of a low penetrance gene.

P348

A CASE OF GLUT1 DEFICIENCY SYNDROME WITH DEVELOPMENTAL DELAY AND ABSENCE OF SEIZURES AND MOVEMENT DISORDER

André Luiz Santos Pessoa[1], Danielle Pessoa Lima[1], Alexandre Bastos Lima[1], Fernando Kok[2]. [1]Universidade de Fortaleza - Unifor, Brazil; [2]Universidade de São Paulo - USP, Brazil

A 3-year-old, male, the second child of a non-consanguineous couple, no pre or perinatal complications had his neuropsychomotor development delayed. He walked and spoke after two years. He had normal head circumference and moderate hypotonia with joint laxity but no motor deficits. Reflexes exalted in lower limbs without Babinski sign. He was investigated with brain MRI, EEG, BAEP, electromyography, complete blood count, transaminases, CPK, ammonia, lactate, molecular test for Fragile X, HPLC of amino acids, urine organic acids analysis, Acylcarnitine profile analysis, karyotype and CGH-Array. These tests were normal. The family refused to collect CSF.

He presented with 6 hour episodes in which he was lethargic, hypotonic and drowsy. These started when he was 1-year-old and happened on average every 3 months. Metabolic changes or epileptiform activity on EEG-video monitoring were never found during crises.

Whole exome sequencing: heterozygous mutation **nonsense** c.724 C>T (p.Gln242*) in SLC2A1 (Glut 1).

GLUT1 deficiency syndrome-1 is caused by heterozygous mutation in the gene (SLC2A1) and rarely by homozygous or compound heterozygous mutation. Presents with infantile-onset epileptic encephalopathy, delayed development, acquired microcephaly, motor incoordination and spasticity. Other paroxysmal findings include intermittent ataxia, confusion, lethargy, sleep disturbance, and headache. Hypoglycorrhachia and low CSF lactate are essentially diagnosis. The phenotype includes individuals with ataxia and mental retardation but without seizures, individuals with dystonia and choreoathetosis, and rarely individuals without seizures and movement disorder. The disorder (a defect in the GLUT1 glucose transporter) causes decreased glucose concentration in the brain. A ketogenic diet results in clinical improvement.

P349

MUTATION SCREENING OF FOXP2 GENE IN AUTISM AND ASPERGER SYNDROME

Michele Gea Guimaraes Pozzato[1,2], Patricia Maria de Carvalho Aguiar[1,2], Marcelo Rodrigues Masruha[1], Luiz Celso Pereira Vilanova[1]. [1]Universidade Federal de Sao Paulo, Brazil; [2]Hospital Israelita Albert Einstein- Instituto do Cérebro, Brazil.

Introduction: The FOXP2 gene, located on human 7q31, was recently linked with autism (A) and Asperger syndrome (AS) in association with previous studies and is involved in the development of speech and language. The objective of this study is to investigate whether there are disruptive molecular changes in FOXP2 present in patients with A and SA and here we present preliminary data from an ongoing study.

Methods: We evaluated 98 patients (45 A and 53 SA), aged 3-18 years of both sexes. All were screened for mutations in the FOXP2 gene through DNA sequencing.

Results: We identified six single nucleotide polymorphisms (SNP), two silent (rs61758964 - p.Gln190= and the original c.1260C>T) and four in intron (rs10227893, rs184212755, rs144807019 and the original c.1769+67G>A), all not found in 200 chromosomes from normal controls.

Conclusions: Silent mutations deserve more detailed investigation because studies have shown that these mutations can lead to profound effects on the production of the transcript. Likewise, SNPs near the intron-exon boundaries may be closely related to the mechanism of splicing. Additional elements (promoters and silencers) are also needed to allow normal splicing in the formation of the transcript which may be close or distant sites of splicing. So far, disruptive mutations in this gene appear to be rare. However, the study of RNA will be required to elucidate whether the changes found so far interfere with transcription, therefore contributing to the pathogenesis of A and SA.

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P350

PONTOCEREBELLAR HYPOPLASIA IN THE DIFFERENTIAL DIAGNOSIS OF FLOPPY INFANT SYNDROME

Ana Paula Rodrigues Lazzari Amâncio[1], Fernanda Veiga Góes[1,2], Alessandra Augusta Penna e Costa [1,2], Flávia Nardes[1], , Denise Santana[1], Carla Quero Cunha[1], Alexandre Lucidi[1], Lúcio José Santa-Ignêz[1], Tania Saad[1,2,3] . [1]Fernandes Figueira Institute (IFF)/Oswaldo Cruz Foundation , [2]Brazilian Academy of Neurology&[3] Brazilian Society of Child Neurology, Brazil.

Introduction: The pontocerebellar hypoplasia type 1 is characterized by cerebellar and brainstem malformation, associated to spinal cord anterior horn degeneration. It is a rare cause of severe global hypotonia of genetic etiology and with poor prognosis.

Case description: M.A.O., female, admitted at 43 days of life for investigation of global hypotonia and facial assimetry. Born at term, appropriate for gestational age, pregnancy and delivery occurred uneventfully, no family history of consanguinity. At examination showed facial dimorphism, hypoactivity and hyporeactivity, severe global hypotonia with diffuse muscular hypotrophy and hyporeflexia, reduced force in all limbs, but no fasciculation.

At follow up presented important psychomotor development delay without seizures. Diagnostic investigation showed MRI (at 3 months) with important reduction of volume in pons, vermis and cerebellar hemispheres and electromyography (at 5 months) compatible with axonopathy in spinal anterior horn at cervical and lumbosacral segments. Other exams like echocardiogram, abdominal USG, muscle enzymes, tandem mass spectrometry, test for pompe disease, karyotype, transferrin isofocusing, lactate, blood gases and EEG all came out normal. It was proposed the diagnosis of pontocerebellar hypoplasia type 1, still waiting genetic confirmation. Recurrent respiratory infections leaded to death at 16 months of age.

Conclusion: The investigation of floppy infant syndrome begins with semiological and topographic differentiation between central and peripheral alterations. Pontocerebellar hypoplasia type 1 affects both central and peripheral levels and should be considered in this differential diagnosis, despite of its rarity.

P351

CASE REPORT: JOUBERT SYNDROME

Giuliana Franzago Salmazo, Rubens Wajnsztejn, Paulo Breinis, Roberta Caramico Pinto, Daniela Fontes Bezerra, Flavio Geraldes Alves, Camila Exposto Alves, Rafael Guerra Cintra, Debora Almeida, Regia Gasparetto, Priscila Passareli, Bruna Da Cruz Beyruth Borges, Patricia Oliveira Meireles Mariano Costa. Faculdade De Medicina Do Abc

Introduction: Joubert syndrome (JS) is a ciliopathy defined primarily by typical cerebellar defect (hypoplasia of the cerebellar vermis) and ocular motility defects. It is an autosomal recessive, or X -linked disease. Exhibit the pathognomonic sign "molar tooth" as well as hypotonia, renal, hepatic and pulmonary changes, and mental retardation. The clinically heterogeneous disease and correlate with 17 genes identified. Estimates of incidence vary between 1:80.000 and 1:100.000 live births. Phenotype variability complicates the diagnosis. The differential diagnosis should include: isolated nephronophthisis and syndromes like Senior- Loken , Bardet - Biedl and Meckel

Objective: To present a case with the diagnosis of JS in two dizygotic twin sisters.

Case description: Twin 1, female, two years old, with an initial complaint of episodes accompanied cephalic version of ipsilateral gaze deviation from four months of life. Evolved with delayed psychomotor development, has coloboma of choroid and change pigmentation temporal retina bilaterally, delayed language acquisition and ataxia. The twin 2, presented the same clinical course, with episodes of ipsilateral ocular and cephalic version, with the same chronological age. In addition delayed psychomotor development, language acquisition and ataxia. Evidenced by examination with coloboma of choroid and change pigmentation temporal retina bilaterally. The diagnosis was possible by MRI demonstrated enlargement of the superior cerebellar peduncle in both patients.

Conclusion: The syndrome should be considered in all children with abnormal eye movements, delayed psychomotor development and ataxia. The identification of genetic mutations allows early prenatal diagnosis, while fetal neuroimaging remains unchanged until the second trimester.

P352

USE OF CYCLODEXTRIN IN TWO BRAZILIAN GIRLS WITH NIEMANN-PICK DISEASE TYPE C

Camilo Vieira Santos, João Gabriel Jagersbacher Passos Oliveira, Igor Dórea Bandeira, Fernanda Costa de Queirós, Rita de Cássia Saldanha de Lucena. Federal University of Bahia, Brazil

Introduction: Niemann-Pick disease type C (NPC) is a lipid storage disease that can present in children or adults. The prevalence of NPC has been estimated at 1:1200.00 to 1:150.000. The classic presentation occurs in mid-to-late childhood with the insidious onset of ataxia, vertical supranuclear gaze palsy (VSGP), and dementia. Until now, there is no effective treatment. The use of 2-hydroxypropyl-b-cyclodextrin has been shown good results.

Methods: Report of two cases of NPC in girls, comparing PET-Scan, films, and NPC Clinical Severity Scale pre-treatment and after three years.

Case description: NBP, 10 years old, with NPC, has a deficit of motor coordination, discrepancy between executive and verbal potential and behavioral symptoms with reduction in all areas. Show deficits in memory and attention and injury of abstraction. In use of Miglustat (Zaveska) and lamotrigine. MBP, 14 years old, with NPC, in use of Miglustat (Zaveska, 400 mg/day), shows an improvement of balance and intelligibility of speech, but with difficulty to memorize and assimilate new information. Presence of axial and appendicular cerebellar syndrome.

Results: They started treatment with cyclodextrin by intravenous infusion twice a week and after one year, they had significantly lower scores for NPC Clinical Severity Scale and improved brain metabolism measured by PET-scan.

Conclusion/discussion: The use of 2-hydroxypropyl-b-cyclodextrin in two NPC patients reduced NPC severity score and improve brain metabolism. This drug can improve the health of NPC patients.

P353

RETT SYNDROME: CLINICAL PHENOTYPES ASSOCIATED TO MUTATIONS IN MECP2 GENE

Paola Santander, Mónica Troncoso, Ledia Troncoso, Sebastián Silva, Andrés Barrios, Patricia Parra, Rodrigo Díaz. Neuropediátra Hospital San Borja Arriarán Universidad de Chile, Chile

Introduction: there are several clinical phenotypes related to mutations in MECP2 gene, being Rett syndrome in females the most frequent in its classical and variants forms, and syndromes in males going from encephalopathy to mental disability.

Objective: to establish the clinical phenotype and evolution of patients with mutations in MECP2 gene and to describe its relation to the phenotype.

Materials and methods: descriptive and retrospective study of patients with mutations in MECP2 gene controlled in our Service between 2005-2009. Cases with positive mutations are studied from the protocol applied to girls with Rett syndrome phenotype.

Results and discussion: 11 girls with Rett syndrome phenotype, 9 classical forms and 2 variants. The 9 girls with the classical form had normal initial development, regression between 6 to 18 months, stereotypies emergence, 7 lost hand propositivity, 6 had epilepsy, 7 acquired microcephaly, 4 achieved gait and none had language. 6 patients had frequent mutations R255X, R168X y R306C with similar clinical severity. The 2 patients with variant forms had normal development until 3 years old, slow progression of language, normocephaly, epilepsy, late stereotypies, preserved gait, with R294X and TRUNC293 mutations.

Conclusion: phenotypes of MECP2 gene mutations manifest as usually is described in females with Rett syndrome. Most are classical forms, with the exceptional gait achievement as highlight. The most frequent mutation is R255X and the severity of the phenotype is not related with a mutation in particular.

P354

DEFECTS IN THE SYNTHESIS OF PROTEOLIPID PROTEIN, DIFFERENT FORMS OF PRESENTATION FOR DEFECTS IN THE SAME GENE.

Mónica Troncoso, Paola Santander, Daniela Muñoz Carolina Quintana, Ledia Troncoso, Patricio Guerra, María José Hidalgo, Rodrigo Diaz, Ana Flandes, Andrés Barrios. Servicio Neurología Infantil Hospital San Borja Arriarán, Universidad de Chile, Santiago Chile.

Background: The proteolipid protein 1 (PLP1) gene encodes the two major proteins of the central nervous system (CNS) myelin: PLP and DM20. Aberrations in PLP1 gene result in altered CNS myelination and manifest as Pelizaeus-Merzbacher disease (PMD) or spastic paraparesis type 2 (SPG2).

Objective: To identify patients with a confirmed genetic defect in PLP1 and to characterize the phenotype and neuroimaging by mutation.

Material and Methods: A retrospective/prospective study, analysis of clinical data and images and their relationship with the genetic defect in patients with impaired PLP synthesis.

Results: 19 patients. (I) 16/19 corresponded to PMD, all affected individuals and their mothers with PLP1 gene duplication. 10 with family history of PMD. Average age of symptoms onset was 3 months (1-8 months). Most frequent initial symptoms were delay in motor development, nystagmus, head tremor. Other clinical signs were global development delayed, cerebellar syndrome, bilateral pyramidal syndrome, dystonia. All neuroimaging showed diffuse hypomyelination. (II) 3/19 corresponded to SPG2, the study confirmed PLP1 gene mutation c.388C> T (p.His130Tyr) exon 3B in patient and mother. A 6 year old boy began at 7 months nystagmus, head tremor, motor development delayed, spastic paraparesis. Neuroimaging showed incomplete myelination regions. 2 cousins on mother's side with spastic paraparesis.

Conclusion: In our series, patients with PLP1 gene duplication exhibit PMD with symptoms and CNS´s hypomyelination more diffuse and severe. Those with a mutation in the gene expressed SPG2.

P355

VANISHING WHITE MATTER DISEASE (VWM): CLINICAL FEATURES, GENETIC STUDY AND EVOLUTION IN 10 CHILEAN PATIENTS.

Mónica Troncoso, Paola Santander, Andrés Barrios, Diane Vergara, Ledia Troncoso, Rodrigo Diaz, María Soledad Rojas, Christian Galleguillos. Servicio neurología infantil, Hospital San Borja Arriarán, Universidad de Chile, Chile

Introduction: VWM is an autosomal recessive hereditary leukodystrophy, linked to mutations in genes encoding the eukaryotic initiation factor 2B (eIF2B). Neurological features and clinical phenotypes are variable. The most common variant has a childhood onset and characteristic abnormalities on cranial MRI.

Methods: Retrospective and prospective study: clinical, neuroimaging and genetic analysis. Patients were divided in groups according to age at onset: Group 1 (<2 years), group 2 (age 2-5) and group 3 (age >5), and according to disability scores (1=gait disturbance to 5=deceased).

Results: 10 patients (7male/3female), 3 siblings. 9/10 had prior normal development. Average age at onset was 7 (1-13years), with gait disturbance (6/10), development regression (3/10) and tremor (1/10). History of cranial concussion (4/10) and febrile infection (1/10). Group distribution: 1 (n=2), 2 (n=1), 3 (n=7). Disability score distribution: 1 (n=6), 2 (n=1), 4 (n=2), 5 (n=1). Phenotypes: late childhood/early childhood onset (7/3). Symptoms: spasticity (7/10), cerebellar ataxia (7/10). Clinical monitoring: 3-12 years, rapidly progressive (n=6), progressive (n=2), fulminant (1) evolution. Brain MRI: diffuse, symmetrical abnormal white matter signal (10/10), most with cystic degeneration. Genetic study (9/10): IF2B5-R113H mutation (homozygous/heterozygous=2/6), IF2B4-R373C homozygous (1).

Conclusion/Discussion: VWM is one of the most prevalent inherited childhood leucoencephalopathies, therefore it must be considered in the differential diagnosis. In this series the classical form was the most frequent, with characteristic white matter abnormalities in MRI, and most with IF2B5- R113H mutation.

P356

THE RELATIONSHIP BETWEEN ACADEMIC PERFORMANCE AND ACADEMIC-RELATED BOREDOM: THE 5-HTTLPR GENE POLYMORPHISM AS A MODERATOR

Yangyang Liu. Nanjing university, China

Objective: In previous research, studies that examine the effects of genes on academic-related negative emotions are largely lacking. The present study sought to examine the moderating effects of the promoter of the serotonin transporter (5-HTTLPR) gene polymorphism on the relationship between students' academic performance and their academic-related boredom.

Method: In a sample of 420 Chinese high school students, we collected data about their academic-related boredom and academic performance. In addition, students' DNA was extracted from cheek cells. Polymerase chain reaction (PCR) was performed to amplify the DNA fragment.

Results: The results indicated that students with the genotype of the 16/16 repeat in their 5-HTTLPR gene were more likely to be influenced by academic performance on their academic-related boredom.

Conclusion: Our findings suggested that the functional polymorphism of the 5-HTTLPR gene moderated the relationship between academic performance and academic-related boredom.

P357

NEXT GENERATION MASSIVELY PARALLEL SEQUENCING OF TARGETED EXOMES TO IDENTIFY GENETIC MUTATIONS IN CHINESE UNKNOWN CAUSE EARLY-ONSET EPILEPTIC ENCEPHALOPATHIES

Jing Peng, Yuping Ma, Liwen Wu, Fei Yin. Xiang Ya Hospital of Central South University, China

Objective Early-onset epileptic encephalopathies (EEEs) is a devastating group of epilepsies which onset inthe first year of life with cognitive arrest or regression, and the majority isetiologically obscure. This disorder is genetically heterogeneous, rendering molecular diagnosis challenging given that mutations in 18 different reported genes account for only approximately 12% of EEEs cases. Moreover, detection technology based on Sanger sequencing is time consuming, expensive and low detection rate. The objective of this study was to investigate the performance characteristics of exon capture technology coupled with massively parallel sequencing for clinical diagnostic evaluation.

Methods We designed a custom array to capture exons from 18 genes with known involvement in EEEs and 290 genes associated with epilepsy, making the total number of genes 308, and sequenced the enriched material using the IlluminaHiSeq 2000 platform. A total of 50 Chinese patients were included. All patients have a confirmed diagnosis of EEEs excluded acquired brain injury, metabolic diseases and other known causes.

Results Eight de novo mutations and one small insertion/deletion mutations were identified and routinely screened with Sanger sequencing. Five of them are known pathogenic gene with unreported mutations. The rest 4 mutations were known epilepsy genes but are the first time involving in EEEs.

Conclusion This is the first report of targeted sequencing including 308 pathogenic c orrelated genes in Chinese unknown cause EEEs. We found 18% (9/50) patients carry pathogenic or likely pathogenic mutations, and 2 of them may be new EEEs pathogenic genes in Chinese population.

P358

ATP1A3 GENE DE NOVO MUTATION CAUSING ALTERNATING HEMIPLEGIA OF CHILDHOOD IN AN ECUADORIAN GIRL.

Bolivar Fabian Quito-Betancourt[1], Kathryn J. Swoboda[2], Tara Newcomb[3]. [1]Hospital IESS "Jose Carrasco Arteaga" Cuenca - Ecuador; [2]University of Utah - USA; [3]University of Utah - USA

INTRODUCTION: Alternating Hemiplegia of Childhood (AHC) is a rare but severe syndrome caused by mutations in the ATP1A3 gene. Onset of symptoms is frequently in the neonatal period. Characteristic features include transient episodes of palsy affecting alternate sides of the body, oculomotor abnormalities, seizures, choreoathetosis and dysautonomia. We describe clinical features in an Ecuadorian girl with a de novo mutation in ATP1A3.

METHODS: Description of medical history and Sanger sequencing of ATP1A3.

CASE DESCRIPTION: Refractory partial seizures began at the age of only two months. Alternating episodes of hemiplegia lasting minutes to 3-4 days become increasingly evident over the next months. She often suffered from asymmetric status dystonicus and partial status epilepticus partially responsive to epilepsy therapies (levetiracetam and benzodiazepines). Motor milestones were severely delayed. She was able to walk with support at the age of three years. Initiation of an antioxidant cocktail therapy and flunarizine appeared to result in ~ 50% reduction in episodes. EEG´s showed focal slowing during partial seizure episodes. MRI, MRA, MR SPECT, CT scan were unremarkable. She ultimately asphyxiated during a choking episode at four years old. A de novo mutation was identified in the ATP1A3 gene in exon 17; c.2401 G to A; D801N.

CONCLUSIONS: The complex nature of symptoms in AHC makes early diagnosis a challenge. Additional research is needed to understand the role of ATP1A3 and the full phenotypic spectrum of this disorder.

P359

RETT SYNDROME,GENOTYPE-PHENOTYPE CORRELATIONS

Lobna Abdelgawad Mansour. Head of Neuropediatric unit, Cairo University,Egypt

Introduction: Rett syndrome is an X linked dominant neurological disorder that affects almost exclusively girls with an estimated prevalence of 10,000---20,000.

Aim: to highlight the clinical manifestations of Rett syndrome & to present genotype phenotype correlations.

Materials & methods : the study included 15 girls (9 months-5years) with typical Rett syndrome according to the international criteria .They were subjected to screening of the whole coding region of the MECP2gene (MECP2A& MECP2B) by DHPLC.

Results: Microcephaly was present in 73.3%, stereotypic hand movement in 100%. Recurrent seizures in 53.3%. Delayed language development in 46.6% deterioration of speech in 53.3%, autistic features in 60%, growth retardation in 46.6%. Three mutations were detected in(66.6%): heterozygous for p.R270X mutation (3 cases) ,heterozygous for p.R255X mutation (3 cases)and heterozygous p.R168X nonsense mutation (4 cases .Phenotype genotype correlation between the group

of mutated gene and those with no mutation showed that microcephaly was present in (80% versus 60% respectively),seizures (70% versus 20%), growth retardation (50% versus 40%) and autistic features (70% versus 40%).But for those with no mutation, they were more frequently able to walk (60% versus 40% with mutation).

Conclusion: Mutations of MECP2 analysis were detected in 66.6% of Rett syndrome cases .Cases with detected mutation had more frequent seizures , microcephaly, growth retardation and autism. Concerning cases with no mutation, further investigations are required for X linked candidate genes.

P360

NOVEL MITOCHONDRIAL MUTATION IN AN INDIAN FAMILY CAUSING AUTOSOMAL RECESSIVE NEURODEGENERATIVE DISORDER

Biswaroop Chakrabarty[1], Sheffali Gulati[1], Rajeshwari R Moganty[1], Dantham Subrahamanyum[1], Rachana Dubey[1], Achal Kumar Srivastava[1], Mohammed Faruq[2]. [1]All India Institute of Medical Sciences, New Delhi, India; [2]Institute of Genomics and Integrative Biology (CSIR), Delhi

Introduction: Recessive mutations in mitochondrial replication machinery primarily affects two genes, viz., c10orf2 and POLG1 (former encoding for helicase and the latter for polymerase), causing mitochondrial depletion syndrome. Mutations in c10orf2 are associated with infantile onset spinocerebellar ataxia.

Case description: Two siblings, one female and one male, born to a nonconsanguinous couple, presented with primarily motor developmental delay from the second half of infancy (till 6-7 months they had normal development). Walking with support was the best attained gross motor milestone, noted at the age of 8 to 10 years in both. By early second decade they became wheelchair bound. Salient features on examination were bilateral claw hands with clubfeet, scoliosis, impaired hearing, distal weakness, choreoathetosis, extensor plantars and pancerebellar involvement with relatively preserved cognition and vision (including saccades) without any obvious dysmorphism or telengiectasia. Currently the female sibling is 18 years and the male is 12 years of age.

MRI Brain had shown pancerebellar atrophy in the female sib (normal in male) and electrophysiology revealed sensory motor axonal polyneuropathy in both. Mutations for Frederich ataxia and spinocerebellar ataxias (1, 2, 3, 6, 7, 8, and 12) were negative. The female sib also had hypergonadotrophic hypogonadism.

Both the sibs are positive for single homozygous nonsynonymous variation (p.237A) in c10orf2 gene and the parents are carriers.

Discussion: This entity is described predominantly in Finnish population. This is the first report of a Caucasian family of Indian origin with a novel mutation in this gene.

P361

TOSCA - TUBEROUS SCLEROSIS REGISTRY TO INCREASE DISEASE AWARENESS

Paolo Curatolo. Tor Vergata University Hospital, Rome, Italy

Introduction Tuberous sclerosis complex (TSC) is a rare, genetic, multisystem disorder associated with marked neurological dysfunction. TOSCA has been designed to address knowledge gaps in the natural history and management of TSC.

Methods TOSCA is a multicentre, international disease registry to assess manifestations, interventions, and outcomes in patients with TSC. Patients of any age diagnosed with TSC, with a documented visit for TSC within preceding 12 months or newly diagnosed individuals are eligible. Objectives include mapping the course of TSC manifestations and their prognostic role, identifying patients with rare symptoms and co-morbidities, recording interventions and their outcomes, contributing to creation of an evidence-base for disease assessment and therapy, informing further research on TSC, and evaluating the quality of life in patients with TSC. TOSCA includes a 'core' section to record general mandatory information on patients' backgrounds and subsections/'petals' to record additional data related to specific disease manifestations. Estimated enrolment is approximately 2000 patients from about 250 sites in over 30 countries. An initial enrolment period of about 24 months and a follow-up observation period of up to 5 years is planned.

Current Status A planned administrative analysis was performed on 'core' data from first 100 patients, to evaluate feasibility of the registry. Results showed a high degree of accuracy of the data collection procedure. Annual interim analyses are scheduled.

Implications Results will help in planning better management and surveillance strategies. This large-scale international registry to study TSC could serve as a model to plan similar registries for other rare diseases.

P362

AICARDI SYNDROME IN A GENOTYPIC MALE. CASE REPORT

Marzhan Lepessova[1], Bakhytkul Myrzaliyeva[1], Gyuzel Khudayberdiyeva[2], Sholpan Tankayeva[1], Aidana Berdaliyeva[1]. [1]Almaty State Institute of Advanced Medical Education, Kazakhstan; [2]Almaty Children's Hospital, Kazakhstan

Objective: to study clinical and diagnostic criteria of Aicardi syndrome in a male patient.

Material and methods: a clinical case of Aicardi syndrome in a 5 month-old 46 XY male child. Results: The boy aged 5 months came in to the hospital with complaints of serial seizures by type of infantile spasms, muscle weakness, lethargy, developmental delay. Seizures debut at age 44 days by type of flexor infantile spasms. Later focal tonic and myoclonic infantile spasms, also generalized tonic-clonic seizures joined. The anticonvulsant polytherapy was without effect.

Neurologic status. The child's condition is serious. Consciousness is violated. There is no adequate response to the inspection. Microcephaly. Facial features: hypoplasia of the mandible, upturned nasal tip. Muscle hypotonia. Skeletal abnormalities: hypoplasia of the fourth finger, disproportionate limbs. Severe psychomotor retardation. The examination: MRI - agenesis of the corpus callosum, ventriculomegaly, gyral anomalies. Neurosonography - agenesis of the corpus callosum, hypoplasia septum pellucidum, choroid plexus cysts. EEG - polymorphic epileptiform activity, modified hypsarrhythmia, expressed hemispheric asymmetry. Ophthalmologist - coloboma of the optic nerve and retina. Karyotyping - male karyotype 46, XY. Genetics - not excluded Aicardi syndrome. Pulmonologist - idiopathic pulmonary fibrosis.

Conclusion. Availability of basic criteria - agenesis of the corpus callosum , infantile spasms, retina and optic nerve pathology, as well as additional - microcephaly, ventriculomegaly, gyral anomalies, facial and skeletal abnormalities and bronchopulmonary pathology - allow us to diagnosis Aicardi syndrome in a 5 month-old 46 XY male child.

P363

NEUROPSYCHIATRIC MANIFESTATIONS IN CHILDREN WITH 22Q11.2 MICRODELETION SYNDROME : SINGLE CENTER STUDY

Eunhee Kim, Mi-Sun Yum, Beom-Hee Lee, Han-Wook Yoo, Tae-Sung Ko. Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea, Republic Of

Objectives: The 22q11.2 microdeletion syndrome is the most common human microdeletion syndrome. Neuropsychiatric (NP) manifestations in this genetic syndrome are not uncommon, but not well-understood and associated with unfavorable outcome. We reviewed the NP manifestations in children with 22q11.2 microdeletion syndrome and tried to identify the associated clinical variables.

Methods: We retrospectively analyzed the medical records of 145 patients (72 males) genetically diagnosed with 22q11.2 microdeletion syndrome at Asan Medical Center Children's Hospital between March 1996 and June 2013. Clinical data included NP and other clinical symptoms, neuroradiologic and electrophysiologic findings, treatments and outcomes.

Results: Among 145 patients with 22q11.2 microdeletion syndrome, 78 (53.8%) developed NP manifestations, most commonly with developmental delay/cognitive impairment (n=71), epilepsy (n=22), and psychiatric illness (n=16). Neuroradologic studies revealed malformation of cortical development in 6, agenesis of corpus callosum in 1, hypoplasia of cerebral artery in 1, and Chiari malformation in 1. In 22 patients with epilepsy, the mean age of epilepsy onset was 3.3 (0-17) years and 9 patients were diagnosed as idiopathic epilepsy including one with juvenile myoclonic epilepsy. Regarding psychiatric illnesses, attention-deficit hyperactivity disorder were identified in 10, mood disorder in 5, and schizophrenia in 3. Clinical variables including prematurity and congenital heart disease were not associated with the development of NP manifestations in this genetic syndrome.

Conclusion: Patients carrying the 22q11.2 microdeletion syndrome are at risk for diverse NP manifestations across the life span. Therefore, diagnostic screening and early proper management for NP manifestation should be considered in these patients.

P364

TUBEROUS SCLEROSIS COMPLEX IN PARAGUAY. REPORT OF 8 CASES.

Laura Patricia Arredondo, Zulma Irene Valenzuela, Carlos Franco, Néstor Waldemar Sánchez, Fabiola Alarcón, Marco Javier Casartelli. Hospital General Pediátrico "Niños de Acosta Ñu", Paraguay

Introduction: Tuberous sclerosis complex (TSC), is a multisystem autosomic dominant genetic disorder, which is clinically diagnosed. The disease manifestations vary significantly among affected individuals. The main neurological symptoms are seizures, cognitive impairment, neuronal migration defects and brain tumors (cortical/subcortical tubers, subependymal nodules [SEN], and subependymal giant cell astrocytomas [SEGA]). The genetic origin of TSC is located in 2 genes encoding hamartin (TSC1) and tuberin (TSC2), which act by regulating cell growth. The incidence varies depending on the series between 1/5800 and 1/6000 births.

Objective: To report the clinical presentations of TSC in Paraguay and our experience in the clinical management of them.

Methodology: Review of cases of patients treated at the Department of Neurology between January 2011 and August 2013. **Cases Reports:** We report eight patients from Paraguay, 4 males and 4 females, aged between 1 and 13 years, diagnosed and treated at the Neurology Department, between January 2011 and August 2013.

Conclusion: The TSC is a relatively low incidence disease, but with a lot neurological symptoms. The knowledge of the disease is critical to Neuropaediatricians, for improve the quality of life of the patients and to prevent the future affectations that are usually presented in this disease.

P365

NOVEL GLRB GENE MUTATION IN A SAUDI BABY WITH HYPEREKPLEXIA

Tamer Rizk. King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia

Aim: We aim to describe a case of hyperekplexia in a Saudi neonate due to Novel mutation in**GLRB**.

Case Presentation: One month old Saudi neonate with hypertonicity, repetitive episodes of jitteriness and exaggerated startle reflex.

Discussion: Hyperekplexia (OMIM:149400, 138492 & 604159) is considered a rare, autosomal dominant neurological disorder that presents early in life with hypertonicity, exaggerated startle response and life threatening neonatal apnea. It has been caused by mutation in the alpha-1subunit (**GLRA1**) on chromosome 5q32, Beta subunit (**GLRB**) gene on chromosome 4q31 of the inhibitory glycine receptor and **GLYT2** gene (**SLC6A5**) on chromosome 11p15 which encodes a presynaptic glycine transporter.

Conclusion: Raising awareness of the presence of this treatable disease may prevent unnecessary exposure to anti-epileptic medications, prevent life threatening apneas and improve long term outcome.

P366

PELLAGRA-LIKE SYNDROME PROVES TO BE A VARIANT OF XERODERMA PIGMENTOSUM-COCKAYNE SYNDROME AND NIACIN CONFERS CLINICAL BENEFIT

Mustafa A Salih[1], Hadia Hijazi[2], Muddathir H Hamad[1], Hamdy H Hassan[3], Shifa B Salih[4], Khalid A Mohamed[5], Maowia M Mukhtar[6], Zein A Karrar[7], Shinu Ansari[2], Fowzan S Alkuraya[2]. [1]Division of Pediatric Neurology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [2]Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [3]Department of Radiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [4]Mafraq Hospital, Abu Dhabi, United Arab Emirates; ; [5]Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates; [6]Institute of Endemic Diseases, Faculty of Medicine, University of Khartoum, Sudan; [7]Department of Pediatrics and Child Health, Faculty of Medicine, University of Khartoum, Sudan

OBJECTIVE: To identify the causal mutation in pellagra-like syndrome and investigate the mechanism by which niacin confers clinical benefit.

BACKGROUND: An extremely rare pellagra-like syndrome (OMIM 260650) has been described in two multiplex Arab families in which extreme skin sensitivity to sun was associated with a multisystem involvement, primarily neurological, and early lethality. The condition was proposed to represent a novel autosomal recessive entity that displayed partial but significant response to niacin supplementation, but the underlying mutation remained unknown for almost three decades.

DESIGN/METHODS: Autozygosity mapping and exome sequencing to identify the causal mutation, and comet assay on patient fibroblasts before and after niacin treatment to assess its effect on DNA damage.

RESULTS: By studying a newly identified relative to the original proband, and another apparently unrelated family, we identified a single disease locus that harbors a novel mutation in **ERCC5** thus confirming that the condition is in fact a variant of xeroderma pigmentosum **-** Cockayne syndrome. Importantly, we also show that the previously described dermatological response to niacin is consistent with a dramatic protective effect against UV-induced DNA damage in patient's fibroblasts conferred by niacin treatment.

CONCLUSIONS: Our findings show the power of exome sequencing in reassigning previously described novel clinical entities, and suggest a mechanism for the dermatological response to niacin in patients with Cockayne syndrome. This raises interesting possibilities about the potential therapeutic use of niacin in Cockayne syndrome and the closely related condition of xeroderma pigmentosum.

P367

PLEXIFORM NEUROFIBROMAS IN SOUTH AFRICAN CHILDREN WITH NEUROFIBROMATOSIS 1

Veruschka Ramanjam. University of Cape Town, Red Cross War Memorial Hospital, Paediatric Neurology and Developmental Association Of South Africa (PANDA), South Africa

Plexiform Neurofibromas are serious complications of Neurofibromatosis 1 remaining a major management dilemma globally. They are both chemo and radiotherapy resistant and often difficult to excise. A viable therapeutic agent is yet to be found. 25% of children attending the multidisciplinary Neurofibromatosis clinic at our hospital presented with plexiform neurofibromas. This series aimed to better characterise this cohort to gain insight into planning future managment approaches in a resource limited setting.

Method: All children with Plexiform Neurofibromas who presented to the clinic from January 2001 to July 2013 were included, Folders were reviewed and relevant clinical details recorded.

Results: 23 children presented with Plexiform Neurofibromas (9 girls, 14 boys). A family history was present in 9 of the 23. Children presented between 6 weeks and 10 years of age. (Median age 3 years)MRI scans of lesions were performed on all children. 12 children had plexiform neurofibromas involving the head and neck, 3 had peri-orbital lesions, 2 were facial and 1 involved occipital soft tissues. The remaining 5 children had lesions involving the lower limb (n=2), upper limb (n=1), buttock/pelvis (n=1) and lumbar paraspinal (n=1) Only 6 children underwent surgery. These will be described. Malignant transformation occurred in one patient who died shortly after symptom progression.

Conclusion: Management of Plexiform Neurofibromas remains a dilemma globally. This is the first series describing children from an African setting many of whom are from poor socio-economic environments with limited access to services.

P368

PREVALENCE OF LIS1 AND RELATED GENES MUTATIONS IN A POPULATION SAMPLE OF 109 PATIENTS WITH STRUCTURAL CNS ABNORMALITIES.

Francisco Carratalá-Marco[1], Patricia Andreo-Lillo[1], Teresa Escamez[2], Arancha Botella[2], Salvador Martínez[2]. [1]Neuropediatric Unit Pediatric Department University Hospital of San Juan de Alicante, Spain; [2]Neuroscience Institute of Alicante (Spain)

Introduction: Mutations inthe LIS1 gene contained in the lissencephaly critical region (LCR) situated in band p13.3 of the short arm ofchromosome 17, have been related tomultiple CNS malformations, as well as other related genes like PAFR, PAFAH1B2,PAFAH1B3, YWHAE,TUSC5, MYO1C, CRK, EN2, FGF8 y PAX2 (LCR-panel). Performing DNA andtranscriptional studies (LCR-panel) in patients with common features likemental retardation and/or epilepsy altogether with CNS malformations, we aimedto find a closer relationship between some gene mutations and the patient'sphenotype.

Patientsand methods: We have compared the LCR-panelmutation prevalence in patients with mental retardation/psychomotor delayand/or epilepsy, with CNS structural abnormalities (Study Group, SG), versus acontrol group (CG). From a compulsory referential area of 33.281 children(<15 y.o.), we included 109 consecutive patients in the Study Group (SG), referredto our outpatients' clinic of a University Hospital.

All of them were submittedto a neurological examination, EEG, which results were registered asindependent variables. All of these patients and 224 healthy controls (CG) werestudied by means of PCR techniques for DNA mutations and for LCRtranscriptional errors (LCR-panel)

Results: Fifteen out of 109 patients met exclusioncriteria during the study. From the remaining 94 patients (SG), 46 were LCR-panel (+) while none of the CG was. (c2=128.15; p=0.0000000000).

Conclusions: Mutations in the LCR-panel, were significantly more prevalent amongpatients suffering from some degree of mental retardation and/or epilepsy, associatingCNS structural abnormalities than the general population.

P369

CONGENITAL FIBROSIS OF EXTRA OCULAR MUSCLES (CFEOM) RESULTING FROM MUTATIONS IN TUBULIN 3 (TUBB3) CAN MIMIC MOEBIUS SYNDROME

Kosmapatabendige Chryshanth Saminda Dalpatadu[1], Peta Sharples[2], Sarah Smithson[3], Anirban Majumdar[2], Kayal Vijayakumar[2]. [1]Deparment of Paediatric Neurology, Frenchay Hospital,North Bristol NHS Trust, UK & Post Graduate institute of medicine, Sri Lanka, United Kingdom; [2]Deparment of Paediatric Neurology, Frenchay Hospital,North Bristol NHS Trust, UK, United Kingdom; [3]Department of Clinical Genetics, St Michaels Hospital, Bristol, United Kingdom

Introduction and Objective: Moebius Syndrome is a widely known rare congenital non-progressive neurological condition with external ophthalmoplegia and facial weakness due to sixth and seventh cranial nerve palsy. There are other conditions with similar and overlapping features, with variable involvement of other cranial nerves, frequently reported as 'Moebius syndrome plus' or 'congenital facial syndrome'.

Case report:A non-consanguineous 10 year old Caucasian boy with an existing diagnosis of Moebius syndrome presented with facial diplegia, ptosis and ophthalmoplegia, Later in childhood developing difficulties in fine motor skills, and frequent falls. Initially this was attributed to impaired vision and learning difficulty. On examination at the age of 10, in addition to above features, he had wasting of hypothenar/thenar muscles, pes cavus and equinovarus deformity. Neurophysiology studies showed axonal motor-sensory polyneuropathy. Genetic testing confirmed a heterozygous missense mutation in TUBB3.

Discussion: Moebius syndrome and CFEOM are classified under the heterogeneous congenital innervation dysgenesis syndrome group2. TUBB3 encodes a beta-tubulin protein that may be involved in neurogenesis, axon guidance and maintenance. Significant mutations in this gene cause CFOEM type 3 with progressive axonal and cranial neuropathy. This case highlights two important principles, firstly the importance of clinical follow up for patients presenting in infancy with Moebius syndrome and careful clinical assessment in order to distinguish other phenotypes. Secondly, the availability of molecular genetic tests allows clinicians to determine the underlying cause so that the families can be given correct advice about prognosis and genetic implications.

P371

A NOVEL VARIANT IN GABRB2 ASSOCIATED WITH INTELLECTUAL DISABILITY AND EPILEPSY

Siddharth Srivastava, Julie Cohen, Jonathan Pevsner, Michael V. Johnston, Ali Fatemi. Hugo W. Moser Research Institute at Kennedy Krieger Institute, Baltimore, Maryland, USA

The γ-aminobutyric acid type A (GABAA) receptor is one of the three main classes of receptors activated by GABA, the principal inhibitory neurotransmitter in the central nervous system. Mutations in genes encoding various subunits of this receptor (GABRA1, GABRA2, GABRA4, GABRA5, GABRB1, GABRB3, GABRD, GABRG1, GABRG2, and GABRG3) are implicated in a number of neurological and developmental disorders, including epilepsy and autism. To date, no human genetics studies have implicated mutations in **GABRB2**, encoding the ß2 subunit of the GABAA receptor, with neurodevelopmental disorders. Here we present a 12 year old girl with intellectual disability and epilepsy, who was discovered by whole exome sequencing to have a **de novo** heterozygous missense variant in exon 4 of**GABRB2** (c.236T>C; p.M79T). This variant is likely pathogenic, based on **in silico** analyses as well as the fact that it results in the non-conservative substitution of a non-polar amino acid with a polar amino acid at a position that is evolutionarily conserved across multiple species. Moreover, there is compelling evidence from structural comparisons between human GABRB2 and the C. elegans glutamate-gated chloride channel GluClα that the M79 residue may play a role in ligand binding. Our findings underscore the need for further investigation into the mechanisms by which mutations in **GABRB2** contribute to neurological and developmental dysfunction.

P372

ADULT ONSET TAY-SACHS AND SANDHOFF DISEASES PRESENT WITH NON-SPECIFIC MOTOR AND PSYCHIATRIC SYMPTOMS

Patricia Hall[1], Claire Teigen[2], Jennifer Hesemann[2], Silvia Tortorelli[2], Dietrich Matern[2], Kimiyo Raymond[2]. [1]Emory University; [2]Mayo Clinic College of Medicine

Importance: Many patients undergo a diagnostic odyssey of several years before a diagnosis of late onset hexosaminidase deficiency (Tay-Sachs or Sandhoff disease) is made. Recognizing the variable presentations of these conditions could allow diagnostic enzyme testing to be performed early in the clinical course.

Objective: To identify the range of clinical presentations for late onset hexosaminidase deficiencies and explore reasons for diagnostic delays.

Design: Clinical information for cases of late onset hexosaminidase deficiencies were gathered as part of routine follow-up of abnormal results in our laboratory. This information was combined with a literature review to identify previously reported cases in an attempt to clearly define potential presentations, ranging from strictly motor symptoms to severe psychiatric problems.

Participants: Individuals with deficient hexosaminidase enzyme activity suggestive of late onset Tay-Sachs or Sandhoff disease.

Results: Individuals with late onset hexosaminidase deficiencies could be classified as presenting with motor symptoms (gait disturbance, ataxia, and muscle weakness), psychiatric symptoms or a combination. Long diagnostic delays (mean > 10 years) were common for these patients.

Conclusions and Relevance: Late onset hexosaminidase deficiencies can be diagnosed using an enzyme assay from a routine blood draw. Despite the ease of testing, many patients wait years before diagnosis. With the trend towards genome and exome sequencing for diagnostic odyssey cases, many of these individuals may be referred to this type of testing, rather than receiving their diagnosis via the timelier enzyme assay ordered based on clinical suspicion.