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

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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 2: 7y.o. male with microcephaly, spastic quadriaparesis, 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 quadriaparesis, refractory epilepsy, dysmorphic features. Brain MRI: agryia-pachygyria complex. 22q11.2 microdeletion. Normal parental testing.


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

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

Nicolas Deconnick1, Kristof Van Schil2, Francois Meire3, Miriam Bauwens2, Hannah P339, Aline Cupertino Lemos, Igor Dórea Bandeira, João Gabriel Jagersbacher Passos Oliveira, Camilo Vieira Santos, Fernanda Costa de Queiroz, Rita de Cássia Saldanha de Lucena, Federal University of Bahia, Brazil

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 anterior greater than posterior lissencephaly gradient. DCX mutation c.907C>T (stop codon). Normal parental testing.

Conclusion/discussion: Botulinum toxin should be considered as an alternative treatment when facial myotony 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.

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

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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: JSS, 18, female, was diagnosed at the first year of life with blepharophimosis, reduced mouth opening, and lip’s 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 myotony 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.

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

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Scare descriptions concerning the phenotype of children with chromosome 14 terminal deletion show the fewness of this genetic pathology. The clinic, neuropychological 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.

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BROWN-VIALETTO-VAN LAERE SYNDROME: A CASE REPORT

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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 retrocacular 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 type 2; 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, hiporimics, 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.

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

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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, cerebroretinodine xanthomatosi 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 paraparesis, 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.

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**INFANTILE POMPE’S DISEASE: A CASE REPORT**

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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 hypotonia 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 macroglia. There was a suspicion for PompeXCHARXs disease and the material for investigation was collected. The procedure diagnostic was performed and AAG enzyme was deficient with 0.3 µmol/L/h level (reference > or = 3.9 µmol/L/h).

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**LISDEXANFETAMINE AS A TREATMENT OPTION FOR NARCOLEPSY**

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Narcolepsy is a chronic disorder. Excessive daytime somnolence, cataplexia (the hallmark of the disease is present in 70% of the cases), hypnagogic 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. Polysomnography 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 workload 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.

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

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**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 3 (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.
The gene sequence of AAG enzyme demonstrated two heterozygous mutations (c.1657C>T p.Q553* and deletion encompassing exon 18). The patient began 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.

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

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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 eletoneuromiography exam, confirmed the dystonic pattern with myoclonic components. There was no response to treatment with levodopa and benzadera 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 epsilone - 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 aminoacid 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.

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

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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 existed 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, complete blood count, transaminases, CPK, ammonia, lactate, molecular test for Fragile X, HPLC of amino acids, urine organic acids analysis, Acetylcholine 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 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. Hypoglycemia and low CSF lactate are essentially diagnosis. The phenotype includes individuals with ataxia and mental retardation but without seizures, individuals with dystonia and choreothetosis, 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**

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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 (rs16758964 - p.Gln190= and the original c.1260C>T) and four in intron (rs10227893, rs184212755, rs144807019 and the original c.1769+67G>C=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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**CASE REPORT: JOUBERT SYNDROME**

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**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, pericentral, hepatic and pulmonary changes, and mental retardation. The clinically heterogeneous disease and correlate with 17 genes identified. Estimates of incidence vary between 1:8000 and 1:10000 live births. Phenotype variability complicates the diagnosis. The differential diagnosis should include: isolated nephropathies and syndromes like Senior-Loken, Bardet–Biedl and Meckel. 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, such as hypotonia, pericentral ataxia and delayed language acquisition. 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.

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

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**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 1:120000 to 1:150000. 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-β-cyclodextrin has demonstrated enlargement of the superior cerebellar peduncle in both patients.

**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, stereotypes 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, normoccephaly, epilepsy, late stereotypes, preserved gait, with R294X and TRUNC293 mutations.

**Conclusion:** phenotypes of NPC2 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.

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

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**Background:** The proteolipid protein (PLP) 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. (II) 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 3 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.
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**VANISHING WHITE MATTER DISEASE (VWM): CLINICAL FEATURES, GENETIC STUDY AND EVOLUTION IN 10 CHILEAN PATIENTS.**

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**Introduction:** VWM is an autosomal recessive hereditary leukoencephalopathy, 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), 3 (n=2), 4 (n=2), 5 (n=1).

Phenotypes: late childhood/early childhood onset (7/3). Symptoms: spasticity (7/10), cerebellar ataxia (7/10). Clinical course: 3-12 years, rapidly progressive (n=8), 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.

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

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**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 on the relationship between students' academic performance and 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.

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

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Objective Early-onset epileptic encephalopathies (EEEs) is a devastating group of epilepsies which onset in the first year of life with cognitive arrest or regression, and the majority histopathologically 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 or related 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.

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

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**Aim:** To report a case of alternating hemiplegia of childhood (AHC) caused by a de novo mutation in ATP1A3 in an Ecuadorian girl. 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 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.2401G to A; D810N.

**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 functional spectrum of this disorder.

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**RET T SYNDROME,GENOTYPE-PHENOTYPE CORRELATIONS**

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**Introduction:** Rett syndrome is an X linked dominant neurological disorder that affects almost exclusively girls with an estimated prevalence of 10,000—20,000. The purpose of this study was 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 MECP2 gene (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 (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.

TOSCA - TUBEROUS SCLEROSIS REGISTRY TO INCREASE DISEASE AWARENESS
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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 and 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.

AICARDI SYNDROME IN A GENOTYPIC MALE CASE REPORT
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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 seizures by type of infantile spasms, muscle weakness, lethargy, developmental delay. Seizures debuted 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.


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

NEUROPSYCHIATRIC MANIFESTATIONS IN CHILDREN WITH 22Q11.2 MICRODELETION SYNDROME: SINGLE CENTER STUDY
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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 by Asan Medical Center Children’s Hospital between March 1996 and June 2013. Clinical data included NP and other clinical symptoms, neuropsychologic 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). Neuropsychiatric 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.
TUBEROUS SCLEROSIS COMPLEX IN PARAGUAY. REPORT OF 8 CASES.

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Introduction: Tuberous sclerosis complex (TSC), is a multisystem autosomal dominant genetic disorder, which is clinically diagnosed. The disease manifestations vary significantly among affected individuals. The main neurological symptoms are seizures, cognitive impairment, neuropsychiatric symptoms and skin lesions, hamartomas in visceral organs, renal angiomyolipomas and tumors, and subependymal nodules. The incidence varies depending on the series between 1/5000 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 of 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.

NOVEL GLRB GENE MUTATION IN A SAUDI BABY WITH HYPEREKPLEXIA

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

Discussion: Hyperekplexia (OMIM:149400, 138492 & 604159) is a rare, autosomal dominant neurological disorder that presents early in life with hypertonicity, exaggerated startle reflex.

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.

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

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OBJECTIVE: To identify the causal mutation in pellagra-like syndrome and investigate the mechanism by which nacin 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.

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

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Introduction: Mutations in the LIS1 gene contained in the lissencephaly critical region (LCR) situated in band p13.3 of the short arm of chromosome 17, have been related to multiple CNS malformations, as well as other related genes like PAFR, PAFAB1B2, PAFAB1B3, YWHAETUSCS, MYO1C, CRK, EN2, FGF8 y PAX2 (LCR-panel). Performing DNA and transcriptional studies (LCR-panel) in patients with common features likemental retardation and/or epilepsy altogether with CNS malformations, we aimed to find a closer relationship between some gene mutations and the patient’sphenotype.

Patients and 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 control group (CG). From a compulsory referential area of 33.281 children(<15 y.o.), we included 109 consecutive patients in the Study Group (SG), referred to our outpatients’ clinic of a University Hospital.

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A NOVEL VARIANT IN GABRB2 ASSOCIATED WITH INTELLIGENT DISABILITY AND EPILEPSY

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The y-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.2367T>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 GluCo 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.