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## SCIENTIFIC WORK

### Doenças neuromusculares

Code: PE010

#### Central nervous system involvement and the genotype-phenotype correlation in CMD-LAMA2

Clara Gontijo Camelo<sup>1</sup>, Mariana Cunha Artilheiro<sup>1</sup>, Cristiane Araújo Martins Moreno<sup>1</sup>, Suely Fazio Ferracioli<sup>1</sup>, André Macedo Serafim Silva<sup>1</sup>, Leandro Tavares Lucato<sup>1</sup>, Antônio José Rocha<sup>2</sup>, Umbertina Conti Reed<sup>1</sup>, Edmar Zanoteli<sup>1</sup><sup>1</sup>Universidade de São Paulo, São Paulo SP, Brazil<sup>2</sup>Universidade Federal de São Paulo, São Paulo, SP, Brazil

**Background:** Patients with LAMA2-congenital muscular dystrophy (CMD) usually present with a severe phenotype characterized by inability to achieve walking capacity, multiple joint deformities, and respiratory insufficiency. However, there is a gravity spectrum, and some patients can walk unassisted. Characteristically, the patients have white matter changes in T2-WI and FLAIR in brain magnetic resonance. More rarely, cortical changes like polymicrogyria in the temporo-occipital regions can be observed and some of these patients can manifest epilepsy and intellectual disabilities.

**Objective:** The aim of this study was to characterize central nervous system manifestations in a large cohort of CMD-LAMA2 and correlate them to genotype and motor function. **Methods:** In this observational study, 52 patients with genetically confirmed CMD-LAMA2 were included. All patients had brain MRI, and the presence of cortical malformations, epilepsy, intellectual disability was correlated to the motor function. The type and location of the LAMA2 variants were correlated to the motor function and central nervous system manifestations.

**Results:** All patients had white matter abnormalities in brain MRI, and ten of them (19.2%) presented cortical malformations (i.e. polymicrogyria, lissencephaly-pachygyria, cobblestone), seven had cerebellar cysts and white matter changes and three had temporal cysts. In addition, ten patients (19.2%) presented epilepsy and six (11.5%) had intellectual disability. Central nervous system manifestations correlated with motor function severity, and to the variants located at LG-domain ( $p=0.029$ ). The presence of cortical malformations correlated to the occurrence of epilepsy and intellectual disability ( $p=0.016$  and  $p=0.0017$ ). A higher frequency of missense, in comparison to null variants, was observed in patients able to

walk ( $p=0.037$ ) and null variants in both alleles were observed in 90% of the patients with cortical malformations.

**Conclusions:** Central nervous system manifestations are frequent among the CMD-LAMA2 patients and correlate with motor function severity and the presence of LG-domain variants in LAMA2.

Code: PE011

#### Early recognition of Duchenne muscular dystrophy: where could we improve?

Marco Antonio Veloso Albuquerque<sup>1</sup>, Karla Daniele Lima<sup>1</sup>, Edmar Zonoteli<sup>1</sup><sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Background:** Duchenne muscular dystrophy (DMD) is caused by a mutation in the dystrophin gene and is the most common form of childhood-onset muscular dystrophy affecting approximately 1 in 3500 newborn boys. The disease is invariably progressive and most patients with DMD exhibit signs of muscle weakness before 5 years of age. Loss of ability to walk usually occurs between 10 to 13 years. Despite all the advances in management and treatment of DMD over the last decades, the mean age at diagnosis of DMD has been reported to be around the age of 4.5-5 years in several countries with a delay of about 2 years between the first symptoms are noted, and the diagnosis.

**Objective:** This retrospective study had objective to investigate the age at diagnosis of disease in a group of Brazilian patients followed in a tertiary center. We compared this age with the age that the symptoms started and age that therapy with steroids initiated. We compared our results with results from other countries that helped us to understand how we can improve pathway to reach an early diagnosis in our country, highlighting its strengths and weakness.

**Methods:** Data from one hundred and twenty-two (122) boys with Duchenne muscular dystrophy (DMD) that have been followed at Outpatient Child Neurology Service for neuromuscular disorders at the Hospital das Clínicas de São Paulo for 8 years (2014-2022).

**Results:** The mean age at onset of the disease was 3,3 years (ranged from 1 to 7 years). The mean age at diagnosis was 6,9 years (range 2-16 years). Steroid therapy was initiated in 120/122 patients (prednisolone in 36/120 and deflazacort 84/120). The mean age at started treatment with steroid was 7.3 years. The mean age of lost the capacity to walk was 10 years. Intragenic deletions, accounting for 58% (71/122) of all mutations was the most common mutational event. Duplications

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accounted for 14% and 20% had a point mutation (including 12/122 with nonsense mutation). In 7 boys (5%) was found an intronic mutation and in 2 the muscle biopsy confirmed the disease.

**Conclusions:** In this group of Brazilian patients with DMD, an important delay in diagnosis was observed which led to a delay in the beginning of steroid therapy. This late onset of therapy is probably related to an earlier age of loss of capacity to walk observed. Despite the availability of access to molecular testing we still observed difficult in recognizing the disease, which may be improved with wider dosage of serum CK in patients with motor/global development delay and weakness.

#### Code: PE012

##### **Long-term follow-up of SMA type 1 treatment with Nusinersen: a single-center experience**

Rodrigo Holanda Mendonca<sup>1</sup>, Graziela Jorge Polido<sup>1</sup>, Ciro Matsui Jr<sup>1</sup>, Umbertina Conti Reed<sup>1</sup>, Edmar Zanoteli<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Departamento de Neurologia, São Paulo SP, Brazil

**Background:** Spinal muscular atrophy (SMA) is a genetic motor neuron disease caused by mutations in the SMN1 (Survival Motor Neuron) gene, which leads to hypotonia, muscle weakness and respiratory involvement. Its most severe form, SMA type 1, starts before 6 months of life and has a high mortality due to ventilatory failure. Nusinersen, the first approved treatment for SMA, is an antisense oligonucleotide for intrathecal use, which leads to greater survival and gain in motor acquisitions. Studies on the safety and efficacy of long-term treatment are still scarce.

**Objective:** To present long-term results (4 years of follow-up) in SMA type 1 patients under treatment with Nusinersen.

**Methods:** We followed a total of 24 patients, all with SMA type 1 (20 patients with 2 copies of SMN2). The patients were evaluated by the functional scale CHOP-INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) and in relation to gain of motor milestones (head control, sitting with or without support, standing and walking).

**Results:** Twelve patients were female, only 11 patients (45.8%) started treatment before 12 months of illness. 22 patients (91.6%) were already using gastrostomy at the beginning of treatment. After 4 years of follow-up, 22 (91.6%) patients were alive, two deaths occurred: one after gene therapy and the other after respiratory failure. Two patients received gene therapy but continued to use Nusinersen (combined therapy). Eight patients gained some motor milestone, all of them started treatment before 12 months disease. The greatest gains in CHOP-INTEND occurred up to 24 months of treatment, and after this period, the scores tended to stabilize, without further gains. 19 patients (79.1%) were already using PV (>16h/day) at the beginning of treatment and 15 patients were using PV after 4 years of treatment. Even in those patients who were on PV, there was a reduction in the duration of ventilation use and an improvement in the management of airway secretion.

**Conclusions:** Nusinersen showed continuous benefit over 4 years of treatment, bringing motor improvement mainly within the first 2 years of treatment and maintaining motor function acquired at 4 years. Only patients who started treatment before 12 months of illness gained some motor

milestone. No new adverse events were reported in this long-term follow-up.

#### Code: PE015

##### **ASPIRO gene replacement therapy trial with resamirigene bilparvovec in XLMTM: pathologic findings in four deceased study participants**

Kennedy Kirk<sup>1</sup>, Lawlor Michael<sup>2</sup>, Perry Shieh<sup>3</sup>, Carsten Bonnemann<sup>4</sup>, Wolfgang Müller-Felber<sup>5</sup>, Nancy Kuntz<sup>6</sup>, Weston Miller<sup>1</sup>

<sup>1</sup>Astellas Gene Therapies, San Francisco CA, United States

<sup>2</sup>Medical College of Wisconsin, Milwaukee WI, United States

<sup>3</sup>University of California, Los Angeles CA, United States

<sup>4</sup>Neuromuscular and Neurogenetic Disorders of Childhood Section, NINDS, NIH, Bethesda MD, United States

<sup>5</sup>Klinikum der Universität München, Munich, Germany

<sup>6</sup>Ann & Robert H Lurie Children's Hospital of Chicago, Chicago IL, United States

**Background:** X-linked myotubular myopathy (XLMTM) is caused by mutations in the MTM1 gene, leading to absent or dysfunctional myotubularin, respiratory failure and profound muscle weakness at birth, and early death.

**Objective:** We report the pathologic findings of 4 deceased XLMTM patients who received investigational MTM1 gene replacement therapy.

**Methods:** ASPIRO (NCT03199469) is an open-label, phase 1/2/3 randomized trial in which young boys with genetically confirmed XLMTM and chronic ventilator dependence received resamirigene bilparvovec (AT132), a single intravenous dose of adeno-associated viral (AAV) vector delivering human MTM1.

**Results:** Three of 17 participants in the higher dose (3.5x10<sup>14</sup> vg/kg) and 1 of 7 participants in the lower dose (1.3x10<sup>14</sup> vg/kg) cohort died. All 4 deceased participants had ongoing hepatobiliary cholestasis with decompensated liver disease at death. Immediate causes of death included sepsis and gastrointestinal hemorrhage. Two serial liver biopsies obtained from 1 participant demonstrated progression to liver fibrosis over the course of ~7 months. All 4 participants had histological similarities. This progressive, cholestatic disease was associated with a previously unrecognized cholestatic tendency, exposure to AT132 with mechanism of cholestatic disease exacerbation not understood, and evidence of decreased expression of bile salt export protein (BSEP) in liver tissue. Retrospective analyses of preclinical mouse and canine XLMTM models and healthy non-human primates treated with AAV8 gene transfer did not reveal evidence of cholestatic disease.

**Conclusions:** Deaths were attributable to AT132-triggered severe exacerbation of cholestatic liver disease; factors that would help predict this susceptibility remain under investigation while the ASPIRO study is currently on hold. aASPIRO Pathology Study Group: James J. Dowling, Benedikt Schoser, Marta Margeta, Hui Meng, Amanda M. Hopp, Laura Wozniak, A. Reghan Foley, Dimah N. Saade, David E. Kleiner, Esra Dikoglu, Christine Jones, Osorio Lopes Abath Neto, Astrid Blaschek, Eberhard Lurz, Susanna Mueller, Nitin R Wadhvani, Saeed Mohammad, Catherine A Chapin, Robyn C. Reed, Evelyn Hsu, Suyash Prasad, Salvador Rico, Michael Murtagh, Nathan Bachtell.

Code: PE017

### Epidemiology of acute flaccid paralysis and vaccination coverage in the pediatric population of Rio Grande do Sul State, Brazil: an analysis from 2010 to 2019

Sara Julia Zorzi de Brum<sup>1</sup>, Augusto Nicaretta<sup>2</sup>, Fabiana de Abreu Getulino<sup>3</sup>, Júlia Pustrelo Moro<sup>3</sup>, Vinicius Estanislau Albergaria<sup>1</sup>

<sup>1</sup>Universidade Federal da Fronteira Sul, Passo Fundo RS, Brazil

<sup>2</sup>Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil

<sup>3</sup>Universidade Federal do Rio Grande, Rio Grande RS, Brazil

**Background:** Acute Flaccid Paralysis or polio is a viral infectious disease that affects the motor neurons of the central nervous system and can be prevented through vaccination.

**Objective:** This study aimed to describe the number of acute flaccid paralysis cases in the pediatric population and to identify the relationship with vaccination coverage in the State of Rio Grande do Sul, Brazil.

**Methods:** An ecological study was carried out in July 2022 from the health information of the Brazilian Health Unified System databases. The analysis comprised the number of notified cases and the % of vaccination coverage from 2010 to 2019 in seven health macro-regions (Valley, South, Mountains, North, Missionary, Metropolitan, and Center-West) in the state of Rio Grande do Sul, Brazil. Descriptive statistics were performed through absolute (n) and relative (%) frequencies.

**Results:** A total of 235 cases of polio were reported, with an increase from 3 cases in 2010 to 35 in 2019. At the same period, there was a decrease in the percentage of polio vaccination coverage in the State, from 92.3% in 2010 to 83.5% in 2019. The missionary region had the lowest numbers of cases in the period (n= 8), with a percentual vaccination coverage close to 100%. The highest number of absolute cases was in the Metropolitan region (n= 124), with vaccination coverage of 86%.

**Conclusions:** We observed a relationship between the increase in polio cases and the decrease in vaccination coverage. Thus, it is necessary to seek the minimum vaccination coverage goal recommended by the World Health Organization ( $\geq 95\%$ ), guaranteeing that morbidity brought by this disease is next to zero.

Code: PE018

### Motor unit number estimation in patients with spinal muscular atrophy using the CMAP scan technique

Felipe Barbosa Magalhaes<sup>1</sup>, Rodrigo Holanda Mendonca<sup>1</sup>, Edmar Zanoteli<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Departamento de Neurologia, São Paulo SP, Brazil

**Background:** 5q-Spinal Muscular Atrophy (SMA) is one of the most prevalent neuromuscular diseases in our country, and still an important cause of lethality, due to genetic disease, in its most severe forms. From a genetic point of view, it is already known that the number of copies of the SMN2 gene drastically influences the phenotype in an inverse relationship with the severity of the disease. Several studies show the reduction of motor unit counts by different techniques. A new Motor Unit Number Estimation (MUNE) technique described in 2016 by Bostock, MScanfit (CMAP Scan MUNE), uses a mathematical model that considers the stimulus-response curve of the compound muscle action potential (CMAP) to estimate the number of motor units. Studies have shown that this technique has greater sensitivity than other conventional techniques (MUNIX and MPS), in addition to not requiring

voluntary activation, facilitating its use in children or patients with marked weakness.

**Objective:** The present study aims to evaluate the usefulness of Mscanfit in patients with SMA at the Hospital das Clínicas-FMUSP neuromuscular diseases outpatient clinic compared to other techniques (MUNIX and CMAP amplitude).

**Methods:** Forty-seven patients with SMA were evaluated, CMAP scan values were obtained with surface electrodes on the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles. MUNIX values were obtained in the same muscles, for comparison, of 40 collaborative patients for the technique. In 8 patients, the same exams were performed with one year of follow-up.

**Results:** Seven patients were SMA type 1, 25 patients were SMA type 2 and 15 were SMA type 3. Mean CMAP scan MUNE values correlated inversely with disease severity, with patients with SMA type 1 having lower values while those with patients with type 3 SMA have higher MUNE values. Among the patients who were controlled at 1 year of follow-up, only 1 patient was SMA type 1, being treated with nusinersen, and the MUNE values obtained by the CMAP scan were the same after 1 year of follow-up. The remaining seven patients who underwent the technique were SMA type 2 or 3 and the values did not differ significantly between the two exams in relation to the use or not of disease-modifying therapy.

**Conclusions:** CMAP Scan can be used to count motor units in patients with spinal muscular atrophy. More ongoing studies should assess its usefulness as a biomarker of disease progression and treatment response parameter.

Code: PE020

### Description protocol used to monitor patients treated with gene therapy

Adriana Banzatto Ortega<sup>1</sup>, Izabela Cristina Macedo Marques<sup>1</sup>, Guilherme Siqueira Gaede<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Background:** The spinal muscular atrophy (SMA) is an autosomal recessive hereditary neuromuscular disease, categorized into 4 types according to the severity. Type 2 is considered the intermediate form. There are three medication options approved by ANVISA for SMA treatment: Spinraza, Ridisplam and Zolgensma.

**Objective:** This article intends describing the protocol in terms of evaluation, infusion of gene therapy and follow-up of treated patients applied in city of Curitiba-PR.

**Methods:** Description of the examinations and evaluations performed before, during and after the infusion of Genic Therapy.

**Results:** Those patients diagnosed with SMA who will receive gene therapy undergoes blood tests two weeks prior to medicine infusion. Those are blood count, liver function, renal function, coagulograma and troponina I. To do the clinical, physical therapist and speech therapist evaluations it is recommended to patient arriving in Curitiba at least four days before the infusion. A day before the infusion undergoes evaluation in the hospital. It must be decided if the venous access will run on peripheral access (two accesses) or central access; in case of central access, there is another evaluation with the anesthesia team. Patient will be guided about the preparation and fasting at preceding day. It'll begin taking Prednisolone at 1 mg/kg/day one day before the infusion and keep it, at least, for five weeks; it should be increased to 2 mg/kg/day if transaminases increase more than ten times the transaminase reference value. It's requested weekly blood tests (blood count, coagulograma, TGO, TGP, gamma-GT, total

and fractions bilirubinas, troponina I) during next five weeks. In case those tests (mainly transaminase one) at 5th week are considered normal, it's allowed reducing Prednisolone at 0.2mg/kg/week. It must repeat all exams every other week next two months. After that period, it will take monthly exams until the 6th month after the infusion, then, exams should be taken every other month in the following four months, and, finally, exams will be taken twice a year until completing two years from starting gene therapy. If transaminase indexes are still increased at 5th week after the infusion, it should be maintained the Prednisolone dose and continue performing weekly blood tests until liver enzymes normalize, and then start withdrawal of corticoides, in the same way as described.

**Conclusions:** Present the protocol used to follow up patients with SMA treated with gene therapy in a referral service in Curitiba.

#### Code: PE024

##### **Intrathecal administration of Nusinersen in children and adolescent SMA type 1 and 2**

Michele Michelin Becker<sup>1</sup>, Lygia Ohlweiler<sup>1</sup>, Josiane Ranzan<sup>1</sup>, Hugo Leonardo Justo Horácio<sup>1</sup>, Ana Clara Bernardi Saul<sup>1</sup>, Layanna Bezerra Maciel Pereira<sup>1</sup>, Renata Yasmin Cardoso Sousa<sup>1</sup>, Dayana de Lima Mariano<sup>1</sup>, Rudimar dos Santos Riesgo<sup>1</sup>  
<sup>1</sup>Hospital de Clínicas de Porto Alegre, Porto Alegre RS, Brazil

**Background:** Spinal muscular atrophy (SMA) is an autosomal-recessive disorder resulting in progressive muscle weakness. In August 2017, the Agência Nacional de Vigilância Sanitária (ANVISA) approved the first treatment for SMA, a drug named nusinersen that is administered intrathecally. However, many patients with SMA have neuromuscular scoliosis or spinal instrumentation resulting in challenging intrathecal access. Many centers use radiological methods to guide lumbar puncture, such as ultrasound, videofluoroscopy or tomography, but these methods are often available only in referral centers.

**Objective:** The authors describe their experience as a reference center in SMA treatment with intrathecal applications of nusinersen.

**Methods:** Electronic medical record review.

**Results:** A total of 107 lumbar punctures were performed for application of nusinersen. In 12 patients with SMA type 1, 71 punctures were performed and 36 punctures in 4 patients with SMA type 2. The age of the patients ranged from 1 month to 15 years. None of the patients had previous spine fusion surgeries. Punctures were successfully performed in all patients without the need for a radiological method. Complications occurred in 6 procedures (5,6%) and the adverse events were attributed to lumbar puncture. These events were headache (n= 6), nausea (n= 2), vomit (n= 1), back pain (n= 1). Performing the analysis only with patients able to verbalize those symptoms (SMA type 1C and type 2), in a total of 46 procedures, adverse effects occurred in 13%.

**Conclusions:** The authors conclude that lumbar punctures for the application of nusinersen are feasible, safe and can be successfully performed without the aid of a radiological method, even in the presence of scoliosis.

#### Code: PE027

##### **Long term preliminary safety and efficacy outcomes for x-linked myotubular myopathy with gene replacement therapy**

Kennedy Kirk<sup>1</sup>, Nancy Kuntz<sup>2</sup>, Perry Shieh<sup>3</sup>, Julie Coats<sup>1</sup>, Cong Han<sup>4</sup>, Weston Miller<sup>5</sup>

<sup>1</sup>Astellas Gene Therapies, United States

<sup>2</sup>Ann & Robert H Lurie Children's Hospital of Chicago, Chicago IL, United States

<sup>3</sup>University of California, Los Angeles CA, United States

<sup>4</sup>Astellas Pharma Global Development, Northbrook IL, United States

<sup>5</sup>Formerly Astellas Gene Therapies, San Francisco CA United States

**Background:** XLMTM is a rare, currently untreated, life-threatening congenital myopathy caused by mutations in the MTM1 gene, with profound muscle weakness and impairment of motor development, congenital respiratory failure, and chronic ventilator dependency.

**Objective:** We report long-term safety and key efficacy outcomes (up to 42 months) for the first 6 participants dosed in the ASPIRO study.

**Methods:** ASPIRO (NCT03199469) is a phase 1/2/3 randomized, open-label study investigating the safety and efficacy of AT132 (resamirigene bilparvovec), a single-dose gene replacement therapy for ventilator-dependent XLMTM. Participants were young boys with genetically confirmed XLMTM. The first 6 participants received the lower dose 1.3 x 10<sup>14</sup> vg/kg and were compared with 15 untreated controls.

**Results:** All dosed participants were ventilator dependent at baseline and then achieved ventilator independence, with 5 remaining so. No control participants achieved this milestone. At baseline, 1/6 dosed participant was able to sit independently without support for 30 seconds and 5/6 did not have full head control. Major motor milestones were achieved in all dosed participants; 5/6 remain independently ambulatory without assistive device (Figure 1). In this cohort, 4 (67%) participants had treatment-emergent severe adverse events. Overall, deaths occurred in the higher-dose cohort (3/17) following severe decompensated liver disease, in the lower-dose cohort (1/7) following liver function test abnormalities, and in the control cohort (3/15 from aspiration pneumonia, cardiopulmonary failure, and hepatic hemorrhage with peliosis, respectively).

**Conclusions:** The substantial improvements observed must be weighed against fatal serious adverse events, for which the ASPIRO program is on clinical hold while investigations continue. Aspiro Study Group: James J. Dowling, (6) Wolfgang Müller-Felber, (7) Astrid Blaschek, (7) Carsten G. Bönnemann, (8) A. Reghan Foley, (8) Dimah N. Saade, (9) Andreea M. Seferian, (10) Laurent Servais, (11) Neema Lakshman, (1) Suyash Prasad, (5) Salvador Rico, (5) (1) Astellas Gene Therapies, San Francisco, CA, USA, (5) Formerly Astellas Gene Therapies, (6) Hospital for Sick Children, Toronto, ON, Canada; (7) Klinikum der Universität München, Munich, Germany; (8) Neuromuscular and Neurogenetic Disorders of Childhood Section, NINDS, NIH, Bethesda, MD, USA; (9) University of Iowa Hospitals and Clinics, Iowa City, IA, USA; (10) I-Motion, Institute of Myology, Paris, France; (11) MDUK Oxford Neuromuscular Centre, Oxford, UK.

**Code: PE028****Long term use of deflazacort or prednisolone in patients with Duchenne muscular dystrophy: experience at a large Brazilian center**

Marco Antonio Veloso Albuquerque<sup>1</sup>, Karlla Daniele Lima<sup>1</sup>, Raquel Diógenes Alencar Sindeaux<sup>1</sup>, Edmar Zanoteli<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Background:** Duchenne muscular dystrophy (DMD) is a severe progressive inherited neuromuscular disorder, caused by mutations in DMD gene. Although onset of disease can be observed during the first age of life, most patients exhibit signs of muscle weakness between 3 to 5 years of age and around 10-12 years of age individuals loss ambulation (LoA). Standard care treatment of DMD include the use of steroids. The two most commonly prescribed in Brazil are prednisolone and deflazacort. Use of steroids modified the natural history of the disease by slowing the progression of motor and pulmonary functional decline and extending survival.

**Objective:** Analise data of a group of 118 ambulatory and non-ambulatory Brazilian boys with DMD in steroid treatment followed in service for neuromuscular disorders at our Institution - Hospital das Clínicas of University of São Paulo, Brazil.

**Methods:** A retrospective cohort analysis 118 patients with DMD in steroid use who attended our clinic in the last 7 years (from 2016 to 2022). Treatment with steroid, prednisolone on intermittent regimen (10 days on and 10 days off) at a dose of 0,75 mg/kg/day, or deflazacort daily at a dose of 0.9 mg/kg/day was started by decision of first author. The outcomes of interest were age at last visit, age of diagnosis, age at steroid was initiated and age at loss of ambulation.

**Results:** The mean age at last clinic visit was 10,1 years. The age at onset of the disease ranged from 1 to 7 years (mean 3,3 years). The mean age at diagnosis was 7,1 years (range 2-13 years). The mean age at starting treatment with steroid was 7,3 years (range 2-14 years). Deflazacort (70%) is more common used than prednisolone (30%), but 20 patients switched prednisolone to deflazacort during follow-up due to side effects or not enough benefit. 37/118 (35,59%) of boys' loss of ambulation. In deflazacort group, LoA occurred by the age of 9.31±2.46 years; and in prednisolone group, LoA was observed at the age of 10.36±1.86 (p > 0.05), without statistical significance.

**Conclusions:** Loss of ambulation (LoA) represents a clinically meaningful milestone in DMD progression. The results of this study showed that in our center the LoA occurred at an earlier age when compared to other studies that may be related to a late diagnosis and treatment. There were no statistical differences between prednisolone or deflazacort use at age of LoA, but weight gain and lack of response to treatment seem to be more evident in patients treated with prednisolone.

**Code: PE030****Muscle ultrasound as a tool for respiratory assessment in patients with LAMA2-MD**

Clara Gontijo Camelo<sup>1</sup>, Ana Lucila Moreira<sup>1</sup>, Mariana Cunha Artilheiro<sup>1</sup>, Pedro Henrique Marte de Arruda Sampaio<sup>1</sup>, Tatiana Ribeiro Fernandes<sup>1</sup>, Cristiane Araujo Martins Moreno<sup>1</sup>, André Macedo Serafim Silva<sup>1</sup>, Umbertina Conti Reed<sup>1</sup>, Edmar Zanoteli<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, São Paulo SP, Brazil

**Background:** LAMA2-muscular dystrophy (LAMA2-MD) is an autosomal recessive disease, and the most common form of

congenital muscular dystrophy (CMD). Most of the patients develop a form of disease characterized by inability to achieve walking capacity, multiple joint deformities, respiratory insufficiency, and some degree of dysphagia. However, there is a gravity spectrum, and some patients never achieve sitting position, while others can walk unassisted. There are still no adequate biomarkers to assess disease progression, and muscle ultrasound can be a useful tool, and also complement the assessment of respiratory and swallowing function.

**Objective:** Evaluate, through muscular ultrasound, the function of the respiratory muscles, tongue muscles and correlate them with respiratory function, degree of dysphagia, disease severity and age.

**Methods:** Ten patients with genetically confirmed LAMA2-MD were divided according to motor severity and evaluated. Muscle ultrasound of tongue, respiratory and paravertebral muscles were made. For muscles comparable to bone echo, the 4-point Heckmatt scale was used, for the others the classifications were hypoechoic, slightly hyperechoic, or very hyperechoic. Patients underwent respiratory function assessment and underwent neuromuscular disease swallowing status scale (NdSSS).

**Results:** 2 patients had severe presentation and were not able to sit without support. They presented geniohyoid and genioglossus muscles very hyperechoic, had level 3 NdSSS dysphagia and required gastrostomy. They both had very affected external oblique, internal oblique and transverse muscles, but presented normal diaphragm, with normal thickening. They had altered polysomnography. 4 patients had maximum motor ability to sit without support and were under six years old. They presented geniohyoid and genioglossus muscles slightly hyperechoic, affected external oblique muscle with normal internal oblique and transverse muscles and normal diaphragm, with normal thickening. They all had total lung capacity (TLC) above 50% and level 7 NdSSS. 3 patients had classic disease presentation but were older than twelve years old. They presented geniohyoid and genioglossus muscles highly hyperechoic, affected external oblique, internal oblique and transverse muscles, with normal diaphragm, with normal thickening. They all had TLC below 35% and level 7 NdSSS.

**Conclusions:** US can be used as a tool to evaluate disease progression and contribute to the assessment of respiratory function and dysphagia in LAMA2-MD.

**Code: PE033****Hypoglycemia in patients with LAMA2-CMD**

Clara Gontijo Camelo<sup>1</sup>, Cristiane Araújo Martins Moreno<sup>1</sup>, Mariana Cunha Artilheiro<sup>1</sup>, André Macedo Serafim Silva<sup>1</sup>, Alullin Tácio Quadros Monteiro Fonseca<sup>1</sup>, Rodrigo Mendonça de Holanda<sup>1</sup>, Umbertina Conti Reed<sup>1</sup>, Edmar Zanoteli<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, São Paulo SP, Brazil

**Background:** Hypoglycemia has been reported in LAMA2-CMD patients, but the frequency, risk factors, and correlation to genotype/phenotype have not been systematically assessed to date.

**Objective:** The aim of this study was to identify the frequency of hypoglycemia in a large cohort of LAMA2-CMD patients and to correlate it with findings of phenotypes and genotypes that enhance possible risk factors and triggers.

**Methods:** A retrospective cohort study was performed on 48 patients with LAMA2-CMD. Patients were divided into 2 groups: a hypoglycemic group, with at least 1 episode of hypoglycemia, and a nonhypoglycemic group. The groups

were compared according to gait function, epilepsy, intellectual disability, constipation, gastroesophageal reflux, gastrostomy, weight percentile, scoliosis, the use of a ventilator device, the use of a feeding device, neuromuscular disease swallowing status scale, and type of mutation.

**Results:** Fifteen patients (31.2%) presented with at least 1 episode of symptomatic hypoglycemia and 8 (16.6% of the cohort) had 2 or more episodes. All patients who had hypoglycemia were in the nonambulant group. A correlation was observed between gait, the use of ventilator and feeding devices, and swallow function with hypoglycemia. Patients with extreme low weight were 5 times more likely to have recurrent episodes of hypoglycemia. The presence of at least 1 missense variant appears to be associated with a lower risk of hypoglycemia.

**Conclusions:** Patients with LAMA2-CMD are at risk of hypoglycemia. The risk is more relevant in patients with severe phenotype and patients with loss of function variants. For patients with extremely low weight, the risk is higher. Blood glucose should be actively measured in patients who are fasting or have infections, and health care providers should be prepared to identify and treat these patients.

#### Code: PE036

##### **Profile of patients diagnosed with spinal cord atrophy treated with an antisense oligonucleotide in a reference service in Minas Gerais**

Thaís de Almeida F. Fonseca Oliveira<sup>1</sup>, Laura Maria Silva Thiersch<sup>1</sup>, Renan Guimarães Santana<sup>1</sup>, Nathalia Jamille Moreira Nascimento David<sup>1</sup>, Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, Karina Soares Loufi<sup>1</sup>, André Vinicius Soares Barbosa<sup>1</sup>, Bruna Ribeiro Torres<sup>1</sup>, Ana Carolina Cardoso Diniz<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

**Background:** Spinal muscular atrophy (SMA) is a disorder caused by homozygous loss of function of the SMN1 gene. This gene produces the survival motor neuron (SMN) protein, which is important in motor neuron homeostasis. The SMN2 gene has homology with SMN1, but only expresses 10% functional full-length SMN protein. The treatment available in the Brazilian public health system is Nusinersen, an antisense oligonucleotide that increases the proportion of functional SMN2 protein.

**Objective:** The aim of this study was to analyze the profile of patients with SMA treated with Nusinersen in a reference service in Minas Gerais.

**Methods:** We conducted a database analysis of patients with SMA followed up between 2020 and 2022.

**Results:** We analyzed the information from 33 patients who were candidates for receiving Nusinersen at our service. The criterias used were established by the Clinical Protocols and Therapeutic Guidelines (CPTG) from Brazilian Ministry of Health published in 2019. The refusals were made for cases that did not meet the criterias, such as permanent invasive ventilatory support, severe contractures or scoliosis and subtypes 0, 2, 3 or 4. Treatment was indicated for 20 patients. Among these, 15% were later excluded due to 1 death, 1 case of clinical worsening, 1 loss of follow-up and 4 changes of treatment to gene therapy. 14 patients received the first 4 doses in our service, whose ages ranged from 2,5 to 29 months with a mean of 10,3 months. 4 patients received it in another service through judicialization, before the medicine became available in the health system. The average time between the molecular diagnosis and the beginning of the treatment after the implementation of CPTG was 89,7 days.

The Chop Intend motor scale implementation was impaired by COVID19 pandemic and patient's respiratory complications. However, it was used to follow up 6 patients, which had, 6 months after the first dose, a mean increment of 11.1 points, ranging from 6 to 22 points. Among these, 4 patients got a mean gain of 16 points at the 1-year evaluation and 1 patient achieved a maximum score at the 2 years follow up. Until now, the total number of Nusinersen's doses administered was 89 and there were no side effects reported.

**Conclusions:** The new treatments are modifying the clinical course of SMA. However, it is important to reduce the time between diagnosis and treatment to optimize results.

#### Code: PE044

##### **Treatment with Ataluren in seven brazilian boys with Duchenne muscular dystrophy (DMD) caused by nonsense mutation: real-world experience**

Marco Antonio Veloso Albuquerque<sup>1</sup>, Karlla Daniele Ferreira Lima<sup>1</sup>, Raquel Diogenes Alencar Sindeaux<sup>1</sup>, Edmar Zanoteli<sup>1</sup>  
<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Background:** Duchenne muscular dystrophy (DMD) is an inherited genetic disorder caused by a mutation in the dystrophin gene that results in progressive skeletal, respiratory and cardiac muscle weakness that ultimately leads to loss of ambulation as well as respiratory and heart failure. About 13% of DMD cases are caused by point mutations leading to premature stop codon (nmDMD). Ataluren was approved in Brazil for treatment of nmDMD, but both the efficacy and safety have been previously reported from clinical trials and few reports exists about real experience.

**Objective:** Report our experience in seven boys with DMD caused by nonsense mutation, confirmed by molecular test. All patients are in treatment with Ataluren, that was initiated in ambulatory stage and are in following in the Outpatient Child Neurology Service for neuromuscular disorders at our Institution.

**Methods:** Clinical data from these 7 patients included were: age at the last visit, age at first symptoms and at diagnosis. We analyzed age that steroid and Ataluren therapy was initiated. Muscle strength, cardiac and pulmonar function tests were performed immediately before the onset of the treatment with Ataluren and at the last visit.

**Results:** The mean age at last visit was 10,8 years (ranged 8 to 16 years). The first symptoms appeared in mean at 2,7 years (ranged from 1 to 5 years). The mean age at diagnosis was 7,6 years (range 5-9 years). Therapy with deflazacort was started in all patients, at mean age 7,9 years. After one year (case 5,6 e 7), two years (cases 2 and 3), three years (case 1) and 5 years (case 4) of treatment with Ataluren, it was observed a stabilization in the muscular strength in patient 3 and 7 and a slight improvement in patients 2 and 5. Three patients (case 1, 4 and 6) lost ability to walk at 9, 10 and 11 years, respectively; In addition, CVF in repeated pulmonary function tests showed no changes in all boys. On cardiac function, two boys (cases 3 and 4) showed worsening on ejection fraction (EF) on echocardiography repeated tests. In the other boys the cardiac function remained stable during the follow-up. Side effects are not related by parents.

**Conclusions:** Even considering the reduced number of patients in our study, we concluded that treatment with Ataluren might ameliorate the clinical course of the disease, but the response depends on the patient's age and disease severity when therapy is initiated. We suggest that treatment should be initiated as soon as the diagnosis is confirmed.

## Epilepsias

Code: PE047

### Tuberous sclerosis complex and west syndrome: an assessment of cognitive aspects

Patrícia do Rocio Litça<sup>1</sup>, Luísa Teixeira dos Santos<sup>1</sup>, Angel Miriade<sup>1</sup>, Laís Faria Masulk Cardozo<sup>2</sup>, Sérgio Antonio Antoniuk<sup>2</sup>, Ana Paula Almeida de Pereira<sup>2</sup>, Ana Chrystina de Souza Crippa<sup>2</sup>

<sup>1</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>2</sup>Universidade Federal do Paraná, Complexo Hospital de Clínicas, Curitiba PR, Brazil

**Background:** Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the development of benign tumors in multiple organs and tissues, especially in the brain, kidneys, heart, lungs, and skin. Brain lesions are frequently associated with cognitive deficits, neuropsychiatric disorders, learning disabilities, and seizures. Seizures occur in approximately 80% of patients and 30% to 60% of them had West Syndrome (WS).

**Objective:** The aim of the present study was to explore and describe cognitive development differences between patients with and without West Syndrome diagnosis. All of them had clinical or genetic diagnosis of TSC.

**Methods:** A sample consisting of 39 patients, from 6 to 27 years of age, answered the neuropsychological assessment. Group A, 10 of them (25,6%) had a history of WS and Group B, 29 of them without WS. Participants were assessed by the Wechsler Intelligence Scale for Children (WISC-IV) or the Wechsler Adult Intelligence Scale (WAIS-III). Data were analyzed using density graphs.

**Results:** There were not significant differences between groups regarding total IQ, verbal comprehension, perceptual organization, and working memory indexes. The processing speed index showed significant differences between groups, with an index of 60 to 80 on most of the participants with TSC and WS, and 80 to 100 on patients with TSC only.

**Conclusions:** The study showed a significant impact on processing speed index on patients with TSC associated with WS. Given that there weren't significant differences between groups regarding the other indexes assessed. The impact on those may be caused by TSC in general, without specific influence by WS. A more in-depth study on processing speed in patients with TSC associated with WS is needed, with investigation of other variables, such as treatment modalities. Considering the developmental impact of WS, it is important to identify and control seizures and infantile spasms in early childhood, avoiding lifetime impacts on cognition as shown by these results.

Code: PE048

### A Brazilian ACTH therapy protocol for west syndrome in environmental treatment

Luciana de Paula Souza<sup>1</sup>, Giovana Memari Pavanelli<sup>1</sup>, Danielle Caldas Bufara Rodrigues<sup>1</sup>, Ana Chrystina de Souza Crippa<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Complexo Hospital de Clínicas, Curitiba PR, Brazil

**Background:** West syndrome (WS) is an epileptic encephalopathy characterized by epileptic spasms, neurodevelopment delay, and hypsarrhythmia on electroencephalography. Infantile spasms have an incidence of about 0.43 per 1000 livebirths and occur between 3 and 12 months of age. The drug's choice is the adrenocorticotrophic hormone (ACTH), with varied response rates and limited efficacy data, relapses, and evolution

to other kinds of seizures in the medium-long term in our country.

**Objective:** This study aims to evaluate the effectiveness of ACTH therapy after failure of vigabatrin in patients with West syndrome.

**Methods:** This retrospective cohort study included WS children from two Neuropediatric ambulatories, aged 2-144 months, treated with synthetic ACTH from 2001 to 2021, that failed with therapeutic doses of vigabatrin. The primary outcome was efficacy on the 7<sup>th</sup> and 30<sup>th</sup> days; secondarily, we registered the relapse rates of hormonal therapy during one year of follow-up.

**Results:** Of 41 patients selected to study, 2 had severe ACTH side effects, and 39 made up the sample. Sixty-eight percent were male, with 87% symptomatic WS presentation. The median of spasms onset, ACTH lag to treat, and VGB dose was 6, 5, and 12 months, respectively. On the 7<sup>th</sup> and 30<sup>th</sup> days, 46,1% and 94,8% had a favorable clinical-electroencephalographic resolution with the drug. Although without statistical significance, the study showed that the favorable clinical response was not associated with the form of WS presentation, etiology, history of other types of seizures, coexistence of two or more diseases, previous diagnosis of epilepsy or gender. Female gender, symptomatic etiology and diagnosis of epilepsy before WS increased the probability of an unfavorable outcome one month after the end of ACTH. The diagnosis of prenatal or perinatal injury also increased the chances of an unfavorable outcome, although these results were not statistically significant.

**Conclusions:** Our data corroborate the higher rates of ACTH therapy efficacy after vigabatrin failure in West syndrome. Also, we demonstrated minor relapse rates compared to ACTH results, attributed to their higher doses.

Code: PE049

### ACTH versus corticosteroid in infantile spasms: a literature review

Saulo Bueno de Azeredo<sup>1</sup>, Eduarda Vogel Wollmeister<sup>1</sup>, Lucas Lizot Pozzobon<sup>1</sup>, Maria Fernanda Guadagnin<sup>1</sup>, Martina Estacia Da Cas<sup>1</sup>, Gabriel Soccol Fassina<sup>1</sup>, Valéria Tessaro Grandi<sup>1</sup>, Nicolle Surkamp<sup>1</sup>, Marcos Vinicius Dalla Lana<sup>1</sup>

<sup>1</sup>Universidade de Passo Fundo, Passo Fundo RS, Brazil

**Background:** Infantile spasms (IS) represent an age-specific epileptic disorder of infancy and early childhood. Children with infantile spasms typically exhibit epileptic spasms along with the electroencephalographic (EEG) pattern known as roceededica. Although rare, 1.6 to 4.5 per 10,000 live births, IS is a significant disorder because of the association with developmental delay or regression, high mortality rate, refractoriness to conventional antiseizure medications, and responsiveness to hormonal therapy. Genetic variants and acquired factors such as hypoxic-ischemic injury, infections, and structural abnormalities of the brain, are some of the insults that are associated with IS.

**Objective:** To summarize the knowledge about corticotropin (ACTH) and corticosteroid in IS available in the literature.

**Methods:** We performed a literature review using PUBMED and SCIELO search engines up to August 2022 with the terms (infantile spasms) AND (corticosteroid) OR (ACTH).

**Results:** The ACTH formulation is the classical treatment for IS given intramuscularly or subcutaneously. Several meta-analyses of randomized trials comparing the effectiveness of ACTH with oral glucocorticoids have found no difference between the two forms of hormonal treatment for outcomes including cessation of IS, roceededica resolution, adverse effects, relapse rate, or subsequent development of epilepsy. Data from the National Infantile Spasms Consortium

prospective multicenter cohort study also support corticotropin and oral glucocorticoids as effective first-line treatments. Of note, conclusions have been limited by the overall poor methodology and small size of most of the available clinical trials and studies. Lack of adherence to standardized case definitions and outcome measures is one problem with many studies. Another is that inclusion of a control group is critical, as the natural history of the disease is that clinical spasms subside and EEG patterns evolve without therapy, yet many clinicians would be reluctant not to treat, particularly since observational data showed that delayed therapy may worsen prognosis. As a result, questions remain regarding the optimal drug, dose, and duration of therapy.

**Conclusions:** Given the advent of data that have suggested, but not proven, that high-dose prednisolone regimens are as effective as ACTH and given considerable reduction in the cost of treatment and ease of administration with oral glucocorticoids, some centers are now using oral glucocorticoids as initial therapy for IS.

### Code: PE053

#### **Rasmussen Encephalitis: drug treatments and results after surgery followed up in a large medical center in Brazil**

Ana Cristina Azevedo Leão<sup>1</sup>, Nicholas dos Santos Barros<sup>1</sup>, Clarice Semião Coimbra<sup>1</sup>, Rafaela Fernandes Dantas<sup>1</sup>, Roberta Diniz De Almeida<sup>1</sup>, Cristiani Rocha Lima Cruz<sup>1</sup>, Joemir Brito<sup>1</sup>, Maria Luiza Giralde Manreza<sup>1</sup>, Letícia Pereira de Brito Sampaio<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Background:** Rasmussen Encephalitis is characterized by epilepsia partialis continua, hemiparesis, cognitive decline and progressive cerebral hemiatrophy<sup>1</sup>. The typical form begins before age 10 and is divided into three phases: prodromal, acute, and residual. The most accepted cause is autoimmunity<sup>3</sup>.

**Objective:** The present study aims to evaluate the epidemiological profile of patients with Rasmussen Encephalitis undergoing hemispherectomy surgery and the outcome of epileptic seizures.

**Methods:** Eighteen patients' medical records were evaluated between the years 2014 and 2022. Children treated at the Hospital das Clínicas da Universidade de São Paulo who met the criteria for Rasmussen Encephalitis were included, totaling 12 children who underwent hemispherectomy surgery.

**Results:** The disease started at age 5.9. Epilepsy was the first symptom in 91% (n.11) except for hemiparesis in one participant. Progressively all developed severe and refractory seizures. epilepsia partialis continua were present at 50% (n. 6). All children had focal motor seizures (between tonic and clonic seizures). Second generalized seizures occurred in 25% and segmental myoclonic seizures in 8.3% (n.1). Evolutionarily, cognitive decline was observed 83.3% (n.10), hemiparesis 75% (n.9), behavioral changes in 16.7% (n.2), language alterations 16.7% (n.2) and psychiatric symptoms in 8.3% (n.1). On resonance, progressive brain hemiatrophy was observed (100%). In the electroencephalogram, focal epileptiform activity was unanimous, multifocal activities were progressively confined to one hemisphere in 16.7% (n.2), and in one patient (8.3%) had bilateral activity. Half of the participants underwent cerebrospinal fluid analysis, being normal in 41.7% (n.5), oligoclonal bands were observed in one (8.3%). Immunotherapies were the primary strategy, being Intravenous Immunoglobulin isolated in 25% (n.3) and 33.3%

(n.4) pulse therapy with Methylprednisolone, and dual therapy 25% (n.3). Two did not use any modality 16.7%. After surgery, 75% (n. 9) had seizure resolution, 16.7% (n. 2) had reduction, and 1 (8.3%) maintained electrographic seizures. Postoperatively, Topiramate, Clobazam (58.3%), and Carbamazepine (33.3%) were maintained, and 25% (n.3) were not taking any medication.

**Conclusions:** The data obtained in this study are similar to the literature<sup>1,4</sup> on the development of the epilepsy<sup>5</sup> and the symptoms of the various stages of the disease<sup>4</sup>. Surgery is a curative treatment for seizures<sup>1</sup>, and children who have undergone surgery show a good response.

### Code: PE054

#### **Comparison between epilepsy hospitalization of Brazilian adult and pediatric patients in Brazil during the last decade** Isabelle Diniz Melo<sup>1</sup>, Luciano de Albuquerque Mota<sup>1</sup>, Deniele Bezerra Lós<sup>1</sup>

<sup>1</sup>Universidade Federal do Ceará, Fortaleza CE, Brazil

**Background:** Epilepsy is characterized by a persistent predisposition of the brain to generate epileptic seizures, due to abnormal neuronal activity reflected as involuntary muscle movement. This disturbance may lead to important hospital admissions, which differ in prevalence based on distinct age groups.

**Objective:** To compare the prevalence of epilepsy hospital admissions between pediatric (0-19 years old) and adult patients (20-59 years old) among the Brazilian regions in a decade (2012-2021).

**Methods:** Epidemiological, retrospective, descriptive study, carried out with data obtained from the Mortality Information System (SIM/SUS) and the Brazilian Institute of Geography and Statistics (IBGE). From these, the number of hospitalizations per million (pm) people of each Brazilian region per year of the period was calculated.

**Results:** In 2012, the national rate of epilepsy hospitalizations per million of patients from 0 to 59 years was 232.06, with the Southern Region having the most hospitalizations (346.61) pm and the Northern, the least (149.56). That year, pediatric patients represented 54% of hospital admissions, having 345.8 cases pm within that group. The adult group, representing 46% of hospital admissions, had 166.67 pm. At the end of the period, in 2021, the national rate of epilepsy hospitalizations pm was 236.30 (an increase of 1.82%). However, the pediatric group had an increment of 15.9% in admissions (ending with 401.03 cases pm), while the adult group rate decreased by 6.3% (ending with 156.15 cases pm). For the pediatric group, the Northeastern region had an increase of 84.4% in admissions, presenting the highest expansion, while the Southern had a decrease of 8.4%. The adults had similar results, with the Northeastern admissions increasing by 31.2% and the Southern decreasing by 19%. During the decade, the prevalence ratio between the pediatric and adult groups ranged from 2.07 to 2.57 (a 23.8% increase).

**Conclusions:** This analysis allowed a comparison of epilepsy hospital admissions rates of the proceeded pediatric and adult population from 2012 to 2021. Although the increase in hospitalizations was small, there was an important rise in the pediatric group, especially in the Northeastern region, while the general ratio of cases in the adult group decreased. The conservation of the prevalence ratio in the 2.07-2.57 range allows the conclusion that the prevalence of



pediatric epilepsy hospitalizations is 2 times higher than the adult.

Code: PE062

**Getting to know the needs of caregivers of children and adolescents with epilepsy for the development of technological tool**

Clarissa Ferraz Rodrigues<sup>1</sup>, Gabriel Rodrigues<sup>1</sup>, Thiago Minossi Oliboni<sup>1</sup>, Roberta Folgieri<sup>1</sup>, Raissa Kalsing<sup>1</sup>, Magda Lahorgue Nunes<sup>1</sup>

<sup>1</sup>Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre RS, Brazil

**Background:** Epilepsy is a chronic disease characterized by the occurrence of recurrent non provoked epileptic seizures. This condition affects the quality of life of those affected as well as their caregivers' not only by the disease itself but also because of comorbidity. It requires daily care and continuous use of anti seizure medication at specific times of the day.

**Objective:** To develop a technological tool to help the planning of the daily routine of children and adolescents with epilepsy.

**Methods:** This is a cross-sectional research. The data was collected remotely through Qualtrics platform. The participants had access to the informed consent form in advance of responding the questionnaire. The sample of participants was composed by caregivers of children ranging from 0-17 years old diagnosed with epilepsy, and the recruitment happened through social media and epilepsy outpatient clinics. The questionnaire was made of 55 questions that approached the knowledge, perceptions and habits of the caregivers as to the daily basis of the child. There were also questions about the use of technologies that helped in the management of the disease.

**Results:** A total of 100 people accessed the questionnaire, from which only 46 answered it thoroughly. From the 46 respondents, 100% affirmed having the habit of using cell phones, 32,61% answered that the child they care for is on monotherapy and 56,52% reported that they use alarms to remember to give the medication. The orientation to record ictal events to help characterize seizures was given, by doctors, to 89,36% of the sample, yet 40% reported finding trouble keeping the recordings. Also, 66% of the respondents think they don't have clear information about the child's condition or treatment.

**Conclusions:** Epilepsy is a condition that interferes in physiological and social ways. Considering such impact in the quality of life of both patient and caregiver, it is believed that the development of an app that carries information about the disease and tools to organize the daily routine of these people will be of great value.

Code: PE069

**Prevalence of use of teratogenic antiepileptic drugs in female patients referred to the transition ambulatory of epilepsy**

Ana Carolina Jorge Fogolin<sup>1</sup>, Helen Ramos Vasconcelos<sup>1</sup>, Michelle Basso Couto Gouvêa<sup>1</sup>, Iris do Vale Miranda<sup>1</sup>, Isadora Cavalcante Olímpio de Melo<sup>1</sup>, Paula Luísa Lopes Schell<sup>1</sup>, Daniela Fontes Bezerra<sup>1</sup>, Rubens Wajnsztein<sup>1</sup>

<sup>1</sup>Faculdade de Medicina do ABC, Santo André SP, Brazil

**Background:** Adolescents diagnosed with epilepsy are patients who need specific care, especially girls of childbearing age. Considering that two of the main antiepileptic medications can have teratogenic effects, it is extremely

important that these patients receive adequate guidance in their process of maturation and introduction to adulthood, without prejudice to seizure control.

**Objective:** To analyze the prevalence of the use of sodium valproate and carbamazepine in female patients of childbearing age diagnosed with epilepsy.

**Methods:** This work is a cross-sectional study in which a survey was carried out of the medical records of the Transition Ambulatory of Epilepsy, in the first half of 2022, of female patients with epilepsy referred from external and internal services.

**Results:** Were identified 16 medical records of female patients, between 12 and 18 years old, with epilepsy undergoing pharmacological treatment. After multivariate analysis, it was found that 50% of these patients were using teratogenic antiepileptic medication.

**Conclusions:** Adolescents with epilepsy constitute a distinct group with physical, psychological and social needs, significantly different from those of adolescents without comorbidities. As a result, they need special attention, mainly young people of childbearing age. Therefore, the Transition Ambulatory of Epilepsy is crucial for these patients throughout their maturation process, in favor of adopting the best therapy, according to their needs and reducing future risks.

Code: PE071

**Relevance of the transition ambulatory of epilepsy**

Iris do Vale Miranda<sup>1</sup>, Paula Luísa Lopes Schell<sup>1</sup>, Isadora Cavalcante Olímpio de Melo<sup>1</sup>, Michelle Basso Couto Gouvêa<sup>1</sup>, Ana Carolina Jorge Fogolin<sup>1</sup>, Helen Ramos Vasconcelos<sup>1</sup>, Daniela Fontes Bezerra<sup>1</sup>, Rubens Wajnsztein<sup>1</sup>

<sup>1</sup>Faculdade de Medicina do ABC, Santo André SP, Brazil

**Background:** Epilepsy is a chronic condition that affects a considerable portion of the population, being one of the most frequent neurological diseases. The high incidence and the losses proceeded from low seizure control, lead to the need to know the peculiarities of epilepsy in order to promote adequate intervention to the patient in transition. Epileptic patients end their childhood and become adolescents and adults with the disease. Therefore, the purpose of the Transition Ambulatory of Epilepsy is to help the patient to gradually assume responsibility for their treatment, assist in the autonomy process and ensure adherence to medical follow-up. Approaches to professions, relationships, habits and addictions are present in the routine of this clinic. These patients need a structured transition plan so that, when responsible for their self-care, they can succeed in the continuity of crisis control.

**Objective:** The objective of this work is to present the relevance of the Transition Ambulatory of Epilepsy. Through knowledge of this, it can be implemented in other services, expanding the specific care for adolescents who need a differentiated approach to their disease.

**Methods:** This work is a cross-sectional study in progress, in which an analysis of medical records is performed based on consultations and a specific questionnaire, which assesses independence from self-medication, knowledge of the disease and the impact on their activities, daily routines and life planning. This questionnaire is applied to the patient and his/her responsible, focusing on their chronic disease, during the first medical consultation and reapplied after 12 months of follow-up. During follow-up, adolescents between 12 and 18 years of age are seen separately from their parents, and then together.

**Results:** Although still in progress, it is already possible to observe that the analyzed patients, when starting specific follow-up, presented better conditions to grow and evolve in all the proposed aspects. Autonomy in care, mastery over the disease, as well as adherence to treatment, became a shared responsibility with patient participation in decision-making. **Conclusions:** Transition Ambulatory of Epilepsy has impacted, directly and indirectly, on the quality life of the patient and his family, contributing to a functional and productive life, becoming crucial for the introduction of the patient to independence.

#### Code: PE075

##### **The first unprovoked seizure in children from a reference tertiary care center in Paraná, Brazil**

Patrícia do Rocio Litça<sup>1</sup>, Mariana Yamamoto Wollmann<sup>1</sup>, Sérgio Antonio Antoniuk, Ana Chrystina de Souza Crippa<sup>2</sup>

<sup>1</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>2</sup>Universidade Federal do Paraná, Complexo Hospital de Clínicas, Curitiba PR, Brazil

**Background:** A seizure occurs as result of a sudden and transitory abnormal electrical brain activity, that causes a variety of changes on behavior, movements and level of consciousness. After a first unprovoked seizure, the risk of recurrence in the three following years varies from 23 to 71%. The recurrence of a seizure after more than 24 hours after the first defines the diagnosis of Epilepsy, which has numerous biological, cognitive, psychological and social consequences. **Objective:** Given this scenario, the objective of the present study is to describe the profile of the pediatric patients with a first unprovoked seizure in an outpatient tertiary reference care center in Paraná, Brazil.

**Methods:** A total of 33 children, ages 3 months to 14 years old, followed-up for a first unprovoked seizure at a reference tertiary care center from 2009 to 2019 were included in this study. Data were obtained from the first 18 months of follow-up, through the patients' medical records. The characteristics examined were gender; age at the first seizure; family history of epilepsy and/or seizures; seizure type; abnormalities in electroencephalogram (EEG), head computed tomography (CT) and head magnetic resonance imaging (MRI); use of antiepileptic medication after the first seizure and which medication was used.

**Results:** Out of the 33 patients, 23 were male and 10 female; 39% were 5-10 years old at the time of the first seizure and 39% were 10-15 years old; 27% have positive first-degree family history of epilepsy and/or seizures. As for the seizure type, 65% had focal onset and 32% generalized onset. Regarding EEG and head scans abnormalities, 97% had an EEG, of which 45% had epileptiform abnormalities; 97% performed at least one head scan, of which 10% presented abnormalities either in head-CT or head-MRI. Antiepileptic medication was used in 94% of the patients at follow-up; 53% used carbamazepine, 19% valproic acid, 13% phenobarbital, 9% oxcarbazepine, 3% clobazam, and 3% more than one medication.

**Conclusions:** This study provides a comprehensive description of the profile of children with a first unprovoked seizure in a reference tertiary care center in Southern Brazil. For a more accurate epidemiological examination of this population, as well as evaluation of recurrence and risk factors for recurrence, prospective studies with a longer follow-up period are needed.

#### Code: PE078

##### **Use of Cannabidiol in pediatric patients with refractory epilepsy of different etiologies**

Isadora Cristina Barbosa Lopes<sup>1</sup>, Mariane Wehmuth Furlan Eulalio<sup>1</sup>, Ana Clarice Bartosiewicz Prestes<sup>1</sup>, Melanie Scarlet Díaz Solano<sup>1</sup>, Eduarda de Boer Furstenberger<sup>1</sup>, Carolina Oliveira de Paulo<sup>1</sup>, José Antônio Coba Lacle<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>

<sup>1</sup>Hospital Universitário Evangélico Mackenzie, Curitiba PR, Brazil

**Background:** Cannabidiol (CBD) is a non-psychoactive substance of Cannabis sativa effective in refractory epilepsy due to Dravet syndrome, Lennox-Gastaut syndrome and Tuberous Sclerosis Complex, with few studies in other etiologies. There are studies that show benefit in the mutual use of clobazam and CBD.

**Objective:** To analyze the response of pediatric refractory epilepsy of different etiologies after CBD introduction.

**Methods:** Analysis of data from medical records using measures of central tendency and dispersion (average and standard deviation) and Student's T-test.

**Results:** In a total of 5 patients, 3 have Doose syndrome, 1 has Miller-Dieker syndrome and 1 has epileptic encephalopathy of unclear etiology, the last 2 with cerebral palsy (CP). Age at CBD introduction was 3±1.9 years. Time of use in months of 9±5. Total anticonvulsants in optimized dose of 3±1, all patients using clobazam in association. Dosage of CBD in mg/kg/day of 11.6±11.1. Maximum number of daily crises before was 28±15 and after 2±1.2, with p < 0.05 (0.002). Number of admissions before of introduction was 2.4±0.9 and after 0.8±0.9, with p < 0.05 (0.03). There was an improvement in development in children with Doose syndrome and in social interaction in the children with CP. Reduction of other medications possible in 2 of the patients. One patient had memory impairment, with no other identified side effects.

**Conclusions:** CBD in pediatric refractory epilepsy needs more studies in different kinds of etiologies. This study suggests that there is benefit in controlling the number of seizures and reduction of hospitalizations, also improving quality of life. The association of clobazam and CBD is encouraged by the literature, which is a combination used in all patients in this study.

#### Erros inatos do metabolismo

#### Code: PE081

##### **Unraveling phenotypes in Brazilian patients with cutaneous porphyrias: the impact of next generation sequencing with a targeted gene panel**

Charles Marques Lourenço<sup>1</sup>, Lilian Sansão<sup>1</sup>, Jordana Bueno<sup>1</sup>, Renan Campi Gomes<sup>1</sup>, Debora Tomaz<sup>1</sup>, Regina Albuquerque<sup>1</sup>, Jacqueline Harouche Rodrigues Fonseca<sup>2</sup>, Amadeu Jose Rodrigues Queiroz<sup>1</sup>, Ieda Bussmann<sup>3</sup>

<sup>1</sup>Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto SP, Brazil

<sup>2</sup>DLE, Bioquímica, Rio de Janeiro RJ, Brazil

<sup>3</sup>Associação Brasileira de Porfirias, Curitiba PR, Brazil

**Background:** Cutaneous porphyrias are a heterogeneous group of both acquired and genetic disorders whose diagnosis rely on clinical features and specific biochemical testing. In Brazil, biochemical testing for acute porphyrias become more accessible in the last years, nevertheless the same was not seen for cutaneous porphyrias, so most of the key laboratory testing are performed only abroad, increasing the costs for analysis. In this context, Next Generation Sequencing (NGS)

became an important tool in the investigation of patients with genetic cutaneous porphyrias.

**Objective:** To report the findings of a genetic comprehensive analysis performed in Brazilian patients with clinical and/or biochemical features of cutaneous porphyrias.

**Methods:** Prospective data of 50 Brazilian patients with suspicion of a genetic cutaneous porphyria were collected by a national referral center for rare diseases over a 2-year period. Extracted DNA samples were analyzed using a short-read next-generation sequencing gene panel.

**Results:** Mutations were identified in 45 patients. All patients with clinical features of erythropoietic protoporphyria (EPP) showed a FECH mutation on one allele trans to a hypomorphic FECH IVS3-48C allele, being classified as having pseudodominant EPP. No compound heterozygotes (recessive EPP) neither ALAS2 mutations were identified in our patients. Biallelic UROS mutations were present in three unrelated patients with features of Congenital Erythropoietic Porphyria (CEP). No UROD mutations were found in 3 patients with a strong family history for Porphyria Cutanea Tarda (PPOX and CPOX mutations were not identified as well). Two pediatric patients born to unrelated families showed biallelic mutations in UROD gene, confirming the diagnosis of hepatoerythropoietic porphyria (HEP) – one of the patients had a previous diagnosis of CEP and was referred for bone marrow transplant that was put on hold after the genetic diagnosis.

**Conclusions:** This is the first report describing genetic variants for all cutaneous porphyrias in a sample of Brazilian patients. A genetic diagnosis allowed not only family genetic counseling but also changes in the management of patients whose clinical features could overlap, such as HEP and attenuated CEP patients. Our results also suggest that a comprehensive clinical history and physical exam can better guide the genetic testing, avoiding unnecessary and expensive laboratory tests which many times become a barrier to families in the pursuit of a rare disease diagnosis.

Code: PE085

#### Next generation sequencing in the diagnosis of Acute Hepatic Porphyrias (AHP): unraveling the molecular basis of AHP in Brazilian patients

Charles Marques Lourenço<sup>1</sup>, Jordana Bueno<sup>1</sup>, Lilian Sansao<sup>1</sup>, Amanda Selvatici<sup>1</sup>, Renan Campi<sup>1</sup>, Debora Tomaz<sup>1</sup>, Regina Albuquerque<sup>1</sup>, Amadeu José Rodrigues Queiroz<sup>1</sup>, Ieda Bussmann<sup>2</sup>

<sup>1</sup>Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto SP, Brazil

<sup>2</sup>Associação Brasileira de Porfirias, Curitiba PR, Brazil

**Background:** In Brazil, analyses of clinical and laboratory features of patients with acute porphyrias are until recently limited to biochemical testing since genetic testing was expensive and not covered by national health system neither private insurance. In partnership with Brazilian Porphyria Association (ABRAPO), during February 2020 until March 2022, genetic testing was offered to patients registered in the patient's database to better allow a specific diagnosis for the families.

**Objective:** To report the findings of a genetic comprehensive analysis performed in Brazilian patients with clinical and/or biochemical features of acute porphyrias.

**Methods:** Individuals aged  $\geq 16$  years from a Brazilian national referral center for porphyrias with a suspected diagnosis or a confirmed history of AHP that underwent genetic testing via ABRAPO between February 2020 and March 2022 were included. Extracted DNA samples from saliva and buccal

swabs were analyzed using a short-read next-generation sequencing gene panel.

**Results:** Overall, of the 122 unrelated individuals referred for AHP molecular diagnostic testing, 80 had an AHP mutation. Although most mutations identified were in hydroxymethylbilane synthase gene (HMBS n= 43), there was an unexpected great number of pathogenic variants in protoporphyrinogen oxidase (PPOX n= 31) in patients with a previous biochemical diagnosis of Acute Intermittent Porphyria (AIP). Just one heterozygous variant in ALAD gene was seen in our cohort in a patient with a pathogenic mutation in PPOX gene. Of the 250 family members of mutation-positive individuals tested for an autosomal dominant AHP, 104 (46.8%) had their respective family mutation. All patients with documented increase in aminolevulinic acid and porphobilinogen had a confirmed molecular diagnosis of AHP.

**Conclusions:** This is the first report describing genetic variants for all four acute porphyrias in Brazilian individuals under AHP investigation. It was worthy of note that a high number of cases of VP was identified with PPOX mutations, being a frequent cause of AHP in our population. These data expand the molecular genetic heterogeneity of the AHP and document the usefulness of molecular testing to confirm the positive biochemical findings in symptomatic patients and identify at-risk asymptomatic family members. A correct genetic diagnosis allows not only better understanding of such disorders but also genetic counseling for affected and at-risk individuals.

Code: PE086

#### Difficulties in treating CLN2 through enzyme replacement therapy

Erlane Marques Ribeiro<sup>1</sup>, Aline Campos Fontenele Rodrigues<sup>2</sup>, Raffaella Neves Mont'Alverne Napoleão<sup>3</sup>, Mariana de Souza Rocha Teixeira<sup>3</sup>, Beatriz Esmeraldo Teixeira<sup>3</sup>, Ester Mara Rodrigues Freire<sup>3</sup>, Rosicler Pereira de Gois<sup>1</sup>, Tamiris Carneiro Mariano<sup>1</sup>, André Luiz Santos Pessoa<sup>1</sup>

<sup>1</sup>Hospital Infantil Albert Sabin, Fortaleza CE, Brazil

<sup>2</sup>Universidade Estadual do Ceará, Fortaleza CE, Brazil

<sup>3</sup>Unichristus, Fortaleza CE, Brazil

**Background:** Neuronal ceroid lipofuscinosis type 2 (CLN2) is a neurometabolic disease whose treatment consists of enzyme replacement therapy (ERT) performed through a syringe pump connected to a catheter surgically implanted in the cerebral ventricle. The therapy brought about a change in the natural history of the disease in these patients. However, there are several barriers to the implementation of this therapy.

**Objective:** Report the difficulties in treating CLN2 through enzyme replacement therapy.

**Methods:** Quantitative, descriptive, retrospective, observational study carried out at a reference center for genetic diseases in the Northeast of the country related to the treatment of CLN2 from 2020 to 2022.

**Results:** At the referral center, we have 3 wheelchair patients treated with CLN2. Delay in drug supply due to judicialization, lack of continuation of therapy due to interruption of medication supply by the government, PCR for COVID-19 in the 48-hour pre-medication period, and delay in organizing the reference center for Brineura® infusion in the post-pandemic period was a problem for all patients. Case 1: 14 years old, male, with the use of medication, the patient became more active, started to feed himself, and showed greater independence to walk, but he fell from his own height and had bleeding in the CSF puncture of the intracerebroventricular catheter (ICRC) pre-infusion, causing the catheter to have to

be evaluated by CT scan of the head and momentarily interrupting the infusions. Over time, the patient also became less cooperative and had infusion losses due to convulsions and strokes. Family problems were also a reason for the lack of infusion. Case 2: 15-year-old male, had an infectious complication after ICRC implantation, lived far from the infusion center, and had frequent transport problems. Case 3: 15-year-old female, had difficulty in scheduling a cranial CT with neuronavigation for planning ICRC implantation and ICRC implantation in the operating room due to the COVID-19 pandemic.

**Conclusions:** There are several barriers to the implementation of ERT in CLN2. Every team that treats CLN2 must be attentive to reduce patients' difficulties in performing the therapy. Families must be connected with the healthcare team to maintain CLN2 therapy and improve patients' quality of life.

### Code: PE088

#### **Hyperphenylalaninemia as a cause of Autism Spectrum Disorder (ASD) in patients from the national neonatal screening program in a Northeastern Brazilian state**

Raffaella Neves Mont'Alverne Napoleão<sup>1</sup>, Tamiris Carneiro Mariano<sup>2</sup>, André Luiz Santos Pessoa<sup>2</sup>, Rosicler Pereira de Gois<sup>2</sup>, Aline Campos Fontenele Rodrigues<sup>3</sup>, Matheus Carvalho Vasconcelos<sup>1</sup>, Beatriz Esmeraldo Teixeira<sup>1</sup>, Ester Mara Rodrigues Freire<sup>1</sup>, Erlane Marques Ribeiro<sup>2</sup>

<sup>1</sup>Unichristus, Fortaleza CE, Brazil

<sup>2</sup>Hospital Infantil Albert Sabin, Fortaleza CE, Brazil

<sup>3</sup>Universidade Estadual do Ceará, Fortaleza CE, Brazil

**Background:** About 20 years ago, the national neonatal screening program (PNTN) was implemented in Brazil for early screening, diagnosis, and treatment of some diseases, such as hyperphenylalaninemia (HP). This condition with inadequate treatment can result in neurological changes such as intellectual disability and autism spectrum disorder (ASD).

**Objective:** Describe the cases of patients with ASD from the PNTN in a center in Northeast Brazil.

**Methods:** Quantitative, descriptive, retrospective, observational study carried out at a referral center for the treatment of PH in Northeast Brazil from 2000 to 2022.

**Results:** Of the 168 patients seen, 9 (5.3%) had ASD. Only 1 case had a late diagnosis (12 years). There wasn't gender prevalence (50% male). The initial age ranged from 1 month to 8 years, with a median of 12 months. In this group, there're 4 families with affected siblings and treatment failure. Only the late case presents consanguinity and does not present recurrence in the family. Only 1 family lived in the capital. The other cases were from the interior of the state. Only 1 case was the genotype known (r408w/l249f). Seizures occurred in 3 cases from 2 families (2 siblings). All cases had an intellectual disability, and they are under outpatient follow-up. All of them showed temporary abandonment of treatment, dietary transgression, suspension of the use of the therapeutic formula, lack of consultation, and failure to perform laboratory tests, except in the case of late diagnosis. The medication used in most cases was risperidone. In 1 case there was a cleft lip and palate associated with HP.

**Conclusions:** Although HP is an autosomal recessive disease, most of the cases weren't consanguineous, in a region where consanguinity is frequent. Most cases followed up by the PNTN did not develop neurological impairment associated with signs of ASD. Although neonatal screening is an excellent

program to prevent neurological impairment due to PH, every effort by the healthcare team must be made to avoid the neurological sequelae caused by this condition. Neurological changes should be avoided in patients with PH, as brain involvement worsens the prognosis and quality of life of these patients.

### Code: PE091

#### **Maple syrup urine disease: past, present, future at the reference center of a state in Northeast Brazil**

Ester Mara Rodrigues Freire<sup>1</sup>, Raffaella Neves Mont'Alverne<sup>1</sup>, Mariana de Souza Rocha Teixeira<sup>1</sup>, Beatriz Esmeraldo Teixeira<sup>1</sup>, Aline Campos Fontenele Rodrigues<sup>2</sup>, Rosicler Pereira de Gois<sup>3</sup>, Tamiris Carneiro Mariano<sup>3</sup>, Andre Luiz Santos Pessoa<sup>3</sup>, Erlane Marques Ribeiro<sup>3</sup>

<sup>1</sup>Unichristus, Fortaleza CE, Brazil

<sup>2</sup>Universidade Estadual do Ceará, Fortaleza CE, Brazil

<sup>3</sup>Hospital Infantil Albert Sabin, Fortaleza CE, Brazil

**Background:** Maple syrup urine disease (MSUD) is an inborn error of metabolism resulting from the accumulation of leucine, isoleucine and valine. The classic form is more common, in which there are neurological signs and symptoms, coma, and death from the third or fifth day of life. Treatment is based on diet and liver transplantation.

**Objective:** To report the past and present experience of a reference center (CR) in leucinos treatment in Northeast Brazil and the perspective for the future.

**Methods:** Retrospective, descriptive, observational study carried out at a reference center for genetic diseases in the Northeast related to the treatment of leucinos from 2000 to 2022.

**Results:** We had 12 cases (5F:7M) without familial recurrence. From 2000-2008 the CR had 2 cases, a geneticist and a nutritionist for treatment. Diagnostic tests were sent to the genetics service at Hospital de Clínicas de Porto Alegre (HCPA) and took 15 days to produce results. The government had no formula, and it was still necessary to wait for a bid to start treatment. All cases evolved to death. From 2009-2017 we had 5 cases and from 2018, 5 cases. We currently rely on the Brazilian Maple Syrup Network (HCPA) and test results began to be delivered in 7 to 10 days. We have 2 neurologists in the group. Some patients did not die, the government started to have a formula for the treatment. Molecular tests gave us an earlier diagnosis, but the difficulty in performing the diet, the lack of knowledge on the part of physicians, especially neurologists and pediatricians, contributed to inadequate therapeutic measures. All cases had neurological impairment. Only 2 cases were consanguineous, and all were from the interior of the state. In the future, we hope that neonatal screening for leucinos will contribute to early diagnosis/treatment, reducing neurological impairment and morbidity and mortality.

**Conclusions:** In the past, all cases were of late diagnosis/treatment. Currently, all cases are neurologically compromised, but we have reduced diagnosis time and improved therapy. In the future, we hope that neonatal screening will contribute to a higher quality of diagnosis/therapy, improving patients' quality of life. Pediatricians and neurologists must learn about the treatment of the disease to reduce neurological damage.

Code: PE094

**Mucopolysaccharidosis III at the reference center for rare diseases of Ceará**

Beatriz Esmeraldo Teixeira<sup>1</sup>, Ester Mara Rodrigues Freire<sup>1</sup>, Raffaella Neves Mont'alverne Napoleão<sup>1</sup>, Mariana de Souza Rocha Teixeira<sup>1</sup>, Aline Campos Fontenele Rodrigues<sup>2</sup>, André Santos Pessoa<sup>3</sup>, Rosicleir Pereira de Góis<sup>3</sup>, Tamiris Carneiro Mariano<sup>3</sup>, Erlane Marques Ribeiro<sup>3</sup>

<sup>1</sup>Unichristus, Fortaleza CE, Brazil<sup>2</sup>Universidade Estadual do Ceará, Fortaleza CE, Brazil<sup>3</sup>Hospital Infantil Albert Sabin, Fortaleza CE, Brazil

**Background:** Mucopolysaccharidosis type III (MPS III) is the type of mucopolysaccharidosis that has fewer systemic signs and symptoms, however, it has the most severe neurological impairment. There are four types of MPS III, determined by the mutation in the gene responsible for the enzyme that becomes deficient in degrading intracellular glycosaminoglycan, which is responsible for the clinical picture.

**Objective:** Describe the cases of MPS III at a Reference Center for Rare Diseases in Ceará.

**Methods:** Quantitative, cross-sectional, retrospective, observational study of MPS III cases from 2000 to 2022 at the Reference Center for Rare Diseases of Ceará. The variables were: type of MPS, sex, age at study, age of onset, age at diagnosis, neurological developmental milestones, neurological signs/symptoms, neuroimaging data, and death (yes/no).

**Results:** We evaluated 12 cases, 6 MPS IIIB, 4 MPS IIIA, and 2 MPS IIIC. Five were female. Three had consanguinity, four had a familial recurrence. The first symptoms occurred between 1 month and 3 years of age and the speech-language disorders were more frequent. The etiological diagnosis was performed between 2-18 years. In all cases, there was a delay in neurodevelopmental milestones. In the clinical picture, the presence of seizures, behavior disorder, intellectual disability, hyperactivity, autism, hydrocephalus, and dysphagia are highlighted. There were three cases of abandonment of follow-up and four deaths, three due to respiratory failure and one due to sepsis in the age group of 13 to 19 years.

**Conclusions:** Severe neurological impairment is evident in all cases of MPS III. Strategies must be implemented to avoid delay in diagnosis, such as happened in the cases presented, including to enable future treatment with gene therapy, possible only for asymptomatic cases or with initial symptoms.

**Malformações do sistema nervoso central**

Code: PE102

**The impact of nutriology on human neurodevelopment: an integrative literature review**

Arthur Carvalho Gonçalves<sup>1</sup>, Jéssica de Moutta Gomes<sup>1</sup>

<sup>1</sup>Universidade Iguauçu, Itaperuna RJ, Brazil

**Background:** Water, vitamins, minerals, proteins and carbohydrates are biomolecules essential for the functioning of the organism. In this context, it is valid to point out that micro and macronutrients are subgroups of nutrients that are essential for an optimal functioning of the organism.

**Objective:** The aim is to describe and understand the relationship between the nutritional effects on the neurological unfolding of the human being.

**Methods:** This is a qualitative and descriptive research, carried out through an integrative literature review, which aims

to synthesize results obtained in research on a particular subject/problem, systematic, organized and comprehensive.

**Results:** Pregnancy is a special phase in a woman's life and is defined by the period in which the fetus develops intra-uterinely until birth. During pregnancy, maternal nutritional demands must be in line with his needs. This is because, as based on the references revisited, nutrition has high relevance in human neurodevelopment, being the link between several areas, such as Neurobiology and Cognitive Neuroscience. From this perspective, it is noted that significant evidence from studies carried out in humans demonstrate that the lack of nutrient intake in the intrauterine and postnatal period has an impact on these aspects, as well as influencing later cognitive performance.

**Conclusions:** From the studies consulted, it was possible to verify that the Nutrologia brings with it several approaches that have a significant impact on the neurological unfolding of the human being. Your contributions – through nutritional genomics and its subdivisions (nutrigenetics, nutrigenomics and nutri-epigenetics) – have allowed Medicine to become increasingly increasingly personalized and, thus, contribute to the health-disease process, above all, towards the promotion of the quality of life of individuals.

**Neoplasias**

Code: PE104

**Opsoclonus-myoclonus-ataxia Syndrome: A Pediatric Oncology Hospital Experience**

Lorena Raulik Cyrino<sup>1</sup>, Ricardo Silva Pinho<sup>1</sup>, Marcelo Melo Aragão<sup>1</sup>, Caroline Corrêa Maranhão<sup>1</sup>, Jose Marcos Vieira Albuquerque Filho<sup>1</sup>, Katrine Freitas Valeriano<sup>1</sup>, Mateus Oliveira Torres<sup>1</sup>, Alulin Tacio Quadros Monteiro Fonseca<sup>1</sup>

<sup>1</sup>Universidade Federal de São Paulo, São Paulo SP, Brazil

**Background:** Opsoclonus myoclonus ataxia syndrome (OMAS) is a rare, immune-mediated neurological disorder that usually starts in the second year of life. The triad of signs is composed of opsoclonus, myoclonus and ataxia. In addition, there is often irritability and sleep disturbance. In about 50% of children there is an underlying neuroblastoma.

**Objective:** The aim of study was to investigate and describe the epidemiology, clinical features, tumor association, treatment profile and outcome of patients with OMAS.

**Methods:** We conducted a retrospective study over 17 years (2005-2022) including all patients aged under 18 years who were managed for OMAS in an oncologic hospital (GRAACC Hospital in São Paulo – SP). Epidemiological and clinical data were analyzed.

**Results:** Eleven patients were included. The male-female ratio was 1:4.5. Median age of onset was 2.15 years (25.8 months). Time to diagnosis ranged between 10 days and 3 years. All patients had ataxia, tremor, dysmetria and irritability at some point. Acute ataxia was the predominant initial symptom, corresponding to 81% of the cases. Opsoclonus was the initial symptom in only 9% of cases. Eighty two percent of the patients had brain magnetic resonance imaging. Eighty one percent realized cerebrospinal fluid analysis. Most patients had association with tumor (72%), with neuroblastoma and ganglioneuroblastoma corresponding to half of the cases each. Time to diagnosis among OMAS and tumor ranged from 0 days to 1 year and 7 months, but the majority (63%) were diagnosed at the same time. Only one patient did not resect the tumor. All patients received immunomodulatory treatment, and 62% received combination therapy (immunoglobulin plus dexamethasone, or immunoglobulin plus methylprednisolone, or immunoglobulin plus prednisolone, or

immunoglobulin plus dexamethasone and rituximab). Comparing the “tumor group” and the “no tumor group”, there were no differences in sex ratio and the main presenting symptom. Children in the tumor group had an earlier age of onset (mean 19.1 vs. 25.8 months). Of the total, there was relapse in 36% and 63% have sequelae, with language and cognition as the most affected areas. The percentage of sequelae was higher in the “Group of tumors” (75% vs 33%). **Conclusions:** OMAS is a rare neurologic condition that can be associated with poor cognitive outcomes. An early diagnosis with aggressive immunomodulation might lead to a better outcome. The disorder requires careful monitoring and longer-term follow-up.

## Neurogenética

Code: PE108

### Levodopa-responsive dystonia (DYT5) in a large family from Minas Gerais: the importance of early diagnosis

Yuri Barcelos<sup>1</sup>, Juliana Gurgel-Giannetti<sup>1</sup>, Lívia Uliana Jácome<sup>1</sup>, Beatriz Vilela Morais de Azevedo<sup>1</sup>, Mariz Vainzof<sup>2</sup>, Aline dos Passos Moraes<sup>1</sup>, Laryssa da Silva Ribeiro<sup>1</sup>, Mariana Braga Valadão<sup>1</sup>

<sup>1</sup>Universidade Federal de Minas Gerais, Hospital das Clínicas, Belo Horizonte MG, Brazil

<sup>2</sup>Universidade de São Paulo, Centro de Estudos do Genoma Humano, São Paulo SP, Brazil

**Background:** Dopa-responsive dystonia associated with mutations in the GCH1 gene (DYT5) is classically described as autosomal dominant but rare cases with recessive inheritance have been reported. The autosomal dominant (AD) form is characterized by a childhood onset and predominates in the females. It usually starts with gait disturbance with foot dystonia (segmental dystonia) with fluctuation of symptoms during the day, and parkinsonism can be present. The treatment consists of low doses of levodopa and diagnosis is confirmed by the identification of pathogenic variant in the GCH1 gene.

**Objective:** To present a family with 7 affected individuals from a large family, originally from small city in Minas Gerais. **Methods:** All the affected members were clinically evaluated. Neuroimaging and molecular study were performed in the index case. The affected individuals were treated with L-dopa and followed from 2 to 5 years.

**Results:** The index case is a female who presented dystonia in right lower limb, at the age of 8 years old. The patient improved her symptoms with L-dopa treatment. The molecular study showed in a heterozygous pathogenic variant in exon 5 of the GCH1 gene (c.607G>A /p.Gly203Arg). A total of nine relatives of the index case that complaint of gait abnormalities was evaluated: 6 females and 3 males. All men did not have dystonia. The 6 females were: the daughter of the index case, who showed segmental dystonia (left foot) at 4 years of age; three first-degree cousins that showed segmental dystonia with the age of onset ranging from 8 - 23 years. More two older third-degree cousins (diagnosed at the age of 50 and 53 years) presented history of segmental dystonia that evolved to diffuse dystonia associated to parkinsonism, and they lost the capacity of walking at the age of 15 and 44 years, respectively. After starting levodopa, all women responded with improvement in walking. The two older relatives who lost the walk ability became able to walk with support, but their improvement was limited by contractures and foot deformities.

**Conclusions:** Early identification of individuals with dopa-responsive dystonia allows for timely initiation of levodopa

therapy. The response to L-dopa could be observed in patients with long course of the disease however the joint contractures and foot deformities were the limiting factor for better results. In addition, through genetic diagnosis the family can be informed about the disease and genetic counseling.

Code: PE117

### Central congenital hypotonia: what is the first genetic test of choice?

Luan Guanais<sup>1</sup>, Patrícia Pontes Cruz<sup>1</sup>, Emília Katiane Embiruçu<sup>1</sup>

<sup>1</sup>Universidade Federal da Bahia, Hospital Universitário Professor Edgar Santos, Salvador BA, Brazil

**Background:** Hypotonia is a frequent neurological manifestation with numerous etiologies, but recognizing the cause is a challenge. First, it's necessary to differentiate hypotonia as peripheral, central or mixed. Signs of central hypotonia are normo/hyperreflexia, developmental delay, cognitive delay and/or epileptic seizures associated and normal creatine phosphokinase (CPK). After ruling out environmental risk factors, genetic causes should be investigated. Brazil lacks epidemiological studies on these diseases. One of the factors that may influence is the difficulty to perform specific biochemical dosage and genetic testing due to the high cost and difficulty to access in the public health network.

**Objective:** To identify the main diagnostic genetic tests for non-environmental central congenital hypotonias.

**Methods:** Descriptive, cross-sectional and retrospective study by reviewing medical records of children evaluated between 2017 and 2022 at the Neurogenetics outpatient clinic at the referral hospital in Salvador-BA. Inclusion criteria were central congenital hypotonia and etiologic diagnosis.

**Results:** Sixty-four children with hypotonia were selected and 14 children met the inclusion criteria. Of this sample, 50% are boys and the age at diagnosis was between 11 and 232 months. Central hypotonia was associated with other neurological syndromes, such as: cognitive (57%), epileptic (43%), neurodevelopment regression (36%), cerebellar (22%), and dyskinetic (14%). The genetic tests performed were karyotype (62.5%), SNP-array (14.5%), genetic panel (21%), whole exome sequencing (14.5%), and whole genome sequencing (50%). The diagnostic non-confirmation rate was 66% karyotype, 32% SNP-array and 7% for clinical exome. In some situations, the genome was the first choice to carry out the diagnostic investigation due to the availability at the reference center. Some patients have had more than one genetic test.

**Conclusions:** Genome sequencing had the highest diagnostic yield among all genetic tests. Anamnesis and neurological examination are important to guide the etiological investigation and genotype-phenotype correlation, especially in cases with dysmorphism or variants of uncertain significance.

Code: PE125

### Genetic profile of patients with developmental and epileptic encephalopathy at a reference center in Northeast Brazil

Aline Campos Fontenele Rodrigues<sup>1</sup>, Tamiris Carneiro Mariano<sup>2</sup>, Erlane Marques Ribeiro<sup>2</sup>, André Luiz Santos Pessoa<sup>2</sup>

<sup>1</sup>Universidade Estadual do Ceará, Fortaleza CE, Brazil

<sup>2</sup>Hospital Infantil Albert Sabin, Fortaleza CE, Brazil

**Background:** The developmental and epileptic encephalopathy (DEE) diseases where there is developmental impairment related to both the underlying etiology independent of

epileptiform activity and the epileptic encephalopathy. Many DEEs have a genetic basis that, by themselves, can alter the neurodevelopmental delay. By August 2022, there were 105 genes associated with DEE according to OMIM.

**Objective:** This study aims to analyze and characterize the profile of patients with DEE followed up in a center in Northeast Brazil.

**Methods:** Quantitative, descriptive, retrospective, observational study carried out at a neurogenetic reference center in Northeast Brazil. Patients with a confirmed genetic diagnosis.

**Results:** The sample has 16 patients, no prevalence between sexes, ages 2 to 13 years. Variants were found in 13 genes; ALG13; CDKL5; CHD2; DNMT1; GNAO1; KCNQ3; KCNT1; PCDH19; PNKP; SCN1A; SCN1A; SCN1A; SLC12A5; STXBP1; WWOX. Only 5 of the variants were previously described as pathogenic. One of the patients had DEE 2 (CDKL5), and had a global cortical volumetric reduction, in addition to l-dopa-responsive movement disorder. The patient with the earlier onset, neonatal, has a variation in the KCNQ3. 3 of the patients analyzed, all boys, had alterations in the SCN1A, among them 2 brothers, non-consanguineous parents, with the same variation, in heterozygosity, both evolving with regression of the neurodevelopmental. The third child with an alteration in the SCN1A had onset of symptoms at 4 months of age and regression at 2 years of age, being the only patient using cannabidiol. Two patients had variants in the KCNT1. One patient had two heterozygous variants in the SLC12A5, never described in the medical literature, started seizures at 2 months, progressing to death at 8 months. The patient with GNAO1 variation had axial hypotonia, in addition to appendicular dystonia. The patient with a change in the PCDH19 has probable somatic mosaicism and evolved with language regression after the onset of seizures.

**Conclusions:** This work demonstrates the variability of signs and symptoms found in DEEs. It is still necessary to carry out more genetic screening for patients with early onset epilepsy and/or difficult to control, (9 out of 16 undescribed variations). In addition, some DEEs present specific therapies, such as SCN1A, which should avoid channel blockers. Therefore, the earlier the diagnosis, the sooner we can initiate adequate treatment to reduce the morbidity and mortality of such patients.

Code: PE134

#### **Eladocagene exuparovec gene therapy improves motor development in patients with aromatic L-amino Acid decarboxylase deficiency**

Paul Wuh-Liang Hwu<sup>1</sup>, Agathe Roubertie<sup>2</sup>, Yin-Hsiu Chien<sup>1</sup>, Antonia Wang<sup>3</sup>, Alexis Russell<sup>3</sup>, Ni-Chung Lee<sup>1</sup>, Pedro Eugenio Pachelli<sup>4</sup>, Andressa Federhen<sup>4</sup>, Chun-Hwei Tai<sup>1</sup>

<sup>1</sup>National Taiwan University Hospital, Taipei, Taiwan

<sup>2</sup>University Hospital of Montpellier, France

<sup>3</sup>PTC Therapeutics, South Plainfield, NJ, United States

<sup>4</sup>PTC Farmacêutica do Brasil LTDA, São Paulo, SP, Brazil

**Background:** Aromatic L-amino acid decarboxylase (AADC) deficiency is caused by mutations in the dopa decarboxylase gene leading to reduced AADC enzyme activity; it is characterized by motor impairments and inability to attain developmental milestones.

**Objective:** To evaluate clinical outcomes in children with AADC treated with Eladocagene exuparovec, a recombinant adeno-associated viral vector serotype 2 carrying the coding sequence for human AADC enzyme.

**Methods:** Eladocagene exuparovec was infused bilaterally in the putamina of 30 children with AADC deficiency in 3

clinical trials (AADC-CU/1601 [n= 8], AADC-010 [n= 10], and AADC-011 [n= 12] in patients aged 18–102 months. Data were extracted on January 4, 2022. Patients receiving a total of  $1.8 \times 10^{11}$  vg (n= 21) or  $2.4 \times 10^{11}$  vg (n= 9; AADC-011) were followed for up to 120 months and assessed for motor milestone attainment using the Peabody Developmental Motor Scale, 2nd edition (PDMS-2). Specific motor skill items of the PDMS-2 were used to assess key motor milestones including head control (partial or full), sitting (supported or independently), standing (with/away from support; up from cross-legged position), and walking (with/without assistance; 10 feet; taped line) Motor milestones and development were measured every 3 months for 1 year following gene therapy, then every 6–12 months for  $\leq 120$  months.

**Results:** At baseline, no patients had mastered head control or more advanced milestones. At year 1 of follow-up, patients were gaining the following skills (n): partial head control (26); full head control (15), sitting unassisted (7), supported standing (2). Progression of development was noted at years 5 and 10. By year 5 of follow-up, more advanced milestones were achieved (n): full head control (24), sitting unassisted (21) assisted walking (5), walking 10 feet (3), or walking up stairs (3). These abilities were maintained for as long as 10 years.

**Conclusions:** The data indicate that eladocagene exuparovec can provide a durable, positive impact on motor development in patients with AADC deficiency.

Code: PE141

#### **Neurogenic oropharyngeal dysphagia in patients with neuronal ceroid lipofuscinoses**

Joice Silva de Santana<sup>1</sup>, Guilsa Silva de Almeida<sup>2</sup>, Luan Guanais<sup>3</sup>, Patricia Pontes Cruz<sup>3</sup>, Emília Katiane Embiruçu<sup>1</sup>

<sup>1</sup>Universidade Federal da Bahia, Hospital Universitário Professor Edgar Santos, EBSERH, Salvador BA, Brazil

<sup>2</sup>Universidade Federal da Bahia, Salvador BA, Brazil

<sup>3</sup>Universidade Federal da Bahia, Hospital Universitário Professor Edgar Santos, Salvador BA, Brazil

**Background:** Neuronal Ceroid Lipofuscinoses (NCL) is a neurodegenerative condition of lysosomal metabolism due to accumulation of lipofuscin in neurons. The predominant symptoms are motor and cognitive regression, seizures, ataxia and retinopathy. Speech-language disorders such as dysarthria, aphasia and dysphagia have been reported.

**Objective:** To describe the degree of oropharyngeal dysphagia and feeding and breathing route in patients diagnosed with NCL assisted at a referral hospital for rare diseases in Salvador-BA.

**Methods:** Descriptive, cross-sectional and retrospective study by reviewing medical records evaluated between 2017 and 2022. Inclusion criteria were diagnosis of NCL confirmed by genetic and/or biochemical examination. The results were tabulated in an Excel® spreadsheet. The variables were age, age at diagnosis, type of NCL, degree of dysphagia, feeding and breathing route. The diagnosis of dysphagia was based on the protocols used in the service.

**Results:** Seven patients aged between 4 and 19 years were selected. The NCL types identified in the sample were 1, 2, 3, 6 and 7. Types 1 and 2 corresponded to 28.5% of cases each and types 4, 6 and 7 to 14.3% each. The age at diagnosis was between 4 and 14 years; 6 (86%) had a diagnosis of dysphagia and 1 had no diagnosis described. The degree of dysphagia ranged moderate to severe in 28,5% and severe in 57%. Gastrostomy was indicated in 57% of patients and tracheostomy in 14,3%. A prospective evaluation was carried out in

two individuals, the patient with NCL 7 had a rapid evolution of the degree of dysphagia from mild to severe in just 9 months after diagnosis requiring gastrostomy. The second patient in follow-up was diagnosed with NCL 2 and treated on enzyme replacement therapy, he remained with stable moderate to severe dysphagia and an exclusive oral diet.

**Conclusions:** Most of the individuals analyzed evolved with the diagnosis of moderate to severe dysphagia and more than half required gastrostomy, it is in agreement with the literature. However, treatment with enzyme replacement can lead to stability.

**Code:** PE156

**Profile of patients with neurological impairment treated at the medical genetics service of reference in Northeast Brazil** Rosicler Pereira de Gois<sup>1</sup>, Ester Mara Rodrigues Freire<sup>2</sup>, Tamiris Carneiro Mariano<sup>1</sup>, Andre Luiz Santos Pessoa<sup>1</sup>, Raffaella Neves Mont'Alverne Napoleão<sup>2</sup>, Beatriz Esmeraldo Teixeira<sup>2</sup>, Mariana de Souza Rocha Teixeira<sup>2</sup>, Aline Campos Fontenele Rodrigues<sup>3</sup>, Erlane Marques Ribeiro<sup>1</sup>

<sup>1</sup>Hospital Infantil Albert Sabin, Fortaleza CE, Brazil

<sup>2</sup>Unichristus, Fortaleza CE, Brazil

<sup>3</sup>Universidade Estadual do Ceará, Fortaleza CE, Brazil

**Background:** Many genetic diseases have multisystem involvement and when they are associated with neurological alterations, they represent chronic diseases with a worse prognosis.

**Objective:** To evaluate the profile of patients with genetic diseases associated with neurological impairment treated at the genetics outpatient clinic of the Albert Sabin Children's Hospital (HIAS).

**Methods:** Quantitative, descriptive, retrospective, observational study. From 2001 to 2022, 581 cases treated at the HIAS Medical Genetics Outpatient Clinic were randomly selected. The variables were sex, diagnosis, age, origin, consanguinity, prenatal care (with/without complications), type of delivery, gestational age, Apgar >7, birth weight, height, and head circumference, neurological development, neurological examination (altered/ normal), presence of seizure, death. Cases of microcephaly by Zika-virus, non-syndromic cleft lip and cleft palate, and phenylketonuria were excluded because they were in specific outpatient clinics.

**Results:** 290 (50%) were female and 6 were of undetermined sex. Regarding the diagnosis, 57 (14%) were chromosomal disorders, 46 (12%) were neuromuscular diseases, 65 (16%) were metabolic diseases, 213 (54%) were monogenic syndromes, 12 (3%) were environmental etiology, 185 (32%) had no diagnosis. Age ranged from 1-330 months with a median of 165 months. 192 (36%) were from the capital. Consanguinity occurred in 77 (15%) cases; 139 (29%) had prenatal complications. 227 (51%) had a cesarean delivery. 58 (16.5%) had Apgar <7 in the first minute of life. 63 (23%) were premature. Birth weight ranged from 556-5,000g with a median of 2,778g, height from 31-55cm, with a median of 43cm, head circumference from 20-45.5cm with a median of 32.75cm; 406 (90.2%) had delayed neurodevelopmental milestones. In 352 (60.4%) the neurological examination was altered; 97 (16.6%) had seizures. The death occurred in 10 (1.8%) cases.

**Conclusions:** There was no gender prevalence. Most of the cases evaluated were from the countryside, without perinatal complications, but had changes in developmental milestones

and neurological physical examination. Consanguinity was prevalent and death occurred in a minority of cases. The most frequent pathologies in descending order were monogenic syndromes, inborn errors of metabolism, chromosomal disorders, and neuromuscular diseases.

**Code:** PE158

**Recessive TTN mutations: Escobar syndrome, arthrogryposis, and congenital heart defect in Brazilian patients**

Sabrina Stephanie Lana Diniz<sup>1</sup>, Yuri Barcelos<sup>1</sup>, Beatriz Vilela Moraes de Azevedo<sup>1</sup>, Lívia Uliana Jácome<sup>1</sup>, Juliana Gurgel-Giannetti<sup>1</sup>, Laryssa da Silva Ribeiro<sup>1</sup>, Mariana Braga Valadão<sup>1</sup>, Aline dos Passos Moraes<sup>1</sup>

<sup>1</sup>Universidade Federal de Minas Gerais, Hospital das Clínicas, Belo Horizonte MG, Brazil

**Background:** The TTN gene is related to a broad phenotype spectrum including tibial muscular dystrophy, hereditary myopathy with respiratory failure, limb girdle dystrophy 2J and dilated or hypertrophic cardiomyopathy. In 2014, Chauveau et al, described phenotypes including cardiac septal defects, left ventricular non-compaction, Emery-Dreifuss dystrophy and arthrogryposis. In 2020, Savarese et al, showed most of patients with biallelic TTN mutations presented as congenital myopathy.

**Objective:** We describe 4 patients with TTN mutations and different phenotypes: one presenting as Escobar syndrome, one with arthrogryposis and cardiac septal defects and two with multiple arthrogryposis, short neck and scoliosis.

**Methods:** Patients were clinically evaluated, and the molecular study was done using whole exome sequencing (WES).

**Results:** A 7-year-old-boy, second child from non-consanguineous parents. He presented multiple pterigia, short stature, scoliosis, bilateral ptosis, muscle weakness and ventilation failure, requiring the use of non-invasive assisted ventilation since he was 3 years old. The muscle biopsy showed myopathic pattern. A diagnosis of Escobar Syndrome was made, and molecular study showed two TTN truncating mutations: c.669+1G>A and c.54769delT Case 2: A 14-month-old-girl, child of a non-consanguineous parents. At six months of age, she presented a motor delay, hypotonia, global muscle weakness and arthrogryposis. The Echocardiogram showed left ventricular non-compaction and ventricular septum defects. WES showed two truncating mutations: c.101608+1 G>A was paternally inherited and the c.46658G>A which was de novo and a novel mutation. Case 3: A 3-year-old-girl, child of a non-consanguineous parents, presenting multiple arthrogryposis, short neck and scoliosis, cervical pterygia, myopathy and severe scoliosis. WES showed two TTN mutations: c.56648-1G>A e c.19744C>T. Case 4: A 10-year-old-boy, child of a non-consanguineous parents, presented multiple arthrogryposis, short neck and scoliosis, myopathy and severe scoliosis. At 7 years of age, was necessary to start with noninvasive ventilation. WES showed two TTN mutations: c.669+1G>A p. and c.18920delG p. Ser6307Ilefs\*17.

**Conclusions:** The TTN gene is associated to a phenotype spectrum. In the present report, the recessive TTN mutations are related to congenital myopathy, arthrogryposis plus congenital heart defects and to the phenotype of Escobar Syndrome. It is very important to have the genetic diagnosis which allows the genetic counseling.



## Neuroimunologia, esclerose múltipla e outras doenças desmielinizantes

Code: PE170

### Epidemiological profile of patients treated at the medical clinic for demyelinating diseases in a specialized pediatric hospital in Brasília, Brazil

Ana Carolina Andrade Lopes<sup>1</sup>, Manuela de Oliveira Fragomeni<sup>1</sup>, Alessandra Andrade Lopes<sup>2</sup>

<sup>1</sup>Hospital da Criança de Brasília José de Alencar, Brasília DF, Brazil

<sup>2</sup>Centro Universitário de Brasília, Brasília DF, Brazil

**Background:** Pediatric demyelinating diseases can affect the optical nerves, spinal cord, brain, brainstem or cerebellum. Their clinical symptoms are associated with the location of the lesions and may be presented in a monophasic or chronic form. The study of demyelinating diseases is considered recently, as its development of therapies, especially drugs. Pediatric demyelinating diseases are even less described in the literature when compared to diseases in adults.

**Objective:** Identify the epidemiological profile of patients treated at the medical clinic of demyelinating diseases in a specialized pediatric hospital in Brasília, Brazil.

**Methods:** A quantitative descriptive cross-sectional study was realized based on data collection in an electronic medical record system at a specialized pediatric hospital in Brasília, Brazil.

**Results:** Multiple sclerosis (MS) was the most prevalent disease among patients. Females are more commonly affected, except in cases of transverse myelitis (TM) and optical neuromyelitis (NMO). The average age was 13.2 years, and the time between the first clinical manifestation and the diagnosis was 1 month. The number of relapses per patient was 2.2 relapses and neurologic disability was low, except in patients with NMO. The main treatments instituted for recurrent diseases were immunosuppression with azathioprine for patients with NMO and interferon beta for patients with MS.

**Conclusions:** The epidemiological profile of patients was like described in other populations. Although fingolimod is the only treatment with a proven effect in a clinical study, its use in Brazil is limited by the unavailability of the medication for the pediatric population by the unified health system (SUS).

## Neuroinfecções

Code: PE187

### Central nervous system complications of pediatric sinusitis

Laila Prazeres Schulz Moreira<sup>1</sup>, Daniela Fernanda Almeida Santos<sup>1</sup>, Guilherme Cordaro Bucker Furini<sup>1</sup>, Isabela Bartholomeu Ferreira da Costa<sup>1</sup>, Saul Didmar Alquez Montano<sup>1</sup>, Amanda Póvoa de Paiva<sup>1</sup>, Maiave Micalle Figueiredo de Matos<sup>1</sup>, Maria Avanise Yumi Minami<sup>1</sup>, Ana Paula Andrade Hamad

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Hospital das Clínicas, Ribeirão Preto SP, Brazil

**Background:** Central nervous system (CNS) involvement in pediatric acute sinusitis is rare. Intracranial complications involve meningitis, sinus thrombosis, empyemas and cerebral abscesses. We present a series of ten cases evaluated in a period of eight months in our tertiary pediatric referral center.

**Objective:** To gain insight into patterns of presentation, epidemiology, imaging, disease course of intracranial complications of sinusitis (ICS), challenging conditions with high morbidity and potential mortality.

**Methods:** Clinical observation of ten children and adolescents treated for sinusitis intracranial complications in a period of eight months between 2021-2022.

**Results:** Ten patients were identified with an average age of 9.8 years old, with a minimum of two and a maximum of 13 years old. 60% were adolescents, 30% were grade-schoolers and, surprisingly, 10% was toddlers. 80% were male. As for the localization, the frontal sinus was affected in all patients and 60% had pansinusitis. The most common symptoms were fever, present in 90%, and headache, present in 70%. Neurological abnormalities such as paraparesis and hemiplegia were present in 30%, all male with 12 and 13 years old. Focal seizures occurred in 30%. Meningitis was the most common complication, present in 80%, followed by intracranial empyemas in 70%. Intracranial abscesses occurred in 30% and 30% evolved with sinus thrombosis, where 20% had superior sagittal sinus thrombosis. One 12-year-old male had extended CNS complications as paraparesis, urinary retention, facial nerve palsy, lagophthalmos, abducens nerve palsy, oculomotor nerve palsy and hypoesthesia secondary to intracranial lesions, multiple ischemic subcortical areas and mielitis. One 11-year-old male had intracranial hypertension due to a massive frontal abscess. Treatment outcomes showed that only 30% of patients were exclusively treated with antibiotics and 70% needed surgical interventions. 30% had nasoscopic surgery, 30% had neurosurgical intervention and 10%, a ten-year-old female, had both surgeries.

**Conclusions:** For the first time, our hospital had so many sinusitis complicated cases in a brief period of time. Fortunately, we had no mortality rate. These complications should be rare, so the question about the reason behind so many serious cases is raised. Also important, sinusitis in a 2 years old is unusual and unexpected, so we highlight the need of early diagnosis and treatment to further prevent complications.

Code: PE188

### Leprosy in the pediatric population from Brazil: notifications from 2010 to 2019

Augusto Nicaretta<sup>1</sup>, Sara Julia Zorzi de Brum<sup>2</sup>, Fabiana de Abreu Getulino<sup>3</sup>, Júlia Pustrelo Moro<sup>3</sup>, Vinícius Estanislau Albergaria<sup>2</sup>

<sup>1</sup>Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil

<sup>2</sup>Universidade Federal da Fronteira Sul, Passo Fundo RS, Brazil

<sup>3</sup>Universidade Federal de Rio Grande, Rio Grande RS, Brazil

**Background:** Leprosy is a chronic disease, caused by the bacterium *Mycobacterium leprae*. It is characterized by a decrease or loss of thermal, pain and tactile sensitivity, as well as muscle strength.

**Objective:** This study aimed to describe the characteristics of the pediatric population with leprosy in Brazil.

**Methods:** An ecological study was carried out in July 2022 from the health information of the Brazilian Health Unified System databases. The analysis comprised the number of notified cases in Brazil from 2010 to 2019. The main variables analyzed were sex, skin color, age (0-14), region of notification, and diagnostic operational class. Descriptive statistics were performed through absolute (n) and relative (%) frequencies.

**Results:** A total of 23,575 leprosy cases were reported, with a decrease from 2,811 in 2010 to 1,725 in 2019. Most patients were male (51.7%), with brown skin color (65.4%) and aged between 10 and 14 years (65.7%). In the distribution by region of the country, it was observed that 48.9% of the total occurred in the Northeast, 26.6% in the North, 14.1% in the

Midwest, 9.5% in the Southeast, and 0.9% in the South. The most prevalent diagnostic operational class was the paucibacillary (51%).

**Conclusions:** There was a total decrease in leprosy cases in Brazil, but there is still vulnerability to this disease in some regions, such as in the Northeast of Brazil. Therefore, prevention and early detection of the disease must be encouraged to combat this public health problem.

Code: PE189

#### Neurological characteristics of Zika virus embryopathy cases in Ceará

Mariana de Souza Rocha Teixeira<sup>1</sup>, Thais Ferreira Campos<sup>1</sup>, Gabriella Maria Abreu Martins<sup>1</sup>, Lorena Passos Queiroga<sup>1</sup>, Rosicler Pereira de Gois<sup>2</sup>, Aline Campos Fontenele<sup>3</sup>, Tamiaris Carneiro Mariano<sup>2</sup>, Andre Luiz Santos Pessoa<sup>2</sup>, Erlane Marques Ribeiro<sup>2</sup>

<sup>1</sup>Unichristus, Fortaleza CE, Brazil

<sup>2</sup>Hospital Infantil Albert Sabin, Fortaleza CE, Brazil

<sup>3</sup>Universidade Estadual do Ceará, Fortaleza CE, Brazil

**Background:** Congenital Zika virus (SCZV) infection is associated with a spectrum of severe neurological abnormalities, mainly microcephaly, and central nervous system malformation. In this way, it becomes relevant to know the main neurological alterations that accompany SCZV in Ceará.

**Objective:** To know the main neurological characteristics that accompany SCZV in Ceará.

**Methods:** A retrospective cross-sectional study, quantitative and descriptive, through the review of data in medical records. The collection was performed in 2 centers and the neurological evaluation was performed in July 2019. The dysmorphic variables were craniofacial disproportion, prominent occipital bone and neurological variables, hypoactivity, hypertonia, opisthotonos, hyperreflexia, clonus, hyperexcitability, irritability, developmental milestones neurological status, in addition to age, sex, anthropometric data, and history of maternal Zika virus infection during pregnancy.

**Results:** The sample had 43 cases and 50% were female. Most cases were 3 years old, mothers with prenatal symptoms of Zika virus infection in the first trimester, born at term, without perinatal complications, with a mean head circumference of 27.5 cm. We had 41 (95.3%) patients with microcephaly, 36 (83.7%) with craniofacial disproportion, and 29 (67.4%) with a prominent occipital bone. Regarding the neurological manifestations, the most common was hypertonia/opisthotonus, present in 31 patients (72.0%). 19 (44.1%) had reduced motor activity status, 30 (69.7%) had hyperreflexia/clonus, 25 (55.8%) had hyperexcitability/irritability and 23 (53.4%) had significant neurodevelopmental delay.

**Conclusions:** Children with SCZV have a significant neurodevelopmental delay and physical examination features that demonstrate the impact on basic activities of daily living. These changes often result in secondary psychological and social impairments that make socialization and school performance difficult. Early recognition and differentiated multidisciplinary follow-up are necessary to minimize health complications, in addition to favoring a better quality of life for this population.

## Neurologia neonatal

Code: PE194

#### Could preterm infants benefit from neuromonitoring with video aEEG/EEG?

Rafaela Fabri Rodrigues Pietrobom<sup>1</sup>, Nathalie Sales Llaguno<sup>1</sup>, Daniela Pereira Rodrigues<sup>1</sup>, Mauricio Magalhães<sup>1</sup>, Gabriel Fernando Todeschi Variante<sup>1</sup>, Paula Natale Giroto<sup>1</sup>, Letícia Pereira de Brito Sampaio<sup>1</sup>

<sup>1</sup>Protecting Brains and Saving Futures, São Paulo, SP, Brazil

**Background:** More than 80% of neonatal seizures are completely subclinical and represent a risk factor for neurodevelopmental delays in preterm infants. Amplitude integrated electroencephalography combined with raw electroencephalography and video images (video aEEG/EEG) provides real-time monitoring for seizure detection.

**Objective:** To analyze the incidence, pattern and treatment of seizures verified on video aEEG/EEG in preterm infants.

**Methods:** Retrospective cohort study carried out from June 2017 to June 2021, including preterm infants with gestational age <32 weeks monitored with video aEEG/EEG for at least 24 hours in the first seven days of life. Data was collected by medical records and database review of monitored infants in 39 hospitals in Brazil. Demographic and clinical data were correlated with video aEEG/EEG findings. Descriptive analysis was performed using absolute and relative frequencies, and nonparametric variables were presented as median and interquartile ranges (IQR).

**Results:** 392 preterm infants were included, 55.8% male and 68.9% born by C-section. The median birth weight was 1060 (815-1325) grams, and for gestational age, 29 (27-30) weeks. The median of the monitoring time was 68.9 (47.7-91.0) hours. 102 (26.0%) newborns presented seizures, 67 (65.7%) repetitive. 89 (87.2%) seizures were subclinical, and 59 (57.8%) were identified in the first 24 hours of monitoring. Pathological background activity pattern was present in 82 (80.4%) newborns that had seizures and 94 (32.4%) of those without seizures ( $p < 0.0001$ ). Newborns <28 weeks had a higher percentage of 60.3% pathological background activity pattern and 30.5% presence of seizures. Very low-weight preterm newborns had a higher percentage of pathological patterns, 59.3%, and the presence of seizures, 32.9%. 96 (94.1%) newborns that presented seizures received antiepileptic drugs. Phenobarbital was the first line treatment in 100% of the cases, and in 59 (60.8%) cases was sufficient for total seizure control.

**Conclusions:** Given the high incidence of subclinical seizures in preterm infants, monitoring with video aEEG/EEG is essential for seizure diagnosis and management, as well as for the feasibility of the intervention in real-time.

Code: PE195

#### The impact of a telemedicine neuromonitoring protocol for perinatal asphyxia in neonatal intensive care units

Gabriel Fernando Todeschi Variante<sup>1</sup>, Daniela Pereira Rodrigues<sup>1</sup>, Nathalie Sales Llaguno<sup>1</sup>, Danieli Mayumi Kimura Leandro<sup>1</sup>, Rafaela Fabri Rodrigues Pietrobom<sup>1</sup>, Mauricio Magalhães<sup>1</sup>, Paula Natale Giroto<sup>1</sup>, Letícia Pereira de Brito Sampaio<sup>1</sup>

<sup>1</sup>Protecting Brains and Saving Futures, São Paulo, SP, Brazil

**Background:** Brain monitoring of high-risk neonates with integrated video amplitude electroencephalography associated with raw electroencephalography (video aEEG/EEG) is promoted by the Protecting Brains and Saving Futures (PBSF) Protocol which works within an advanced model of

telemedicine for specialized neonatal neurological care in neonatal ICUs.

**Objective:** To compare the incidence of clinical and electrographic seizures, and drug treatment of newborns assisted by the PBSF Protocol with those who did not, to assess the impact of implementing this protocol on the immediate outcome of neonates.

**Methods:** Prospective multicenter clinical study carried out in 12 NICUs between Feb/2021 and Feb/2022, six with the PBSF protocol implemented and six not. All newborns submitted to therapeutic hypothermia (TH) due to perinatal asphyxia with gestational age  $\geq 35$  weeks and birth weight  $\geq 1800$ g were included.

**Results:** 167 newborns were included and divided into PBSF group (n= 87) and non-PBSF group (n= 80). Video aEEG/EEG was performed in the PBSF group. PBSF group: Presence of more moderate or severe results on the modified Sarnat score (p= 0.002) compared to non-PBSF. TH was provided by active cooling in 67 (77.0%) and passive cooling in 20 (23.0%). All newborns were monitored with video aEEG/EEG, and 24 (27.6%) newborns presented electrographic seizures. Seizures were completely subclinical in 7 (29,2%) and clinical followed by subclinical in 6 (25%) newborns. Antiepileptic drugs were used in all newborns that presented electrographic seizures, and a single drug was able to achieve seizure control in 9 (37.5%) infants. Non-PBSF group: TH was provided by active cooling in 39 (48.7%) and passive cooling in 41 (51.3%). 46 (57.5%) newborns presented clinical suspicion of seizures and received antiepileptic drugs, with a significant difference (p<0.0001) compared to the PBSF group. A single drug achieved seizure control in 20 (43.5%). In both groups, seizure onset was most frequent between 1 to 12 hours of life and the first line treatment was phenobarbital. In the cranium MRI, 25 (62.5%) newborns in the PBSF and 10 (50%) in the non-PBSF group presented favorable results. Early outcomes were similar in both groups.

**Conclusions:** Non-PBSF group, without electrographic assessment, diagnosed seizures and used antiepileptic drugs twice times more than the PBSF group. It demonstrates the importance of implementing continuous neuromonitoring in high-risk newborns in the NICU.

#### Code: PE196

##### **The role of the continuous brain monitoring with video AEEG/EEG for neonates with suspected seizures**

Nicolas Rodrigues<sup>1</sup>, Daniela Pereira Rodrigues<sup>1</sup>, Nathalie Sales Llaguno<sup>1</sup>, Rafaela Fabri Rodrigues Pietrobom<sup>1</sup>, Mauricio Magalhães<sup>1</sup>, Paula Natale Giroto<sup>1</sup>, Letícia Pereira de Brito Sampaio<sup>1</sup>, Gabriel Fernando Todeschi Variane<sup>1</sup>

<sup>1</sup>Protecting Brains and Saving Futures, São Paulo SP, Brazil

**Background:** Seizures affect 1.5 - 1.3/1000 live births at term and are associated with worse neurodevelopmental outcomes. 80-90% of neonatal seizures are subclinical. Amplitude integrated electroencephalography associated with raw EEG and video images (video aEEG/EEG) is an alternative for seizure assessment at the bedside.

**Objective:** To assess, among neonates with clinical suspicion of seizures, which had seizures confirmed by video aEEG/EEG and to evaluate the characteristics of these patients, clinical signs most often associated with seizures and early outcomes.

**Methods:** Retrospective and descriptive study including neonates monitored with video aEEG/EEG, whose indication was clinical suspicion of seizure between August 2017 and October 2021. Data was collected by medical record review.

Categorical variables were described in absolute and relative numbers, and numerical variables were as median, 1st and 3rd interquartile range (IQR), or mean and standard deviation (SD).

**Results:** 80 monitoring of 66 newborns were included, 62% males and 53% born by cesarean section, with a median and IQR for birth weight of 2127 (1420-2960) grams. The mean monitoring duration was 38,3 (24-76,8) hours. The median gestational age was 35 (32-38) weeks. Newborns were divided into two groups, 13 (19.7%) with electrographic seizures and 53 (80.3%) without. Autonomic changes frequently led to the suspicion of a seizure in both groups, 10 (66.7%) in the seizures group and 27 (41.5%) in the non-seizure. The seizures group presented more than one sign in 7 (46.7%), while 16 (24.6%) were in the non-seizure group. In the seizure group, 1 (6.7%) had only clinical seizures, 3 (20%) had clinically followed by subclinical, and 11 (73.3%) were only subclinical. Phenobarbital was the most commonly used drug as a first-line treatment. Both groups had similar mortality, with 2 (15.4%) and 6 (11.3%) deaths in the seizure and non-seizure groups, respectively.

**Conclusions:** Diagnosis of neonatal seizures based on clinical signs is inaccurate. Video aEEG/EEG is an important tool to assess and monitor newborns at risk for brain injury. Brain monitoring makes the diagnosis accurate, avoiding the inadvertent administration of antiepileptic drugs in children with seizures and contributing to better long-term neurodevelopment.

## Outros

#### Code: PE201

##### **Epidemiologic profile of pediatric patients with signs and symptoms of intracranial hypertension and monitoring of brain compliance using a non-invasive device in a referral pediatric hospital in Brazil**

Simone Carreiro Vieira Karuta<sup>1</sup>, Caroline Mensor Folchini<sup>1</sup>, Maraine Campos Ricieri<sup>1</sup>, Fabio Araujo Motta<sup>1</sup>, Guilherme de Rosso Manços<sup>1</sup>, Adriano Keijiro Maeda<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Background:** Intracranial hypertension (IH) is a secondary clinical condition due to the loss of brain compensatory mechanisms, leading to increased intracranial pressure (ICP) and changes in cerebral blood flow, which can result in hypoxia, brain injury, and herniation. Brain4care (b4c) is a device that explores variations in intracranial compliance and allows the measurement of ICP in a non-invasive and serial way, in addition, it can predict the evolution trend of the IH clinical syndrome.

**Objective:** To characterize the epidemiological profile of patients with signs and symptoms of IH in the pediatric age group and describe the results of the tests used to assess the clinical condition.

**Methods:** Observational and cross-sectional study has been carried out in a reference pediatric hospital in Brazil, in patients with signs and symptoms of IH. After a neurological medical evaluation, the following tests were performed – non-invasive ICP monitoring with B4C, ophthalmoscopy, tomography (CT), magnetic resonance imaging (MRI), and lumbar puncture.

**Results:** To describe the epidemiological profile of IH 58 patients were evaluated, of which 32 were female (55.2%), 26 were male (44.8%), and the median age was 10 (3-17). Most patients had symptoms such as drowsiness (81%),

nausea (77.6%), headache (74.1%), vomiting (63.8%), and dizziness (53.4%). Ophthalmoscopic examination on 77.6% (n= 58) patients did not show signs of papilledema. On CT and MRI, no changes were found in 84.5% (n= 58), and 69.2% (n= 26), respectively. Lumbar puncture was abnormal in 57.1% (n= 21). Based on the published studies of the b4c values in the adult population, monitoring with the device (n= 58) showed a possible change in the sitting and lying position, respectively, of 46.3% and 38.9% in pediatric patients.

**Conclusions:** It was possible to describe the profile of pediatric patients monitored by a non-invasive device with signs and symptoms of IH, which so far has not been described in the literature. Furthermore, it was found that the b4c device provides a possible complement of clinical information in the process of monitoring brain compliance.

## Code: PE202

### Quality of life in down syndrome in Brazil

Beatriz Elizabeth Bagatin Veleda Bermudez<sup>1</sup>, Ana C. S. Crippa<sup>1</sup>, Iolanda Maria Novadzki<sup>1</sup>, Leo Coutinho<sup>1</sup>, Gustavo L. Franklin<sup>2</sup>

<sup>1</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>2</sup>Pontifícia Universidade Católica de Curitiba, Curitiba PR, Brazil

**Background:** Down syndrome (DS) is the most common identified genetic cause of developmental delay and intellectual disability. DS is characterized by a regular trisomy 21 in 95% of the cases and 5% in the form of translocation and/or mosaicism (Malt et al., 2013). Because of the presence of extra genetic material from chromosome 21, children with Down syndrome have medical conditions, cognitive impairment, multiple malformations, such as congenital heart defect, present in 50% of the patients. While there have been scientific advances in general health, a few people with DS have an independent life, most of them live with their parents, some work and few are married or have a post-secondary education. Their potential and capacity are not considered, nor are effective therapeutic approaches used to develop them to the fullest.

**Objective:** To assess the major determining factors of quality of life among patients with Down syndrome in a large cohort in Brazil.

**Methods:** Data were gathered from the medical files of 1,187 patients with Down syndrome. Patients older than 4 years-old were included, and assessed to factors of quality of life, based on a Portuguese validated version of the Personal Outcomes Scale.

**Results:** Parents finished high school education or higher of 44%. The percentage of professionally active mothers was 54.8%. The prenatal follow-up was 94.8% and the pregnancies progressed to normal delivery in 52.8%. The prematurity index was 13.4%. Good quality of life was associated with female sex, age at medical first visit less than four months, higher parental education, active professionally mother, prenatal care, no use of alcohol or family psychiatric disorder, genetic mosaicism, no autism nor epilepsy.

**Conclusions:** Many factors may influence the quality of life of patients with DS and should be the object of health policies and attention to patient care. Good quality of life was associated with female sex, age at medical first visit less than four months, higher parental education, active professionally mother, prenatal care, among others.

## Code: PE205

### Hospital morbidity from nervous system diseases in the pediatric population in the Brazilian health system

Sara Julia Zorzi de Brum<sup>1</sup>, Augusto Nicaretta<sup>2</sup>, Fabiana de Abreu Getulino<sup>3</sup>, Julia Pustrelo Moro<sup>3</sup>, Vinicius Estanislau Albergaria<sup>1</sup>

<sup>1</sup>Universidade Federal da Fronteira Sul, Passo Fundo RS, Brazil

<sup>2</sup>Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil

<sup>3</sup>Universidade Federal de Rio Grande, Rio Grande RS, Brazil

**Background:** Hospital morbidity corresponds to the percentage distribution of hospital admission by groups of selected causes.

**Objective:** The aim of this study was to describe the hospitalizations for diseases of the nervous system in the pediatric population in Brazil from 2010 to 2019.

**Methods:** An ecological study was carried out in July 2022 from the health information of the Brazilian Health Unified System databases. All hospital pediatric admissions resulting from the international classification of diseases (ICD), chapter VI in Brazil from 2010 to 2019 were included. The main variables analyzed were sex, age (0-14), elective or urgency character, regime of hospitalization and geographic region. Descriptive statistics were performed though absolute (n) and relative (%) frequencies.

**Results:** A total of 387,472 hospital admissions were identified for diseases of the nervous system in children, with an increase from 36,386 in 2010 to 43,722 in 2019. Most patients were male (55.1%), aged between 1 and 4 years old (33.9%) and urgent service (80%). Most frequent comorbidities, according to the ICD, were epilepsy (53.2%), other diseases of the nervous system (28.5%) and cerebral paralysis and other paralytic syndromes (7.7%). The largest number of hospitalizations occurred in the Southeast (38.8%), followed by the Northeast (27.6%), South (18.9%), Central-West (8.5%) and North (6.2%).

**Conclusions:** There was an increase in hospitalizations for diseases of the nervous system in the pediatric population, with emphasis on the number of emergency care. In order to reduce hospitalizations, it is necessary to expand the screening and early diagnosis of such diseases.

## Code: PE207

### Child neurology residency in Brazil: current scenario

Paula Thaís Bandeira Elias<sup>1</sup>, Maria Luiza Benevides<sup>1</sup>, Tarcízio Brito<sup>2</sup>, Larissa Torres<sup>2</sup>, Leticia Pereira Brito Sampaio<sup>2</sup>, Ana Carolina Coan<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas SP, Brazil

<sup>2</sup>Universidade de São Paulo, São Paulo SP, Brazil

**Background:** Child neurology is a complex medical specialty which involves distinct areas of knowledge. Presently, in Brazil, there are 26 child neurology residency programs. Science and education have considerably developed in the last twenty years, so data about the present scenario in this area are needed.

**Objective:** To investigate the current scenario of child neurology residency programs in Brazil.

**Methods:** The medical in charge of each of the 26 residency child neurology programs in Brazil were invited to fulfill an online structured questionnaire that included information about the hospital's physical structures, accessibility to exams and medical specialties, medical teams, and residents' performance. A descriptive analysis characterized the sample. Quantitative and qualitative variables were expressed as means and standard deviations (SDs), and as frequencies and percentages, respectively.

**Results:** Twenty-three (23/26; 88%) invited directors fulfilled the questionnaire. Considering the physical structure, 21 (91.3%) residencies are located in teaching hospitals. Child neurology is a consultant medical specialty in 13 (56.5%) hospitals. The average number of hospital beds in pediatric ward is 72.9 (SD±91.7), and in child neurology ward is 2.4 (SD±3.9). Referring to neuroimaging, brain ultrasonography and brain CT are available in all centers, and MRI in 16 (69.6%). The genetic, neurosurgery, psychiatry, and radiology specialties are accessible in most centers. Epilepsy, general child neurology, and neurodevelopmental disorders represent the higher number of patients in the outpatient clinics. The child neurology staff is formed by a mean of 5.9 (SD±2.6) tutors. There is a mean of 2.9 (SD±1.3) annually vacancies for child neurology medical residents. Around 2.5 candidates per year are pediatricians, and 0.7 are neurologists. Considering medical residents' performance, professors evaluated that by the end of their training, their ethical posture as excellent or good. The knowledge about neuroanatomy, neurophysiology, and semiology was rated as good, as well as interpretation and understanding of genetic tests. Their ability to indicate neuroimaging exams, such as CT or MRI, was considered excellent.

**Conclusions:** This survey comprehended almost all child neurology residency programs in Brazil, delineating the physical structure, medical team, availability of exams, and residents' performance. Future studies might use this scenario to establish improvement measures in residency programs.

#### Code: PE211

##### **Study of factors associated with the level of autism spectrum disorder in a clinical sample**

Mariane Wehmuth<sup>1</sup>, Sérgio Antônio Antoniuk<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Centro de Neuropediatria, Curitiba PR, Brazil

**Background:** Autism Spectrum Disorder (ASD) is a heterogeneous Neurodevelopmental Disorder that causes an impairment of social communication and repetitive behaviors. It can be divided into levels 1 to 3, depending on the level of support required. Language and Cognitive Development are the most determining factors to ASD level. However, other situations can interfere with the level of ASD, such as perinatal risk factors, gender, delay or language regression, self-injury, neurological conditions and psychiatric behaviors.

**Objective:** To analyze how these factors can be related to the ASD.

**Methods:** This is a cross-sectional analytical observational study of 470 individuals aged 1 to 18 years diagnosed with ASD in outpatient follow-up.

**Results:** There was a predominance of males in a 4:1 ratio and ASD level 1 in 46% of the sample. There was no association between gender and level of commitment. Among perinatal risk factors, prematurity was the most frequent and is associated with ASD level 3, with a prevalence 2.6 times higher than in the rest of the sample. 12% presented language regression and 70% language delay, being more frequent in levels 2 and 3. Self-injury behaviors was present in 11% of the sample, being more common also in ASD level 3. Between the psychiatric disorders symptoms, the attention deficit hyperactivity disorder were more frequent in ASD level 1, as well as depressive symptoms and suicidal ideation. There was no

correlation between anxiety symptoms and ASD level. Sleep disorders were reported in 15% of the sample, with no relation to ASD level. Apraxia of speech was more common in patients with ASD level 3. Epilepsy was present in 5% of the sample, with a prevalence 5 times higher in ASD level 3 and the presence of an abnormal Electroencephalogram, with or without Epilepsy had a prevalence 1.9 times higher in ASD level 3.

**Conclusions:** ASD is a heterogeneous disorder and specific factors can interfere with its level of impairment and life quality of these individuals.

#### Code: PE212

##### **The use of artificial intelligence tools in the elucidation of cases of neurodevelopmental disorders**

Carlos Magno Leprevost<sup>1</sup>

<sup>1</sup>Instituto de Genética Médica Dr. Carlos Leprevost, Ribeirão Preto SP, Brazil

**Introduction:** Neurodevelopmental disorders (NDD) form a complex set of differential diagnoses in clinical practice. Research tools, neuroimaging, cytogenetics, and next-generation sequencing (NGS) aid in elucidation. Still, the complexity of phenotypes, the absence of local genetic data leading to many variants of uncertain significance (VUS) and barriers to accessing such tests are limiting factors.

**Objective:** Case presentation, showing how the use of artificial intelligence (AI) tools can help target the etiology of NDD.

**Methods:** Male, 13 years old, with developmental delay, moderate intellectual disability, and extensive diagnostic journey by more than 40 specialists, with conflicting diagnoses, including guilt for the family for the lack of patient adequate stimulation. On examination was observed hyper-telorism, downward palpebral fissure, long nasolabial philtrum, large ears, thick eyebrows, short nose with wide columella, thick and everted lips. Investigational testing with no changes except for brain MRIs from 2019 and 2022 with T2 and flair hypersignal in the periventricular and subcortical white matter in the frontal lobes. NGS panel of leukodystrophies with 835 genes was performed reporting VUSes in heterozygosity 13 of them (ACY1, CNTNAP2, CYP2U1, FGFR1, NIPBL, RPS6KA3, NT5C2, SLC1A2, SLC46A1, WDR73, ZNF335, ACADS, GALC).

**Results:** The refinement started by discarding variants in genes with a recessive pattern or not consistent with the case phenotype. Afterwards, the Face2Fene® AI tool was used, which indicated a high gestalt for Coffin-Lowry Syndrome, a X-linked NDD syndrome caused by RPS6KA3 mutations. A segregation study was carried out in the mother, concluding that it was a de novo mutation. The updated information was shared with the laboratory, which reclassified the variant RPS6KA3 c.709C>T (p.Pro237Ser) from VUS to Pathogenic, confirming the diagnosis of Coffin-Lowry Syndrome.

**Conclusions:** The finding of VUS is common when requesting genetic panels and exome, especially in Hispanic population. The case presented showed how the association of the phenotype with analysis of family segregation and the use of AI tools are allies in shortening the journey of patients with NDD, enabling proper follow-up and treatment.

Code: PE213

**Video Head Impulse Test (VHIT) in preadolescents with dizziness could be a safe choice?**

David Greco Varela<sup>1</sup>, Luciana Cristina de Carvalho Santos<sup>2</sup>, Monique Medeiros de Moura Barreto Alves<sup>3</sup>, José Gilvan Gama de Jesus Dias<sup>1</sup>, Rilvan Galileu Fernandes Oliveira do Nascimento<sup>1</sup>, Mateus Gomes da Silva Serra<sup>1</sup>, Antonio de Souza Andrade Filho<sup>1</sup>

<sup>1</sup>Fundação de Neurologia e Neurocirurgia, Instituto do Cérebro, Salvador BA, Brazil

<sup>2</sup>Instituto de Medicina Especializada da Bahia, Salvador BA, Brazil

<sup>3</sup>Hospital Santa Izelabel, Serviço de Otorrinolaringologia, Salvador BA, Brazil

**Background:** The detection of objective changes in the vestibulo-ocular reflex (VOR) in preadolescents with complaint of dizziness is not easy to be registered. The Video Head Impulse Test (VHIT) is an objective exam that quickly analyzes this subject in adults and could be an alternative to this age group.

**Objective:** Verify the feasibility of performing the Video Head Impulse Test (VHIT) in preadolescents with dizziness.

**Methods:** Preadolescents with dizziness crisis in the last thirty days were included in the study. They should not have had cervical or visual diseases and must be collaborative to the head movements during the exam. Audiometry was performed and might be normal. Middle and outer otitis were excluded. Video Head Impulse signal were captured from the eye with the best visual acuity. Stimulation was performed in three axes: 1) from the right anterior semicircular canal to the left posterior one (RALP); 2) from the left anterior semicircular canal to the right posterior one (LARP) and 3) from the right lateral canal to the left one. At end, vestibulo-ocular gain could be measured in each six semicircular canals. The sample consisted of three boys (3/5) and two girls (2/5). Age ranged between 10 and 13 years. Mean was 11.4 years and median was 11 years.

**Results:** The analysis of the vestibulo-ocular reflex in every six semicircular canals could be performed because it was possible to be obtained between seven and fifteen reliable samples of signals for the five participants. None of them had any complaints during or after the examination. The gain means of the right and left lateral semicircular canal was 0.87. The gain mean of the right posterior semicircular canal was 0.90 and 0.95 for the left one. The gain mean of the right anterior semicircular canal was 0.93 and 1.09 for the left one. Gain was considered normal for two participants of the sample, decreased gain was found in a single lateral semicircular canal for two preadolescents and decreased gain was found in a single posterior semicircular canal for another one.

**Conclusions:** In the current study, Video Head Impulse Test (VHIT) was safely applied and the vestibulo-ocular signals obtained were reliable for the studied group with dizziness. The gain analysis can help the physician in the propaedeutic of diseases that affect the semicircular canals and the vestibular nerve of preadolescents.

## Reabilitação

Code: PE214

**Animal-assisted therapy in the process of physical and mental rehabilitation of patients with disabilities**

Arthur Carvalhal Gonçalves<sup>1</sup>, Livia Coutinho Silveira<sup>1</sup>

<sup>1</sup>Universidade Iguazu, Itaperuna RJ, Brazil

**Background:** Animal-assisted therapy is the use of animals in the therapeutic environment for the healing and rehabilita-

tion of the patient. This intervention is still not widespread; however, clinical practice shows the great and positive impacts that this treatment promotes in the process of physical and mental rehabilitation of patients with disabilities.

**Objective:** The main objective of this paper is to show how animals can be used in the therapeutic environment to promote the physical and mental rehabilitation of patients with disabilities.

**Methods:** For this study the "systematic literature review" method was used by means of carrying out retrospective observation of articles and studies or experimental studies of recovery and critical analysis of the literature.

**Results:** In order to talk about TAA (animal-assisted therapy), a trained multidisciplinary team is needed, so that each one in his/her specialty may contribute to the success of such a complex relationship that involves the animal, the therapist and the human patient). It is also important that a veterinarian is part of the team to manage the animal's behavior, knowing how to intervene in case any adverse situation occurs. It is possible to establish a great affective bond between the patient and the animal, making the intervention more effective and reaching the goals programmed by the professionals involved in the treatment. Animals may improve cognitive ability, balance, and motor coordination through stimuli (sensory, motor or affective) besides being part of several other activities that encompass the assisted person.

**Conclusions:** Animal-assisted therapy can be very beneficial for people of all ages, whether an elderly person or a child. Several patients – carriers of various diseases – can achieve great improvement with such kind of intervention. Patients with Alzheimer's disease; the emotionally and mentally ill; developmentally delayed children and adults; and children with Down's syndrome, cerebral palsy, brain damage and learning disabilities, all these diseases may improve potentially with the help of animal therapists. However, it is important to point out that it is necessary a specialized professional in the training of this kind of animal and in the training of other therapists involved in the treatment.

Code: PE215

**Short, medium and long term pituitary neuroradiological follow-up in children and adolescents after traumatic brain injury**

Eliane Cespedes Paes Huard<sup>1</sup>, Luis Claudio Gonçalves Castro<sup>2</sup>, Bernardo Jose Alves Ferreira Martins<sup>1</sup>

<sup>1</sup>Associação das Pioneiras Sociais, Hospitais de Reabilitação, Rede SARAH, Brasília DF, Brazil

<sup>2</sup>Universidade de Brasília, Brasília DF, Brazil

**Background:** Pituitary Radiological study is important to evaluate hypothalamus/hypophysis axis problems. There are studies that describe correlation between pituitary radiological abnormalities and hipopituitarism at general population, but few studies describe neuroradiological abnormalities after traumatic brain injury in pediatric population, and, when they do, it's only at isolated case reports.

**Objective:** Studying routine traumatic brain injured patients' magnetic resonance images (MRI), evaluating pituitary morphology and volume in a pediatric population.

**Methods:** It is a longitudinal retrospective cases serie study, including 78 children and adolescents that are being followed at our Rehabilitation Center between 2009 and 2021. MRI Technique 1,5 or 3,0 millimeter contiguous sagittal and coronal plain through the sella were obtained using

superconducting MRI units. A Developmental and Rehabilitation Pediatrician has been trained by a Neuroradiologist and performed at the morphological pituitary analysis. Pituitary volume was measured using the formula: coronal width X coronal height X sagittal width X 0,5. The results were compared to pre-existing parameters for age and sex. We used the Program AquariusNet Viwer (AqNet) Versão V4.4.13.P4 (522).

**Results:** We studied 47 males and 31 females. Some patients had more than one sequential study, so, totally, we evaluated 151 images. Age at MRI test went from 11 months old to 18 years old. Age at traumatic brain injury went from 0,2 to 16,9 years old. Time after traumatic brain injury went from 0,2 to 14 follow up years. We found pituitary abnormalitie at 29 from 123 MRI exams (23%) or in 25 from 74 patients (32%). All patients with radiological pituitary abnormalities had previous severe traumatic brain injury, according to Glasgow Coma Scale. From those patients, 72% were females. We found two “empty sella syndrome” situations, one caused by “pituitary stalk transection syndrome”; one pituitary cyst (Rathke); and 22 cases with pituitary volume inferior to normal references. with pituitary hormone deficiency. These abnormalities are more prevalent in MPHD. In both adults and children, ectopic posterior pituitary bright spot (EPPBS) at the median eminence was a universal finding in all patients.

**Conclusions:** Structural pituitary abnormalities have been found in 32% of our patients. It is important to closely follow-up these patients in the long-term so that their natural history of progressive radiological and hormonal deterioration can be ascertained.

#### Code: PE216

##### **Cuevas Medek exercises a neurological rehabilitation for children, the effect in developmental hip dysplasia in a patient with cerebral palsy: case study**

Andreas Dreckmann Ferreira<sup>1</sup>, Laís Rodrigues Gerzson<sup>1</sup>, Carla Skilhan de Almeida<sup>1</sup>, Gislaïne Bacarin Lopes<sup>2</sup>

<sup>1</sup>Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil

<sup>2</sup>Clínica Pro Forma, Curitiba PR, Brazil

**Introduction:** Cuevas Medek Exercises is a physical therapy approach for child with abnormal motor evolution affecting the Central Nervous. The corrections of the movements are done through sensory input from the therapist's hands and sensory-motor system to organize coordinating structures by a neural group selecting theory.

**Objective:** To evaluate the effect of CME on the Developmental Dysplasia of the Hip (DDH) in a patient with Cerebral Palsy (CP).

**Methods:** The research is characterized as a case study, having as a participant a six-year-old girl with CP, tetraparesis and bilateral hip dysplasia. The interventions started after an initial evaluation developed exclusively with the CME method, hip radiography and classification in the Gross Motor Function Classification System (GMFCS) levels. The child went through CME therapy to treat DDH for 10 months, totaling 136 sessions (45 minutes each), consisting of four to six repeated exercises, six times on average. The time and/or how many repetitions she managed to perform were recorded. At the end, the evaluations were done again.

**Results:** Evolved from 55 to 61 points in the CME score, improved her motor age and, in the hip radiography, the left went from subluxated to at-risk hip.

**Conclusion:** The patient improved motor age, trunk control and bipedestation, autonomy, and hip fitting on both sides.

#### Code: PE218

##### **Pharmacological management of chronic pain in children and adolescents with cerebral palsy and hip dislocation**

Betânia Souza Oliveira<sup>1</sup>, Erica Ueno Imamura<sup>1</sup>, Eliana Valverde Magro Borigato<sup>1</sup>, Oton Naziazene Lima<sup>1</sup>, Clarissa Miranda Carneiro Albuquerque Olbertz<sup>1</sup>, Bruno Barbosa Oliveira Silva<sup>1</sup>

<sup>1</sup>Hospital SARAH Brasília, Brasília DF, Brazil

**Background:** Chronic pain is a common and significant issue in individuals with cerebral palsy, more frequent in those with greater neurological impairment, predominantly in the lower limbs, hip, and abdomen. Hip dislocation is one of the main causes of pain in this population, even in those submitted to orthopedic treatment, leading to difficulty in sleeping, eating, positioning, and daily care. The use of chronic pain medications in this context can assist in the management of these patients.

**Objective:** To present the response to drug treatment for chronic hip pain in patients with cerebral palsy.

**Methods:** Prospective study with evaluation of chronic hip pain complaints in patients with bilateral cerebral palsy starting from December 2020 at SARAH/Brasília Hospital. A pain scale (Pediatric Pain Profile – PPP) validated in Brazil for this population (Inventory of Pain Behavior in Neurological Disability – ICDDN) was used and treatment with amitriptyline and/or gabapentin was instituted.

**Results:** We followed 32 patients with bilateral cerebral palsy and chronic hip pain, 28 with hip dislocation, and four with subluxation, mean age of 14 years, 48% female. In the GMFCS (Gross Motor Function Classification System) classification two patients were level IV and 30 level V. Fourteen had undergone hip surgery (tenotomy, reconstruction surgery, or salvage surgery) and 15 had undergone one or more intra-articular injections (infiltration) with depomedrol and anesthetic associated with the anterior branch of the obturator nerve block for pain treatment but maintained this complaint. Amitriptyline was indicated for 22 patients, gabapentin for 19, with nine patients requiring a combination of both medications. All patients took the pain inventory (ICDDN) before and after the introduction of medication. Improvement of pain complaints was observed in 81% of patients. There was a significant reduction in pain scores ( $p < 0.0001$ ). Persistent or recurrent pain was observed in six patients (19%), four of whom underwent hip infiltration and two reconstruction surgery. The mean follow-up was 12 months. **Conclusions:** The use of amitriptyline and/or gabapentin for the treatment of chronic hip pain in individuals with cerebral palsy resulted in better pain control, being a good coadjuvant therapeutic option in the follow-up of these patients.

## Transtornos do sono

#### Code: PE229

##### **Changes in the sleep latency time of adolescents seen at the hebiatria service of a tertiary hospital in Paraná state after confinement of the COVID-19 pandemic**

Liara Bohnert<sup>1</sup>, Ana Chrystina de Souza Crippa<sup>1</sup>, Leticia Pugim Ferreira<sup>1</sup>, Beatriz Elizabeth Bagatin Veleda Bermudez<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Hospital de Clínicas, Curitiba PR, Brazil

**Background:** Sleep characteristics vary throughout life, with a well-documented night preference among adolescents from 12 years of age onwards, with a predilection for later times to sleep and waking up. The COVID-19 outbreak caused an impact on the adolescent sleep patterns, including sleep

duration, latency, time, quality and onset of insomnia symptoms.

**Objective:** This study aimed to evaluate the sleep latency time of adolescents treated at the Hebiatrics service of a tertiary hospital after the period of lockdown due to the COVID-19 pandemic, checking this sleep behavior in adolescents with return of present learning.

**Methods:** A cross-sectional observational study was carried out in 55 patients treated at the Hebiatry Service of the Hospital de Clínicas do Paraná, aged between 12 and 18 years, with the application of the Pittsburgh Sleep Quality Index questionnaire (1989).

**Results:** The sleep latency time of adolescents after a period of social isolation with home-schooling ranged from 0 to 120 minutes and was greater than 15 minutes in 27 patients (49%), with an average of 26.5 minutes and a median of 15 minutes, which refers to an increase in latency time compared to studies that occurred in periods prior to the pandemic.

**Conclusions:** There was a change in the sleep pattern of adolescents after the period of social isolation, which may represent a worsening in sleep quality. It is important to be aware of changes in the sleep behaviors of adolescents, since changes in sleep patterns in this age group can have consequences for a decline in cognitive and physical performance, in addition to an increase in the morbidity and mortality rate, so it is important to intervene in this stage of life so that there are no future consequences.

Code: PE230

#### Sleep disturbances in children with learning difficulties

Débora Cristina Przybysz<sup>1</sup>, Ana Chrystina Crippa<sup>1</sup>, Isac Bruck<sup>1</sup>, Ana Paula Lopes Luiz<sup>2</sup>, Ana Paula Dassie Leite<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>2</sup>Faculdade Evangélica Mackenzie do Paraná, Curitiba PR, Brazil

**Background:** For most children, the process of learning how to read, write and math skills happens without great difficulties. However, in some cases, as a result of several factors, this process can be impaired and altered. Learning difficulties are increasingly frequent and can be impacted by environmental aspects. Children with learning difficulties may experience worsening of their conditions due to several factors, such as sleep, attention, memory, routine changes, changes in the way of teaching, among others. The quality of sleep is fundamental for the individual's overall health and for school learning, with impacts on attention, memory, concentration and logical reasoning.

**Objective:** To investigate the sleep quality of children with learning difficulties and the association among sleep disturbances and learning difficulties.

**Methods:** Observational, cross-sectional, retrospective research. For sleep investigation, the Sleep Disturbances Scale for Children was used. The research sample consisted of children referred to the Neuropediatrics center, who were later referred to the School Disorders' Outpatient Clinic and received a diagnosis of learning difficulties after evaluation by a multidisciplinary team.

**Results:** The sample consisted predominantly of boys, totaling 56%, while 44% were girls. As for school failure, 4% have already failed. Quantitative data revealed that 88.3% of children with learning difficulties also have sleep-related complaints, with high rates of associated sleep disorders. Of the group surveyed, 25% wake up in the morning feeling tired.

**Conclusions:** The data collected revealed that most children with learning difficulties also have sleep-related complaints,

with high rates of associated sleep disturbances. The research also revealed that the worse the sleep quality of these children, greater the learning complaints. This indicates the importance of sleep for child development and learning, as well as the need for an integral look at the child learning process, considering environmental aspects.

## Transtornos neuropsiquiátricos e distúrbios de aprendizagem

Code: PE232

#### Analysis of aspects and impacts of attention deficit and hyperactivity disorder in child neurodevelopment: a narrative review of the past 10 years (2012-2022)

Eduardo Crístian Oliveira de Souza Mota<sup>1</sup>, Jonas Gabriel Araripe Dantas<sup>2</sup>, Gabriel Vitor Oliveira de Souza Mota<sup>1</sup>, Alyssa Maria Rigon Bueno<sup>1</sup>, Kauê Magalhães Castro dos Santos<sup>1</sup>, Douglas Machado da Costa<sup>1</sup>, Lucas Sousa e Souza<sup>1</sup>, Ana Paula Palheta Faria<sup>1</sup>, Renato Lobato da Costa Nunes<sup>1</sup>

<sup>1</sup>Universidade Federal do Amapá, Macapá AP, Brazil

<sup>2</sup>Centro Universitário Aparício Carvalho, Porto Velho RO, Brazil

**Background:** Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental pathology characterized by persistent degrees of inattention, hyperactivity and impulsivity - manifested in various spheres in which the individual is inserted - and is associated with neural aspects of the prefrontal cortex. In this sense, the disorder directly affects the learning and development of children.

**Objective:** To understand the main pathophysiological and symptomatic aspects of ADHD in children and the impact of such a disorder on the quality of life of patients.

**Methods:** Literature Review Study based on research in PubMed, CAPES Journal and SCIELO databases using the descriptors "Attention Deficit Hyperactivity Disorder", "Physiopathology" and "Impacts". The inclusion criteria were articles published between the years 2012-22 in Portuguese or English; and, as exclusion methods, articles that preceded the period 2012.

**Results:** After the research and application of the filters, 13 articles were selected for discussion regarding physiology: 70% of the articles found deal with the pathology of the disorder being intrinsic to deficits in the neural circuits of the prefrontal cortex and the action of neurotransmitters of the dopaminergic and noradrenergic pathway. On the other hand, 30% of the articles address other aspects such as a delay in myelination of the prefrontal cortex, impacting on anatomical and functional aspects of the region. Under another bias, it was analyzed the impact that the symptoms of ADHD brings to children living with the disorder: it was highlighted in 12 studies that ADHD has an impact on learning and school development and may result in damage to adulthood. Moreover, it was denoted, through 6 studies, that children with ADHD tend to have losses in their personal relationships and in the development of personal aspects - such as trust and security.

**Conclusions:** Therefore, it is concluded from the study presented that ADHD is a disorder of pathophysiological complexity that acts, in general, on the prefrontal cortex. Consequently, it brings losses to the development of children with the disorder - especially those inserted in the school environment, who may acquire difficulties in their learning if there is no adequate management of the disorder.



Code: PE233

**Application of a questionnaire for screening anxiety disorder in adolescents**

Estela Cristina Giglio de Sousa<sup>1</sup>, João Victor Pereira de Sousa<sup>1</sup>, André Curioletti Pereira<sup>1</sup>, Amanda Fontana Gouveia<sup>1</sup>, Ana Claudia de Araujo Argentino<sup>1</sup>, Rafaela Sorpile Araujo<sup>1</sup>, Carmem Denise Royer<sup>1</sup>, Gleice Fernanda Costa Pinto Gabriel<sup>1</sup>, Marcos Antonio da Silva Cristovam<sup>1</sup>

<sup>1</sup>Universidade Estadual do Oeste do Paraná, Cascavel PR, Brazil

**Background:** Anxiety disorder involves physiological, cognitive, and behavioral components. When the anxious response becomes distorted and/or dysfunctional, the adolescents experience losses in several environments (school, family, and social). The causes of the anxiety disorders are multifactorial; therefore, high prevalence and difficult prognosis justify the necessity of studies and investments in programs that reduce the incidence of anxiety disorders in adolescents. **Objective:** To administer a Generalized Anxiety Disorder Screening questionnaire in adolescents assisted at an outpatient clinic of medicine of adolescents and other sectors of a university hospital.

**Methods:** To application the Multidimensional Anxiety Scale for Children (MASC) questionnaire, which is a self-report scale used to assess anxiety in children and adolescents in the affective, physical, cognitive, and behavioral domains. The cutoff point adopted for this research was 56 points, situation in which assessment by a mental health professional would be indicated. The questionnaire was administered to adolescents whose age ranged from 11 to 16 years, treated at an outpatient clinic for adolescents and in other sectors of a university hospital.

**Results:** 60 questionnaires were administered to the adolescents, three of which (5%) were invalidated due to being incompletely filled. The age ranged from 11 to 16 years, and the average age was 13 years. Among the 57 (97%) adolescents who completed the questionnaire properly, 31 (54.3%) were male and 26 (45.6%) were female. 21 (36.8%) scored for generalized anxiety disorder, six of which (28.5%) were male and 15 (71.4%) were female.

**Conclusions:** Anxiety disorder is a common situation in teenagers, usually in girls. In this study, there was a prevalence of anxiety in girls, which corroborates findings in literature.

Code: PE234

**Application of conners rating scale on school with underachievement academic**

Sthefanny Josephine Klein Ottoni Guedes<sup>1</sup>, Giovana Pereira de Oliveira<sup>1</sup>, João Victor Pereira de Sousa<sup>1</sup>, André Curioletti Pereira<sup>1</sup>, Guilherme Fernandes Kula<sup>1</sup>, Carmem Denise Royer<sup>1</sup>, Mariana Defazio Zomerfeld<sup>1</sup>, Fernanda Bortolanza Hernandes<sup>1</sup>, Marcos Antonio da Silva Cristovam<sup>1</sup>

<sup>1</sup>Universidade Estadual do Oeste do Paraná, Cascavel PR, Brazil

**Background:** Attention deficit hyperactivity disorder (ADHD) is one of the most frequent behavioral disorders diagnosed in childhood, causing damage to the child's neurocognitive development.

**Objective:** The aim of this study was to apply the Conners Rating Scale- Francisco Rosa Neto's Brazilian Version on schoolchildren with academic underachievement.

**Methods:** Application of the Conners Rating Scale filled by psychologist during evaluation in academic underachievement outpatient clinic from a university hospital, to assess the prevalence of ADHD and its subtypes in the context of academic failure, ranging grade from preschool to ninth grade.

**Results:** The questionnaire was applied to 34 children, 20 males and 14 females, between 6 and 13 years. The majority (71.4% girls, 50% boys) presented attention deficit. Similarly, hyperactivity and inattention (64.2% girls, 45% boys), hyperactivity/impulsivity (21.4% girls, 20% boys), conduct disorder (CT) (35.7% girls, 35% boys) and overall ADHD (42.8% girls, 30% boys) were more prevalent in girls. The mean age among students with attention deficit was 9.05 years; with hyperactivity/impulsivity, 9.21 years; with hyperactivity and inattention, 8.81 years; with CT, 8 years; and with predominance of global ADHD was 8.58 years. No relation between obesity and ADHD was observed in the present study. 50% of obese children did not score for any of the behavioral disorders. In addition, 57.1% of the girls and 55% of the boys were eutrophic.

**Conclusions:** The relation with academic impairment was evidenced by the high prevalence of attention deficit symptoms alone, diverging from the literature, in which the predominance is of the combined type. Regarding gender, the result – higher absolute number of boys and higher prevalence of CT in females – differed from the literature data. However, there was agreement in the predominance of inattention, which was more frequent in females. There was little variation in average age for each sex concerning specific age for each learning disorder. No relationship was found between obesity and ADHD.

Code: PE235

**Application of pediatric symptoms checklist in students with academic underachievement**

Eduarda Stritthorst<sup>1</sup>, Bruna Freire Ribeiro<sup>2</sup>, Sthefanny Josephine Klein Ottoni Guedes<sup>1</sup>, Taynara Cristina Paixão<sup>1</sup>, Fernanda Bortolanza Hernandes<sup>1</sup>, Carmem Denise Royer<sup>1</sup>, Mariana Defazio Zomerfeld<sup>1</sup>, Gleice Fernanda Costa Pinto Gabriel<sup>1</sup>, Marcos Antonio da Silva Cristovam<sup>1</sup>

<sup>1</sup>Universidade Estadual do Oeste do Paraná, Cascavel PR, Brazil

<sup>2</sup>Faculdade Assis Gurgacz, Cascavel PR, Brazil

**Background:** Validated instruments for screening of behavioral and emotional problems, although not being diagnostic tools, allow the survey of positive cases for various mental health problems of childhood and adolescence. Students with academic underachievement are more likely to present some psychosocial or emotional problem which corroborates the lack acquisition of knowledge. The objective of this research was carried out a screening to emotional and psychosocial problems in children with academic underachievement by application of Pediatric Symptoms Checklist (PSC).

**Objective:** Analysis of a cohort of children and adolescents, age ranging from 6 to 14 years old, in follow-up at the academic underachievement outpatient clinic of a University Hospital in West Paraná State. Analyzed variables were PSC score, sex, age, grade and Body Mass Index and their correlation. To this research the cut off to PSC was  $\geq 28$ , situation in which children or adolescents should be referred to specialist in mental health.

**Methods:** It was included 117 children, of which 80 (68.4%) were male and 37 (31.6%) female. Average age was 8,71 ( $\pm 1.71$ ). 85 (72.65%) presented negative PSC score and 32 (27.35%) were positive PSC score. The analysis of covariance showed that, in addition to age, positivity on the PSC scale was a direct and independent predictor of school grade ( $P < 0.001$  and  $P = 0.004$ , respectively).

**Results:** It was included 117 children, of which 80 (68.4%) were male and 37 (31.6%) female. Average age was 8.71 ( $\pm 1.71$ ). 85 (72.65%) presented negative PSC score and 32 (27.35%) were positive PSC score. The analysis of covariance showed that, in addition to age, positivity on the PSC scale was a direct and independent predictor of school grade ( $P < 0.001$  and  $P = 0.004$ , respectively).

**Conclusions:** Sex, grade and BMI were not factor of risk to mental disorders in children and adolescents with academic underachievement in this study. Positivity on PSC scale showed as a factor of risk determinant and independent to academic underachievement. Mental disorders screening tool, as PSC questionnaire, can be useful to medical evaluation of these children and adolescents, which can detect psychosocial and emotional problems, leading to an evaluation by mental health professional (psychologist and/or psychiatrist).

#### Code: PE236

##### **Application of SNAP-IV scale on children with academic underachievement**

Isabela Bulhões Faganello<sup>1</sup>, Mariana Defazio Zomerfeld<sup>1</sup>, Rebeca Eloíse de Oliveira<sup>1</sup>, Taynara Cristina da Paixão<sup>1</sup>, Hisadora Gemelli<sup>1</sup>, Melissa Dornelles de Carvalho<sup>1</sup>, Gleice Fernanda Costa Pinto Gabriel<sup>1</sup>, Marcos Antonio da Silva Cristovam<sup>1</sup>

<sup>1</sup>Universidade Estadual do Oeste do Paraná, Cascavel PR, Brazil

**Background:** Attention Deficit Hyperactivity Disorder (ADHD) is the most frequent neurobehavioral syndrome in childhood, causing significant impairment in family, social and academic performance of children. A tool to help both diagnosis and follow-up of the schoolchildren is the SNAP-IV scale, which evaluate 18 behaviors, according to the answers of parents and/or teachers.

**Objective:** This study aimed to describe the prevalence of symptoms of ADHD in schoolchildren with academic underachievement, using the SNAP-IV questionnaire.

**Methods:** Application of SNAP-IV scale and analysis of the answers filled by teachers.

**Results:** The questionnaire was applied to 30 children, 23 males and 7 females, ranging age from 6 to 12 years, registered between the first and eighth grades of elementary school. The majority (71.43% girls; 39.13% boys) presented attention deficit. Hyperactivity and both symptoms (attention deficit + hyperactivity) were found only in the boys (13.04% and 34.79%, respectively). Overall ADHD was more prevalent in boys (86.95% boys; 71.42% girls). In the study, most children were eutrophic, but the overweight was more related to attention deficit (75%). Considering the grade enrolled, all the students in seventh and eighth grades there was predominance of attention deficit, as well as 50% in second grade and 63.63% in fourth grade. Besides, every fifth-grade schoolchild had both of symptoms (attention deficit + hyperactivity). The mean age among students with attention deficit was 8.92 years; with hyperactivity/impulsivity, 8 years and with hyperactivity and inattention, 8.875 years.

**Conclusions:** ADHD was more prevalent in males according to literature data and the results of the present study. The predominance of attention deficit was the most prevalent subtype found, followed by the combined one. The teacher's assessment provided evidence of a high prevalence of symptoms in students with academic underachievement during classes. Thus, the SNAP-IV questionnaire shows the context where symptoms can manifest and can be used as an important tool in supporting the diagnosis of ADHD.

#### Code: PE237

##### **Autism and sexuality: review and discussion**

Carla Gruber Gikovate<sup>1</sup>, Clara Gruber Telles<sup>2</sup>

<sup>1</sup>Faculdade de Medicina de Petrópolis, Petrópolis RJ, Brazil

<sup>2</sup>Centro Universitário Arthur Sá Earp Neto, Petrópolis RJ, Brazil

**Background:** In the majority of cases, the autism spectrum disorder (ASD) diagnosis is received during childhood. However, considering the high prevalence of the disorder (over 1% of total population) and the fact that children with the diagnosis will grow up, it is urgent to deeply understand matters of autism in teenagers, adults and elders. Focusing on a complete health perspective for individuals with ASD, the lack of scientific articles on sexuality draws attention.

**Objective:** To review literature regarding sexuality in individuals with ASD, using data obtained from the perspective of patients themselves. Possible hypotheses related to the results found will be discussed.

**Methods:** A search was performed in June 2022 on PubMed with the keyword combinations: autism AND sexuality, as well as a search on Capes' Theses and Dissertations Catalogue, with the same keywords in Portuguese. Only articles that contained information from patients with ASD themselves where selected, excluding articles based on narratives from family members.

**Results:** 79 articles were found on PubMed and, after reading, 5 were selected. In the Capes Theses and Dissertations Catalogue, 4 articles were found, only 1 containing qualitative interviews with nine ASD adults. From the review articles, data were found that points to heterosexuality as less frequent in individuals with ASD, if compared to the general population. Difficulties fitting within the socially expected standards of gender were also described. In addition, people with autism are more likely to engage in inappropriate sexual behaviors that offer risks to themselves or their partners.

**Conclusions:** It is essential to understand sexuality aspects in the autism spectrum disorder group, in order to promote better education and support to patients, the families and society as a whole.

#### Code: PE239

##### **Difficulties related to the diagnosis and treatment of autism spectrum disorder in the SUS network in Salvador-BA**

Emmanuelle Souza Vasconcelos<sup>1</sup>

<sup>1</sup>Universidade Federal do Recôncavo Baiano, Salvador BA, Brazil

**Background:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder that encompasses difficulties in social communication/social interaction and the presence of stereotyped and repetitive behaviors, associated or not with sensory changes. The diagnosis is based on clinical criteria and has been updated in recent years. The most recent scientific data indicate that the prevalence of ASD has grown a lot and in the United States, it is estimated that 1 in 30 children are autistic. In Brazil, there are still no reliable data, but epidemiological studies bring the probability that there are about 2 million autistic people across the country. One of the factors that contribute to the imprecision of epidemiological data is related to early access to diagnosis. Especially in Public Health, finding qualified professionals to perform the diagnosis is a difficult task. The early diagnosis makes it easier for autistic children to receive the appropriate treatment as early as possible, improving the prognosis.

**Objective:** To know the main difficulties in relation to the diagnosis and treatment of autistic children in relation to the

public services offered by the Unified Health System (SUS) network.

**Methods:** An online questionnaire was used with objective questions about the diagnosis and treatment of families of autistic children attended at a reference center of the SUS network, in the city of Salvador, Bahia, in April 2022.

**Results:** In all, 119 families responded to the questionnaire. Of these, 55.5% took more than one year between the referral and the consultation with the neuropediatrician. The definitive report with the diagnosis was only achieved after one year of the first consultation with the neuropediatrician for 50% of the families. After the definitive diagnosis, access to therapies by the SUS was only achieved after one year for 42% of the families. Of the families that obtained some therapy through the SUS, 41.2% had access to a speech therapist at most once a week, 26.7% had access to a psychologist and only 19.3% had access to an occupational therapist at most once a week.

**Conclusions:** The process of diagnosis and initiation of treatment for autistic children dependent on the SUS network is still very time consuming. This fact can harm their development, worsening their functional prognoses, since windows of neurological opportunities are lost over time.

#### Code: PE240

#### **CBD-rich Cannabis Sativa on core and comorbid symptoms of autism spectrum disorder: a prospective observational study**

Alysson Madruga Liz<sup>1</sup>, Rafael Mariano Bitencourt<sup>2</sup>, Paulo César Trevisol Bittencourt<sup>1</sup>, Raquel Alberti<sup>3</sup>, Kelsner de Souza Kock<sup>2</sup>

<sup>1</sup>Universidade Federal de Santa Catarina, Florianópolis SC, Brazil

<sup>2</sup>Universidade do Sul de Santa Catarina, Tubarão SC, Brazil

<sup>3</sup>Associação Terapêutica de Pacientes de Cannabis Medicinal, Florianópolis SC, Brazil

**Background:** Autism spectrum disorder (ASD) is a heterogeneous condition of early neurodevelopment defined by deficits in social interaction and social communication, along with repetitive patterns of behavior, interests or activities. The pathogenesis of ASD is incompletely understood, although there is general agreement that it is caused by genetic factors that modify brain development, specifically neural connectivity. This process is likely related to the role that microglia can play in controlling synaptic pruning and neuroinflammation. The Endocannabinoid System exerts control over microglial activity and therefore offers a possibility of intervention in ASD. Preclinical studies indicate that anandamide administration induces an increase in IL-10 (anti-inflammatory cytokine) production by microglia cells. Furthermore, stimulation of CB2R leads to a protective phenotype in microglia, responsible for decreased secretion of IL-1.

**Objective:** There is no established pharmacological treatment for the core symptoms of ASD and the psychotropic drugs used in adjuvant symptoms have limited effectiveness and expressive adverse effects. In this context, new medications are needed to control ASD-related symptoms and to promote quality of life for patients and their families.

**Methods:** This observational study was designed to evaluate the effects of CBD-rich Cannabis s. oil on core and comorbid symptoms of ASD over 24 weeks, simultaneously with the withdrawal of commonly used psychotropic drugs. The primary outcomes assessed the core symptoms of ASD. The

secondary endpoints assessed neuropsychiatric manifestations and adverse effects. For all participants, a fixed dose of 5 drops of the cannabis oil distributed 3 times daily was started (CBD: 18.8 mg/d; THC: 1.3 mg/d).

**Results:** 27 participants completed the follow-up (mean±SD age, 7.2±2.9 years). There was significant ( $p<0.001$ ) improvement in all core ASD symptoms: communication, sociability, and stereotyped behavior. Of the neuropsychiatric comorbidities, Avoidant Restrictive Food Intake Disorder had the greatest significant improvement at 40%. Attention Deficit Hyperactivity Disorder and Insomnia Disorder also improved significantly ( $p<0.05$ ). The three most common side effects were restlessness, increased appetite and nervousness and/or aggression.

**Conclusions:** The present study strengthens the evidence that CBD-rich Cannabis s. oil is an effective and safe therapeutic possibility for the treatment of core and comorbid symptoms of ASD.

#### Code: PE241

#### **Families with children in the autism spectrum disorder: tracing difficulties and support strategies**

Carla Gruber Gikovate<sup>1</sup>, Clara Gruber Telles<sup>2</sup>

<sup>1</sup>Faculdade de Medicina de Petrópolis, Petrópolis RJ, Brazil

<sup>2</sup>Centro Universitário Arthur Sá Earp Neto, Petrópolis RJ, Brazil

**Background:** Considering that the autism spectrum disorder (ASD) is a frequent condition that, in many cases, will have difficulties persisting throughout an individual's lifetime, it is essential to understand the impact on a family context.

**Objective:** To trace emotional repercussions that occur in families with children in the autism spectrum disorder, as well as evaluate the results of intervention programs that provide mental health support for these families.

**Methods:** A search was made on MEDLINE using the terms (autism + family) with the "systematic Review" filter on the last 10 years. The data obtained in the selected articles will be correlated with concepts and approaches proposed by Salvador Minuchin (family subsystems) in his structural family therapy model.

**Results:** 161 articles were found and, after reading, 4 systematic review articles were selected based on the main objective of this study (to understand the family impact of having children with autism and possible interventions to reduce stress). From the 4 review articles, new articles mentioned by the authors were used and included in the references of this study. In this review, data found show parents of children with autism to have higher levels of stress, depression and anxiety (especially in mothers), reduced sleep quality, low levels of happiness in marriage, higher divorce rates and a need to increase work hours to afford special treatment for the child. These data are directly related to the severity of the child's clinical condition, being irritability, aggressiveness and sleep difficulties aggravating factors for family symptoms.

**Conclusions:** It is essential that professionals involved in the treatment of children with ASD understand the impacts the condition can have in a family environment and that mental health services are widely available, inserted in the local culture, focusing on the guidance, care and support for these families.

## Code: PE243

**Perception of family physicians regarding identification of autism spectrum disorder**Yan Victor Araújo Rodrigues<sup>1</sup>, Renata Orlandi Rubim<sup>1</sup><sup>1</sup>Hospital Regional de Sobradinho, Brasília, DF, Brazil

**Background:** Autism Spectrum Disorder is the term used to describe a constellation of deficits in social communication and repetitive sensory and motor behaviors. It is characterized by an early onset and a robust genetic component. In Brazil, in addition to difficulties inflicted by the disease itself, there are structural limitations assignable to underdevelopment. There is a pilgrimage of these children and their caregivers in search of clarification, which obviously results in a delayed diagnosis. Once Primary Care is the main entrance for these children into the health system, the role of family physicians is discussed to achieve better care for autistic children.

**Objective:** To assess the perception of family physicians regarding the early identification of autism spectrum disorder in their clinical practices, in the Northern region of Brazilian Federal District.

**Methods:** The research performs a descriptive, cross-sectional, qualitative study, using a semi-structured questionnaire. The subjects of the study are the family physicians with a Brazilian board certification, allocated in the delimited area. Each interview was recorded for later transcription of the content. Ultimately, the number of physicians to be heard was defined by coding operations, according to Laurence Bardin's Content Analysis method, which proposes an exhaustive reading and a thematic grouping of ideas.

**Results:** Physicians reported barely any discussion concerning autism in college. Through residency, the first cases arose, and, consequently, a theoretical basis began to be required. Notwithstanding, after the training years, interviewees refer to have actively searched for an autism spectrum approach once patients' demand continues to escalate. Family doctors tend to suspect autism in children over 2 years old, especially when the main caregiver or the kindergarten carer identifies speech and language delay, as well as poor socialization and stereotyped movements. Common complaints mentioned were the lack of transdisciplinary follow-up, the absence of longitudinal medical capacitation and scarce feedback regarding children referred to other levels of care.

**Conclusions:** The increase in diagnoses seen worldwide is reflected in primary care. Family physicians demonstrate concern and responsibility regarding autistic patients. However, due to the lack of structured, intuitive and widespread flowcharts and limited transdisciplinary support, these children are belatedly diagnosed, missing opportunities to be nurtured.

## Code: PE244

**Prevalence of intellectual disability as a comorbidity of autism spectrum disorder in patients with multidisciplinary examination at the specialized learning center (NEA) of Faculdade de Medicina do ABC**Kleitton Rodolfo Silveira Rufino<sup>1</sup>, Rubens Wajnsztein<sup>1</sup>, Alessandra Bernardes Caturani Wajnsztein<sup>1</sup>, Keila Paula Pereira Chaves<sup>1</sup>, Vanessa Ferreira Horta<sup>1</sup>, Damaris Alcídia Gaester Fakler<sup>1</sup>, Ketlyn Gil Garcia<sup>1</sup>, Carina Cássia Zaneli<sup>1</sup>, Sandra Ramos Gonçalves<sup>1</sup><sup>1</sup>Faculdade de Medicina do ABC, Santo André SP, Brazil

**Background:** Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by clinically signifi-

cant and persistent deficits in communication and social interactions associated with restricted and repetitive patterns of behavior, interests and activities<sup>1</sup>. ASD can be associated with several comorbidities, including Intellectual Disability, ADHD, anxiety, depression, epilepsy and sleep disorders<sup>2</sup>. In the context of ASD comorbidities, intellectual disability (ID) is among those whose presence is directly related to the level of support of patients, and its assessment is important from the point of view of functionality of each individual. According to data from the CDC<sup>3</sup>, 35.2% of ASD patients with cognitive examination data were classified as having ID. Overall, the proportions of this comorbidity in girls and boys were similar (35.6% and 35.1%, respectively).

**Objective:** Assessing the total prevalence of ID as a comorbidity of ASD and compare the prevalence of this comorbidity in male and female patients.

**Methods:** Data from the medical records of a sample of patients who underwent a multidisciplinary examination at the Specialized Learning Center (NEA) of the Faculdade de Medicina do ABC (FMABC) were used. The sample consists of 1321 patients who underwent cognitive examination. We analyzed the prevalence data of patients diagnosed with ASD in the sample and, in these, ID as a comorbidity, as well as the proportion between male and female patients. Diagnoses made before the 2013 DSM-V, which included Pervasive Developmental Disorder and Asperger Syndrome, were discarded.

**Results:** The sample had 28 patients with ASD, 7 of whom had ID as a comorbidity (25%). In the group of girls (n= 4) 1 had ID (25%) and in the group of boys (n= 24) 6 had this comorbidity (25%).

**Conclusions:** The prevalence of ID as an ASD comorbidity in the sample presented was slightly lower than that observed in previous data in the literature. However, there were no significant differences in the proportions of this comorbidity between girls and boys, which corroborates the hypothesis that the prevalence of ID in patients with ASD is similar in both genders.

## Code: PE247

**Screening for psychosocial and emotional problems on children with atopic dermatitis**Melissa Dorneles de Carvalho<sup>1</sup>, André Curioletti Pereira<sup>1</sup>, Andressa Naomy Tamura<sup>1</sup>, Estela Cristina Giglio de Sousa<sup>1</sup>, Hisadora Gemelli<sup>1</sup>, Ana Cláudia de Araújo Argentino<sup>1</sup>, Hirofumi Uyeda<sup>1</sup>, Fernanda Bortolanza Hernandez<sup>1</sup>, Marcos Antonio da Silva Cristovam<sup>1</sup><sup>1</sup>Universidade Estadual do Oeste do Paraná, Cascavel PR, Brazil

**Background:** Atopic dermatitis (AD) is the most common chronic dermatitis in childhood. Its prevalence is currently around 15 to 20% of the pediatric population. Chronic diseases such as AD negatively affect the quality of life and the emotional aspects of its patients. Studies show that AD patients have a higher rate of attention deficit hyperactivity disorder, and that both these children and their caregivers are at greater risk of developing anxiety and depressive symptoms. These data point to the long-term effect caused by this condition on child behavior and development and on the psychosocial scope.

**Objective:** Screening for psychosocial and emotional problems in children with AD by application of the Pediatric Symptoms Checklist (PSC).

**Methods:** Application of the PSC in children assisted in a dermatology outpatient clinic of a university hospital in West State of Paraná. Children and adolescents aged between seven

and eighteen years with a confirmed diagnosis of AD were included in the study. After approval by the Research Ethics Committee under protocol number 5.224.128 the PSC was applied to screen for emotional and psychosocial disorders. **Results:** Twenty-one subjects were included in the study, thirteen (62%) female and eight (38%) male. Age ranging from seven to fifteen years (mean: 10.5 years and median: 10 years). PSC score ranging from two to forty-three points (mean: 16.8 points and median: fourteen points). Three patients (14.3%) had a score higher than 28 points on PSC, with a positive result and indication of referral for mental health assessment by a specialist. Three patients (14.3%) had a score very close to 28, however, with a negative result, but indicating that mental health surveillance in AD patients is essential.

**Conclusions:** AD is a condition that affects the quality of life of children and adolescents by triggering physical and psychological signs and symptoms, requiring screening for emotional and psychosocial disorders in order to provide the necessary support to these patients and prevent progression to more serious psychosocial conditions. The percentage of children with a tendency towards mental disorders was higher than the general population, according of literature (10%).

#### Code: PE248

##### **Severe and moderate autism spectrum disorder: serial cases treated with combined usage of Cannabidiol and Tetrahydrocannabinol, in a university hospital**

Jeanne Alves de Souza Mazza<sup>1</sup>, Carlos de Almeida Dias Neto<sup>1</sup>, Lisiane Seguti Ferreira<sup>2</sup>, Carla Lenita Coelho Siqueira<sup>1</sup>, Paulo Emídio Lobão da Cunha<sup>1</sup>, Isadora Oliveira Cavalcante<sup>1</sup>, Júlia Lopes Vieira<sup>2</sup>, Vinícius Paulo Lima de Menezes<sup>2</sup>, Julia Carvalho Maia<sup>2</sup>

<sup>1</sup>Hospital Universitário de Brasília, Brasília DF, Brazil

<sup>2</sup>Universidade de Brasília, Brasília DF, Brazil

**Background:** 15 patients diagnosed with autism spectrum disorder (ASD) from a neurodevelopment outpatient clinic in combined use of Cannabidiol (CBD) and Tetrahydrocannabinol (THC), in 100 mg/ml CBD concentration and 3 mg/ml of THC, with initial dosage of 1 mg/kg/day and maximum of 5 mg/kg/day for a six-month period. The patients were all non-syndromic, without epilepsy, and with ASD level 2 or 3, with or without associated intellectual deficiency.

**Objective:** The parameters analyzed prior and after treatment were aggressiveness, social cognition, learning capabilities, language, sleep, appetite, and collateral effects, through clinical evaluation, neuropsychological testing, and questionnaire answered by the parents.

**Methods:** Level 2 and 3 ASD patients present a higher degree of compromise in their social cognition and communication, with more disruptive behaviors (self-injury, Hetero-Aggressiveness) and higher inflexibility of repetitive and/or restrictive interests. Out of the 15 patients selected, 13 were male and 2 were female; 12 were ASD Level 2 and 3 were Level 3. The average age was 11,1 years old.

**Results:** Among the evaluated patients, 12 (80%) showcased improvement in their social cognition, with higher frequency of eye contact; 10 (66%) had less aggressiveness, both Hetero-Aggressiveness and self-injury; 10 (66%) presented a higher degree of interest in communication and language usage, both receptive and expressive; 7 (46%) demonstrated better learning capabilities. Regarding the appetite: 7 showcased

enhanced food selectivity behavior, though 4 (53%) of them got better; out of the 6 that previously had overeating disorders, 4 (66%) demonstrated some improvement in regulating their appetite. All the 3 patients that previously had sleeping disorders showed improvement. Regarding collateral effects, one patient initially had nausea and vomiting, which later stopped; another patient had an increase in their overeating disorder habits.

**Conclusions:** This work brings to light therapeutic possibilities in the management of more severe ASD cases, since it is common that, in spite of commonly requiring the use of several drugs, many patients remain with a high number of maladaptive behaviors. Even with the reduced sample size, this research contributes by demonstrating the treatment used presented an improvement in social-related symptoms, such as eye contact and communication interest, which is the main concern of this disorder, and that other therapeutic options did not tackle as efficiently.

#### Code: PE249

##### **Speech disorders in children with learning disabilities**

Débora Cristina Przybysz<sup>1</sup>, Ana Chrystina Crippa<sup>1</sup>, Isac Bruck<sup>1</sup>, Ana Paula Lopes Luiz<sup>2</sup>, Ana Paula Dassie Leite<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>2</sup>Faculdade Evangélica Mackenzie do Paraná, Curitiba PR, Brazil

**Background:** Speech disorders can be prejudicial to child development as a whole. There may be losses in social interaction, literacy and the development of reading and writing. The literature on speech and language development points out that children who had speech delay are at increased risk for difficulties in reading and writing.

**Objective:** To investigate the frequency of speech disorders (speech delay, exchanges, omissions or deviations) in children diagnosed with learning difficulties.

**Methods:** Observational, cross-sectional, retrospective research. For speech assessment, the ABFW test – Child Language Test, phonoarticulatory album and oromyofunctional clinical assessment were used. The research sample consisted of children referred to the Neuropediatrics center, who were later referred to a School Disorders' outpatient clinic and received a diagnosis of learning difficulties after evaluation by a multidisciplinary team.

**Results:** The sample consisted predominantly of boys, totaling 56%, while 44% were girls. Quantitative data revealed that 54.2% of the children had some type of speech disorder. 27.3% present exchanges between phonemes and 26.9% had some kind of delay in speech and language development. The data also revealed that 72% of the children had a family history of speech disorders.

**Conclusions:** The research reveals that learning difficulties may be associated with speech disorders. The family history of these children indicates that those with family members with some type of speech disorders are more likely to present the same difficulties in child development. The development of speech and language is directly related to the development of reading and writing. It is possible to emphasize the importance of early intervention in cases of speech and language difficulties, since such difficulties can harm the development of reading and writing, as well as the school learning process.

## Reabilitação

Code: TL01

### Hip dislocation in children with congenital Zika virus syndrome

Lenamaris Mendes Rocha Duarte<sup>1</sup>, Eliana Valverde Magro Borigato<sup>1</sup>, Adriana Gonçalves da Silva<sup>1</sup>, Alvaro Massao Nomura<sup>1</sup>, Clarissa Miranda Carneiro de Albuquerque Olbertz<sup>1</sup>, Oton Naziasene Lima<sup>1</sup>

<sup>1</sup>Rede SARAH de Hospitais de Reabilitação, Brasília DF, Brazil

**Background:** Hip displacement is defined as a percentage of migration of the femoral head over 33% and affects children with cerebral palsy. The risk of dislocation is higher in children classified as IV and V levels in the gross motor function classification system. In November 2015, there was an increase in congenital microcephaly that was associated with Zika virus infection during pregnancy, and it was considered a public health problem in Brazil.

**Objective:** This retrospective cohort study aimed to analyze the hip dislocation in children with cerebral palsy due to congenital Zika virus syndrome at one Rehabilitation Hospital, from June 2015 to September 2017.

**Methods:** The study included 46 children with cerebral palsy, GMFCS IV and V and congenital Zika virus syndrome. Children with laboratory tests positive for STORCH or suspected genetic syndrome were excluded from the study. The children included underwent serial anteroposterior radiographs of the pelvis as part of the hip surveillance protocol. 110 exams were studied, and these parameters analyzed. The following symptoms were analyzed from the medical records: pain and complaints during daily care.

**Results:** In the group, 57% of the cases were male, 98% GMFCS level V, with a current average age of 3.6 years. According to Reimers' Percentage of Lateral Migration, 50% had a subluxated hip at an average age of 1.10 years and 20% dislocated at 2 years. In 20% of cases the acetabular index was  $\geq 30^\circ$  with an average age of 1.6 years. The Shenton Line was broken in 83% of cases with an average age of 1.9 years. 39% of caregivers reported hip pain. Complaints related to difficulties in positioning, hygiene and clothing were mostly due to spasticity. 35% of cases underwent soft tissue surgery with an average age of 3.2 years.

**Conclusions:** It is important to include children with cerebral palsy affected by congenital Zika virus syndrome as early as possible in hip surveillance programs because hip dislocation occurs at an early age in this group compared to children with cerebral palsy due to other etiologies.

## Doenças neuromusculares

Code: TL02

### Nemaline myopathy in Brazilian patients: clinical, muscle imaging and molecular characterization

Juliana Gurgel-Giannetti<sup>1</sup>, Guilherme Yamamoto<sup>2</sup>, Marina Belisario<sup>1</sup>, Lucas Santos Souza<sup>2</sup>, Erasmo Casella<sup>3</sup>, Edmar Zanoteli<sup>3</sup>, Umbertina Reed<sup>3</sup>, Laing Nigel<sup>4</sup>, Mariz Vainzof<sup>2</sup>

<sup>1</sup>Universidade Federal de Minas Gerais, Belo Horizonte MG, Brazil

<sup>2</sup>Universidade de São Paulo, Bioscience Institute, São Paulo SP, Brazil

<sup>3</sup>Universidade de São Paulo, São Paulo SP, Brazil

<sup>4</sup>University of Western Australia, Australia

**Background:** Nemaline myopathy (NM) is one of the most common structural congenital myopathies, with a significant

clinical and genetic heterogeneity. Nowadays, more than 15 genes are related to NM, including TPM3, NEB, ACTA1, TPM2, TNNT1, KBTBD13, CFL2 (COFILIN2), KLHL40, KLHL41, LMOD3, MYO18B, MYPN, RYR3, TTN3, ADSSL1, Filamin C and MYH2. Most of these genes encode structural or regulatory proteins associated with the thin filament in the skeletal muscle fiber. NM is considered a rare condition and there are no national studies with a large cohort of Brazilian nemaline patients.

**Objective:** To characterize the clinical, molecular and muscle MRI data from a Brazilian cohort of patients with nemaline myopathy.

**Methods:** Patients were clinically evaluated and followed for 2 to 20 years. Exams were performed including muscle biopsy, muscle MRI and next generation sequencing (exome).

**Results:** 30 patients, 15 males and 15 females, from 25 unrelated families were evaluated. Five families presented more than one affected patient, one of them with a clear autosomal dominant inheritance and 4 with autosomal recessive form. The remaining 20 families presented with sporadic cases. Patients were classified based on the severity of the disease: 24 with the typical form, three with the mild form and three with the severe neonatal form. We identified pathogenic mutations in NM-related genes in all 25 studied families. NEB variants were present in 20 patients from 16 families (all patients had 2 NEB variants and 11 of these variants were novel). Five families showed heterozygous mutations in ACTA1 gene (one mutation was novel), in 4 families, mutations in the following genes were found: TPM2, TPM3, and KLHL40. In 28 patients, the muscle biopsy was performed and showed rods inside of muscle fibers. Type I predominance was present in all patients, and in some there was total predominance. Muscle MRI could show different patterns of muscle involvement associated with the affected gene.

**Conclusions:** Molecular analysis in the present study showed that mutations in the NEB are the most common cause of NM, followed by mutations in the ACTA1. A total of 12 mutations were novel. The NEB mutation c. 24579 G> C was recurrent in 3 unrelated patients, but from a region with a high frequency of consanguinity, suggesting a common ancestor. Two unrelated patients with severe form of the disease presented the same KLHL40 mutations. Respiratory involvement was very common in NM patients and can be out of proportion to the weakness of the limbs.

Code: TL03

### Safety and efficacy of gene therapy for patients with spinal muscular atrophy: a real-life study in a Brazilian cohort

Rodrigo Holanda Mendonca<sup>1</sup>, Adriana Banzatto Ortega<sup>2</sup>, Ciro Matsui Jr<sup>1</sup>, Luis Fernando Grossklauss<sup>3</sup>, Elizabeth Lemos Silveira Lucas<sup>4</sup>, Edmar Zanoteli<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Departamento de Neurologia, São Paulo SP, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

<sup>3</sup>Hospital Infantil Sabará, São Paulo SP, Brazil

<sup>4</sup>Hospital Moinhos do Vento, Porto Alegre RS, Brazil

**Background:** Spinal muscular atrophy (SMA) is a genetic motor neuron disease caused by mutations in the SMN1 (Survival Motor Neuron) gene, which leads to hypotonia and muscle weakness with high mortality related to respiratory involvement. Gene therapy (GT) (onasemnogeno aberpavovec) for SMA, through an adeno-associated viral vector 9 (AAV9) was recently approved in our country, but its safety

and efficacy outside the context of clinical trials is still poorly understood.

**Objective:** To present early results regarding safety and efficacy in SMA patients treated with GT.

**Methods:** We followed a total of 33 patients treated with GT for SMA from 6 months to 1 year of treatment. The patients were evaluated by the functional scales CHOP-INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) and in relation to gain of motor milestones. In addition, assessment of survival and use of continuous ventilation (CV) was performed and also data regarding transaminase elevation, liver function, hematological data, elevation of troponin and duration of corticosteroid use.

**Results:** 33 patients were included, 26 SMA type 1 and 7 SMA type 2. The mean age at dosing was 18.5 months (14.0 - 23.2), with a mean weight of 9.9 kg (8.3 kg. - 16.3) and 28 patients (87.5%) were using nusinersen previously. After 1 year of treatment 32 patients (96.9%) were alive, 7 patients (21.2%) remained on CV (>16h/day) versus 11 (33.3%) patients at dosing. Regarding the gain in the CHOP-INTEND score, the mean baseline score was 30.50 (19.50, 40.75) to 46 (40.00, 52.00) at 6 months and to 56 (50.00, 58.00) points at 12 months. Regarding motor milestones, from those with SMA type 1, nine patients (42.9%) sat and four patients (19%) stood with support, and three patients acquired gait with support among SMA type 2. In terms of safety, the highest transaminase peak occurred in weeks 3 and 6 after infusion. Only 10 patients (30.3%) had transaminase levels similar to baseline at week 8. 15 patients (45.4%) had thrombocytopenia in the first week and one patient met criteria for thrombotic microangiopathy. The mean time of prednisolone use was 105 days (60.0 - 122.2).

**Conclusions:** GT is effective in real life but with the potential for serious adverse events. There is a need for strict monitoring of transaminases, platelets and troponin and the occurrence of liver damage beyond 2 months of drug use, especially in patients with an older profile than in clinical studies.

**Code:** TL04

#### **Skeletal and cardiac function are correlated in dystrophinopathies: a study using cardiac MRI and the MFM scale**

Antônio Rodrigues Coimbra Neto<sup>1</sup>, Leticia Silva Sousa<sup>1</sup>, Thiago Junqueira Ribeiro de Rezende<sup>1</sup>, Cristina Iwabe<sup>1</sup>, Tauana Bernardes Leoni<sup>1</sup>, Thiago Quinaglia Araújo Costa Silva<sup>1</sup>, Otávio Rizzi Coelho Filho<sup>1</sup>, Anamarli Nucci<sup>1</sup>, Marcondes Cavalcante França Junior<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas SP, Brazil

**Background:** Cardiomyopathy is almost universal in dystrophinopathies and the leading cause of death in this population. Despite this, there are few studies that correlated cardiac structural changes with motor function in dystrophinopathies.

**Objective:** This cross-sectional study aims to characterize myocardial tissue remodeling in patients with Duchenne and Becker muscular dystrophies (DMD/BMD) and investigate its correlation with motor function.

**Methods:** In the same week, 27 patients with DMD and 23 with BMD aged 7 years and older and 10 sex-matched healthy individuals underwent to a comprehensive evaluation including laboratory workup, MFM-32 scale and 3.0 T cardiac magnetic resonance imaging.

**Results:** The BMD group presented mean age of 27.1 ± 16.4 years, disease duration of 19.9 ± 14.2 years and MFM-32

score of 64.8 ± 22.0%. The DMD group presented mean age of 12.8 ± 5.3 years, disease duration of 8.0 ± 6.1 years and MFM-32 score of 53.3 ± 21.8%. Both BMD and DMD groups presented subepicardial late gadolinium enhancement (LGE) and lower LVEF values compared to controls (respectively 53.49 ± 12.82% versus 62.65 ± 2.81%, P= 0.008 and 60.43 ± 6.94% versus 62.65 ± 2.81%, P= 0.037). The LVEF values correlated directly with MFM-32 scale in BMD and DMD (respectively R= 0.73 P < 0.001 and R= 0.536 P = 0.007). DMD presented higher Native T1 than controls (1252.27 ± 62.21 ms versus 1180.59 ± 59.40 ms, P= 0.016) and BMD group presented higher ECV than controls (0.31 ± 0.07 versus 0.27 ± 0.03, P= 0.042). This parameter correlated directly with duration of disease (R= 0.66 P < 0.001) and inversely with MFM-32 (R= -0.64 P= 0.002) in BMD group, while T1 native correlated with pro-BNP levels in DMD (R= 0.51 P= 0.01). In the multiple regression model, LVEF correlated with the MFM-32 scale in the DMD group (R<sup>2</sup> adjusted= 0.22 Regression coefficient= 0.158, P= 0.031), but not with the disease duration.

**Conclusions:** This study indicates that ECV and T1 native proved useful to detect myocardial microstructural remodeling in dystrophinopathies. Cardiac and motor function are related processes, which are driven by the amount of dystrophin underexpression.

## **Neuroimunologia, esclerose múltipla e outras doenças desmielinizantes**

**Code:** TL05

#### **Use of plasmapheresis in acquired demyelinating syndromes**

Roberta Diniz de Almeida<sup>1</sup>, José Albino da Paz<sup>1</sup>, Renata Barbosa Paolilo<sup>1</sup>, Clarice Semião Coimbra<sup>1</sup>, Rafaela Fernandes Dantas<sup>1</sup>, Nicholas dos Santos Barros<sup>1</sup>, Ana Cristina Azevedo Leão<sup>1</sup>, Renata Silva de Mendonça<sup>1</sup>, Cristiani Rocha Lima Cruz<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Background:** Patients with acute inflammatory demyelination of the central nervous system (CNS) may present with severe neurological impairment, including flaccid quadriplegia and amaurosis. Plasmapheresis (PLEX) is an alternative treatment for patients who do not immediately improve clinically or for whom symptoms worsen despite corticosteroid dosing and is preferred in the context of serious events.

**Objective:** Describe the profile of the patients with demyelinating diseases that were submitted to PLEX from July 2012 until July 2022 in a tertiary center in the city of Sao Paulo.

**Methods:** Retrospective cohort study of patients <18 years with acute CNS demyelinating events seen at a single tertiary referral center who received PLEX as second- or third-line therapy between 2010 and 2022. Through chart review of clinical notes.

**Results:** Total of 80 patients who received diagnosis of demyelinating disease: Multiple Sclerosis (MS), Acute Disseminated Encephalomyelitis (ADEM), Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), Neuromyelitis Optica Spectrum Disorder (NMOSD) or optic neuritis (NO), 18 were to PLEX. From a total of 18 patients, the most prevalent diagnosis was MS, with 7 patients, followed by NMOSD with 5 patients, MOGAD 3 patients, ADEM 1 patient and 2 patients that presented a NO bilateral, that so far did not fulfil a specific disorder. The youngest patient submitted was 5 years old, and the oldest were 16. From the

18 patients, 11 were in its first clinical event. All received at least 5 days of metilprednisolone as first line therapy. The clinical neurology syndrome was 5 with NO bilateral, 3 with NO unilateral, 6 with myelitis and 4 patients with more then 1 syndrome (myelitis with NO or with a stem brain syndrome). Only one was submitted to PLEX more then once. None of our patients presented severe complications related to plasmapheresis, and all of them showed some improvement.

*Conclusions:* Demyelinating diseases acute events are potential cause of sequelae in young patients and sometimes require more aggressive therapeutics in order to prevent amaurosis or severe motor disfunction. Access to PLEX is not an easily available, and require trained personel, as the limitations are also related with weight and access to ICU. There is room for improvements over clinical protocols and categorization of patients eligible for PLEX.



## CASE REPORT

### Cefaleias e demais transtornos paroxísticos não epiléticos

Code: PE001

#### Clinical case report: headache due to cerebrospinal fluid hypotension treated with caffeine

Nicholas Pili Monteiro<sup>1</sup>, Vitor Reis de Souza<sup>1</sup>, Fernanda Silveira de Quadros<sup>2</sup>, Liselotte Menke Barea<sup>2</sup>, Francisco Scornavacca<sup>2</sup>

<sup>1</sup>Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre RS, Brazil

<sup>2</sup>Irmãdade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre RS, Brazil

**Case presentation:** A 16-year-old male patient with a previous history of WHO Grade IV Medulloblastoma in the posterior fossa, resected at the age of 14, also submitted to radiotherapy and adjuvant chemotherapy. He sought medical attention referring episodes of headache associated with the orthostatic position, with criteria for hospitalization. Upon evaluation, the patient reported continuous headache, with biparietal and occipital location, associated with fatigue, nausea, dizziness and blurred vision, refractory to analgesia. He presented with ataxia, diplopia and preserved ocular motricity, without other alterations. During hospitalization, brain and neuraxial images showed no relevant changes. Lumbar puncture with spinal manometry showed cerebrospinal fluid (CSF) hypotension, with an opening pressure of 10 cmH<sub>2</sub>O measured in lateral decubitus, thus establishing the diagnosis of headache due to CSF hypotension. Clinical measures were taken to provide analgesia, with little response. Scintigraphy with cisternography was performed, without signs suggestive of CSF leak. It was decided to associate oral caffeine citrate, at a dose of 200 mg a day, to the drug regimen. Then, the patient reported a progressive decrease in episodes of headache in orthostatism, presenting criteria for hospital discharge and outpatient follow-up. At this time, the patient was instructed to consume coffee during meals, except at night, and anhydrous caffeine was prescribed orally at a dose of 100 mg daily. After that, the patient remained without new episodes of headache until the present moment.

**Discussion:** The headache due to CSF hypotension is attributed to venodilation compensatory to CSF volume depletion in the brain. Caffeine has been used as part of conservative clinical management because of its vasoconstrictor action, attenuating symptoms attributed to compensatory venous engorgement, although there is a need for studies whose results corroborate its use in clinical practice. The present report has great clinical relevance as it demonstrates a case of headache due to CSF hypotension refractory to analgesia occurring in the absence of significant imaging changes, in which caffeine was used for empirical symptomatic treatment, with therapeutic success.

**Final comments:** This case report supports the hypothesis that the use of caffeine may represent an important and effective therapeutic option for the clinical management of orthostatic headaches attributed to CSF hypotension.

Code: PE002

#### Family hemiplegic migraine as differential diagnosis of stroke: series of 2 case reports

Gabrielle Gruppelli Good<sup>1</sup>, Giulia Vilela Silva<sup>2</sup>, Daniel Almeida do Valle<sup>1</sup>, Lucas Procopiak Gugelmin<sup>1</sup>, Maria Fernanda Jara Maldonado<sup>1</sup>, Maria Vitória Correa<sup>1</sup>, Marina Massuchin Prêcoma<sup>1</sup>, Ana Luiza de Rezende e Cota<sup>1</sup>, Maria Vitória Ruiz Fatuch<sup>1</sup>

<sup>1</sup>Universidade Positivo, Curitiba PR, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Case 1: Female patient, hospitalized at 15 years for investigation of hemiplegia and right hemiparesis accompanied by vomiting and fever without local history signs. At 16 years hospitalized for similar condition, with unchanged resonance and complete remission in two weeks. Genetic investigation was performed for hemiplegic migraine, with identification of heterozygous mutation in the ATP1A2 gene (c.2563G>A). Case 2: An 11-year-old female patient complaining of severe intermittent occipital headache, followed by syncope. It evolved with confusion, disorientation and vomiting followed by left hemiparesis, rhyming deviation to and bilateral eye tremor lasting ~30 minutes. In view of the normality of neuroimaging, a molecular investigation was performed that showed heterozygosity in the PRRT2 gene (c.650651 insC).

**Discussion:** Migraine is classically characterized as pulsatile hemicranian headache, accompanied by photophobia, phonophobia, nausea and vomiting, with great impairment in daily life. It is a common condition that is difficult to diagnose in the pediatric population due to greater variability in clinical presentation when compared with adults. It may or may not be preceded by visual, auditory, and sensory symptoms called aura. Family hemiplegic migraine (HFS) is a type of migraine whose aura is characterized by hemiparesis, hemianopsia, aphasia, lethargy, and acute-onset mental confusion, simulating ischemic event in the central nervous system. Due to its autosomal dominant character, it affects first and second degrees relatives, a fact that should increase suspicion for diagnosis. Mutations already identified for EHF are localized in the ATP1A2, CACNA1A, PRRT2 and SCN1A genes. Although in the reported cases the mutation is distinct, the clinical presentation has many similarities to each other, and both were initially hospitalized with the suspicion of stroke and evolved with complete remission of symptoms.

**Final comments:** The reported cases illustrate that the suspicion of family hemiplegic migraine should be considered in patients with acute focal neurological deficits without neuroimaging alterations compatible with ischemic event and without exuberant pain. Molecular testing can help in the diagnosis to avoid unnecessary hospitalizations and investigations and guide patients and family members affected regarding prophylactic treatment, prognosis and transmission in dominant inheritance pattern.

Code: PE003

#### Pott puffy tumor: a rare case of secondary headache

Jamile Nascimento Souza Fernandes<sup>1</sup>, Ana Cleide Silva Souza<sup>1</sup>, Filipe Souza Azevedo<sup>1</sup>

<sup>1</sup>Hospital Infantil Cosme Damião, Porto Velho RO, Brazil

**Case presentation:** F.L.A.R., 12 years-old, male, reporting severe frontal headache with fever and emesis for 7 days, with edema in the frontal cephalic and periorbital region, diagnosed as sinusitis and prescribed amoxicillin+clavulanate (A/C). Due to the persistence of symptoms on third day, he was admitted in hospital. On physical examination, the

center of his forehead had a soft, tender, warm, swollen area that caused an obvious bulge. Facial ultrasound showed a frontal abscess. Skull computed tomography showed frontal subcutaneous abscess, epidural and subdural empyema, and associated local osteomyelitis. This finding confirmed the diagnosis of Pott puffy tumor. On the third day of hospitalization, he underwent a neurosurgical procedure to drain the empyema. Abscess culture with *S.aureus*. Used Ceftriaxone for 21 days, Clindamycin for 10 days. He was discharged from hospital on the 21st day with indication of domiciliary use of A/C for 10 days.

**Discussion:** The case is an important complaint of severe acute headache secondary to a less prevalent pathology. A Pott puffy tumor (PPT) is defined as swelling of the forehead, usually from the anterior extension of frontal sinusitis, and associated osteomyelitis of the frontal bone. It was first described by Sir Percival Pott as a complication of forehead trauma and after, in relation to sinusitis. When not treated promptly, osteomyelitis of the frontal bone and the resulting subperiosteal abscess gives rise to the characteristic PPT. It is a rare entity that is generally seen in older children. It can be associated with subdural empyema, epidural or brain abscess, and cortical veins. Intracranial involvement is possible, with or without direct erosion of the frontal bone. Treatment must contain broad-spectrum intravenous antibiotics and analgesics. A CT scan with contrast and MRI should be done to confirm the diagnosis and rule out intracranial complications. Surgical intervention may be necessary and neurosurgical consultation is always required in the case of intracranial involvement.

**Final comments:** Headache is one of the most frequent medical symptoms in outpatient clinics. The case reported is a typical presentation of a rare diagnosis and therefore not considered among the usual hypotheses. PPT should be among the likely diagnostic hypotheses of severe secondary headache. Prompt diagnosis and proper treatment will decrease the morbidity and mortality associated with this rare condition.

## Doenças cerebrovasculares e terapia intensiva em neurologia infantil

Code: PE004

### Atrial myxoma's embolization and stroke causing aphasia in a bilingual (Persian and Portuguese) Iranian girl: a case report

Eliane Cespedes Paes Huard<sup>1</sup>, Marcus Vinicius Teles Rodrigues<sup>1</sup>, Bernardo Jose Alves Ferreira Martins<sup>1</sup>, Ana Luisa Louisenço Moretto<sup>1</sup>

<sup>1</sup>Associação das Pioneiras Sociais, Rede Sarah de Hospitais de Reabilitação, Brasília DF, Brazil

**Case presentation:** A 12 years old Iranian girl, who lived in Brazil for 5 years previously to the stroke and was bilingual (Persian and Portuguese). On October 2016 the girl suddenly presented seizures, hemiparesis and aphasia. Tests for immunological, infectious and coagulation diseases were normal; echocardiogram showed a 39 × 17 mm tumor in the left atrial cavity, that was surgically excised 20 days after. The patient came to our Rehabilitation Hospital only 6 months later. Her first language was Persian, and she started learning Portuguese when she was 5 years old. Prior to the stroke, she was fluent for both languages, either for speaking, reading and writing. After, she developed aphasia for both languages, facing more problems with her first language. In Portuguese, she presented expression aphasia, with anomias, semantical, phonemic and morphemic para-

phasias, besides paralexias and paraphasias. Magnetic resonance (08/08/2017) showed ancient ischemic vascular accident at left medial cerebral artery, justifying patient's aphasia. Sequential brain images, including a tractography study prior and 9 months after the rehabilitation program, initially showed important reduction at the number of the left arcuatus fasciculus, which affects connections at the primary language areas at the left cerebral hemisphere, that were damaged by the stroke. Tractography at 01/11/2018 showed a small increase at the number of the right arcuatus fasciculus, that represents neuroplasticity with increase at the number of connections at areas on the right cerebral hemisphere.

**Discussion:** Although aphasia is one of the most common sequelae after a stroke episode, it is a rare condition in children, specially when it is related to primary cardiac tumors, like the myxomas. Tractography findings showed that even 9 months after the stroke, at the primary area of language, at the dominant hemisphere, still there was anatomic changes, after the intervention. The most expressive increase at the right arcuatus fasciculus may suggest that the right hemisphere might be compensating the language deficits secondary to damage at primary language areas at the dominant hemisphere.

**Final comments:** It's very important to consider rare conditions as a cause for a stroke in children and teenagers. The existence of independent linguistic subsystems to process different languages at the bilingual person might be the reason why both languages were damaged at different degrees.

Code: PE005

### Case report: central nervous system vasculitis due to COVID-19

Matheus de Souza Rosa<sup>1</sup>, Rodrigo Santana Arruda<sup>1</sup>, Alicia Carolina Coraspe Gonçalves<sup>1</sup>, Guilherme Cordaro Buckner Furini<sup>1</sup>, Daniela Fernanda de Almeida Santos<sup>1</sup>, Laila Prazeres Schulz Moreira<sup>1</sup>, Amanda Póvoa Paiva<sup>1</sup>, Maria Avanise Yumi Minami<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto SP, Brazil

**Case presentation:** A two year-old previously-healthy male was admitted at the emergency room due to severe acute respiratory syndrome. Initial evaluation detected right pneumonia and ipsilateral pleural effusion. A nasopharyngeal SARS-COV-2 RT-PCR test was positive. He was admitted for intravenous treatment and, after 7 days, presented a decreased level of consciousness and left hemiparesis. CT scan was normal and spinal fluid showed pleocytosis, elevated protein and low glucose, suggesting meningitis. Antimicrobial therapy was scalonated. After 3 days, the patient deteriorated (GCS 7) and presented focal seizures, requiring intubation and transference to the PICU. A new CT was performed, showing a hypodense lesion in the right thalamus. Then, an AngioMRI was performed and demonstrated multiple acute infarcts in the brainstem, right thalamus and temporal lobes probably caused by an arteritis due to the infection in process. The child improved clinically in the following weeks. During his stay, a control MRI was performed 11 days later and indicated a new acute infarct at the brainstem. Due to the event recurrence, despite his clinical improvement, he received a methylprednisolone pulse for 3 days. It was repeated monthly for the next 3 months. He also received enoxaparin and acetylsalicylic acid.

**Discussion:** Neurologic involvement associated to COVID-19 is not uncommon, either as in the acute disease or associated

with MIS-C. However, life-threatening neurologic complications occur in a minority of patients and are rare in previously healthy children. They can manifest as severe encephalitis, ischemic or hemorrhagic stroke, acute infection of the central nervous system, acute fulminant cerebral edema and Guillain Barré Syndrome. At this moment, the pathogenic mechanisms are uncertain. It is suggested to involve neuroinvasive mechanisms directly linked to the virus, neuroinflammatory by the elevated production of cytokines, dysregulation of the post-infectious immune system or even secondary to complications of systemic inflammation.

*Final comments:* As a recent outbreak, COVID-19 is yet being comprehended. Our case reinforces the possibility of CNS vascular involvement complicating this disease in previously healthy children. Therefore, further studies are necessary for better understanding of its pathogenesis. Also, children affected will require follow-up for evaluation of the morbidity.

#### Code: PE006

##### **First thrombolysis in a 2-year-old child with ischemic stroke at HC FMUSP: case report**

Nicholas dos Santos Barros<sup>1</sup>, José Albino da Paz<sup>1</sup>, Clarice Semião Coimbra<sup>1</sup>, Suely Fazio Ferracioli<sup>1</sup>, Roberta Diniz de Almeida<sup>1</sup>, Ana Cristina Azevedo Leão<sup>1</sup>, Rafaela Fernandes Dantas<sup>1</sup>, Renata Keiko Watanabe<sup>1</sup>, Gabriel Frizzo Ramos<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

*Case presentation:* Female patient, 2 years and 3 months old, previously followed up by pediatric cardiology due to complex congenital heart disease characterized by pulmonary atresia and intact interventricular septum and atrial septal defect with important right-to-left shunt in the late postoperative period of blalock surgery taussig modified on 04/30/2020 and Glenn's surgery on 04/26/2021. Child was referred to pediatric neurology on 8/16/2022 due to complete left hemiparesis and ictal anarthria, at evaluation around 3 hours after the onset of the event scored on the NIHSS 11 scale (Item 4: 2 points | Item 5a: 4 points | Item 6a: 3 points | Item 10: 2 points), performed CT of the skull that showed ischemia of the caudate nucleus, lentiform and right internal capsule, estimated ASPECTS of 8. Talked with parents and explained about the lack of consensus, possible adverse and beneficial effects of thrombolysis with intravenous alteplase, after discussion between the assistant teams together with those responsible for the child, thrombolysis was indicated, which was performed three hours and thirty minutes after the event, with an improvement in the NIHSS to 6 (Item 4: 0 point | Item 5a: 3 points | Item 6a: 2 points | Item 10: 1 point) and no evidence of CNS bleeding after control neuroimaging.

*Discussion:* Despite the higher incidence of stroke in the population over 18 years of age, in the pediatric age group, data around 5 to 10 for every 100,000 children annually have been reported, with mortality around 6% and of those who survive, around 75% have sequelae neurological signs that impair the quality of life and development of these children. The treatment of the acute phase in cases of ischemic stroke is very well studied and conducted in adult patients, but in the pediatric age group there are few published studies with a small number of patients who underwent reperfusion therapies, in view of this, to date, there is no there are well-established guidelines on the subject.

*Final comments:* We highlight the important relevance of the report of this pioneering case in thrombolysis in a 2-year-old

child with a favorable clinical outcome, to open more discussions regarding the indication of vascular reperfusion therapies in the pediatric age group.

#### Code: PE007

##### **Ischemic arterial stroke, epileptic status and choreoathetosis in late vasculitis COVID-19: a case report**

Saul Didmar Alquez Montano<sup>1</sup>, Eduardo Vaz de Sousa Ferreira<sup>1</sup>, Laura Defensor Ribeiro de Melo<sup>1</sup>, Laila Prazeres Moreira<sup>1</sup>, Guilherme Furini<sup>1</sup>, Marcela Lopes Almeida<sup>1</sup>, Maria Avaniise Yumi Minami<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Hospital das Clínicas, Ribeirão Preto SP, Brazil

*Case presentation:* A 3-year-old patient started with runny nose and fever onset treatment for pneumonia, without improvement with amoxicillin and Clavulanic Acid for 10 days; later with azithromycin 5 days, without improvement and joined our service due to impaired respiratory function, when performing chest computer tomography (CT): seen opacities in matte glass bilaterally. Screening tests for COVID-19 in the initial care unit were negative. The patient evolved with pleural effusion, convulsive status, and left complete hemiplegia. Due to the worsening breath was intubated, cranial-CT showed multiple infarctions, compromising bilateral left-wing of middle cerebral artery (MCA) territory, associated with diffuse brain edema, cranial CT angiography: occlusion of the proximal segment of cervical and top of intracranial right internal carotid artery (ICA), occlusion of the right MCA and left anterior cerebral artery (ACA) A2 segment. There wasn't no history of cervical trauma. We performed a study of vascular wall by MRI ("black blood") that showed parietal thickening in the thrombosed segments, as well as foci of concentric parietal enhancement, representing vascular inflammatory process. After extubation, she developed paroxysmal autonomic instability, dystonia; and, but later, choreoathetosis in the right side. Performed viral panel in liquor including research for COVID-19: negative; but serology for this virus IgG and IgM were positive. Rare causes of stroke in children were negative in investigations. During the evolution, anticoagulation was performed, achieved adequate control of seizures, currently in deformity prevention and motor rehabilitation.

*Discussion:* Virus-induced endotheliopathy leading to thrombosis is observed in SARS-CoV-2 infections in several organs, although research by nasopharyngeal swab testing, and cerebrospinal fluid was negative, serology showed COVID-19 infection, which has already been reported in the literature, probably due to the low viral load in the sample, transient viremia or due to delay in the test after the onset of symptoms. Latency time between the infection and late-onset vasculitis varies from 2–5 weeks, due to delayed immune reactivation triggered by the virus.

*Final comments:* Due to the technical difficulties for viral research, it is of great importance to pay attention to the signs of focal neurological deficit, as well as an adequate evaluation with neuroimaging given the potential of COVID-19 to affect the central nervous system.

**Code: PE008****New inflammatory and genetic condition manifesting with recurrent strokes at young age: DADA-2**

Maria Luiza Benevides<sup>1</sup>, Paula Thaís Bandeira Elias<sup>1</sup>, Fernanda Ferrão Antônio<sup>1</sup>, Larisse Souza de Morais Somavilla<sup>1</sup>, Ana Carolina Piauilino Santos Falcão<sup>1</sup>, Isabelle Salgado Castellano<sup>1</sup>, Karine Couto Sarmiento Teixeira<sup>1</sup>, Ana Carolina Coan<sup>1</sup>, Kátia Maria Ribeiro da Silva Schmutzler<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas SP, Brazil

**Case presentation:** A 8-year-old girl, born in southeast Brazil, was taken to the neurologist by her parents to investigate repeated unexplained neurological deficits. When she was 4 years old, she presented with livedo reticularis, abdominal pain, fever, and lower digestive hemorrhage. She was extensively investigated, showing increased ESR and RCP, and negative tests for ANA, rheumatoid factor, ANCA, cryoglobulin, antiphospholipid antibody, and serological screening for infectious diseases. This event was interpreted as a possible polyarteritis nodosa (PAN), and treatment with corticoids and azathioprine was prescribed. Despite of treatment, at 7 years old, she presented with focal seizures followed by left hemiparesis, dysarthria, and dysphagia. Three months later, she progressed with right amaurosis, due to ischemic neuritis of the optic nerve; and one year later, with tetraparesis, worse in lower limbs. Her MRI showed midbrain, cerebral peduncles, basal ganglia, and thalamic ischemic lesions of different times of occurrence. Besides, parenchymal microhemorrhages and hemosiderin deposits in right middle temporal gyrus were identified. She did not have any similar history among her family, and her parents were not consanguineous. Considering complete rheumatologic investigation, inflammatory proofs persistently elevated, and vasculopathy involving small and medium-sized vessels, the diagnosis of adenosine deaminase-2 deficiency (DADA2) was plausible. Enzymatic test showed that the patient was deficient in plasma ADA2 activity (0.3mU/g protein; reference: 25–285mU/g protein). Immunosuppressive treatment was prescribed with Adalimumab.

**Discussion:** DADA-2 is an autoimmune genetic disease, caused by homozygous or compound heterozygous mutations in the CECR1 gene, characterized by vasculopathy in small and medium-sized vessels. Clinical manifestations are stroke in young people, and varied systemic manifestations, such as PAN, livedo reticularis, and recurrent infections.

**Final comments:** The reported case highlights the importance of considering DADA-2 as a differential diagnosis in patients with PAN symptoms and recurrent neurological deficits at a young age, especially regarding prompt treatment.

**Code: PE009****Thrombolysis in pediatric acute ischemic stroke: two case reports**

Ana Clara Bernardi<sup>1</sup>, Gabriel Lellis Neto<sup>1</sup>, Hugo Leonardo Justo Horácio<sup>1</sup>, Renata Yasmin Cardoso Sousa<sup>1</sup>, Layanna Bezerra Maciel Pereira<sup>1</sup>, Rudimar Santos Riesgo<sup>1</sup>, Michele Michelin Becker<sup>1</sup>, Maria Isabel Bragatti Winckler<sup>1</sup>, Josiane Ranzan<sup>1</sup>

<sup>1</sup>Hospital de Clínicas de Porto Alegre, Porto Alegre RS, Brazil

**Case presentation:** Male, 13 years old, previously diagnosed with autism spectrum disorder and epilepsy, arrived in the emergency room with acute dysarthria, lethargy and ataxia. Asymptomatic the night before, he woke up showing focal neurologic signs. At examination, he was lethargic, disoriented, dysarthric and ataxic. Head computed tomography (CT) showed signs of recent ischemic injury in both cerebellar hemispheres and hyperdensity in the basilar artery, sugges-

tive of thrombus, confirmed by angiography. Thus, it was opted to start thrombolysis with alteplase 0,9mg/kg, with no complications and showing improvement of the symptoms during the infusion. Further investigation found patent foramen ovale (PFO) by transesophageal echocardiography. Cardiac evaluation suggested there was a possible benefit in performing percutaneous PFO closure. At the time of discharge, the patient maintained only a discrete wide-based gait and was using rivaroxaban. Female, 11 years old, obese, presented with an acute case of complete left-sided hemiparesis and dysarthria. She was taken to the emergency room, where her head CT showed no abnormalities, but due to the highly suggestive acute ischemic stroke (AIS) presentation, she started thrombolysis with alteplase 0,9mg/kg, 3 hours after symptom onset. The next morning, she showed partial improvement of the motor signs. Head CT was repeated and, this time, it showed hypodensity in the right internal capsule. After 24 hours, secondary prophylaxis with AAS and simvastatin was started, as well as deep venous thrombosis prophylaxis with subcutaneous heparin. No etiology was found for the event. Patient was discharged with slurred speech and brachial predominance of complete left-sided hemiparesis.

**Discussion:** Pediatric AIS can be a multifactorial disease, and all patients must undergo comprehensive investigation. Thrombolysis should be considered, especially due to the benefits shown in adults. Case reports support the use of alteplase in patients aged 13 years or older, but some centers use it in younger patients with satisfactory results.

**Final comments:** Thrombolysis can be the treatment of choice in pediatric AIS, despite the lack of clinical trials in this population.

**Doenças neuromusculares****Code: PE013****Nemaline myopathy with severe congenital manifestation**

Izabela Cristina Macedo Marques<sup>1</sup>, Rui Carlos Silva Junior<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Nildo Vilacorte de Araújo Júnior<sup>1</sup>, Daniel Almeida do Valle<sup>1</sup>, Anderson Nitsche<sup>1</sup>, Adriana Banzatto Ortega<sup>1</sup>, Mara Lucia Schmitz Ferreira Santos<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Full-term newborn with reduced fetal movements during pregnancy, elective cesarean section, first child of a non-consanguineous couple with no family history of neurological disease. Apgar 5–5, severe respiratory distress, cyanosis and cardiorespiratory arrest. He required cardiopulmonary resuscitation and mechanical ventilation, persisting with hypotonia. On examination, facial hypomimia and carp mouth with jaw drop, severe hypotonia, immobile in bed, weak and exhaustible deep tendon reflexes, absence of sucking reflex and other primitive reflexes. Proximal strength of limbs 1+ and distal 2+. Arthrogryposis, myokymia and tongue fasciculation absent. The exams showed normal CPK, mild asymmetric dilatation of the lateral ventricles on MRI of the brain, echocardiogram with moderate functional tricuspid regurgitation with slight increase in pulmonary pressure, patent ductus arteriosus with left-right flow, and patent foramen ovale. The initial hypotheses were: SMA type 0, congenital myasthenia and congenital myopathy. The neuromuscular diseases panel showed a heterozygous pathogenic mutation in the ACTA1 gene that is associated with nemaline myopathy with autosomal recessive or dominant inheritance. This congenital myopathy has no curative treatment so far. The patient was discharged home with supportive care.

**Discussion:** Nemaline myopathy is a disease with variable phenotype whose most common expression is bulbar muscular weakness and congenital severe peripheral weakness. Of the 12 genes associated with the disease, the most frequently involved are NEB and ACTA1. Diagnosis depends on molecular testing or biopsy with electron microscopy and immunohistochemistry. Severe early-onset cases are associated with poor prognosis and high mortality.

**Final comments:** The severe hypotonic baby is a great challenge in the delivery room, thinking about neuromuscular causes enables a more aggressive approach and delivery in a specialized center. The diagnosis depends on expensive and difficult-to-access techniques in Brazil, however, it allows for notions of prognosis and establishment of the risk of recurrence.

#### Code: PE014

##### **An unusual cause of non-5q spinal muscular atrophy: DYNCH1-related disease**

Fernanda Ferrão Antonio<sup>1</sup>, Alexandre Motta Mecê<sup>1</sup>, Maria Luiza Benevides<sup>1</sup>, Paula Thais Bandeira Elias<sup>1</sup>, Isabelle Salgado Castellano<sup>1</sup>, Ana Carolina Coan<sup>1</sup>, Anamarli Nucci<sup>1</sup>, Jr. Marcondes Cavalcante França<sup>1</sup>

<sup>1</sup>Universidade de Estado de Campinas, Campinas SP, Brazil

**Case presentation:** This is a five-year-old boy, admitted with global development delay associated with limb deformities. He was born prematurely at 35 weeks, by cesarean delivery due to pelvic presentation. During pregnancy, the mother noticed reduced fetal movements, and at birth, neonatal resuscitation with hospitalization was required. He was born with congenital arthrogryposis (CA), with thumbs in bilateral adduction, restricted plantar movement, global hypotonia, and facial dysmorphisms. Later, behavioral and cognitive changes became evident, leading to the diagnosis of autism spectrum disorder. Laboratorial work-up revealed mild CPK elevation. Genetic testing identified a heterozygous DYNCH1 pathogenic variant (p.Arg1201Ser), confirming the diagnosis of Spinal Muscular Atrophy Lower Extremity - predominant (SMALED - OMIM: 158600).

**Discussion:** CA is diagnosed in the presence of joint contractures in at least two areas of the body from birth with muscle wasting and abnormal joint configuration. The most common causes for this condition are disorders of the neuromuscular junction, congenital muscular dystrophies, congenital infections, and causes of fetal intrauterine immobility. There is, however, a smaller group referred to as neurogenic CA in which there is loss of motor neurons and subsequent denervation of muscle. Although the most frequent cause of neurogenic CA is 5q spinal muscular atrophy (SMA), SMN1-related, there is another group of diseases referred to as non-5q SMA, which include SMALED. This is a rare autosomal dominant condition caused by pathogenic DYNCH1 variants. Mutations in this last gene are associated with three different phenotypes: Charcot Marie-Tooth disease, axonal, type 20, intellectual developmental disorder, and SMALED. Patients with SMALED typically present muscle weakness, symmetric proximal and predominantly of the lower limbs, muscle atrophy, and deformities of joints. Cognitive delay can be present but is usually mild.

**Final comments:** This case describes DYNCH1-related SMALED, an unusual cause of non-5q SMA, in a Brazilian patient. This mutation is associated with variable phenotypes, leading to motor and cognitive disabilities. Neuro-

pediatricians should be aware of this rare entity in the differential diagnosis of CA and/or SMA. Proper diagnosis enables adequate management and genetic counseling of the family.

#### Code: PE019

##### **Charcot Marie Tooth disease type 4C with overlap of chronic inflammatory demyelinating polyneuropathy: a case report**

Luiza Oliveira Prata Silveira<sup>1</sup>, Loiane Dante Correia Rocha<sup>1</sup>, Anna Carollina Eulalio Amorim Baratta<sup>1</sup>, Marcela Gonçalves de Souza Machado<sup>1</sup>, Pedro Zambuzi Naufel<sup>1</sup>, Sérgio Rosemberg<sup>1</sup>, Roberta Paiva Magalhaes Ortega<sup>1</sup>

<sup>1</sup>Irmadade Santa Casa de Misericórdia de São Paulo, São Paulo SP, Brazil

**Case presentation:** Patient female, born of a cousin marriage with history of respiratory distress at birth requiring oro-tracheal intubation and was diagnosed with dysphagia requiring gastrostomy for 1 year. Presented neuropsychomotor developmental delay and at the age of 6 started with symptoms of paraesthesias and lower limbs cramps. At the age of 12, the patient presented muscle weakness and pain in the lower limbs with progressive worsening associated with frequent falls. The patient was referred to our service at the age of 13 years old. At clinical evaluation, the patient could easily stand up, initiate independent gait, with a wide-based gait and tendency to fall. She could stand without support for a short period of time. Presented Grade III muscle strength in lower limbs and grade IV in the upper limbs associated with hypotrophy in lower limbs and at reflex and sensitivity examinations presented hypoactive osteotendinous reflexes in upper limbs and absent in lower limbs with distally reduced sensitivity in the lower limbs. Electroneuromyography demonstrated severe peripheral sensorimotor demyelinating polyneuropathy and cerebrospinal fluid shown hiperproteynorraquia. During follow-up, the patient presented an unstable course of symptoms, with worsen of weakness especially in association with an infectious condition. Therefore, pulse therapy with steroids was chosen as a treatment, with expressive improvement of the clinical symptoms. PMP22 genetic test was performed, which ruled out Charcot Marie Tooth type 1A. An expansion of the genetic test was performed, which revealed CMT4C alteration with mutation in the SH3TC2 gene.

**Discussion:** Charcot Marie Tooth 4C disease is a chronic sensorimotor demyelinating polyneuropathy. It's the most frequent mutation among the recessive subtype but is considered a very rare form. In general, the mutation in the SH3TC2 gene characterizes a late-onset condition. In the case reported, we considered the coexistence between Charcot Marie Tooth disease type 4C and chronic demyelinating inflammatory polyneuropathy (CIDP). The findings that favor the diagnosis of overlap are the unstable course of symptoms, sensory symptoms, hyperproteynorraquia and clinical improvement after pulse therapy.

**Final comments:** The diagnosis of inflammatory polyneuropathy overlap in patients with Charcot Marie Tooth with unstable clinical course is important, due to the possibility of the clinical improvement when immunomodulatory and/or immunosuppressive therapy is indicated.

**Code: PE021****A case report of a response to onasemnogen abeparvovec in a 7-year-old child with SMA Type 2**  
**Tainara Zappia Tessaro<sup>1</sup>**<sup>1</sup>Hospital Grupo de Assistência à Criança com Câncer, São José dos Campos SP, Brazil

**Case presentation:** A male patient, 8 years old, son of non-consanguineous parents, who presented delayed motor development. At 10 months, he underwent genetic testing for Spinal Muscular Atrophy (SMA) with absence of copies in exon 7 and 8 of the SMN1 gene and 3 copies of the SMN2 gene, being then classified as SMA type 2. He was using Nusinersine (he received 16 doses of medication), with a good response to treatment. In January 2022, at the age of 7 years, he received a dose of Onasemnogeno Abeparvovec (adjusted to 21 kg, according to the European package insert), as instructed in the package insert, he used prednisolone (2mg/kg/day), started on the eve of the application and maintained for 4 weeks with slow drug taper to date. After 6 months of receiving gene therapy, he showed a gain of 5 points on the "Expanded Motor Functional Scale for AME Hammersmith (HFMSE)," he had 22 points in January 2022 and in July of the same year he increased his score to 27 points. In addition to improvement in this motor scale, reductions in foot and chest deformities were also noticed, as well as improved hand strength, fine motor coordination, ensuring more autonomy in his daily care, such as bathing and brushing his teeth. After the first month of treatment, during the corticosteroid reduction phase, he evolved with an increase in liver enzymes (AST and ALT), corrected with a pulse of Methylprednisolone for 3 days. Even during treatment, he remained asymptomatic. Now, he maintains a gradual reduction in corticosteroids.

**Discussion:** Although the child is above the age of recent studies on the medication, the patient had a good response to treatment, without severe adverse events. An important point to be evaluated in this case is that the child did not present motor involution when he received the gene therapy (unlike the cases shown in studies with children older than 2 years), in addition to the fact that this child has a complete multidisciplinary care network. Wouldn't it be necessary to evaluate the patient's clinical conditions to indicate the medication beyond the age group?

**Final comments:** Spinal Muscular Atrophy (SMA) is a progressive and degenerative disease, gene therapy becomes a viable treatment option for patients with the disease. More studies with older patients are needed to better assess the profile of treatment candidates. It would be possible to consider the clinical condition of these patients to indicate gene therapy, although they are outside the ideal age group.

**Code: PE022****First Brazilian case of rare mitochondrial myopathy and ataxia associated to MSTO1 variants**

Mateus Oliveira Torres<sup>1</sup>, José Marcos Vieira Albuquerque Filho<sup>1</sup>, Katrine Freitas Valeriano<sup>1</sup>, Caroline Corrêa Maranhão<sup>1</sup>, Lorena Raulik Cyrino<sup>1</sup>, Bryan Silva Marques Cajado<sup>1</sup>, Marcelo Melo Aragão<sup>1</sup>, Alulin Tacio Quadros Monteiro Fonseca<sup>1</sup>, Ricardo Silva Pinho<sup>1</sup>

<sup>1</sup>Universidade Federal de São Paulo, São Paulo SP, Brazil

**Case presentation:** A 9-year-old Brazilian girl, second child of healthy non-consanguineous parents, born full term after an uneventful pregnancy and delivery. Family history was unremarkable. Developmental milestones were achieved without delay. She presented to our service at the age of 7 with a

history of difficulty walking, climbing stairs and frequent falls since the age of 3 associated with truncal ataxia and lumbar pain. First neurological examination revealed myopathic gait, with retained reflexes, unimpaired balance and coordination. There were no other abnormalities on the physical exam. She evolved with worsening of dorsal pain but had no episodes of overt rhabdomyolysis. The first reassessment, 6 months later, physical examination showed slight worsening of proximal hip girdle weakness, reflexes become hypoactive in superior and hyperactive in lower limbs. Complementary tests showed: normal EKG, minimal degree tricuspid valve regurgitation on echocardiogram. Baseline blood investigations were normal. Plasma CK level: 324 U/L (normal range 32–211U/L). EMG was normal. Neuromuscular directed genetic panel was performed and revealed two variants, heterozygous state, in MSTO1 gene: c.887\_888delTT;p.(p.Leu296Argfs\*26), classified as likely pathogenic and c.1115C>T;p.(p.Ala372Val), classified as variant of uncertain significance (VUS).

**Discussion:** MSTO1 pathogenic variants have been shown to cause clinical manifestations suggestive of mitochondrial dysfunction, an extremely rare condition characterized by early-onset myopathy and cerebellar ataxia. Both autosomal dominant and recessive modes of inheritance have been suggested. Patients with biallelic MSTO1 mutations presented with a quite homogeneous phenotype, characterized by early-onset muscle impairment and ataxia in all, whereas retinopathy, facial dysmorphisms or skeletal abnormalities were variably present. It is noteworthy that patients present different evolutions, and like our patient, others present with a relatively stable or slowly progressive condition, which may mimic other causes. Cognitive impairment is also described in these patients but not present in our patient.

**Final comments:** We report a rare case of mitochondrial myopathy and ataxia due to compound heterozygous MSTO1 mutation, clinically characterized by muscle weakness, myalgia and ataxia. This clinical phenotype matches the few cases described in current literature and, to date, the first Brazilian case of this condition.

**Code: PE023****Gene therapy treatment in SMA with positive AAV9 antibodies**

Adriana Banzatto Ortega<sup>1</sup>, Guilherme Siqueira Gaede<sup>1</sup>, Izabela Cristina Macedo Marques<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** To describe the outcome of the clinical evolution of two SMA patients with positive test for the AAV9 antibody, treated with gene therapy. Case report: Patient 1, C. M.M., currently 2 years and 11 months, was diagnosed with spinal muscular atrophy type C at 7 months due to the loss of cervical tonus and reduction of lower limbs movement, associated with weight loss caused by the dysphagia, with initiation of Spinraza treatment at 10 months. At 33 months, he received gene therapy, with a positive test for the AAV9 antibody (titer 1:100). The patient had no adverse events, only a slight increase in the transaminases, not higher than twice the reference value. Only two weeks after receiving the gene therapy, it was already possible to observe effective cough and improvement in torso strength; After 45 days, he was able to stand with only a short orthosis. Patient 2, T.E.S., currently 2 years and 3 months old, was diagnosed with SMA type 2 at 17 months of age. He started treatment with nusinersena at 19 months of age. At 25 months old, he received an infusion of gene therapy (Zolgensma) for SMA with an AAV9 test titer of 1:100, while two weeks earlier the titer was 1:200. He received 1mg/kg/day of prednisolone,

without the need to increase the dose. He did not present any major adverse event, other than an increase in the transaminases up to 4 times the reference value, which allowed the suspension of the corticosteroid therapy 60 days after the infusion.

**Discussion:** The cases in question are part of the presentation of SMA, which were early diagnosed due to the precocious identification of suggestive symptoms of the disease, such as generalized muscle hypotonia, areflexia and loss of developmental milestones. The possibility of early treatment, associated with non-pharmacological therapies, allows greater possibility of motor skill gains and improvement in quality of life. Although current drug leaflet guidelines only recommend the use of gene therapy for the treatment of SMA in patients with AAV9 antibody titers below 1:50, two patients with titers of 1:100 received the treatment and did not show any immunological side effect. On the contrary, after 2 weeks, they were already showing motor skill improvements.

**Final comments:** Based on the cases presented, it is suggested the possibility of considering a higher titration for AAV9 antibodies to avoid the gene therapy in SMA patients.

#### Code: PE025

##### **Intrauterine diagnosis of SMA type 1 and early initiation of therapy: case report**

Amanda Regina Farias Teixeira<sup>1</sup>, Flavia Nardes dos Santos<sup>1</sup>, Marlos Melo Martins<sup>1</sup>, Maria Lina Giacomino de Almeida Passos<sup>1</sup>, Hanid Gomes Fontes<sup>1</sup>, Caroline Scantamburlo Martins<sup>1</sup>, Sofia Russi<sup>1</sup>, Jessica Kayene Souza Ferreira<sup>1</sup>, Lana Correa Paschoal<sup>1</sup>

<sup>1</sup>Universidade Federal do Rio de Janeiro, Instituto de Puericultura e Pediatria Martagão Gesteira, Rio de Janeiro RJ, Brazil

**Case presentation:** Female patient, second daughter of a healthy couple, was first brought for neuropsychiatric evaluation with three days old already with the diagnosis of spinal muscular atrophy 5q (SMA) type 1. The firstborn of this couple had the same diagnosis (deceased one month after her first birthday) therefore they decided to test the second child while still in the uterus. PCR (Polymerase Chain Reaction) for SMA was performed in a vilochorial sample, which showed a homozygous deletion of exon 7 SMN1. On physical examination, she presented mild global hypotonia, tongue myofasciculation, suction reflex and no apparent malformations. She scored 22 of 64 on CHOP-INTEND evaluation. MLPA (Multiplex Ligation-Dependent Probe Amplification) collected, showing two copies of SMN2. At the end of her first month of life, hypotonia was more accentuated. The patient underwent the first intrathecal infusion of nusinersen at thirty five days of life. Three months old evaluation, (after three infusions) improvement of hypotonia was observed. The patient had partial cervical support, social smile, palmoplantar prehension and was following human face, scoring 39 of 64 on CHOP INTEND. Tongue myofasciculation was not observed but polimyoclonus of the hands was present. No ventilation support was required, and feeding was orally.

**Discussion:** Spinal muscular atrophy (SMA) presents progressive degeneration of motor neurons located in the anterior horn of the spinal cord and has an incidence of 1 in every 10,000 births. SMN1 gene mutations comprise the most common form of the disease and their severity is related to the age of onset of symptoms. It is classified into types I, II, III and IV. Type I presents symptoms before six months of life and has a more severe presentation, with death occurring in most cases before two years of life. Nusinersene is indicated in cases of mutation or deletion of SMN1, and acts by increasing

the amount of functional survival motor neuron (SMN) protein from the SMN2 gene.

**Final comments:** With the initiation of nusinersen therapy, a significant improvement in hypotonia was observed, the patient continued with oral feeding (breast on demand), without sialorrhea, presented fully expanded chest, without tachypnea or dyspnea, which reinforces that nusinersen therapy has been modifying the course of the disease, offering better quality and life expectancy for patients with SMA.

#### Code: PE031

##### **Mutations in the gene MEGF10 causing a recessive congenital multimimicore myopathy**

Thaís de Almeida Fonseca Oliveira<sup>1</sup>, Laura Maria Silva Thiersch<sup>1</sup>, Renan Guimaraes Santana<sup>1</sup>, Nathalia Jamille Moreira Nascimento David<sup>1</sup>, Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, Karina Soares Loutfi<sup>1</sup>, André Vinicius Soares Barbosa<sup>1</sup>, Bruna Ribeiro Torres<sup>1</sup>, Ana Carolina Cardoso Diniz<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

**Case presentation:** 5-year-old girl, born from a consanguineous couple, is referred to our service due to weakness and hypotonia. It was necessary hospitalization, after birth, due to respiratory insufficiency and a severe motor delay was already evident in the first months of life. At 6 months she did not have head control and at 12 months she was not able to sit without support. She developed respiratory problems with apneas and hypercapnia, at 3 years of age, that was treated with bilevel positive airway pressure ventilation. Because of aspiration pneumonia gastrostomy was indicated at the age of 4. In her evaluation she had axial and proximal muscle weakness, facial weakness, scoliosis and hypernasal speech. Despite presenting with hypotonia and gait difficulties, she was able to walk independently and did not present cognitive impairment. At the neurological workup a muscle biopsy was performed and suggested a multimimicore myopathy. A genetic investigation resulted in a homozygous mutation of MEGF10 gene.

**Discussion:** Congenital myopathies result from a variety of genetic defects. They are classified into five main types: core myopathies, nemaline myopathies, centronuclear myopathies, congenital fiber-type disproportion, and myosin storage myopathies. Core myopathies such as central core disease and multimimicore disease are the most common forms of congenital myopathies. Despite their phenotypic diversity, patients demonstrate common symptoms including hypotonia, muscle weakness, dysmorphic features, and respiratory problems. There are several mutations in MEGF10 that have been reported to cause autosomal recessive congenital myopathy, areflexia, respiratory distress, muscle weakness, dysphagia with early or late-onset syndrome, mimicore myopathy and limb girdle muscular dystrophy. Affected individuals frequently become ventilator dependent or die secondary to respiratory failure.

**Final comments:** MEGF10 mutations should be considered in the differential diagnosis of individuals presenting with respiratory insufficiency and myopathy, particularly when accompanied by facial weakness, scoliosis or dysphagia. The phenotypic similarities with other congenital neuromuscular disorders may cause difficulties in reaching a definite diagnosis. Treatment with a multidisciplinary team is important and family counseling is essential since consanguineous unions play a role in recessive genetic mutations manifestations.

**Code: PE032****Mutilating hereditary sensory and autonomic neuropathy associated with WNK1 gene**

Bryan da Silva Marques Cajado<sup>1</sup>, Pedro Henrique de Almeida Fraiman<sup>1</sup>, Vinicius Alves Lima<sup>1</sup>, Felipe Arthur de Almeida Jorge<sup>1</sup>, Mateus Oliveira Torres<sup>1</sup>, José Marcos Vieira Albuquerque Filho<sup>1</sup>, Alulin Tácio Quadros Santos Monteiro Fonseca<sup>1</sup>, Marcelo de Melo Aragão<sup>1</sup>, Ricardo da Silva Pinho<sup>1</sup>

<sup>1</sup>Universidade Federal de São Paulo, São Paulo SP, Brazil

**Case presentation:** A 17-year-old girl presented recurrent skin injuries on both feet with onset at 2 years old. She had labile skin temperature with unexplained hyperthermia episodes. Parents were consanguineous and had two healthy younger brothers. Past medical history included chronic osteomyelitis of the right foot after recurrent skin cellulitis. On examination, there are acral mutilations on both hands and feet and dry skin; reduced bilateral and symmetrical length-dependent pain, touch and vibratory sensation to knees and elbows, absent on hands and feet. Deep tendon reflexes are globally absent, except triceps and pronator teres. Orthostatic hypotension and urinary or fecal incontinence are absent. Nerve conduction studies revealed absent sensory nerve action potentials on four limbs, with normal compound muscle action potentials. Hereditary sensory and autonomic neuropathies were suspected and a genetic panel confirmed a homozygous pathogenic variant c.3226C>T (p.Arg1076\*) in WNK1 gene associated with autosomal recessive hereditary autonomic and sensory neuropathy type 2A (HSAN2A), but also a single pathogenic variant in DST gene, c.4152del (p.Glu1384Aspfs\*2), associated with HSAN6.

**Discussion:** HSAN2A is a childhood-onset disorder that typically presents numbness affecting the hands and feet, reduced sensitivity to pain, and loss of touch and temperature. Although autonomic functions are not classically affected, HSAN6 is similar but with dysautonomia – including impaired sweating and heat intolerance. Our patient also presented several episodes of unexplained hyperthermia and dry skin. Besides, the phenotype is typical of HSAN2A and genetic analysis confirmed homozygous mutation of WNK1 gene. In the long term, reduced sensitivity of extremities causes acral mutilations and infectious complications due to ulcerations. Autonomic features seen in our patient are unexpected in HSAN2A. Oddly, she is a carrier of single copy mutated DST gene associated with HSAN6, an autosomal recessive condition, more associated with autonomic features than HSAN2A.

**Final comments:** Despite HSAN2A phenotype and confirmed mutation of WNK1 gene, our patient is also a carrier of a single copy of DST gene mutation associated with HSAN6 phenotype. Oddly, some autonomic features presented in our case are not expected on HSAN2A but in HSAN6. Therefore, a single copy mutation of DST gene is insufficient to cause autosomal recessive DST-related conditions such as HSAN6, besides the reproductive risk of a carrier.

**Code: PE034****PLEKHG5 mutation: a rare cause of Charcot-Marie-Tooth disease**

Cristiani Rocha Lima Cruz<sup>1</sup>, Ana Beatriz Arruda Carvalho Oliveira<sup>1</sup>, Renata Silva Mendonça<sup>1</sup>, Daniel Shoji Hayashi<sup>1</sup>, Joemir Jabson Conceição<sup>1</sup>, Clarice Semião Coimbra<sup>1</sup>, Clarissa Bueno<sup>1</sup>, Marco Antonio Veloso Albuquerque<sup>1</sup>, Fernando Kok<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, São Paulo SP, Brazil

**Case presentation:** Fifteen year-old male, brown skin, with non-consanguineous parents and a previous diagnosis of

intellectual deficiency and attention deficit hyperactivity disorder. When the patient was ten years old the symptoms began with gait impairment, bilateral foot drop and calf pain. The symptoms progressed and 7 months before our clinical evaluation the patient also started presenting muscle contracture in both upper limbs with no sensitive complaints. In the physical exam there was distal limb muscle weakness in the regions from ulnar, mediane and fibular nerve and bilateral claw hand. There was no muscle atrophy and the only area with sensitive impairment was apalesthesia on the left hallux. Bilateral slapping gait was also noticed. The findings included a brain MRI with a discreet prominence in the lateral ventricles and elevated serum creatine kinase (1400mg/dl). Needle electromyography showed a chronic sensory-motor polyneuropathy affecting all four limbs with a myelin-axonal pattern. The genetic panel presented a pathogenic mutation in heterozygous on the HINT1 and in homozygous on PLEKHG5, both associated with an intermediary type C form of Charcot-Marie-Tooth (CMT).

**Discussion:** CMT comprises a clinically and genetically heterogeneous group of peripheral neuropathies characterized by progressive distal limb weakness, atrophy, foot deformities, sensory impairment and hypo or areflexia. The two main clinical forms, demyelination and axonal, were described based on electromyographic findings. There is also the intermediary group that combines findings from the above. Mutations on PLEKHG5 can lead to a wide set of manifestations, such as intermediary CMT. The clinical manifestation is typically associated with missense mutations in homozygous. Our patient presented similar symptoms even though the mutation was heterozygous. The second mutation found on the HINT1 gene is correlated with axonal neuropathy associated with neuromyotonia. However, the patient's electromyographic study showed a myelinic-axonal form, which is not present on the classic manifestations of this disease. Therefore, our patient's diagnosis would not be completely explained by this variant alone.

**Final comments:** The case addressed a heterozygous mutation of the PLEKHG5 gene as a cause of CMT. There are rare descriptions of such an association in the literature, as well as a well-established genotype-phenotypic correlation.

**Code: PE035****Rare case of congenital myopathy associated with the FXR1 gene**

Isadora Cavalcante Olímpio de Melo<sup>1</sup>, Paula Luisa Lopes Shell<sup>1</sup>, Ana Carolina Jorge Fogolin<sup>1</sup>, Michelle Basso Couto Gouveia<sup>1</sup>, Iris do Vale Miranda<sup>1</sup>, Helen Ramos Vasoncelos<sup>1</sup>, Ana Elisa Ribeiro de Faria<sup>1</sup>, Rafael Guerra Cintra<sup>1</sup>

<sup>1</sup>Faculdade de Medicina do ABC, Santo André SP, Brazil

**Case presentation:** A.M.M., 14 years old, consanguineous parents; term, pregnancy and delivery without complications, mother without history of abortion. Healthy parents, 19-year-old sister and healthy 12-year-old brother. At 4 months, the mother noticed the absence of head support, difficulty in sucking and swallowing. She evolved with repeated hospitalizations due to aspiration pneumonia. At 10 months she sat up with support; she did not crawl and at 15 months walked with support. She acquired independent gait at 2 years of age, but had many falls, stood up with the help of her arms and did not climb steps. Cognitive apparently preserved. At age 5, she was often tired on short-distance walks and needed bipap assistance during sleep. She was always carried by her parents to get around, due to weakness and frequent falls, so at age 7 she started using a wheelchair.



She did not eat solid food due to choking. At 8 years old, she started to eat only through a gastrostomy. At 10 years of age, she had scoliosis and significant lordosis, winged scapula, axial and appendicular hypotonia, dropped head, grade 2 muscle strength in the proximal upper limb and distal lower limb, grade 3 in the distal upper limb and proximal lower limb. Hypoactive osteotendinous reflexes, without signs of pyramidal release. Broad DNA panel for neuromuscular diseases was requested, and a rare mutation was identified in the FXR1 gene in homozygosis.

**Discussion:** Homozygous pathogenic variants in the FXR1 gene were associated with 2 phenotypes: congenital myopathy with respiratory failure and bone fractures characterized by a very early and severe myopathy leading to hypotonia, dysphagia, respiratory failure and fracture of long bones. Another phenotype presents as congenital myopathy with “minicore” lesions, which has an early onset and mainly affects the proximal muscles. It is characterized by muscle weakness, hypotonia and delay in gait acquisition, slowly progressive course, difficulty running and climbing stairs. There is no cardiac involvement, but obstructive sleep apnea may occur. The patient described presented early manifestation and progressive evolution, with gait delay, loss of strength to stand and walk, swallowing difficulty requiring gastrostomy and obstructive sleep apnea.

**Final comments:** The patient described has a congenital myopathy phenotype with minicore lesions. This condition was previously described in the medical literature in only two families, hence the importance of this report.

**Code: PE037**

**Recurrent rhabdomyolysis due to long chain Hydroxyacyl-CoA dehydrogenase deficiency (LCHAD): a case report**

Victoria Faustino Silva Reis<sup>1</sup>, Joanna Sousa Fonseca Santana<sup>1</sup>, Lara Cordeiro Magalhães<sup>1</sup>, Marcela Camara Machado Costa<sup>1</sup>, Daise Larissa Ribeiro França<sup>1</sup>, Adriele Ribeiro França Viriato<sup>1</sup>, Juliana Silva Almeida Magalhães<sup>1</sup>

<sup>1</sup>Escola Bahiana de Medicina e Saúde Pública, Salvador BA, Brazil

**Case presentation:** J.A.P.N., male, 7 years old, born at full-term, without gestational complications. He presented significant delay in motor development, started crawling at 8 months, but never acquired gait. In addition, he presented palpebral ptosis since birth. He evolved throughout his life with a pattern of distal atrophy in the upper and lower limbs, in addition to recurrent episodes of hospitalizations due to rhabdomyolysis (~7 episodes). In addition, he also had drowsiness and worsening of ptosis during these events. On neurological examination, he presented bilateral palpebral ptosis, muscle strength grade IV in upper limbs and grade III in lower limbs, besides the presence of distal atrophy and retractions in hands and feet. He was able to crawl, but did not ambulate. To elucidate the diagnosis, a genetic panel (NGS) for neuromuscular diseases was performed, which revealed a homozygous mutation in the HADHA (Hydroxyacyl-CoA Dehydrogenase Trifunctional Multienzyme Complex Subunit Alpha) gene, position chr2:26,232,203, confirming the diagnosis of Long Chain Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD).

**Discussion:** Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is an autosomal recessive inherited condition caused by pathogenic variants of the trifunctional protein (TFP), encoded by the HADHA gene, which has 3 subunits: long-chain hydroxyacyl-CoA dehydrogenase, long-chain enoyl-CoA hydratase, and long-chain thiolase. This

deficiency in the metabolism of long-chain fatty acids results in insufficient energy production as well as an accumulation of fatty acid intermediates. The clinical course of the disease usually begins in the first months of life with growth deficits, hypotonia, peripheral neuropathy, hepatomegaly, cardiomyopathy, and retinopathy. In addition, symptoms may be intensified by prolonged fasting or infections, presenting with idiopathic episodes of cramping and rhabdomyolysis.

**Final comments:** Despite being a rare disease, LCHAD should be considered as a differential diagnosis in patients presenting with a compatible clinical picture, because there is treatment that modifies the course of the disease, which can be performed starting with diet. In addition, it is important that the patient is properly followed up with the specialties, neurologist, gastroenterologist and cardiologist, for assistance in the progression of the disease.

**Code: PE038**

**Report of two cases of Walker-Warburg Syndrome: clinical and radiological aspects**

Ana Paula Resende Silva<sup>1</sup>, Daniel Almeida Valle<sup>1</sup>, Mara Lucia S. F. Santos<sup>1</sup>, Adriana Banzatto Ortega<sup>1</sup>, Izabela Cristina Marques<sup>1</sup>, Anderson Nitsche<sup>1</sup>, Lisandra C. F. Rigoldi<sup>1</sup>, Rui Junior<sup>1</sup>, Alfredo Lohr<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** T.V, F, 4 years-old. Consanguineous parents. G1PN1A0. At birth, diagnosis of Congenital Retinal Detachment. Hypotonic patient, at 6 months of age, she had her first seizure, since then using anti-seizure drugs without good control. Positive family history for epilepsy and intellectual disability. Patient without head support. It has hypertelorism, high palate, corneal opacity. Grade 2 strength in the upper and lower limbs, Global hypotonia, with axial predominance. CPK: 4500U/L. Neuroimaging: CCT - diffuse hypodense area in white matter, in addition to an alteration of the sulci between cerebral gyri, predominantly in the frontal lobe, and dilatation of the lateral ventricles. Cranial MRI shows imaging findings suggestive of Walker-Warburg Syndrome, corroborating clinical findings. of a patient with myopathy associated with ocular changes and epilepsy. Molecular analysis by genetic panel shows POMCGNT1 mutation in homozygous variant c.546\_576del(p.Ala189\*) M.I.M, F, 2 years. Non-consanguineous parents. Child evolved with hypotonia, did not acquire cephalic support skills, dysphagia. He started seizures at ~1 year of age. Family History - Sister died at 4 years old with epilepsy, hypotonia, ophthalmologic alteration. Mother had speech delay. Examination: Spontaneous eye opening. Incoordination of gaze, microphthalmia with leukocoria. Convergent strabismus. Right eye fixed. Light stimulus follows. No changes in the other cranial nerves. More accentuated hypotonia in lower limbs. MRI of the skull Dec 2020 - Simplification of the giriform pattern and thickening of the gray matter of the frontal, insular and mesial temporal lobes bilaterally (perisylvian polymicrogyria?). Medialization and verticalization of the body of the hippocampi in the coronal plane. Symmetrical hippocampal signal strength. Increase in the dimensions of the ventricular system, especially supratentorial and with significant dysplasia of the midbrain ceiling. Brainstem with Z-morphology, showing anterior angulation and hypoplasia in the midbrain region. Volumetric reduction of the bridge, especially the left. Cerebellar morphological changes with a dysplastic appearance. Molecular analysis - POMCGNT1 mutation in compound heterozygosis.

**Discussion:** Walker-Warburg Syndrome is an autosomal recessive disorder characterized by congenital muscular

dystrophy with CPK elevation, major brain malformations, brainstem and cerebrosplinal defects.

*Final comments:* The phenotype is variable. There is no specific treatment.

**Code: PE039**

**Severe case of myotonic dystrophy type 1 associated with syringomyelia**

Teodora Roballo Durigan<sup>1</sup>, Marina Hideko Kinoshita Assahide<sup>2</sup>, Leticia Sayuri Kinoshita Assahide<sup>1</sup>

<sup>1</sup>Universidade Positivo, Curitiba PR, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

*Case presentation:* A 11-year-old Brazilian boy, without family history of neurological disease, presented at 1 year and 6 months of age with pain crisis after a reconstructive surgery to correct hypospadias, and, during the postoperative period, evolved with lack of sphincter control and difficulty walking. During this period, was diagnosed with syringomyelia and, at 4-year-old, underwent surgical treatment (Filum System® method), with total improvement for 4 months. Soon after, presented with metabolic, endocrine, respiratory, cardiac, locomotor and neurocognitive deterioration, requiring a transdisciplinary approach. The final diagnosis of DM1 was confirmed by molecular genetic testing of DM protein kinase (DMPK), which showed a CTG triplet repeat expansion of 97. Although the diagnosis was established, the disease management remains a challenge, due to the multiple systems affected and lack of established therapy for DM1.

*Discussion:* DM1 is a genetic neuromuscular disorder, inherited in an autosomal dominant fashion of variable penetrance, caused by unstable repeat expansions of the CTG triplet in the DMPK gene (locus 19q13.3). The clinical manifestations are extremely miscellaneous, patients with childhood-onset DM1 are usually associated with cognitive and behavioral symptoms, differently from what happened in the present case. Cardiorespiratory problems, although rare, are potentially life threatening to these patients. Due to the low occurrence of DM1 associated with syringomyelia, it is not possible to associate both diseases yet. Disagreements in the literature about the management of patients and about the association between the size of the CTG codon expansion and the severity of symptoms are extremely prevalent.

*Final comments:* This is a severe case of childhood-onset DM1 associated with syringomyelia, in which the patient presented deterioration of multiple systems, requiring a transdisciplinary approach. Due to the miscellaneous presentations of DM1, disagreements are prevalent in the literature on the management of patients, so there is great need to deepen knowledge about this disease to improve the clinical outcome of patients.

**Code: PE040**

**SMA type I - report of the evolution of a patient with treatment**

Caroline Scantamburlo Martins<sup>1</sup>, Lana Correa Paschoal<sup>1</sup>, Amanda Regina Farias Teixeira<sup>1</sup>, Jessica Kayene Souza Ferreira<sup>1</sup>, Maria Lina Giacominato de Almeida Passos e Azevedo<sup>1</sup>, Sofia Russi<sup>1</sup>, Desirée Louise Procópio Alves<sup>1</sup>, Mariana Sathler Pereira Dantas<sup>1</sup>, Flavia Nardes dos Santos<sup>1</sup>

<sup>1</sup>Universidade Federal do Rio de Janeiro, Instituto de Puericultura e Pediatria Martagão Gesteira, Rio de Janeiro RJ, Brazil

*Case presentation:* School girl, female, 9 years, evaluated at four months with maternal report of hypotonia similar to another child, now deceased, who was diagnosed with SMA type 1. On this occasion, it was possible to observe tongue

myofasciculations, generalized muscle weakness, global areflexia and hypotonia accentuated when the diagnosis was already suspected. At 6 months she started nocturnal ventilatory support and at 7 months she underwent GTT due to frequent choking. At 1 ½ years old, she had ¾ strength in her upper limbs and ⅔ in her lower limbs. She performed a genetic test that confirmed the homozygous deletion in exon 7 of the SMN1 gene and 2 copies of SMN2. At 2 and a half years old, she was evaluated by the Chop Intend scale with a score of 13/64. In 2018, at age 6, the patient showed a worsening on the Chop Intend scale with a score of 10/64. In 2019, at 6 ½ years, she started the intrathecal infusion of nusinersene. During treatment, there was improvement in cervical support, less dependence on ventilatory assistance, motor gains mainly in the extremities that allow the use of cell phones, in addition to the ability to phonate short words. In July 2022, she was evaluated again with a score of 29/64 on the Chop Intend scale, proving the gains.

*Discussion:* SMA is a genetic disease of autosomal recessive, degenerative inheritance, its classification is based on the age of onset of symptoms, being divided into five subtypes. In children with type I, the average survival is seven months, with respiratory infections being the main cause of death. In April 2019, the MS incorporated nusinersene into the SUS for the treatment of SMA type I. The drug is indicated for the treatment of patients with SMA with a deletion or mutation in the SMN1 gene located on chromosome 5q and acts on the production of the SMN protein, reducing the loss of motor neurons improving muscle strength and tone. It is important to have multidisciplinary follow-up, reducing complications such as respiratory infections, tendon retractions and reduced joint mobility, so that the gains with the medication are maximum.

*Final comments:* SMA is a degenerative disease and for many years it remained with a reserved prognosis, now with the evolution of the treatment we can observe a gain in quality and years of life. In this case, there was an improvement in the movement of fingers and hands, axial and ventilatory strength, corroborated by the increase in the scores on the scales, even with a late start of the medication.

**Code: PE041**

**Spinal muscular amyotrophy of lower limb predominance - SMALED1: case report**

Nicholas dos Santos Barros<sup>1</sup>, Fernando Kok<sup>1</sup>, José Albino da Paz<sup>1</sup>, Clarice Semião Coimbra<sup>1</sup>, Rafaela Fernandes Dantas<sup>1</sup>, Ana Cristina Azevedo Leão<sup>1</sup>, Roberta Diniz de Almeida<sup>1</sup>, Ana Beatriz Arruda Carvalho de Oliveira<sup>1</sup>, Joemir Jabson da Conceição Brito<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

*Case presentation:* Male patient, 1 year-old, born and resident in Maranhão. Mother reported reduced fetal movement, after birth some dysmorphisms were identified such as deformity in the lower limbs, characterized by arthrogyposis, bilateral congenital clubfoot, bilateral congenital dislocation of the hip and fracture of the right femur perceived on the fifth day of life. During development, generalized hypotonia and significant motor delay were noticed, predominantly affecting the lower limbs. The evaluation identified blue sclera, hyperelasticity mainly of the upper limbs, batrachian posture, osteotendinous and plantar cutaneous reflexes not obtained, bilateral congenital clubfoot, without apparent sensory and cranial nerve changes. A complementary workup was performed with the collection of a panel for neuromuscular diseases with evidence of a mutation in the DYNC1H1 gene, indicative of Predominant Lower Limb Spinal Muscular Amyotrophy (SMALED1) of autosomal dominant inheritance.

**Discussion:** A small portion of muscle atrophies (AME) is not related to the 5q13 locus, so it is called non-5q AME. These forms represent a group of different genetic and clinical features, so they are classified by their inheritance pattern and by the distribution of muscle weakness (proximal, distal or bulbar). As for the case of the patient with SMALED1, the clinical picture generally starts in infants and is characterized by weakness predominantly in the lower limbs with early deformities and delay, especially in the sitting and gait milestones, in some cases hyperelasticity has been observed in limbs. superior, it is important to consider the differential diagnosis with diseases related to collagen mutation, but sparing the spine, without significant scoliosis.

**Final comments:** We considered the case of interest for exposure, considering the confirmed diagnosis of non-5q SMA is less common when compared with those related to the classic 5q13 locus and the importance of disseminating knowledge about cases alike for the correct diagnosis and follow-up of these patients.

#### Code: PE042

##### **Steinert's myotonic dystrophy: a case report**

Anna Paula Monteiro de Souza<sup>1</sup>, Raimundo Maurício dos Santos<sup>1</sup>, Elisandra Andreia da Rosa<sup>1</sup>, Jackson Pagno Lunelli<sup>1</sup>, Andressa Schuh<sup>1</sup>, Gabriel Lemos Da Veiga<sup>1</sup>, Patrícia Marcolin<sup>1</sup>, Guilherme Alves de Araujo<sup>1</sup>, Eliezer Naudal Dertelmann<sup>2</sup>

<sup>1</sup>Universidade Federal da Fronteira Sul, Passo Fundo RS, Brazil

<sup>2</sup>Hospital São Vicente de Paulo, Passo Fundo RS, Brazil

**Case presentation:** 9-year-old female, born at term by vaginal delivery without complications. Referred to the neurologist due to learning difficulties and gait imbalance. She was born with mild hypotonia, presenting with difficulty in breast-feeding, but did not need any ventilatory support. She was diagnosed with congenital clubfoot which was successfully treated until the age of 2 years and 4 months. Extended screening for inborn errors of metabolism and karyotype did not show any abnormalities. Brain MRI showed hypoxia. Regarding developmental milestones, she walked and spoke her first words at 1 year and 6 months. She did not have any family history of neurological disorders. However, her mother has mild cognitive impairment. On physical examination, he was able to understand and respond to all requests but presented rhinophonia, mandibular hypotonia, mild bilateral and symmetrical palpebral ptosis, hyporeflexia in all limbs, diffuse muscular hypotonia with strength grade 4 distal and 5 proximal in the upper limbs and foot drop bilaterally with strength grade 1 and 2 to the extension of the right and left feet respectively, strength grade 4 in the rest of the lower limb muscles, without fasciculations. Also, bilateral flexor plantar reflex, a myotonic phenomenon to thenar region percussion, and bilateral scrambling gait. The mother had bilateral eyelid ptosis, mild frontal baldness, and a clear myotonic phenomenon on percussion of the thenar region and when closing her eyes. Molecular genetic testing was requested for myotonic dystrophy type 1 (DM1), DMPK gene expansion, which was positive.

**Discussion:** DM1, or Steinert's myotonic dystrophy, is an autosomal dominant disease caused by an expansion in the DMPK gene. It is the most common type of muscular dystrophy in adults, being a multisystem disease. In the vast majority of cases, the diagnosis of DM1 can be made clinically and confirmed with genetic tests. Detailed medical history, family history, and physical examination are crucial.

**Final comments:** The reported case highlights the importance of clinical detailing in the pediatric consultation in the

presence of neurological symptoms, as well as a thorough family history investigation, especially under suspicion of syndromes with an autosomal inheritance pattern, such as Steinert's disease. Moreover, we emphasize the importance of genetic counseling in the management of patients affected by this condition.

#### Code: PE043

##### **Treatment of spinal muscular atrophy with onasemnogene abeparvovec: off-label case report and follow-up protocol proposal**

Elisa Victória Costa Caetano Funck<sup>1</sup>, Adriana Banzatto Ortega<sup>2</sup>, Rodrigo de Holanda Mendonça<sup>3</sup>, Sabrina Aparecida Prado Lucas<sup>4</sup>, Sabrina Cavalcanti de Barros Fonseca<sup>1</sup>

<sup>1</sup>Hospital Infantil Nossa Senhora da Glória, Vitória ES, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

<sup>3</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

<sup>4</sup>Consultório Particular, Vitória ES, Brazil

**Case presentation:** Male patient whose hypotonia was observed around 2 months-old. He was diagnosed with Spinal Muscular Atrophy (SMA) when he was 4 months-old - heterozygous deletion of the SMN1 gene (1 copy of exon 7 and exon 8), 2 copies of SMN2 (2 copies of exon 7 and exon 8). In the copy of SMN1, a p.Pro246Thrfs\*10 variant is observed, characterizing a compound heterozygosity. This patient always had an excellent multidisciplinary follow-up - motor and respiratory physiotherapy, speech therapy, occupational therapy, several times per week. He is periodically evaluated by pediatrician, child neurologist, orthopedist, pulmonologist and nutritionist. He uses BIPAP and has a gastrostomy to supplement oral feeding. He has never been hospitalized for respiratory or other complications, only for elective gastrostomy. He began the treatment with nusinersene when he was 8 months-old, having applied 12 doses. The last dose was at 3 years and 5 months-old. At 3 years and 6 months-old, he had the onasemnogene abeparvovec application. He evolved with an increase in hepatic transaminases and required corticosteroid therapy for 19 weeks. In general terms, he always had a good evolution, but, apparently, he increased the speed of gaining points on the CHOP INTEND scale after the application of gene therapy. He also improved his ventilometry. In addition, he has been able to feed more quickly, better handling the accumulation of saliva in the mouth and his speech is less interrupted and presents a more audible tone.

**Discussion:** The new era of therapies for SMA broke paradigms and created a new reality. Currently, there is extensive discussion about which therapy would be most suitable for each case. Thus, the need arises to define parameters that can guide and assist in these choices, especially in patients considered off-label. The case has shown a better evolution compared with its peers described so far in the literature - patients who have received gene therapy older than 24 months-old. We believe that this is highly related to the good clinical condition of the patient, combined with the therapies and the fact that he has a compound heterozygosity.

**Final comments:** Through this case report, we would like to share the clinical experience with an off-label patient who received gene therapy, presenting a suggestion for a protocol of pre-infusion and follow-up exams, which can provide greater confidence in the diagnosis and management of possible complications - more incidents in this profile of patient.

## Epilepsias

Code: PE045

### Insular cortex epilepsy in Rasmussen Syndrome: a case report

Jeddson Rêgo Nascimento<sup>1</sup>, Adélia Maria Miranda Henriques-Souza<sup>2</sup>

<sup>1</sup>Universidade de Pernambuco, Hospital Universitário Oswaldo Cruz, Recife PE, Brazil

<sup>2</sup>Instituto de Medicina Integral Professor Fernando Figueira, Recife PE, Brazil

**Case presentation:** Male patient, 7 years old, first child of a non-consanguineous couple, previously healthy and with normal neuropsychomotor development, presented with recurrent nausea and vomiting associated with facial paresis. Neurological examination was initially normal. 3 months after the onset of the condition, he started daily myoclonic seizures and was hospitalized for investigation. During clinical investigation, an electroencephalogram was performed, which showed disorganized basal activity, frequent fronto-temporal epileptiform paroxysms in the right cerebral hemisphere, with propagation to contralateral homologous areas, and magnetic resonance imaging that showed an increase in the signal from the cortex of the right frontal lobe and homolateral insula. On neurological examination, mild left hemiparesis was noted. The patient progressed to drug-resistant epilepsy and control magnetic resonance imaging showed signal alteration and atrophy in the right cerebral hemisphere, compatible with Rasmussen syndrome. He underwent immunoglobulin, pulse therapy with methylprednisolone and nine anti-seizure drugs, but showed no clinical response. A video electroencephalogram was performed, which showed autonomic crises with insular characteristics. Due to poor seizure control and progression of brain atrophy, hemispherectomy surgery was indicated. As he presented recurrence of crises after the first surgery, he was surgically approached twice more. After surgery, the patient presented seizure control and developed behavioral disorder and left hemiparesis.

**Discussion:** Rasmussen syndrome is a rare disease, with an incidence of 1.7–2.4 per 10 million individuals. Progressive hemispheric atrophy is seen on neuroimaging. The cause of this is unknown, and no causative antibody has been identified. Patients have focal seizures (usually motor seizures, including epilepsy partialis continua), which progress over time in frequency and severity. A progressive contralateral hemiparesis develops. The diagnosis is based on the characteristic clinical presentation and imaging findings.

**Final comments:** Insular lobe seizures are an under-recognized seizure type and great mimicker of temporal, frontal, and parietal seizure semiology. Understanding seizure semiology is one of the most important and crucial steps in diagnosing a seizure disorder. We present a case of Rasmussen syndrome that started with insular seizures, a clinical presentation rarely reported in the world literature.

Code: PE046

### Landau-Kleffner Syndrome: the challenges of its treatment

Beatriz Borba Casella<sup>1</sup>, Leticia Pereira de Brito Sampaio<sup>2</sup>, Alexandre Serafim<sup>2</sup>, Erasmo Barbante Casella<sup>2</sup>

<sup>1</sup>Hospital Israelita Albert Einstein, São Paulo SP, Brazil

<sup>2</sup>Universidade de São Paulo, Faculdade de Medicina, São Paulo SP, Brazil

**Case presentation:** A previously healthy 3-year-old boy presented with difficulty understanding commands and devel-

oped impairment of spoken language that lasted four months and remitted spontaneously. After 10 months, he suffered again language regression. Electroencephalogram (EEG) revealed electrical status epilepticus during sleep (ESES). He was treated with sulthiame, sodium valproate and clobazam with partial improvement. One year later, after an episode of COVID-19 infection, symptoms worsened and he was prescribed lamotrigine, levetiracetam and low dose prednisolone with partial response. After a few months, following an episode of otitis, he became severely ataxic and completely aphasic and searched our hospital. He was unable to sit and stand without support and also presented few episodes of absences. EEG persisted with ESES. Brain MRI was normal. He was started on 5 days of methylprednisolone and 5 days of immunoglobulin. By the time he was discharged, he was already able to speak a few words and walk independently. We decided to perform monthly steroid pulse therapy and associated ketogenic diet. After the third month of treatment, he showed significant EEG improvement and ESES was not observed. After the fifth course of methylprednisolone, he was able to surf and skateboard and evolved with marked speech improvement. He is currently on steroid tapering and his last EEG shows rare centrotemporal paroxysms.

**Discussion:** Landau Kleffner Syndrome (LKS) and epilepsy with continuous spike-waves during slow-wave sleep (CSWS) comprise a spectrum of diseases with strong activation of interictal epileptiform activity during sleep. LKS is a rare epileptic encephalopathy characterized by language regression and behavior abnormalities. Seizures occur in 70 - 85% of patients. It usually manifests in 3-to 8-year-old children with normal development. There are no controlled clinical trials investigating the therapeutic options for LKS and some authors have reported the use of immunotherapy with variable effects. We present a case of dramatic response with steroid pulse therapy, immunoglobulin and ketogenic diet.

**Final comments:** LKS should be suspected in previously healthy children with subacute aphasia and seizures. Treatment is challenging and literature on the subject is scarce. Although the etiology is not well established, the potential involvement of the immune system could justify the response to steroids. We suggest that pulse therapy with methylprednisolone and ketogenic diet should be considered.

Code: PE050

### Acute encephalopathy and brain abnormalities on magnetic resonance imaging during combination therapy with adrenocorticotropic hormone and vigabatrin for infantile spasms

Karina Lúcia Soares de Oliveira<sup>1</sup>, Ana Claudia Marques Gouveia de Melo<sup>1</sup>, Felipe Augusto Poli de Souza<sup>1</sup>, Pedro Paulo Gomes do Nascimento<sup>2</sup>, Maria Durce Costa Gomes Carvalho<sup>1</sup>

<sup>1</sup>Instituto de Neurologia, Neurocirurgia e Coluna do Nordeste, Recife PE, Brazil

<sup>2</sup>Universidade Federal de Pernambuco, Recife PE, Brazil

**Case presentation:** A 11-month-old female patient with Trisomy 21 (Down Syndrome) who developed infantile spasms at 6-months-old. She was diagnosed with West Syndrome and first treated with Vigabatrin (VGB). A positive response was observed, with control of the spasms and regression of hypsarrhythmia at the electroencephalogram register. She was well controlled until 10-months-old, when the spasms returned with developmental regression. A treatment with synthetic adrenocorticotropic hormone (ACTH) was started in a low dose, but with partial control of the spasms. It was decided to increase the dose of the ACTH and

we observed regression of spasms and recovery of developmental milestones. An oral corticosteroid withdrawal was maintained. She evolved drowsiness, diarrhea, tachycardia, hypotension and abnormal movements, characterized by sudden limb movements (ballismus) and chorea on the face. A treatment for sepsis was initiated, with improvement in laboratory parameters and hypotension, but she persisted with encephalopathy, abnormal movements, paroxysmal tachycardia and diarrhea. A cranial tomography (CT) was performed, showing a symmetrical and bilateral image of hypoattenuation in the basal nuclei. All the clinical abnormalities stopped after withdrawing the VGB. Magnetic Resonance Imaging (MRI) findings showed T2/FLAIR hypersignal in basal nuclei with diffusion restriction.

**Discussion:** VGB, ACTH and prednisone are first-line treatments for IS. Benefits from the use of combination VGB and hormonal therapy are already established. Acute encephalopathy with extrapyramidal symptoms, dysautonomic features and vigabatrin-associated brain abnormalities on magnetic resonance imaging (VABAM) has been reported after the use of combination-therapy for IS. Asymptomatic VABAM is common and appears to be associated with the use of higher doses of VGB. Main locations for MRI abnormalities included globi pallidi, brainstem, followed by thalami and dentate nuclei. MRI abnormalities usually to be resolved following VGB discontinuation, in a mean interval of 3 months. A literature review supports increased risk of fulminant, symptomatic VABAM in patients receiving VGB in association with hormonal therapy. Patients with Trisomy 21 seem to be particularly sensible to evolve it.

**Final comments:** This report and review raise concerns regarding the safety of combination therapy with adrenocorticotropic hormone and Vigabatrin for Infantile Spasms, mainly in Trisomy 21 patients.

#### Code: PE052

##### **CDKL5 deficiency disorder: case report of a possible new pathogenic variant**

Alicia Carolina Coraspe Goncalves<sup>1</sup>, Amanda Povoia Paiva<sup>1</sup>, Regina Maria Franca Fernandes<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup>, Carla Andrea Cardoso Tanuri Caldas<sup>1</sup>, Matheus de Souza Rosa<sup>1</sup>, Rodrigo Santana Arruda<sup>1</sup>, Maria Avandise Yumi Minami<sup>1</sup>, Ursula Thome Costa<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto SP, Brazil

**Case presentation:** A previously healthy full term 4 month-old boy, presented by 1 months with tonic jerks of the upper limbs and slight behavior arrest. He had no signs of infection and no history of recent vaccination. These jerks became daily, more intense, lateralized and associated with oral automatisms and blinking. They had a very brief duration, mostly 20–30 seconds each. EEG showed bilateral temporo-occipital sharp transients and right temporal slow. Phenobarbital was started with partial seizure control; pyridoxine had no effect. Hence, levetiracetam was initiated. A second EEG by the age of 3 months revealed multifocal epileptiform discharges, as well as seizures characterized by pedaling and swimming movements with parietal origin, mostly on the right hemisphere. By this age, he had predominantly axial hypotonia and lost the ability to fix and follow an object. A whole-exome sequencing test showed a chrX:18.598.499 C>G CDKL5 mutation, known as a variant of uncertain significance (VUS) up to now.

**Discussion:** CDKL5 Deficiency Disorder (CDD) is a rare genetic disorder caused by a mutation in the cyclin-dependent

kinase-like5(CDKL5) gene. It is now considered to be a developmental and epileptic encephalopathy because of the early onset of seizures in association with severe global delay. It's an important cause of early-onset epilepsy (younger than 3mo) associated with severe hypotonia. Seizures are mostly tonic, infantile spasms and, occasionally, hypermotor-tonic-spasms sequence seizures. Other types of focal as well as generalized seizures may occur. Cerebral visual impairment and dysmorphic features are also reported. It is known that CDD enrolled some clinical variants.

**Final comments:** Our case has the typical clinical presentation of this disease although the mutation found is still classified as VUS. Therefore, there is a possibility that this mutation, never described before, can be also responsible for the CDD. This case highlights the importance of the genetic tests and the description of these phenotypes in DEE to promote a better understanding of the CDD spectrum.

#### Code: PE055

##### **Drug-resistant seizures in a teenager with a variant of uncertain significance in PCDH19**

Maria Lina Giacomino de Almeida Passos<sup>1</sup>, Aline Chacon Pereira<sup>1</sup>, Amanda Regina Farias Teixeira<sup>1</sup>, Caroline Scantamburlo Martins<sup>1</sup>, Hanid Fontes Gomes<sup>1</sup>, Jéssica Kayene Souza Ferreira<sup>1</sup>, Lana Correa Paschoal<sup>1</sup>, Sofia Russi<sup>1</sup>

<sup>1</sup>Universidade Federal do Rio de Janeiro, Instituto de Puericultura e Pediatria Martagão Gesteira, Rio de Janeiro RJ, Brazil

**Case presentation:** The case reported is about a 15 years old girl who presents drug-resistant epilepsy (currently using four different antiepileptic drugs), besides Intellectual disability. Her parent reported her first seizure at 6 months of age, during sleep, afebrile, with ocular version and behavioral arrest. Another four episodes occurred that day (some evolving to tonic postures). After a brief hospitalization, she was discharged with multiple antiepileptic drugs. No relevant perinatal history was found. After a new increased frequency of seizures, she was hospitalized again. Magnetic resonance imaging showed no abnormalities and initial screening for inborn errors of metabolism was normal. Electroencephalogram registered paroxysmal discharges consisting of diffuse sharps and waves. The patient's evolution was unfunded, presenting different types of seizures (some of them starting with screaming), sometimes sustaining four months with no seizures, sometimes presenting thirty seizures on the same day. Antiepileptic drugs combinations (sodium valproate, carbamazepine, phenobarbital, phenytoin, vigabatrin and lamotrigine) were readjusted multiple times during follow up and benzodiazepines were added both for synergism and for emergency uses. She was two and a half years old at her first evaluation with a neurologist: significant speech impairment was recorded, despite normal gross motor development. Intellectual disability is present. The Epilepsy and Ataxia Genetic Panel's report describes a variant of uncertain significance (VUS), c.365A>G; p.(Leu122Pro), in heterozygosity in the PCDH19 gene.

**Discussion:** The PCDH19 gene is located on Xq22 but despite being positioned as a X-linked mode of inheritance, the pedigree exhibits a peculiar pattern: affected females were connected through unaffected male relatives. This gene encodes the protein protocadherin-19 and is constituted by six exons. Pathogenic variants (in heterozygosity) were associated with early onset epilepsy (before three years of age), in clusters, typically induced by fever, often drug-resistant and also with a significant risk of intellectual disability and autism spectrum disorder.

**Final comments:** The variant of uncertain significance found in this patient genetic panel is absent in ~62 thousand individuals of the population bank and was not previously described in literature. Pathogenic variants were described in neighbor codons of the reported VUS.

#### Code: PE056

##### **Epilepsy related to GLUT1 mutation and treated with ketogenic diet: a case series**

Laura Maria Silva Thiersch<sup>1</sup>, Thais de Almeida Fonseca Oliveira<sup>1</sup>, Nathalia Jamille Moreira Nascimento David<sup>1</sup>, Renan Guimarães Santana<sup>1</sup>, Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, André Vinícius Soares Barbosa<sup>1</sup>, Ana Carolina Cardoso Diniz<sup>1</sup>, Karina Soares Loutfi<sup>1</sup>, Bruna Ribeiro Torres<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

**Case presentation:** We conducted a descriptive study of 4 cases with GLUT1 Deficiency (Glut1D) diagnosed in our service in the past 2 years. The diagnosis was established by: hypoglycorrhachia, clinical symptoms and SLC2A1 mutation. Our first patient, a 4-year-old boy, presented with developmental delay, hypotonia, myoclonic jerks and drop attacks at 11 months of age. MRI brain image showed bilateral hippocampal atrophy. Valproic acid and clobazam were started with partial seizures control. After introduction of ketogenic diet (KD), the patient achieved full seizure control, and anti-seizures drugs were discontinued. The second case is a 7-year-old boy, with seizures started at 3 months of age, characterized by generalized hypotonia and eye deviation. He had a delay of motor and language milestones and failed to achieve seizure control despite treatment with oxcarbazepine, valproic acid and levetiracetam. After the initiation of KD, a better seizure control and an improvement of muscle tone, speech and coordination were noticed. The third case is a 2-year-old girl, with tonic-clonic seizures started at 2 months of life. Diagnosis of Glut1D was established right after the first seizures, and she achieved an excellent control with levetiracetam and KD. Her development has been normal since. A 5-year-old girl is the fourth case, and presented with hypotonia, delay of speech and gait disturbance noticed around 1 year of age. Treatment with valproic acid and clobazam achieved partial control of seizures. Glut1D was diagnosed 3 years later, and better seizure control was noticed 1 year after the initiation of KD associated with levetiracetam.

**Discussion:** GLUT1 Deficiency is a rare and treatable metabolic encephalopathy. Around 80% of patients carry mutations in the SLC2A1 gene, located on chromosome 1. Transmission is autosomal dominant, with complete penetrance and most mutations are de novo. The syndrome is caused by a defect in the glucose transporter, GLUT1, located in the blood-brain barrier. The poor glucose transport is reflected by hypoglycorrhachia and manifests in many ways, from refractory seizures to developmental delay and movement disorder. The treatment of choice is a ketogenic diet, a high fat and low carbohydrate diet, that provides ketones as an alternative fuel to the brain.

**Final comments:** Early recognition of Glut1D is important to initiate KD and achieve adequate management.

#### Code: PE057

##### **Epileptic and developmental encephalopathy 14 associated with KNCT1 gene mutation: a case report**

Melanie Scarlet Diaz Solano<sup>1</sup>, Mariane Wehmut<sup>1</sup>, Clarice Prestes<sup>1</sup>, Isadora Cristina Barbosa Lopes<sup>1</sup>, Carolina Oliveira de Paulo<sup>1</sup>, José Antonio Coba Lacle<sup>1</sup>, Eduarda Furstenberger<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>

<sup>1</sup>Hospital Universitário Evangélico Mackenzie, Curitiba PR, Brazil

**Case presentation:** Male patient, with no history of comorbidities or consanguinity. Normal neurodevelopment up to two months, when started with daily focal epileptic seizures, with bilateral tonic-clonic progression. EEG with reentrant epileptic activity with onset of rhythmic theta activity located in the left posterior quadrant and then in the right central parietal region. Investigation by neuroimage without alterations. Genetic exam with heterozygous mutation of the KNCT1 Gene, which encodes a sodium-activated potassium channel and is expressed in the central nervous system. During the period, he used multiple drugs in optimized doses without complete improvement of the crises.

**Discussion:** Epileptic and Developmental Encephalopathy 14 associated with mutation of the KNCT1 Gene is a serious disease characterized by refractory focal seizures in children younger than 6 months and severe neurodevelopmental impairment. The mutation alters the central nervous system's sodium-activated potassium channels, which modulate the hyperpolarization of neurons after repetitive firing of action potentials. These channels are also found in the heart muscle contributing to the development of arrhythmias. It is a very rare disease, with ~200 cases described. The EEG of those affected shows ictal discharges that arise randomly from both hemispheres and migrate from one region to another. The diagnosis is made by identifying a heterozygous pathogenic variant in KCNT1. There is no specific treatment for this pathology and traditional drugs are not effective. Some authors approach treatment with Quinidine, still with inconsistent data regarding clinical efficacy, which may vary from complete to no response. Few can benefit from partial seizure reduction at the expense of cardiotoxic effects. Another option is the ketogenic diet, a limiting strategy for our patient due to being an infant.

**Final comments:** Epileptic and developmental encephalopathy 14 is a rare genetic disease, with refractory epilepsy and severe neurodevelopmental impairment. Due to the small number of children affected by this disease, diagnosis and treatment are a challenge for the team.

#### Code: PE058

##### **Epileptic and developmental encephalopathy associated with GABRA1 gene mutation: case report**

Luize Costa Soncini<sup>1</sup>, Maria Helena Romano Santin<sup>1</sup>, Ísis Feldens Müller<sup>1</sup>, Mariana Reis Caram<sup>1</sup>, Marcelo Vitória Reinehr<sup>1</sup>, Emanuele Fonseca Barbosa<sup>1</sup>, Juliana Costa Maia<sup>1</sup>, Luiza Vieira da Silva Magalhães<sup>1</sup>, Claudia Fernandes Lorea<sup>2</sup>

<sup>1</sup>Universidade Federal de Pelotas, Pelotas RS, Brazil

<sup>2</sup>Empresa Brasileira de Serviços Hospitalares, Pelotas RS, Brazil

**Case presentation:** A.B.P., 5 years and 1 month, female, born at term, APGAR 9/10, manifested neuropsychomotor development (NPMD) delay at 8 months and, at 1 year and 3 months, after a fever, she had her first epileptic seizure, with generalized tremor. Since then, she has shown regression of NPMD milestones, self-aggression and swallowing difficulties. The seizures persisted, occurring up to 6 times a day, generalized tonic-clonic seizures and myoclonic seizures. In the first neurological evaluation, at 1 year and 6 months, she was

not very interactive, without fixing her gaze, with incomprehensible speech, right convergent strabismus, and axial and appendicular hypotonia, unable to sit without support. General laboratory tests, amino acid chromatography, urine organic acid chromatography, acylcarnitine profile and transferrin isoelectrofocalization were unaltered. Electroencephalogram detected acute left temporal waves and synchronous and symmetrical bilateral spike-wave complex burst. Genetic testing identified a pathogenic variant in the GABRA1 gene. Treatment was started with phenobarbital alone and, later, with valproic acid, without seizure control. In evolution, the association of the latter with topiramate and clobazam provided a satisfactory therapeutic response.

**Discussion:** The identification of a mutation in the GABRA1 gene was fundamental for a better understanding and management of the case. GABRA1 consists of one of the genes encoding the  $\alpha 1$ ,  $\beta 2$ ,  $\beta 3$ ,  $\gamma 2$  or  $\delta$  subunits of the GABA A receptor. This mutation, through a possible mechanism of haploinsufficiency, causes impairment of the inhibitory function of GABA, causing a wide spectrum of epilepsy phenotypes, with myoclonic and tonic-clonic seizures common features. De novo pathogenic variants are more frequent than hereditary ones. Most patients have severe childhood-onset epilepsies with associated cognitive and behavioral deficits. Also, generalized spike-wave complexes and photoparoxysmal response are often present on the EEG.

**Final comments:** The present case highlights the importance of genetic knowledge in clarifying the etiopathogenesis of epileptic and developmental encephalopathies, as well as highlighting the need for further studies for a better therapeutic approach and prognostic elucidation.

#### Code: PE059

##### **Epileptic Encephalopathy due cyclin-dependent kinase type 5 (CDKL5) gene changes: a case report**

Patricia Gomes de Almeida Lopes<sup>1</sup>, Letícia Fillos<sup>2</sup>, Michelle Silva Zeny<sup>3</sup>, Ana Isabel Zambrana<sup>1</sup>

<sup>1</sup>Hospital Universitário Regional dos Campos Gerais, Ponta Grossa PR, Brazil

<sup>2</sup>Universidade Estadual de Ponta Grossa, Ponta Grossa PR, Brazil

<sup>3</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** S.S.A, 2 years old, female, born at term, with no complications during pregnancy, intrapartum, or neonatal period, and no history of neurological diseases in the family. At 2 months and 20 days of age, she presented her first convulsive crises, initially with 3 and 8 crises in successive days, with duration of seconds, in which the patient expressed muscular rigidity in the upper and lower limbs. Due to the progressive increase of seizure episodes, she was evaluated by a neurologist and a diagnostic investigation was initiated. The initial cranial imaging, electroencephalogram, and echocardiogram exams showed no alterations that could justify the crisis. At one year of age, a genetic panel was performed, which showed developmental epileptic encephalopathy 2 due to the CDKL5 gene. Due to the absence of specific treatment, she continues to use phenobarbital, valproic acid, cannabidiol, clonazepam, and oxcarbamazepine. Currently, the child presents, on average, 2 seizures a day even while taking these medications. The patient presents significant neuropsychomotor developmental delay with partial axial tone, absence of speech, and signs of extrapyramidal release in follow-up with a multidisciplinary team.

**Discussion:** Cyclin-dependent kinase type 5 (CDKL5) deficiency is an X-linked genetic disorder with mutations in the CDKL5 gene, whose patients suffer severe neurodevelopmental disorders, including early onset childhood epileptic encephalopathy, hypotonia, visual impairment, autism

spectrum disorders, and intellectual disability. Intractable epilepsy, a widespread symptom associated with CDKL5 deficiency, can occur from a few hours after birth and extend to ~2 years of life, causing distress to children and burden to caregivers. The incidence of CDKL5 deficiency is ~1:40,000 to 60,000 live births, and is more prevalent in females (4:1), since males do not have the normal CDKL5 gene and thus may not survive intrauterine life. The response of patients with traditional antiepileptic medication treatment is unsatisfactory. Thus, to date, the pathogenic mechanisms of CDKL5 deficiency are not fully understood and there are still no effective therapies.

**Final comments:** Genetic epileptic encephalopathy due to alteration of the CDKL5 gene is a disease that deserves further study to find more effective therapies and improve the quality of life of patients.

#### Code: PE060

##### **Epileptic encephalopathy due to GLUT1 deficiency: a case report**

Mariana Reis Caram<sup>1</sup>, Marcelo Vitória Reinehr<sup>1</sup>, Emanuele Fonseca Barbosa<sup>1</sup>, Luize Costa Soncini<sup>1</sup>, Maria Helena Romano Santin<sup>1</sup>, Ísis Feldens Müller<sup>1</sup>, Juliana Costa Maia<sup>1</sup>, Luiza Vieira da Silva Magalhães<sup>1</sup>, Cláudia Fernandes Lorea<sup>2</sup>

<sup>1</sup>Universidade Federal de Pelotas, Pelotas RS, Brazil

<sup>2</sup>Empresa Brasileira de Serviços Hospitalares, Pelotas RS, Brazil

**Case presentation:** H.M.B.R., female, 5 years, mother with gestational diabetes. Birth weight of 4240 g, full term, APGAR 9/9, neonatal hypoglycemia as intercurrent. At the age of 11 months and 14 days had her first epileptic seizure, being hospitalized and treated with phenobarbital, with no effective response. Family history of epilepsy. At 2 years and 8 months, was reassessed for the worsening of refractory epilepsy associated with neurological regression, presenting 6 or more daily episodes of generalized tonic-clonic seizures, followed by absence seizures, in addition to speech delay. She was diagnosed with myoclonic epilepsy and delayed neuropsychomotor development. EEG concluded paroxysmal abnormality through the occurrence of bursts of spike-slow wave complexes, 3–4 cm/s, generalized, prevalent in fronto-central areas. Even with the use of other antiepileptic drugs (levetiracetam, valproic acid, topiramate and clobazam) in a regimen of polytherapy combinations and in full doses, the patient remained with seizures.

**Discussion:** GLUT1 deficiency syndrome is caused by mutations in the SLC2A1 gene, responsible for encoding the type 1 brain glucose transporter. Due to its heterogeneous characteristics, few cases described in the literature and not being among the main known hypotheses of childhood epilepsies, the syndrome is often underdiagnosed. The first diagnosis of H.M.B.R. was based on clinical aspects. The picture of epilepsy refractory to orthodox treatment jointly with the regression of neuropsychomotor development, induced the realization of a Genetic Panel associated with epilepsy. The identification of the p.Gly76Ala variant, probably pathogenic in the SLC2A1 gene, was central for the understanding and managing of the case. The ketogenic diet, treatment initiated to the patient through follow-up with nutritionist and neurologist, consists of a diet high in fat and low in carbohydrates. The diet is considered the gold standard treatment of the syndrome. It supplies ketone bodies as a source of energy to the brain, generating an anti-epileptogenic and neuroprotective effect.

**Final comments:** After the introduction of a ketogenic diet combined with levetiracetam as treatment, at the age of 3.5 years, H.M.B.R. achieved total remission of the epileptic seizures during the period of 1 year, even with a gradual reduction of the medication dose. It is important to

understand this pathology for the early diagnosis, since the syndrome affects significantly the quality and development of patients' lives.

**Code: PE061**

**Epileptic encephalopathy: is it avoidable?**

Camila Yoko Martins Hatae<sup>1</sup>, Gabriela Schmitt Trevisan<sup>1</sup>, Renata Cristine Alves<sup>1</sup>, Gabriel André Silvério<sup>1</sup>, Mateus Pinto Marchetti<sup>1</sup>, Pedro Arthur Possan<sup>1</sup>, Tatiana Von Hertwig F.O. Kumer<sup>1</sup>, Vera Cristina Terra<sup>1</sup>

<sup>1</sup>Hospital Nossa Senhora das Graças, Curitiba PR, Brazil

**Case presentation:** Female, 8 years old, with onset of seizures at 2 months, evolving with refractory epilepsy. The seizures were characterized by behavioral arrest and vacant gaze, in addition to episodes of loss of tone and head turn to the right with intense salivation. Patient has used topiramate, nitrazepam, carbamazepine and valproate. On examination, he is moderately mentally retarded and does not speak. Prolonged videoelectroencephalogram demonstrated focal seizures in the right cerebral hemisphere and resonance image showed right frontal cortical dysplasia associated with right occipital heterotopic nodule. Surgery was performed with intra-operative monitoring. After complete resection of the lesion and the initial epileptiform discharges, a greater extension of the epileptiform pattern was observed, which became more diffuse with each resection extension. At follow up patient persisted with seizures with only a discrete frequency reduction.

**Discussion:** Epilepsies in childhood have several causes, including genetic and structural ones, emphasizing the importance of overlapping etiologies. Encephalopathy, characterized by diffuse brain dysfunction, should be considered even in patients with predefined lesions, as it is an important cause of epileptic seizures.

**Final comments:** The case in question shows persistence of epileptiform paroxysms even with resection of the lesion and the initial epileptiform discharges. This finding may be related to the epileptic encephalopathy that patients with early onset epilepsies present. Although it is not possible to absolutely affirm, earlier surgery could have avoided this pattern of secondary epileptogenesis.

**Code: PE063**

**Is it seizures? Non-epileptic events in a child with Tay-sachs disease**

Gabriela Schmitt Trevisan<sup>1</sup>, Camila Yoko Martins Hatae<sup>1</sup>, Pedro Arthur Possan<sup>1</sup>, Mateus Pinto Marchetti<sup>1</sup>, Renata Cristine Alves<sup>1</sup>, Gabriel Andre Silverio, Vera Cristina Terra<sup>1</sup>

<sup>1</sup>Hospital Nossa Senhora das Graças, Curitiba PR, Brazil

**Case presentation:** Male, 4 years old, diagnosed with Tay-Sachs syndrome. Patient with neuropsychomotor developmental delay, presented with polymorphic behaviors such as arrests, tonic posturing and laughter that were treated in another facility with a series of anti-crisis medications with no response. At first evaluation patient was in use of Levetiracetam, Clobazam, Phenobarbital, Oxcarbazepine and Cannabidiol. A 24-hour prolonged videoelectroencephalogram (VEEG) was performed, and 18 clinical events were recorded, however, none of them were accompanied by electrographic changes. Progressive and gradual withdrawal of anticrisis medication was performed and patient evolved with improvement in sedation, without significant modification of events previously considered as epileptic seizures.

**Discussion:** Mental retardation is a condition that can be present in several conditions in children and adolescents,

usually associated with some comorbidity. The condition encompasses a series of behaviors, whether motor or non-motor, which can be confused with epileptic seizures. It is important to differentiate such events from epileptic seizures to avoid overtreatment that can worsen the patient's clinical condition. Prolonged VEEG is an available diagnostic method and should be indicated in patients with cognitive impairment who have a history of refractory epileptic seizures, being the best method to identify non-epileptic events.

**Final comments:** Non-epileptic events are common in patients treated with suspected epilepsy. In patients with cognitive impairment unspecific movements are usually confused with epileptic seizures. Studies have demonstrated that almost 40% of children treated as having epilepsy may have no-epileptic events. Correct diagnosis may avoid unnecessary use of anticrisis medication and consequently its side effects.

**Code: PE064**

**Lafora disease and metformin therapy: a case report**

Cristina Detoni Trentin<sup>1</sup>, Nicole Zanardo Tagliari<sup>1</sup>, Laurize Palma Hendges Zanette<sup>1</sup>, Felipe Kalil Neto<sup>1</sup>, Alessandra Marques dos Anjos<sup>1</sup>, Osvaldo Artigalás<sup>1</sup>, Silvana Palmeiro Marcantônio<sup>1</sup>, João Ronaldo Mafalda Krauzer<sup>1</sup>

<sup>1</sup>Hospital Moinhos de Vento, Porto Alegre RS, Brazil

**Case presentation:** We report a case of Lafora Disease (LD) in a 16-year-old boy with prior diagnosis of learning disabilities. Symptoms appear almost 1 year ago, with myoclonic seizures and tonic clonic generalized. After he develop a few episodes of sudden transient blindness, dysarthria, ataxia, frequent myoclonic jerks prominently in the upper limbs and face and cognitive impairment. Multiple anticonvulsants therapy produced no effect or a slight and unstable effect. Liquor analysis was normal, including gradient lactate/glucoses. Optic nerve and funduscopy was normal. electroencephalogram (EEG) showed delta rhythmic activity generalized spikes/polyspikes on a slow background activity, during sleep Brain 3 tesla MRI (magnetic resonance imaging) with spectroscopy slight increase in choline in talomoscapsular region. Epilepsy panel was realized and Lafora disease was diagnosed by genetic test detected homozygosis gene EPM2A. Also detected mutation heterozygosis of PGAP3 (associated with autosomal recessive PCAP3-congenital disorder of glycosylation). The patient was receiving topiramate, levetiracetam and clonazepam with partial improvement of the attacks. It was then decided on therapeutic initiation of metformin. After 24 hours of starting metformin 1500 mg per day, there was improvement in epileptic seizures. 48 hours after starting metformin, there was improvement in cognitive function.

**Discussion:** Lafora disease is a rare fatal autosomal recessive form of progressive myoclonus epilepsy. The clinical diagnosis of LD is based on presentation of myoclonus epilepsy, progressive neurologic deterioration and characteristic EEG. The diagnosis is confirmed genetically, by the presence of mutations in the EPM2A gene, present in all patients.

**Final comments:** Metformin is generally a safe drug. Studies have shown a delay in the progression of the disease, although we need more time to follow up and confirm long-term benefit in our patient. Unfortunately, until now, no definitive curative treatment exists.



Code: PE065

**Myoclonic status epilepticus in a pediatric patient: case report**

Jennyfer Katheryne Klein Ottoni Guedes<sup>1</sup>, Fernanda Lorena de Souza<sup>1</sup>, Sthefanny Josephine Klein Ottoni Guedes<sup>2</sup>, Wendell Paiva Vita<sup>1</sup>, Adriana Koliski<sup>1</sup>, Maria Monica Machado Ulsenheimer<sup>1</sup>, Marcelo Rodrigues<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Hospital de Clínicas, Curitiba PR, Brazil

<sup>2</sup>Universidade Estadual do Oeste do Paraná, Cascavel PR, Brazil

**Case presentation:** Female patient, 14 years old, healthy, with a history of ingestion of an unknown amount of rodenticide. A few hours after, she presented vomiting, diarrhea, bradycardia, myotic pupils and generalized tonic-clonic seizures, evolving with two cardiorespiratory arrests. It was performed the first cardiopulmonary resuscitation maneuvers, including sedation and intubation; atropinization and vasoactive drugs was administered at the intensive care unit. During hospitalization, she developed generalized myoclonus. Electroencephalogram showed a myoclonic status epilepticus, which was reversed with the use of high doses of thiopental, having no response to other anticonvulsants. She progressed with the absence of some brainstem reflexes, but did not complete a brain death diagnosis, maintaining cerebral blood flow on Doppler; brain magnetic resonance revealed severe hypoxic-ischemic encephalopathy. After prolonged hospitalization, she required gastrostomy and tracheostomy for dehospitalization. Currently, bedridden and with important neurological sequelae, the patient maintains outpatient follow-up.

**Discussion:** Post-hypoxic myoclonus, particularly myoclonic status epilepticus (MSE), is uncommon in infants and a marker of poor prognosis. Patients who survived long cardiorespiratory arrest, can develop severe neurological deficits, including post-hypoxic myoclonus. This status may be divided into: MSE and Lance-Adams Syndrome (LAS). MSE is a condition that makes the patient have generalized myoclonus for more than 30 minutes. It occurs shortly after cardiopulmonary resuscitation, with an electroencephalogram showing epileptiform activity. On the contrary, LAS appears days, weeks or months after an ischemic event. The electroencephalogram usually does not show epileptiform activity, with a pattern of diffuse slowing – which is different from the case of the patient under discussion. The treatment of MSE is challenging and not well established. Administration of phenytoin, valproic acid, phenobarbital, and various benzodiazepines may be ineffective.

**Final comments:** Although there is no specific treatment, it is important that physicians pay attention to this diagnosis, after a long cardiorespiratory arrest. Early measures define survival and avoid limited prognosis, including brain injury.

Code: PE066

**Neuronal ceroid lipofuscinosis type 7: a case report**

Eduarda de Boer Furstenberger<sup>1</sup>, Mariane Wehmuth Furlan Eulalio<sup>1</sup>, Ana Clarice Bartosievicz Prestes<sup>1</sup>, Isadora Cristina Barbosa Lopes<sup>1</sup>, Melanie Scarlet Diaz Solano<sup>1</sup>, Carolina Oliveira de Paulo<sup>1</sup>, José Antonio Coba Lacle<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>

<sup>1</sup>Hospital Universitario Evangelico Mackenzie, Curitiba PR, Brazil

**Case presentation:** Female patient, 5 years old, from the countryside of Paraná. Admitted to the pediatric service due to regression of neuropsychomotor development and epilepsy with change in seizure pattern. The patient had an adequate development for her age until she was three years old. When she started with focal seizures associated with

ocular eversion and loss of gait and speech ability. At hospital admission, the mother reported more frequent generalized tonic-clonic seizures than usual, associated with ataxia. On physical examination, patient with globally reduced strength, especially in the lower limbs. Spastic limbs and cogwheel sign to passive mobilization. Right hyporeflexia. Positive Babinski sign in lower limbs. Facial hypotonia. Initiated investigation for progressive encephalopathy. Electroencephalogram with almost continuous generalized epileptiform activity, starting with Valproic Acid 20mg/kg/day. Skull MRI with alteration in periventricular white matter in cerebral hemispheres determining volumetric loss of regional white matter. Evaluated by the ophthalmology team, with description of pale retina, nerve with increased excavation and macular color change. Panel on Epilepsies and Ataxias was performed with a result of neuronal ceroid lipofuscinosis type 7.

**Discussion:** Neuronal ceroid lipofuscinosis type 7, caused by a mutation in the MFSD8 gene, leads to neuropsychomotor development regression, epilepsy and visual changes. The age of onset of symptoms ranges from two to eleven years, with an average of five years. There is no specific treatment for the presented disorder, however, the early recognition of symptoms allows a more complete neurological follow-up and a more adequate control of the presented symptoms.

**Final comments:** The report of neurodegenerative diseases contributes to greater knowledge in the management of these patients. Neuronal ceroid lipofuscinosis type 7 does not present a curative treatment, but the correct diagnosis provides a better follow-up of these patients.

Code: PE067

**New mutation in SCN8A gene associated severe developmental and epileptic encephalopathy type 13: the importance of genetic test and genotype-phenotype correlation**

Aline Rocha Anibal<sup>1</sup>, Patrícia Pontes Cruz<sup>1</sup>, Luan Guanais Soriano<sup>2</sup>, Emília Katiane Embiruçu<sup>1</sup>

<sup>1</sup>Universidade Federal da Bahia, Hospital Universitário Professor Edgard Santos, Salvador BA, Brazil

<sup>2</sup>Hospital Martagão Gesteira, Liga Álvaro Bahia Contra a Mortalidade Infantil, Salvador BA, Brazil

**Case presentation:** Boy, 10 months, late premature infant. His parents aren't consanguineous. He had recurrent and refractory spasm-like seizures, and neurodevelopmental regression started at 4 months. On physical examination, he had lack of visual and social interaction, microcephaly, central hypotonia, upper motor neuron syndrome and dyskinesias. He had seizure control with Levetiracetam for just one month. It was identified worsening of cortical and subcortical atrophy in two comparative his neuroimaging exams at 4 and 9 months. His electroencephalogram (EEG) was normal at 4 months. It was identified fragmented hypsarrhythmia at 5 months and diffuse attenuation of brain activity at 7 months in serial EEG. Five variants of uncertain significance (VUS) were reported in his exome sequencing (ES): variants in the ABCA2 gene were identified in compound heterozygosity and in the CBL, HUWE1 and SCN8A genes in heterozygosity.

**Discussion:** The clinical features are compatible with Developmental and Epileptic Encephalopathy (DEE) type 13 (MIM #614558) that is associated the pathogenic variants in SCN8A gene, autosomal dominant inheritance. The symptoms in DEE type 13 are epilepsy difficult to treat that worsened with Levetiracetam, developmental delay (DD), hypotonia e movement disorders. Initial EEG and neuroimaging exams may be normal with progressive changes, such as worsening brain

atrophy. SCN8A gene encodes voltage-gated sodium channels, and it is widely expressed in neurons of the central and peripheral nervous systems. Gain-of-function variants in the SCN8A gene cause severe DEE with early epilepsy. The variant c.409A>G:p.(Ile137Val) was identified in the patient and it was never described in the ClinVar, VarSome, AbraOM and Lovid databases. It's concluded that variant c.409A>G is as highly likely to be pathogenic after genotype-phenotype correlation by clinical features, natural history of the disease and pathogenicity predictors LRT, MutationTaster, and SIFT classified this variant as deleterious, disease-causing, and harm-causing, respectively.

*Final comments:* We emphasize the importance of molecular tests in case of refractory epilepsies and DD with the aim of providing the best therapeutic choice and prognosis.

### Code: PE068

#### Post-herpetic encephalitis presenting with epilepsy partialis continua

Gabriela Schmitt Trevisan<sup>1</sup>, Camila Yoko Martins Hatae<sup>1</sup>, Gabriel Andre Silverio<sup>1</sup>, Renata Cristine Alves<sup>1</sup>, Pedro Arthur Possan<sup>1</sup>, Mateus Pinto Marchetti<sup>1</sup>, Tatiana Von Hertwig Fernandes de Oliveira Kumer<sup>1</sup>, Vera Cristina Terra<sup>1</sup>

<sup>1</sup>Hospital Nossa Senhora das Graças, Curitiba PR, Brazil

*Case presentation:* Male, 9 years old, healthy, after a dental procedure, he started with clonic seizures on the left side and an episode of tonic-clonic seizure. In the evolution patient developed Epilepsia Partialis Continua (EPC) at the left side. Liquor investigation was positive to herpes virus and despite acyclovir treatment for 21 days patient persisted with seizures. Resonance image demonstrated an atrophic lesion at the left frontobasal region. There was no response to anticrisis medication (phenobarbital, oxcarbazepine, levetiracetam, lacosamide and cannabidiol). A partial response was observed with corticosteroid therapy. Patient underwent left frontal resection with electrocorticography and evolved with complete seizures remission. Anatomopathological was consistent with unspecified gliosis.

*Discussion:* EPC is a rare condition that is usually reported in patients with chronic brain inflammatory diseases. The main exponent related to this condition is Rasmussen Encephalitis. Natural history consists of an initial infectious or inflammatory peripheral disease that after a latent period evolve to EPC. Our patient had a similar evolution, related to herpetic encephalitis. This presentation form is rarely described in the literature.

*Final comments:* The present case shows atypical presentation of herpetic encephalitis, progressing to chronic EPC. This case is an example of the challenge in the etiological investigation of patients with epilepsy.

### Code: PE072

#### SCN2A mutation presenting with autism and epilepsy

Giuseppe Dick Bonato<sup>1</sup>, Glaucio Kody Nagata<sup>1</sup>, Tatiane Morgana da Silva<sup>1</sup>, Leticia Bassani Devens<sup>1</sup>, William Alves Martins<sup>1</sup>

<sup>1</sup>Pontifícia Universidade Católica do Rio Grande do Sul, Hospital São Lucas, Porto Alegre RS, Brazil

*Case presentation:* The parents of a 38 months-old male patient seek neurological consultation for refractory seizures. He was previously treated with phenobarbital 4,7mg/kg/day and valproate 41mg/kg/day for febrile seizures that started at 30 months. The parents described generalized myoclonic seizures following staring. The patient presented seizures every 2 to 3 weeks when it was added clobazam 0,55mg/kg/day, oxcarbazepine 33,3mg/kg/day and cannabidiol 3,33mg/

kg/day. He was diagnosed with autism spectrum disorder after presenting speech regression at the age of 18 months old. There was no known familiar history for epilepsy. No metabolic disorder was found, and the only significant prenatal finding was prematurity at gestational age of 34 weeks. He presented cryptorchidism. Electroencephalography recorded when he was 40 weeks-old was normal. The patient underwent a genetic panel for epilepsy, being discovered a heterozygous genetic variant of the SCN2A, chr2:165.313.721 G >A. The patient was seizure free for at least 3 months after oxcarbazepine suspension and dose adjustment of both valproate and phenobarbital.

*Discussion:* Mutations variants in SCN2A were proven to result in a wide spectrum of phenotypic disorders, ranging from benign familial neonatal-infantile seizures to more severe neurological conditions with delayed development (developmental and epileptic encephalopathy; intellectual disability, or autism with possible late-onset seizures). This case represents a new potentially pathogenic variant to the SCN2A gene presenting with epilepsy and autism. According to gene data banks, there is no evidence of it being a conserved benign variant. Additionally, it was once submitted as potentially pathogenic for development and epileptic encephalopathy, although it remains a variant of unknown significance (VUS). Since the gene in question encodes the voltage-gated sodium channel NaV1.2, there is a correlation to the response to treatment with sodium channel blockers.

*Final comments:* This case highlights the potentially deleterious effect of the mentioned variant and reflects the relevance of genetic tests to guide therapeutic choices. Some studies suggest that this gene is not only linked to epilepsy or autism but also to delay in neurological development as a whole. Furthermore, the genetic testing of both parents would help establish the pathogenic nature of the variant, differentiating a de novo mutation from a hereditary condition.

### Code: PE073

#### SEEG in a child with focal cortical dysplasia: is it safe?

Gabriela Schmitt Trevisan<sup>1</sup>, Camila Yoko Martins Hatae<sup>1</sup>, Renata Cristine Alves<sup>1</sup>, Gabriel Andre Silverio<sup>1</sup>, Mateus Pinto Marchetti<sup>1</sup>, Pedro Arthur Possan<sup>1</sup>, Tatiana Von Hertwig Fernandes de Oliveira Kumer<sup>1</sup>, Vera Cristina Terra<sup>1</sup>

<sup>1</sup>Hospital Nossa Senhora das Graças, Curitiba PR, Brazil

*Case presentation:* Male, 6 years old, presenting seizures since the age of 4 and evolving with refractory epilepsy, in use of several medications for focal seizures, including Lacosamide, Cannabidiol, Phenobarbital and Sulthiame. A 24-hour electroencephalogram showed bursts of bilateral sharp waves and focal seizures in front rolandic region, with no adequate localization of the epileptogenic zone. Resonance imaging examination revealed a right lesion compatible with focal cortical dysplasia close to motor strip. Patient was submitted to stereoEEG (SEEG) evaluation, with deep electrodes implanted in the left frontal and rolandic region. After seizures mapping patient was submitted to lesionectomy and became seizure free.

*Discussion:* SEEG is a technique that is being used to investigate refractory epilepsy in adults for many years. However, there are few reports addressing the utility and safety of the SEEG methodology applied to children. The main age limitation is related to bone thickness and fear of surgical complications. Although surgical strategies can often be defined based on non-invasive diagnostic procedures, and despite the recent advances in this field, an increasing number of more complex cases requires invasive EEG to provide precise information on the localization of the epileptogenic zone,

its relationships with eloquent cortex, and the feasibility of a tailored surgical resection.

*Final comments:* Our data supports current literature that SEEG is a safe and effective method of electrophysiological evaluation in children with refractory epilepsy, with no difference in complication rates when compared with adults.

#### Code: PE074

##### **Seizures in pediatric emergency and autoimmune encephalitis, an essential and challenging differential diagnosis: a case report**

Larissa Firme Rodrigues<sup>1</sup>, Monique Frank de Vasconcelos<sup>1</sup>, Lorena Fernanda Costa Oliveira<sup>1</sup>, Rafaella Castro Gama<sup>1</sup>, Luísa de Assis Marques<sup>1</sup>, Lucas de Brito Costa<sup>1</sup>, Cláudia Ambrosio Polloni<sup>1</sup>

<sup>1</sup>Universidade Santo Amaro, São Paulo SP, Brazil

*Case presentation:* Three-years-old male attended with a generalized tonic-clonic seizure. No history of traumatic brain injury, fever or associated flu-like symptoms. Days before, aggressive behavior, slurred speech, visual hallucination. Only one previous tonic-clonic seizure, one month ago, without status epilepticus. Electroencephalogram (EEG): brush pattern extreme delta, cerebrospinal fluid (CSF) with IgG+ for herpes and normal brain magnetic resonance. This condition corroborates the diagnosis of autoimmune encephalitis, and pulse therapy was instituted empirically. He also required anticonvulsant drugs with improvement in epileptic seizures and wakefulness. However, also developed significant psychosis, agitation, extrapyramidal syndrome with dystonia and involuntary movement, and also required anti-psychotic drugs. Diagnosis was confirmed with positive CSF for anti-N-methyl-D-aspartate receptor (anti-NMDAR). He remained hospitalized for 97 days, being discharged with hypotonia limited to bed, severe encephalitic condition and gastrostomy. Received eight pulse therapy cycles with complete improvement of neurological condition.

*Discussion:* Autoimmune encephalitis is characterized by antibodies production against neurons' surface and synaptic molecules. Herpes simplex-1 virus encephalitis seems to trigger anti-NMDAR as in this case. It is possibly underdiagnosed in developing countries in Latin America due to delay and scarcity of diagnostic methods. Manifestations include behavioral or psychiatric changes, dysautonomia and epilepsy. In this case, it's noted that neuropsychiatric encephalitic disorder was neglected by the family and initially by health professionals as well. EEG often changes and extreme delta brush pattern described in anti-NMDAR encephalitis supports this diagnosis. Pathogenic anti-NMDAR autoantibodies may be present in serum and CSF, the latter being chosen in this case for greater sensitivity. First-line therapy is performed with high doses of corticosteroids. Plasmapheresis and rituximab may be considered. Prognosis is usually good when therapy is instituted early.

*Final comments:* Recognizing autoimmune encephalitis is often difficult and late, although disorders can be severe and highly responsive to immunomodulatory therapies. Therefore, it's necessary to implement pulse therapy empirically, as soon as there is a diagnostic suspicion, both because it allows maximizing full recovery chances and diagnostic tests are generally time consuming little available.

#### Code: PE076

##### **The use of cannabidiol in refractory epilepsy**

Ana Carolina Jorge Fogolin<sup>1</sup>, Michelle Basso Couto Gouvêa<sup>1</sup>, Helen Ramos Vasconcelos<sup>1</sup>, Iris do Vale Miranda<sup>1</sup>, Isadora Cavalcante Olímpio De Melo<sup>1</sup>, Paula Luísa Lopes Schell<sup>1</sup>, Daniela Fontes Bezerra<sup>1</sup>, Rubens Wajnsztein<sup>1</sup>

<sup>1</sup>Faculdade de Medicina do ABC, Santo André SP, Brazil

*Case presentation:* H.C.D.M., 6 years old, female, white, single, student. Patient born by cesarean section, at term, with adequate weight. Fruit of the 2nd pregnancy, from non-consanguineous parents. Gestation, childbirth and post childbirth without complications. Father with an epileptic history. The patient started epileptic condition at 1 year of age, in 2017, with recurrent spasms that were difficult-to-control. In July/2020, at 4 years of age, she had 3 types of seizures - atonic, spasms and absence - with an average of 60 to 80 seizures a day, in addition to aggressive behavior, psychomotor agitation and NPMD with speech delay. She was using phenobarbital, clobazam and levetiracetam.

*Discussion:* The patient started follow-up in July/2020 at the Pediatric Epilepsy Ambulatory due to refractory epilepsy. At first, the doses of medications in force at the time were adjusted. She progressed without significant clinical improvement, and doses were adjusted and/or medications replaced at each medical visit. There were several therapeutic failures. The patient used sodium valproate, sodium divalproate, levetiracetam, vigabatrin, ACTH and corticosteroids. She did ketogenic therapy for a certain time, in an external service. During the follow-up, the patient evolved with a change in one of the types of crisis, presenting atonic, absence and bilateral tonic-clonic. In May/2022, when she was using phenobarbital, clobazam, topiramate, risperidone and pyridoxine, it was opted to start using cannabidiol gradually, in an incessant attempt to control the crises, adding it to the other current medications. It started with 1mg/kg/day of cannabidiol, reaching a dose of 3.5mg/kg/day (cannabidiol 6000mg - 100mg/ml). Evolved with significant improvement in epileptic seizures, behavior and NPMD. The patient had days with only 1 episode of crisis and even days without crisis, after the introduction of cannabidiol in his treatment. Exams already performed described below: Skull CT (August/2018): Exam within the normal range. Skull MRI (August/2020): Exam within the normal range. EEG (September/2020): Exam in spontaneous sleep, showing disorganization and diffuse and bilateral slowing, multifocal pattern and generalized discharges of short duration. Rare Genome Project (June/2021): Result in progress.

*Final comments:* Epilepsy is a chronic disease, of varied etiology and evolution, treated with anticonvulsant drugs to stop epileptic seizures as early as possible, minimizing cognitive, motor and social damage that directly harm the life of the patient and their families. However, 30% of cases are refractory to treatment. In this scenario, the use of cannabidiol, alone or associated with other medications, has been shown to be a safe and effective alternative in reducing the frequency and severity of seizures, especially in drug-resistant epilepsies. The absence of adverse effects and severe toxicities, together with the absence of neurological and psychiatric alterations, are relevant points in its use. However, clinical studies are necessary to evaluate the ideal dose, drug interactions and effects with prolonged use. Currently, the patient in question shows a significant improvement in her epileptic condition after the introduction of cannabidiol in her pharmacological therapy - she maintains a good clinical evolution and follows in a diagnostic investigation of her difficult-to-control epilepsy.

Code: PE077

**Use of cannabidiol in child with refractory seizures: sustained clinical improvements**

Mariana Martins Dantas Santos<sup>1</sup>, Natalie da Silveira Donida<sup>1</sup>, Pedro Rodrigues Neves<sup>1</sup>, Gabriel Rodrigues<sup>1</sup>, Andressa Luise Matte<sup>1</sup>, Flávia Seidler<sup>2</sup>, Gustav Peter Foerster<sup>1</sup>, Kléber Cavalcante Santos<sup>3</sup>

<sup>1</sup>Pontifícia Universidade Católica do Rio Grande do Sul, Escola de Medicina, Porto Alegre, RS, Brazil

<sup>2</sup>Pontifícia Universidade Católica do Rio Grande do Sul, Escola de Ciências da Saúde e da Vida, Porto Alegre RS, Brazil

<sup>3</sup>Secretaria de Saúde do Governo do Distrito Federal, Brasília DF, Brazil

**Case presentation:** A 7 month-old was admitted for presenting a clinical condition suggestive of an Inborn Error of metabolism, as she showed development delay, early onset refractory seizures and generalized dystonia associated with infectious events. After 3 years, she remained unresponsive to treatment, presenting over 15 tonic-clonic events per day, and complementary exams were nonspecific, as EEG showed left temporo-occipital intermittent slow activity and MRI revealed hypersignal on T2, with diffusion restriction in the medial longitudinal fascicles. Also, genetic testing was inconclusive, though it indicated mitochondriopathy. Due to this suspicion, Valproate was suspended and Cannabidiol (400 mg/day) was recommended for seizure control, along with Phenobarbital (5 mg/kg/day), Oxcarbazepine (35 mg/kg/day), Clobazam (1 mg/kg/day) and co-factors (L-carnitine, thiamine and riboflavin). Since this therapy was established, she presented full control of the seizures and increased her development process. Therefore, it is understood that the relevance of the case is closely linked to the need for an adequate and appropriate prescription.

**Discussion:** Even though refractory epilepsy is a recurrent and morbidity associated condition, its management is not fully mastered. In this context, cannabidiol (CDB) treatment has gained prominence, as it has been shown that it might reduce seizure frequency and have an adequate safety profile in these patients. Although its mechanism is not completely known, it is known that CBD is a potent inhibitor of the CYP3A and CYP2C enzymes, which are responsible for metabolism of clobazam and other antiseizure medications, suggesting that metabolite levels of this drugs can rise with concomitant use of CBD. These findings corroborate with the benefit obtained after the concomitant treatment of CBD and Phenobarbital, Oxcarbazepine, Clobazam in this case report.

**Final comments:** Worldwide medicinal use of CBD is rapidly escalating, despite limited evidence of its efficacy from preclinical and clinical studies. Yet, recent clinical trials of cannabidiol in refractory epilepsy support its clinical efficacy for reduction of seizure frequency. So, though we reinforce that patients receiving cannabinoids should be monitored, we showed here that CBD treatment can have an acceptable safety profile and lead to sustained clinical improvements. Considering this, the absence of this treatment can determine not only a great negative impact on the development, but also the death of the child.

Code: PE079

**West syndrome: the importance of early diagnosis**

Monique Frank de Vasconcelos<sup>1</sup>, Guilherme Ramos de Faria<sup>2</sup>, Larissa Firme Rodrigues<sup>1</sup>, Camila Assis Bertollo<sup>3</sup>, Marcia Regina Ribeiro<sup>1</sup>, Rafaella Castro Gama<sup>1</sup>, Luísa de Assis Marques<sup>1</sup>, Lucas de Brito Costa<sup>1</sup>, Cláudia Ambrosio Polloni<sup>1</sup>

<sup>1</sup>Universidade Santo Amaro, São Paulo SP, Brazil

<sup>2</sup>Hospital Sírio Libanês, São Paulo SP, Brazil

<sup>3</sup>Hospital Infantil Nossa Senhora da Glória, Vitória ES, Brazil

**Case presentation:** Term newborn, appropriate for gestational age, female, normal neonatal screenings, vaginal birth, Apgar 7/8. Diagnosed with congenital syphilis, pulmonary hypertension, convulsive syndrome and altered thyroid-stimulating hormone by maternal levothyroxine use during pregnancy. At maternity, infant presented with frequent seizures, receiving levetiracetam and phenobarbital, in addition to crystalline penicillin. Magnetic resonance image showed diffuse signs of severe intracranial multicystic encephalomalacia, with significant cortex loss. Received discharged after 36 days with levetiracetam and persistence of epileptic seizures. Was referred to a neuropediatrician, but without follow-up. It evolved at 4 months of life, requiring hospitalization, presenting no neuropsychomotor development, conjugated supraversion of eyes, regular sucking, without fixation of look and support of head, no social smile or palmar grip sign, convulsive episodes as fast spasms and nystagmus that are repeated several times a day. Electroencephalogram (EEG) with abundant epileptic paroxysm of acute waves and multifocal projection spicules, suggestive of hipsarrhythmia. Diagnosed as West Syndrome, he received vigabatrin, valproic acid, associated with adrenocorticotrophic hormone, with fewer daily seizures.

**Discussion:** West syndrome is an epileptic encephalopathy, with predominant incidence in the first year of life, characterized by clinical trial of infantile spasms, delayed neuropsychomotor development and EEG with hipsarrhythmia pattern. Males are more affected. Infantile spasms are often confused with primary reflexes or scares, not being interpreted as an alarm signal for investigation. It usually has an unfavorable prognosis, with frequent stagnation or regression of neuropsychomotor and cognitive development. The importance of early diagnosis is to preserve maximum neuropsychomotor development. In this case, lack of follow-up with neuropediatricians and rapid diagnosis culminated in irreversible significant neurological sequelae, reinforcing poor prognosis and faster diagnosis.

**Final comments:** West syndrome has, mostly, a reserved prognosis, with severe intellectual and motor loss. Raising awareness and educating health professionals about suspicion signs, diagnostic and therapeutic agility is the best way to reduce neurological loss and ensure quality of life for patients and family members. And treatment with a multi-disciplinary team may decrease possible body deformities allowing global rehabilitation.

Code: PE080

**West syndrome associated with hypoxic brain injury caused by intoxication: a case report**

Ana Carolina Andrade Lopes<sup>1</sup>, Alessandra Andrade Lopes<sup>2</sup>

<sup>1</sup>APAE Anápolis, Anápolis GO, Brazil

<sup>2</sup>Centro Universitário de Brasília, Brasília DF, Brazil

**Case presentation:** M.S.G, 1 year old, previously healthy, suffered intoxication by acaricide (organophosphate and pyrethroid) in November 2021. Patient presented seizures, vomiting, bronchoaspiration, pneumonia, severe respiratory

distress and two cardiorespiratory arrests. The magnetic resonance imaging showed hemorrhagic laminar cortical necrosis and slight accentuation of cortical sulci and brain fissures. He was taken to the pediatric neurology using phenobarbital and baclofen. The electroencephalogram (EEG) presented an electrographic status epilepticus, and it was started levetiracetam and nitrazepam, once there wasn't the possibility of hospitalization. The second EEG presented an epileptic encephalopathy, with the persistence of the electrographic features, multifocal epileptiform activity and in burst-suppression occupying more than 80% of the record. Although the tracing was not typical of a hypsarrhythmia, due to the absence of slow high-voltage activity, the presence of semiology compatible with epileptic spasms led to the possibility that it was an evolution to West Syndrome. Therefore, it was decided to start corticosteroid (prednisone 3mg/kg/day). A new EEG presented abundant multifocal epileptiform activity in the tracing; no burst-suppression episodes were observed, nor was the pattern of electrographic status epilepticus on the record. The patient showed improvement in infantile spasms after treatment with corticosteroids for 3 months. However, after the withdrawal from prednisone, the patient started seizures again.

**Discussion:** West Syndrome is the combination of infantile spasms, hypsarrhythmia and developmental regression. It is caused sometimes by an injury to the brain. Other times, it is caused by developmental anomalies of brain structure, genetic mutations or metabolic disorders. In current practice, ACTH and vigabatrin are the main treatments. As the ACTH is not available in Brazil, high-dose oral of corticosteroids are used. Its use is as effective as ACTH, with fewer adverse effects and it can control between 33–63% of the infantile spasms.

**Final comments:** The prognosis of West Syndrome is usually poor. About 65–70% of children will have spasms fully controlled. Unfortunately, most children will have other kinds of seizures in later childhood including Lennox-Gastaut Syndrome. In this particular case, the patient has severe brain injury, which makes it even more difficult to control his seizures.

## Erros inatos do metabolismo

Code: PE082

### 3-hydroxy-3-methylglutaryl-coenzyme a lyase deficiency: a case report

Jose Antonio Coba Lacle<sup>1</sup>, Mariane Wehmuth Furlan Eulalio<sup>1</sup>, Ana Clarice Bartosievicz Prestes<sup>1</sup>, Melanie Scarlet Díaz Solano<sup>1</sup>, Eduarda de Boer Furstenberger<sup>1</sup>, Isadora Cristina Barbosa Lopes<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>, Carolina Oliveira de Paulo<sup>1</sup>  
<sup>1</sup>Hospital Universitário Evangélico Mackenzie, Curitiba PR, Brazil

**Case presentation:** Male patient, 6 months old, admitted due to seizure associated with severe refractory hypoglycemia. Patient had been experiencing unusual sleepiness for 8 days, and vomiting after feedings. Brain CT showed prominence of the bilateral frontotemporal extra-axial space and of the Sylvian fissures, EEG revealed a slow diffuse moderate disturbance of the background activity and the MRI revealed extensive areas of diffusion restriction involving the white matter of the cerebral hemispheres as well as the globus pallidus and central fragmentary tracts in the brainstem, without mass effect or enhancement by the contrast. A hypothesis of inborn error of metabolism was raised and therapy was initiated with diet adjustments and L-carnitine, and, in the following days, the patient was clinically and hemodynamically stable, with no new episodes of hypoglycemia or seizures. The result of the biochemical analysis of

organic acids in urine showed a marked increase in 3-hydroxy-isovaleric, glutaric, 3-methyl-glutaric, 3-methyl-glutaconic, 3-hydroxy-3-methylglutaric and 3-methyl-crotonylglycine acids. Genetic testing demonstrated 3-hydroxy-methylglutaryl-CoA lyase deficiency (3HMG) with the homozygous mutation of the HMGCL gene.

**Discussion:** 3HMG usually starts with a metabolic decompensation. Clinical manifestations are due to excessive consumption of glucose, since they do not have enough ketone bodies for energy consumption. Acute decompensations are mainly presented by vomiting, lethargy, hypotonia, tachypnea/apnea, metabolic acidosis, seizures, hepatomegaly and other less common manifestations, and may progress to comatose states. The hypothesis of 3HMG was raised when the metabolic alterations were added to the results of the brain images, which showed enlargement of the sylvian fissure, and globus pallidus alteration.

**Final comments:** 3HMG is a hereditary disease of the final metabolism of leucine and the ketogenic pathway due to an enzyme deficiency and manifests as a metabolic decompensation. The earlier the disease is discovered, the better the patient's prognosis, aiming to reduce possible complications and sequelae.

Code: PE083

### Case report: metachromatic leukodystrophy, its clinical evolution and diagnostic management

Jéssica Kayene Souza Ferreira<sup>1</sup>, Hanid Fontes Gomes<sup>1</sup>, Marlos Melo Martins<sup>1</sup>, Maria Lina Giacomino de Almeida Passos e Azevedo<sup>1</sup>, Amanda Regina Farias Teixeira<sup>1</sup>, Sofia Russi<sup>1</sup>, Lana Correa Paschoal<sup>1</sup>, Caroline Scantamburlo Martins<sup>1</sup>

<sup>1</sup>Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil

**Case presentation:** We report a case of a female infant, with a normal previous neuropsychomotor development, at 21 months of age had presented a sudden regression of development after an infectious condition. Initially its courses were composed by ataxia, vomiting, hypotonia and behavior alteration, loss of gait and language in a period of two months, associated with focal seizures, relevant dystonia (opisthotonus) and spasticity. Levetiracetam, baclofen and clobazam were prescribed, with seizure control and partial control of spasticity and dystonia. The initial investigation was directed to inborn errors of metabolism, revealing metabolic acidosis, elevated lactorrachia, proteinorrachia and increased serum creatine phosphokinase, and abnormal amino acid chromatography. Cranial magnetic resonance imaging evidenced signs of intense demyelination, with diffuse and symmetrical T2 hypersignal, affecting mainly the periventricular region and the left cerebellar hemisphere. At first, the diagnostic hypothesis of mitochondrial disease was raised, which was excluded after the genetic panel (ARSA-intron2-c.465+1G>A), which is associated with metachromatic leukodystrophy.

**Discussion:** Metachromatic leukodystrophy has an estimated worldwide prevalence of 1/40,000–160,000. It is a lysosomal storage disease, of autosomal recessive inheritance, characterized by the demyelination of the central and peripheral nervous systems, associated with clinical developmental regression syndrome. The late infantile form has an incidence of 50–60% of cases and presents with a developmental regression syndrome up to thirty months of age, which is more severe, due to rapid neurodegenerative progression, and the diagnosis is confirmed by genetic testing or arylsulfatase dosage. To date, supportive therapeutic strategies are: warfarin, simvastatin, prednisolone, and immunoglobulin to reduce neuroinflammation, in addition to baclofen and

anticonvulsants. Stem cell transplantation, enzyme replacement therapy and viral vectors are currently being studied. *Final comments:* The case refers to the late infantile form, without correlating genotype-phenotype with the course of the disease. Laboratory findings are consequences of lysosomal system dysfunction, which secondarily alters other organs, and radiological findings with a demyelinating pattern. These results are similar to the leukodystrophies group, and genetic testing concludes the diagnosis. In the presence of clinical worsening, supportive therapeutic measures will be reassessed.

#### Code: PE084

##### **Case series on type I gangliosidosis at a reference service for inborn errors of metabolism: from diagnostic strategies to therapeutic perspectives**

Laura Defensor Ribeiro de Melo<sup>1</sup>, Saul Alquez Montano<sup>1</sup>, Maria Avanise Yumi Minami<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Hospital das Clínicas, Ribeirão Preto SP, Brazil

*Case presentation:* Three cases of type I Gangliosidosis were diagnosed and followed up in our service from 2013 to 2022. These cases were reviewed in clinical relevance, diagnostic measures and therapeutic proposals. The patients onset symptoms when they were infants, presenting refractory epilepsy, developmental regression and weight deficit. In clinical investigation, one of the patients presented suggestive ophthalmological characteristic with a cherry red spot in macula. After extensive investigation, including metabolic research, the enzymatic alterations in common as  $\beta$ -galactosidase dysfunction and alterations in quantitative tests, chromatography of oligosaccharides and sialyloligosaccharides in urine, have already suggested a biochemical diagnosis for Gangliosidosis type I. In addition, two patients had diagnosis corroborated with the identification of a mutation in the GLB1 gene, after sequencing all the coding exons of this gene. Currently, one of the patients is being followed up at the service, being a child followed up for 8 years, showing a favorable performance in terms of longevity associated with this disease.

*Discussion:* Type 1 Gangliosidosis is a rare disease characterized by ganglioside substrate accumulation in lysosomes due to  $\beta$ -galactosidase enzyme deficiency. The clinical course can be variable, highlighting neurodegeneration, skeletal changes and findings suggestive of the disease, such as ophthalmological particularities. Laboratory diagnosis can be made through analysis of enzymatic activity or biochemical identification of the metabolite. Confirming the diagnosis, genetic mutation can be a predictor of the severity of the clinical manifestation and helps to direct research therapeutic strategies.

*Final comments:* The objective of the description of this case series is to record the diagnostic progress of a poorly disseminated metabolic disease, detailing the propaedeutic evidence in an evolutionary and rationalized way. In addition, to contribute with recognition of the disease as a differential diagnosis for eventually trivial complaints in the context of Child Neurology, as seizures and delay in neuropsychomotor development, reinforcing the importance of Inborn Errors of Metabolism as an etiological entity.

#### Code: PE087

##### **Early-onset epilepsy in complex II mitochondrial disorder related to the SDHA gene**

Giulia Vilela Silva<sup>1</sup>, Mara Lúcia Schmitz Ferreira Santos<sup>1</sup>, Daniel Almeida Valle<sup>1</sup>, Rui Carlos Silva Junior<sup>1</sup>, Guilherme Siqueira Gaede<sup>1</sup>, Mariah Pereira Andrade Valim<sup>1</sup>, Lorena Vilela Rezende<sup>1</sup>, Izabela Cristina Macedo Marques<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

*Case presentation:* A 2-year-old girl with refractory epilepsy since 4 months of age and persistent daily seizures even with optimized therapy. At 15 months of age, she was presented with global delay in neuropsychomotor development, axial hypotonia, and no interaction. There was also hyperreflexia, clonus, and delayed dentition. Initial metabolic screening and MRI were standard. The electroencephalogram displayed slowed and disorganized baseline activity. She was born at term in good general condition, with early jaundice requiring phototherapy. When asked about other complaints, chronic diarrhea and difficulty gaining weight were raised. Her family members were healthy except for migraine in her mother and maternal half-siblings. At 20 months she was hospitalized for epileptic status, requiring continuous sedation. MRI at the time exhibited diffuse atrophy and intensity signal changes in the basal ganglia. Exome sequencing test showed a compound heterozygous mutation in the SDHA gene confirming the diagnosis of complex II mitochondrial disease.

*Discussion:* So far, more than 400 mutations have been described in mitochondrial and nuclear DNA that lead to primary mitochondrial defects. Because they are present in all human cells, their dysfunction leads to multisystemic involvement in varying degrees. The complex II of the respiratory chain is the only one in which proteins are all encoded by nuclear DNA. It is known that mutations in the A subunit of the SDH gene lead to early epileptic encephalopathy with a phenotype similar to Leigh's syndrome. So far, just over 20 cases have been reported. Out of these, most patients have epilepsy, ataxia, hepatosplenomegaly, optic atrophy, cardiomyopathy, and lactic acidosis, with onset usually at preschool age. There is also a strong association with stromal tumors. Regarding the mutations found in the patient, one of them - paternal inheritance - has already been described in association with pheochromocytomas and heterozygosity in a patient with epilepsy. The second (of maternal inheritance) has not yet been reported.

*Final comments:* The present report indicates the phenotypic variability of the complex II mitochondrial disease related to the SDHA gene. Our patient showed early onset and predominant epileptic manifestation without multisystemic involvement, which differs from the case reports of this condition so far.

#### Code: PE089

##### **Initial manifestations of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) at an infant**

Maria Lina Giacomino de Almeida Passos<sup>1</sup>, Amanda Regina Farias Teixeira<sup>1</sup>, Caroline Scantamburlo Martins<sup>1</sup>, Hanid Fontes Gomes<sup>1</sup>, Jessica Kayene Souza Ferreira<sup>1</sup>, Lana Correa Paschoal<sup>1</sup>, Marlos Melo Martins<sup>1</sup>, Sofia Russi<sup>1</sup>

<sup>1</sup>Universidade Federal do Rio de Janeiro, Instituto de Puericultura e Pediatria Martagão Gesteira, Rio de Janeiro RJ, Brazil

*Case presentation:* The following case is a description of two-year-old girl whose diagnostic for Mitochondrial Myopathy was considered after presenting two episodes of impaired consciousness. At first, she was admitted at a pediatric

emergency with fever, nasal discharge and sleepiness, at eight months old. Cerebrospinal Fluid analysis came normal. After a short period of clinical observation, consciousness was improved, and the patient was discharged. Ten days later, the girl presented irritability alternating with sleepiness. Computerized Tomography head scan showed hypodense areas: cortex- subcortical in anterior convexity of frontal lobes, in parietal parasagittal area in left cerebral hemisphere and in right cerebellar hemisphere (suggesting stroke-like episodes, not limited to a vascular territory). No mass effect was seen. The patient was admitted for meningoencephalitis' treatment while clinical condition progressed to neurodevelopmental regression with irresponsiveness events and choreic movements. Valproic acid, carbamazepine and clonazepam were prescribed for seizures suppression with-out satisfactory results. Haloperidol was used to control the chorea. Increased serum levels of Creatine Phosphokinase was found as well as high lactate levels in Cerebrospinal Fluid (CSF), suggesting a Metabolic disease. Levetiracetam was initiated to replace valproic acid and carbamazepine. Food supplements were prescribed. Muscular biopsy evinced abnormal subsarcolemmal accumulations of eosinophilic material (that may correspond to mitochondria) when colored by Gomori's modified Trichrome.

*Discussion:* Initially described in 1984 and still with uncertain prevalence in global population, Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS) has been widely used as a model to study Mitochondrial diseases. The adenine-t-guanine transition at point 3243 of the mitochondrial genome (m.3243A>G) is described as responsible for up to eighty per cent of this metabolic disease, but the same mutation was found in other genetic diseases, and some other mutations were found in MELAS. Three almost invariable criteria were described for diagnosis of MELAS: Stroke-like episodes before age of 40 years old, encephalopathy (dementia, seizures, or both) and Lactic Acidosis or Ragged-red fibers (or both).

*Final comments:* The exposed case fulfils all the three criterions. The patient had eventually stopped taking Levetiracetam and is currently neurologically stable.

#### Code: PE090

##### **L2-hydroxyglutaric aciduria in a 5-year-old child: a case report**

Marcela Gonçalves de Souza<sup>1</sup>, Debora Carinhato Thomaz<sup>1</sup>, Luiza Oliveira Prata Silveira<sup>1</sup>, Loiane Dante Correia Rocha<sup>1</sup>, Eduardo Ferraz Troijo<sup>1</sup>, Manuel Jacinto de Abreu Neto<sup>1</sup>, Anna Carolina Eulalio Amorim Baratta<sup>1</sup>, Pedro Zambusi Naufel<sup>1</sup>

<sup>1</sup>Irmandade Santa Casa de Misericórdia de São Paulo, São Paulo SP, Brazil

*Case presentation:* EMS, 5 years old, 1st child of a non-consanguineous couple, with no relevant antecedents, have started a neuropsychomotor development regression at 2 years old. The parents noticed a slower speech, in addition to a bad concentration. At the first appointment at a tertiary pediatric neurology service in the city of São Paulo, the patient had a lowered cognitive level for his age, in addition to bradylalia and dysarthria. He had an unsupported gait, on tiptoe, with a slightly enlarged base. The eye examination, inborn error of metabolism trial, cerebrospinal fluid and general serum exams were normal. Cranial magnetic resonance imaging showed bilateral and symmetrical involvement of the basal ganglia and dentate nuclei, associated with changes in the supratentorial white matter. A genetic panel was collected, confirming L2-glutaric aciduria, with 2 pathogenic variants of L2HGDH.

*Discussion:* L-2-hydroxyglutaric aciduria is a rare, autosomal recessive disease caused by mutations in the L2HGDH gene (14q22.1) that encodes mitochondrial 2-hydroxyglutarate dehydrogenase. It consists of an organic cerebral aciduria of insidious onset, with slow progression, generating neurological symptoms. L-2-hydroxyglutaric acid accumulates in urine, blood, and CSF. Cranial MRI shows characteristic abnormalities: symmetrical lesions in the white matter and corpus callosum, in addition to changes in the basal ganglia and cerebellum. Clinical manifestations consist of mild to moderate NPMD delay, cerebellar ataxia, epilepsy, and spasticity. Macrocephaly and extrapyramidal symptoms are present in 50% of cases.

*Final comments:* The presentation of this case report is justified due to the rarity of this genetic condition, with ~200 cases reported so far. Although the clinical picture is nonspecific, imaging changes may suggest the diagnosis, which must be confirmed by molecular test.

#### Code: PE092

##### **Mitochondrial trifunctional protein (MTP) deficiency presenting with late-onset cardiomyopathy phenotype**

Catarina Falleiros Nogueira Rojas<sup>1</sup>, Micaelle Smaniotti de Oliveira<sup>1</sup>, Eloisa Barros Pessoa<sup>1</sup>, Melina Giroto Tazinassi<sup>1</sup>, Camila Garcia Ferrari Jacob<sup>1</sup>, Lia de Oliveira Rosa Gazola<sup>1</sup>, Ana Luiza Gomes de Souza<sup>1</sup>

<sup>1</sup>Faculdade de Medicina de Marília, Marília SP, Brazil

*Case presentation:* Female, 4 years old, hospitalized for coughing and reduced level of consciousness. Physical examination revealed tachycardia, no response to stimuli, isochoric and photoreactive pupils. Diagnostic hypotheses of viral encephalitis and myocarditis were raised after laboratory tests did not suggest sepsis. During admission to the Intensive Care Unit, skull computed tomography and cerebrospinal fluid were normal. Anti-cytomegalovirus serum dosage IgM positive. Evolved with hemodynamic decompensation and prolonged cardiorespiratory arrest, creatine phosphokinase of 23.971, creatine kinase-MB fraction of 950, elevation of transaminases, troponin levels of 703. Post-arrest cranial resonance showed images suggestive of bilateral hypoxic-ischemic white matter lesions. Due to the brother's history of early death at 18 months due to sepsis, we chose to perform tandem mass spectrometry and plasma acylcarnitine profile, which indicated a probable diagnosis of Very Long-Chain Acyl-CoA Dehydrogenase deficiency (VLCADD) with subsequent confirmation of Mitochondrial Trifunctional Protein (MTP) deficiency through specific molecular genetic test. Treatment with triheptanoin was initiated and a gradual improvement in the level of consciousness, cognitive functions, cardiac parameters and reduction of muscle and liver enzymes were observed.

*Discussion:* MTP deficiency is a rare autosomal recessive disorder affecting long-chain fatty acid oxidation caused by mutations in the HADHB gene and is associated with 3 main clinical phenotypes: early-onset of a severe and lethal cardiomyopathic disease, infantile-onset of a hepatic dysfunction and recurrent hypoketotic hypoglycemia and late-onset of skeletal myopathy and peripheral neuropathy. Reports and clinical trials of anaplerotic therapy with triheptanoin have demonstrated an improvement in cardiac symptoms, muscle weakness, hypoglycemia, and hepatomegaly with good security profile and reduced hospitalizations.

*Final comments:* In view of the clinical history of non-specific presentation, severe and acute evolution, premature death of a sibling, our objective is to present a challenging diagnosis with an unusual onset, which must be recognized on hospital admission of children with supposedly infectious disease, to

modify the course of the disease with the treatments already available and reduce morbidity and mortality.

#### Code: PE093

##### **Molybdenum Cofactor Deficiency with Cerebral Atrophy** Teodora Roballo Durigan<sup>1</sup>, Izabela Cristina Macedo Marques<sup>2</sup>, Daniel Almeida do Valle<sup>2</sup>

<sup>1</sup>Universidade Positivo, Curitiba PR, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Full term newborn, Apgar 9/9, with no family history of neurological diseases, developed breathing and feeding difficulties, reason why was admitted at the hospital on her 7th life day. On examination, presented craniofacial dysmorphic features, anisocoria reactive to light, absence of blink reflex, divergent strabismus with discreet skew deviation, hypertonia of limbs and clonic movements, rough skin with diffuse maculopapular lesions, with furfuraeous scaling. The patient was hospitalized and stabilized in the UCI, needing OTI. In the first investigation, the infectious triage and cerebral USG were normal. The MRI of the 9th day of life evidenced cerebral edema, bilateral injury of the thalamus and a high lactate at spectroscopy. The patient progressed with seizures crisis of difficult control, due to that, hypoproteic diet was initiated, with good response. The treatable diseases panel showed absence of variants that isolated would justify the clinical picture. A complete sequencing of the genome revealed variant c.377+1G>A, p.(?) on the intronic region that succeeds the exon 5 of the MOCS2 gene, in homozygous, diagnosing molybdenum cofactor deficiency B. MRI of the 7th month of life revealed plenty of areas with cystic degeneration, important volumetric encephalic reduction and reduction of the N-acetylaspartate peak. Nowadays she's at home, being treated with Phenobarbital, Lev- etiracetam, Oxcarbazepine, L-carnitine, Pyridoxine and Clonazepam.

**Discussion:** The molybdenum cofactor deficiency is an autosomal recessive disease with variable phenotype. Individuals with the early-onset disease usually manifest in the first days of life encephalopathy refractory seizures, opisthotonus, hypotonia, feeding difficulties and apnea. Neuroimaging findings are often loss of white and gray matter differentiation, gyral swelling, edema, sulci injury, diffusely elevated T2-weighted signal and panlobar diffusion restriction. The definitive diagnosis is molecular, with tests that demonstrate biallelic pathogenic variants GPHN, MOCS1, MOCS2 or MOCS3. The serious cases with early-onset are associated with bad prognosis and elevated mortality.

**Final comments:** The molybdenum cofactor deficiency is a rare disease, of poor prognosis, that manifests itself mainly as seizures, and can lead to cerebral atrophy. The diagnosis depends on expensive and difficult-to-access techniques in Brazil, however it allows of prognosis and exclusion of differential diagnosis.

#### Code: PE095

##### **Tay-Sachs disease with atypical evolution: case report** Iris do Vale Miranda<sup>1</sup>, Helen Ramos Vasconcelos<sup>1</sup>, Michelle Basso Couto Gouvêa<sup>1</sup>, Paula Luísa Lopes Schell<sup>1</sup>, Ana Carolina Jorge Fogolin<sup>1</sup>, Isadora Cavalcante Olimpico de Melo<sup>1</sup>, Laís Russo Carneiro Peruzzi<sup>1</sup>, Paulo Breinis<sup>1</sup>

<sup>1</sup>Faculdade de Medicina do ABC, Santo André SP, Brazil

**Case presentation:** Patient R.P.C., birth 06/10/2019, female, referred from pediatric clinic at two years old due to speech regression. In August 2021, she underwent routine funduscopy, due to prematurity, showing a red cherry spot. In her

neuropsychomotor development, she presented cephalic support at three months of age, sat up at eight months, walked at 11 months, started two-syllables at nine months, but regressed, and currently only emits sounds. No story of seizures. On neurological examination, she walks without support. Motor coordination apparently preserved. Diagnostic screening tests performed: Fundoscopy (2021): Red cherry spot. Electroencephalogram (2022): Within normal limits. Investigation of Tay-sachs Disease performed on 01/13/2022, with Lysosomal gene sequencing analysis, identifying two pathogenic variants in HEXA, associated with the autosomal recessive gene of Tay-sachs disease, confirmed with Hexosaminidase A and B Dosage performed day 03/12/2022, with the following result: HEXOSAMINISADE A: 16.9 nmol/h/mL; HEXOSAMINIDASE A (Activity): 1.6%.

**Discussion:** Tay-Sachs disease is within the GM2 gangliosidosis group. The infantile type has progressive neurological deterioration until, at two years of age, patients develop decerebrate posture, dysphagia, non-responsive and vegetative state. An early and persistent manifestation is the 'startle reaction'. The most frequent pathology associated with the presence of cherry-red spot is Tay-sachs disease infantile type, found in all patients up to 6 months of age. In the juvenile type of the syndrome this manifestation is less frequent. Our patient best fits the infantile entity, due to the age of onset of symptoms, presence of cherry red spot in addition to 'startle reaction'. However, its clinical presentation is considered atypical since it does not present all the commemorative ones described in the literature for her age: 3 years of age maintains preserved gait and swallowing and has no convulsive episodes to date. There is no efficient treatment for Tay-Sachs disease, but anti-epileptics can be prescribed. A treatment aimed at inhibiting gangliosides synthesis (Miglustat) is currently being investigated for the slowly progressive forms.

**Final comments:** Tay-Sachs disease is a genetic autosomal recessive inheritance pattern with progressive neurology evolution. As described in this report, the disease has rapid and degenerative evolution, however, the diagnosis cannot be ruled out in patients with delayed progression.

#### Code: PE096

##### **Use of carginic acid in propionic acidemia: a case report**

Renan Guimarães Santana<sup>1</sup>, Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, Nathália Jamille Moreira Nascimento David<sup>1</sup>, Thais de Almeida Fonseca Oliveira<sup>1</sup>, Laura Maria Silva Thiersch<sup>1</sup>, Fernando Nascimento Dias Carneiro<sup>2</sup>, André Vinicius Soares Barbosa<sup>1</sup>, Ana Carolina Cardoso Diniz<sup>1</sup>, Bruna Ribeiro Torres<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

<sup>2</sup>Universidade de Itaúna, Itaúna MG, Brazil

**Case presentation:** The case is about a 1 year and 9 month old infant, child of consanguineous parents, born at term, Apgar 9/10, with respiratory distress, vomiting and hypoactivity starting at 48 hours of life, laboratory tests were performed that showed severe metabolic acidosis, in addition to not being suggestive of infection and blood culture without microorganisms growth. At the time, a measurement of organic acids in urine, amino acids in plasma and acylcarnitine profile on filter paper were gathered, with results suggestive of propionic acidemia, which was confirmed with molecular examination showing a mutation in the PCCA gene in homozygosity. The patient sporadically presented vomiting and hypoactivity associated with hyperammonemia, and then during one of these episodes, on 05/27/2022, carginic acid was started and the patient showed



significant improvement of these symptoms and ammonia within normal range.

**Discussion:** Carglumic acid is a synthetic analogue of N-acetylglutamate (NAG) synthase, an enzyme produced by the liver that activates carbamoyl-phosphate synthetase I (CPS-I), the enzyme of the first limiting step of the urea cycle, stimulating ureagenesis. It is indicated for the treatment of hyperammonemia in patients with NAGS deficiency or patients with isovaleric, methylmalonic, or propionic organic acidemia, which affect NAG function. In case of patients with organic acidemia, it should be used during hyperammonemia crises, as high levels of ammonia can cause neurological complications, coma, and even death.

**Final comments:** Patients with isovaleric, methylmalonic, or propionic organic acidemias constantly present hyperammonemia during infectious processes, prolonged fasting, or protein intake above limit. The use of carglumic acid can thus help reduce morbidity and mortality in these patients and improve their quality of life.

## Malformações do sistema nervoso central

Code: PE097

### A case of unidentified prenatal holoprosencephaly and the need for a chromosomal study to guide management in future pregnancies

Anna Rita Barcelos Martin<sup>1</sup>, Bruna Bavaresco Barros<sup>1</sup>, Bruna Flegler Braun<sup>1</sup>, Thaís Moura Avelar Fonseca<sup>1</sup>, Gabriela Oliveira Anjos<sup>1</sup>, Hellen Kássia De Lima Alves<sup>1</sup>, Amanda Silva Moura<sup>1</sup>, Stéphanie Lara Pereira Lopes<sup>1</sup>, Mariana Almeida Correa<sup>1</sup>

<sup>1</sup>Universidade Federal do Triângulo Mineiro, Uberaba MG, Brazil

**Case presentation:** Newborn was born on 07/25/22 in UFTM clinics hospital, premature at 36 weeks and 5 days, iterative cesarean section, APGAR 7%, aspiration of 11 ml of meconium fluid and gastric lavage were performed without complications. He presented hypotonia and central cyanosis in the 1st minute, requiring oxygen therapy in the first 20 minutes of life. At birth, head circumference was lower than expected (30.5cm - 4.6th percentile). The mother performed serial ultrasounds during prenatal care, but without descriptions regarding the fetal brain circumference, serological tests performed during pregnancy did not show any changes. A microcephaly investigation protocol was started on the first day of life, laboratory tests and serology were performed, with no changes, Karyotype was collected soon after the diagnosis of holoprosencephaly, but until now awaits results. Transfontanella ultrasound showed semilobar holoprosencephaly. Computed tomography with diagnosis of holoprosencephaly. Laboratory tests, serology and cerebrospinal fluid without alterations. The patient remained in good general condition since birth, hemodynamically stable, breathing room air, breastfeeding, with good suction, and at the neurological examination, primitive reflexes were present, without alterations. He was discharged from the hospital on 07/28/22, referred to the neuropediatric outpatient clinic of the hospital for follow-up.

**Discussion:** Holoprosencephaly is a rare brain malformation, the embryonic forebrain does not go through the complete process of segmentation and cleavage and can be identified during prenatal care through intrauterine ultrasound. The 3 main types of holoprosencephaly, in decreasing order of severity are: Lobar, Semilobar and Lobar. Semilobar holo-

prosencephaly is a partial cleavage in the posterior hemispheres, constituting an intermediate form of the disease. Due to the high risk of associated genetic and chromosomal syndromes, a detailed genetic study of the newborn is required. The recognition, at the time of delivery, of a previously unsuspected case of holoprosencephaly, results from the presence of facial anomalies, an equally important prognostic indicator for the child in question, because the more severe the facial alterations present, the greater the probability that holoprosencephaly is lobar, with low survival prospects.

**Final comments:** This diagnosis is also important to recognize the need for a chromosomal study to guide management in future pregnancies.

Code: PE098

### Arteriovenous malformation of the vein of Galen in the pediatric patient: a case report

Anna Paula Monteiro de Souza<sup>1</sup>, Raimundo Maurício dos Santos<sup>1</sup>, Guilherme Graff<sup>1</sup>, Sara Julia Zorzi de Brum<sup>1</sup>, Vinicius Lemos Menegoni<sup>1</sup>, Felipe Eberhart Figur<sup>1</sup>, Marília Gabriela Valuta<sup>1</sup>, Eliezer Naudal Dertelmann<sup>1</sup>, Stefânia Simon Sostruznik<sup>1</sup>

<sup>1</sup>Universidade Federal da Fronteira Sul, Passo Fundo RS, Brazil

**Case presentation:** V.R.P., 2 days old, male, gestational age of 39 weeks and 6 days, born by c-section, weighing 2.970kg, breech presentation, Apgar score 8 and 9. In the home postpartum period, evolved with several seizures, which motivated the family to seek medical attention. The initial patient assessment and the physical examination showed normal vital signs, capillary glycemia of 76mg/dL, good general condition, intensity 4-5 on the Wong-Baker Scale, isochoric and reactive pupils, no signs of meningeal irritation and presence of symmetric superficial and deep reflexes. Three hours later, he had 3 focal seizures with retained awareness and automatisms, which were reversed with a loading dose of phenytoin. The transcranial doppler showed germinal matrix hemorrhage grade 3 on the Papile Scale. On the next day, presented with 5 new seizures with automatisms, when a loading dose of phenobarbital was used, followed by a maintenance dose. The EEG showed no alterations and the cranial CT without contrast revealed hyperdense content next to the brain scythe and the tentorium and between the cortical gyri's grooves on the frontal lobe, bilaterally, as well as extrinsic compression in the III ventricle. An external ventricular derivation catheter was placed on an urgent basis to treat the hydrocephalus. After the procedure, the patient had clinical improvement. The requested cranial MRI exhibited malformation at the vein of Galen territory.

**Discussion:** The vein of Galen aneurysmal malformation (VGAM) is a rare anomaly responsible for less than 1% of all congenital vascular malformations. It is characterized by the formation of multiple arteriovenous fistulas between the choroidal circulation and the median vein of the prosencephalon, an embryonic vessel precursor of the vein of Galen that dilates. About 94% of the cases are diagnosed in the neonatal period, the first manifestation being heart failure and hydrocephalus. Transarterial embolization is the treatment of choice, which can be delayed until the patient is 6 years old, when the formation of the venous sinus is complete.

**Final comments:** There are few studies concerning the VGAM, in spite of its high mortality rates in late diagnosed patients. Therefore, this report is important, since it brings information

about the condition and stimulates future research on the matter.

**Code: PE099**

**Dandy Walker malformation variant associated with refractory seizures in a 6-month-old baby: case report**

Heloísa Augusta Castralli<sup>1</sup>, Bruna Gularte da Conceição<sup>2</sup>, Antônio Diniz da Rosa Pereira<sup>2</sup>

<sup>1</sup>Universidade Federal de Santa Maria, Santa Maria RS, Brazil

<sup>2</sup>Hospital Universitário de Santa Maria, Santa Maria RS, Brazil

**Case presentation:** Female, 6 months of age, only child of unrelated parents. Born at term, weighing 3335 g, by uneventful cesarean delivery. At 2 months of age, the infant started with episodes of seizures, bringing both arms close to the trunk and pushing both lower limbs back, happening once a day, and lasting a few seconds. There was ocular eversion during the episodes and eventual drowsiness after them. Over the time, a worsening of the seizures was observed by her parents, with an increase in the daily frequency (ranging from 3 to 15 a day) and duration (1 to 3 minutes). Eventually, she had peripheral cyanosis after seizures, which improved with oxygen. She was referred to the pediatric service to optimize anticonvulsivant treatment, which consisted of Phenytoin 18 mg/kg/day, Valproic Acid 40 mg/kg/day and Phenobarbital 4,5 mg/kg/day. Upon neurological examination, absence of meningeal signs, axial force reduced, plantar/palm grip absent and global hyperreflexia. The child presented a congenital ocular malformation, with irregular contours and reduced dimensions of the right eyeball. A cranial MRI of the supratentorial region showed complete agenesis of the corpus callosum, irregular contours and increased dimensions of the lateral ventricles and III ventricle, signs of colpocephaly, presence of subependymal nodular gray matter heterotopia in the right lateral ventricle frontal horn and hippocampi with rounded appearance, which may be related to poor rotation. In the infratentorial region, the exam showed the absence of visualization of part of the inferior vermis, with a retrocerebellar fluid collection, that communicated with the fourth ventricle, which had increased dimensions. Based on the radiological findings, the diagnosis of Dandy Walker malformation (DWM) variant was established. At the moment, the child is under clinical observation and remains hospitalized to control the seizures, which are still refractory, despite treatment with Phenobarbital 5 mg/kg/day, Phenytoin 5 mg/kg/day, Carbamazepine 2% 35 mg/ml, Clobazam 5 mg at night, Levetiracetam 40 mg/kg/day for 12/12 hours. No other complaints or complications.

**Discussion:** The Dandy Walker variant is a less severe and more common form of DWM. Regarding neurological manifestations, little is addressed in the literature on the management of refractory seizures in children with this diagnosis.

**Final comments:** Physicians should be aware of the neuroimaging features of DMW and its variants to provide proper support.

**Code: PE100**

**Fowler syndrome: a case report**

Paula Thais Bandeira Elias<sup>1</sup>, Maria Luiza Benevides<sup>1</sup>, Fernanda Ferrao Antônio<sup>1</sup>, Larisse Souza Morais Somavilla<sup>1</sup>, Ana Carolina Piauilino Santos Falcão<sup>1</sup>, Isabelle Salgado Castellano<sup>1</sup>, Ana Carolina Coan<sup>1</sup>, Karine Couto Sarmento Teixeira<sup>1</sup>, Kátia Maria Ribeiro Silva Schmutzler<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas SP, Brazil

**Case presentation:** A 10-year-old boy, presented with early onset epilepsy, at three months of age, characterized by

myoclonic and tonic seizures, associated with global developmental delay. He has never developed gait or speech. Neurologic examination showed spastic tetraparesis. Cranial resonance imaging showed diffuse polymicrogyria, with calcifications, cortical and subcortical atrophy, and ventriculomegaly. There was no history of consanguinity, neither a family history of similar disorders. Since gestational and perinatal data were unremarkable for congenital infections, whole exome sequencing (WES) was requested. WES showed compound heterozygous pathogenic missense variants in FLVCR2 (chr14:75.633.650 A>G;G and chr14:75.634.909 G>C; C, p. Tyr325Cys and c.1021-1G>C). This variant is related to proliferative vasculopathy and hydranencephaly-hydrocephaly syndrome – Fowler Syndrome.

**Discussion:** Fowler syndrome is a rare, autosomal recessive, usually prenatally lethal disorder. The mechanism by which mutations in FLVCR2 cause this syndrome is not well defined, however, the encoded protein may play a role in the development of brain vascular endothelial cells, as variants at this locus have been associated with proliferative vasculopathy and hydranencephaly-hydrocephaly syndrome. Hydranencephaly, a distinctive vasculopathy in the central nervous system and retina, and diffuse ischemic lesions of the brain stem, basal ganglia, and spinal cord with calcifications might be present. Few cases survive until young adulthood, all young cases described had intracranial calcifications, although an association between the variants of FLVCR2 and severity of clinical presentation has not been found yet.

**Final comments:** Fowler syndrome is a rare condition, mainly prenatally lethal or occurring in infancy. It is important to consider Fowler syndrome in patients with gross ventriculomegaly, cortical malformations, and cerebral calcifications on brain imaging. Genetic testing allows the diagnostic of this condition, and hereafter will allow the delineation of the genotype-phenotype relationship.

**Code: PE101**

**Septo-optic dysplasia plus: case report**

Heloísa Augusta Castralli<sup>1</sup>, Bruna Gularte da Conceição<sup>2</sup>, Antônio Diniz da Rosa Pereira<sup>2</sup>

<sup>1</sup>Universidade Federal de Santa Maria, Santa Maria RS, Brazil

<sup>2</sup>Hospital Universitário de Santa Maria, Santa Maria RS, Brazil

**Case presentation:** Female, 3 months old, born preterm, weighing 2285 g, by vaginal delivery. With 25 days of life, she was hospitalized due to jaundice, with total bilirubin at admission of 23 mg/dL, dehydration and low weight gain. The infant remained on phototherapy for one day, with partial improvement of jaundice, remaining, however, dehydrated, presenting hypernatremia, with serum sodium levels reaching 170 mmol/L. A free water deficit was started for treatment, but there was little response, and the patient maintained high sodium levels and had a worsening of renal function (GFR 15.6). Laboratory tests with ACTH 19; cortisol 0.32; TSH 9.35; prolactin 95.9. Lumbar puncture was performed, which showed no changes, and cranial CT, which showed a hyperdense focus in the left frontal region and adjacent to the frontal horn of the right lateral ventricle, without mass effect or adjacent edema, of undetermined etiology, probably corresponding to foci of calcification, not totally excluding small areas of bleeding. Ill-defined hypodensity located in the right parietal region adjacent to the corresponding lateral ventricle. Obliteration of the frontal horn of the right lateral ventricle and apparent obliteration of the cerebral sulci on this side. Elongated hypodensity with cerebrospinal fluid density located in the left frontal and temporal regions, determining an impression on the adjacent brain parenchyma, with an indeterminate aspect, which may

correspond to an arachnoid cyst. An MRI was performed, which result showed absence of septum pellucidum, left frontal schizencephaly, lissencephaly, adenohypophysis with reduced dimensions, markedly tapered pituitary stalk - not being possible to exclude discontinuity - and hypoplastic optic chiasm. Ophthalmological evaluation showed absence of direct and indirect photomotor reflex and increased bilateral optic nerve excavation. In view of the findings, the diagnosis of septo-optic dysplasia (SOD) plus was considered. Currently, the child is in outpatient follow-up with the pediatric service.

**Discussion:** SOD is a rare developmental malformation that includes hypoplasia/dysplasia of the optic nerve, hypothalamic-hypophyseal dysfunction, and midline abnormalities. The term SOD-plus was suggested to differentiate SOD with associated malformations of cortical development.

**Final comments:** SOD-plus is a differential diagnosis to be considered in the face of cortical malformations associated with endocrine and ophthalmological alterations.

## Manifestações neurológicas das doenças sistêmicas

Code: PE103

### Reversible posterior leukoencephalopathy syndrome in a pediatric patient

Carolina Oliveira de Paulo<sup>1</sup>, Isadora Cristina Barbosa Lopes<sup>1</sup>, José Antônio Coba Lacle<sup>1</sup>, Maria Eduarda Souza Amaral<sup>1</sup>, Eduarda de Boer Furstenberger<sup>1</sup>, Melanie Scarlet Díaz Solano<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>, Ana Clarice Bartosiewicz Prestes<sup>1</sup>, Mariane Wehmuth Furlan Eulalio<sup>1</sup>

<sup>1</sup>Hospital Universitário Evangélico Mackenzie, Curitiba PR, Brazil

**Case presentation:** C.S.Y.A., ten years old, female, previous diagnosed with panniculitis-like subcutaneous T cell lymphoma, Systemic Lupus Erythematosus (SLE) and lupus nephritis secondary to arterial hypertension. She presented digestive hemorrhage due to a perforated duodenal ulcer and mucosal laceration in the distal esophagus. In the follow up, she presented three episodes of clonic seizures and a report of headache with nocturnal awakening one hour before the onset of the crisis. She was admitted to the emergency room convulsing, requiring the use of antiseizure treatment to control the crisis. The electroencephalogram showed disorganized and symmetrical electrical activity, composed of slow waves in the theta-delta range, with a predominance of delta, irregular, medium amplitude, diffusely distributed and  $\beta$  rhythm around 20 to 25 Hz predominating in frontal from slow moderator to severe base. Magnetic resonance imaging (MRI) presented extensive vasogenic edema in both posterior cerebral hemispheres (parieto-occipital lobe), thalamus and pons, suggesting Posterior Reversible Encephalopathy Syndrome (PRES).

**Discussion:** Subcutaneous T cell lymphoma panniculitis-like is a subtype of primary cutaneous lymphoma, a rare disease, representing less than 1% of all cutaneous T cell lymphomas, which may be associated with rheumatologic diseases such as systemic SLE, a chronic autoimmune inflammatory disease with clinical variability in terms of severity. PRES in patients with SLE was first described in 2006 and its pathogenesis is multifactorial. PRES is a clinical radiographic syndrome of heterogeneous etiologies that are grouped together because of similar findings on neuroimaging studies. The typical

clinical syndrome includes headache, visual symptoms and seizures. Typical MRI findings are consistent with vasogenic edema in the subcortical white matter and are predominantly localized to the posterior cerebral hemispheres.

**Final comments:** A wide variety of conditions have been implicated as causes. Autoimmune diseases (such as SLE) are often associated with PRES due to side effects as hypertension with autoregulatory failure or immunosuppressive therapy used during treatment.

## Neoplasias

Code: PE105

### Central nervous system juvenile xanthogranuloma: a case report

Ana Clarice Bartosiewicz Prestes<sup>1</sup>, Sergio Antonio Antoniuk<sup>1</sup>, Mara Lucia Schmitz Ferreira Santos<sup>2</sup>, Adriano Kejiro Maeda<sup>2</sup>, Ana Paula Kuczynski Pedro Bom<sup>2</sup>, Victor Horácio de Souza Costa Junior<sup>2</sup>

<sup>1</sup>Universidade Federal do Paraná, Hospital de Clínicas, Centro de Neuropediatria, Curitiba PR, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Boy, 7 years old. Born at term, with no history of consanguinity or complications. Previously healthy patient. Child with a history of Attention Deficit and Hyperactivity Disorder, with adequate neuropsychomotor development. He evolved with spastic paraparesis, frequent falls, enuresis, focal epilepsy, reduced strength in the lower limbs and cutaneous plantar reflex in extension. In the investigation, neuraxial resonance showed nodular thickening of the roots of the cauda equina and the roots of the neural foramina throughout the lumbar segment, with contrast enhancement around the conus medullaris and thickening and contrast enhancement of the roots emerging from the lower thoracic segment, which may represent myelopathy or neoplasia, and nodular images located on the surface of the parietal and left frontal lobes, also increased T2/FLAIR signal in the white matter adjacent to the nodular lesions, suggesting vasogenic edema. Increased signal diffusion in the largest lesions of the right parietal lobe, with low signal on the ADC map, which may correspond to high cellularity, also suggestive of neoplasia. CSF with high protein and low glucose. Anatomopathological exam of the cerebrospinal fluid showed histiocytes and anatomopathological exam of the lesion showed xanthomatous histiocytes and lymphoplasmacytic infiltrate. Immunohistochemical profile consistent with infiltration of meninges by xanthomatous histiocytes.

**Discussion:** Juvenile xanthogranuloma is the most common non-Langerhans cell histiocytosis in children, mostly benign. Intracranial involvement occurs in only 2% of children and is strongly associated with leukemia. When it occurs in the nervous system, it has inexorable evolution and the treatment depends on the resectability of the lesion.

**Final comments:** Juvenile xanthogranuloma of the Central Nervous System is a rare neoplastic disease of severe evolution and the treatment depends on the resectability of the lesion, performed using a Langerhans cell histiocytosis protocol, due to the aggressiveness of the condition.

Code: PE106

**Ependymoma as a final diagnosis of pneumonia suspect: case report**

Eduarda Vogel Wollmeister<sup>1</sup>, Saulo Bueno de Azeredo<sup>1</sup>, Maria Fernanda Guadagnin<sup>1</sup>, Valéria Tessaro Grandi<sup>1</sup>, Lucas Lizot Pozzobon<sup>1</sup>, Martina Estacia Da Cas<sup>1</sup>, Gabriel Soccol Fassina<sup>1</sup>, Nicolle Surkamp<sup>1</sup>, Marcos Vinicius Dalla Lana<sup>1</sup>

<sup>1</sup>Universidade de Passo Fundo, Passo Fundo RS, Brazil

**Case presentation:** A 1 year and 5-month-old female patient presented with 14 days of continuous fever. Initial consultation led to amoxicillin treatment followed by ceftriaxone and cefuroxime for bacterial pneumonia, remaining afebrile since then. Vomiting ~2 times a day, however, remained. Three days after this, there was a worsening of vomiting, now occurring 8 times a day, without other gastrointestinal symptoms, which led her parents to the hospital. The history told motivated to hospitalize the patient for a more careful evaluation. New laboratory showed microcytic anemia, leukocytosis with a predominance of segmented (59%), moderate hypokalemia, elevated alkaline phosphatase, LDH and ESR. Chest X-ray taken on admission showed mild bilateral infiltrate. On the same day of admission, the patient had sensorineural lowering (ECG 13/15), onset of horizontal nystagmus without signs of neck stiffness. The following day, there was an increase in nystagmus, with an episode of opisthotonia lasting until diazepam administration. CT and MRI of the skull revealed a bleeding tumoral lesion in the posterior fossa and hydrocephalus. The patient followed for cranioplasty for tumor biopsy and installation of cerebrospinal fluid fistula. Anatomopathological lesion attested grade 2 ependymoma. The patient evolved well in the postoperative period, however, developed aphasia, deviation of the mouth's gaze to the right, and hemiparesis to the left.

**Discussion:** Ependymomas are tumors derived from ependymal cells lining the brain ventricular surface. This tumor has a peak in childhood with a higher incidence in males. The median age of diagnosis is 5 years, and ~25% are diagnosed under 2 years old. Ependymoma can occur anywhere in the ventricular system or spinal canal, but the most common site is the fourth ventricle. Histologically, they are classified into grades 2 and 3, with grade 2 being classic and grade 3 anaplastic. Symptoms are based on increased intracranial pressure due to hydrocephalus, which results in headache, nausea, vomiting, ataxia, vertigo, and hemiparesis may occur. The therapy consists of resection of the tumor mass.

**Final comments:** The present work emphasizes the importance of valuing the patient's complaints, considering that the patient was treated repeatedly with antibiotics for the vomiting and fever without a proper etiological investigation for the warning signs. Rapid diagnosis and adequate treatment could prevent sequelae development.

**Neurogenética**

Code: PE107

**Complex encephalopathy associated to mutation in the GRIN2B gene: case report**

Laryssa da Silva Ribeiro<sup>1</sup>, Mariana Braga Valadão<sup>1</sup>, Juliana Gurgel Gianetti<sup>1</sup>, Maria Juliana Silverio Nahim<sup>1</sup>, Beatriz Vilela Morais de Azevedo<sup>1</sup>, Yuri Barcelos<sup>1</sup>, Aline dos Passos Moraes<sup>1</sup>

<sup>1</sup>Universidade Federal de Minas Gerais, Hospital das Clínicas, Belo Horizonte MG, Brazil

**Case presentation:** 17-year-old female patient, single child of non-consanguineous healthy parents. The pregnancy and delivery were uneventful. She presented a normal psycho-

motor development until 4 months of age, when she started with epileptic seizures and evolved with central hypotonia, appendicular hypertonia, and dystonia. After, she presented autistic features, stereotypies, lack of response to pain, self-harm and did not develop speech. The epileptic seizures were refractory, with different seizure types: absence, myoclonic, tonic, tonic-clonic and gellastic seizures. In the first year of life the EEG revealed disorganization of the background activity predominating in the left cerebral hemisphere and multifocal epileptogenic activity. Video-EEG showed focal epileptic seizures with interictal discharges of generalized projection and predominance to the left, not associated with the abnormal movements presented by the patient. Complementary tests were normal including karyotype, molecular study for Rett Syndrome, Angelman and screening for IEM. Serial MRI scans of the brain revealed mild brain atrophy. Genetic study by NGS revealed a heterozygous mutation in the GRIN2B gene, which promotes the substitution.

**Discussion:** Heterozygous pathogenic variants in the GRIN2B gene were initially associated to two main phenotypes: autosomal dominant intellectual disability (ID) 6 and epileptic and developmental encephalopathy 27. However, more recent studies show a broadening of the phenotype, including movement disorders, microcephaly and malformation of cortical development in addition to ID and epilepsy, compatible to an encephalopathy with different manifestations. The mutation (p.Gly820Ala) was previously described in the literature and it is associated with different clinical manifestations, either alone or in combination. In the present study, this mutation was associated with a broad spectrum of manifestations: severe ID without speech acquisition, refractory epilepsy, movement disorder (dystonia) and behavioral disorder.

**Final comments:** The manifestations of the GRIN2B gene overlap with those described in different genes linked to neurodevelopment disorders, highlighting the importance of using NGS in the definitive diagnosis, which allows a more adequate family counseling.

Code: PE109

**4H leucodystrophy phenotypical variation among two brothers: a case report**

Rui Carlos Silva Júnior<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Izabela Cristina Macedo Marques<sup>1</sup>, Lorena Vilela Rezende<sup>1</sup>, Mariah Pereira de Andrade Vallim<sup>1</sup>, Lisandra Coneglian de Farias Rigoldi<sup>1</sup>, Elisabete Coelho Auersvald<sup>1</sup>, Daniel Almeida do Valle<sup>1</sup>, Michelle Silva Zeny<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Patient 1: V.U.F, male, 14 years old. When he was 3 years old the patient presented with ataxic gait and recurrent falls. Ataxia worsened during the 8 years after the first presentation. He had low school performance and developed myopia. Family history: great-grandmother developed ataxia at the age of 32 and died when she was 59. Patient has a brother with similar clinical condition. The patient presented with adequate height, absence of the lower central incisor teeth, upper and lower limb dysmetria and Tanner G1P1. Dysdiadochokinesis, ataxic and unstable gait with amplitude reduction, without Romberg signal, and tendril dancing were observed. Scale for the Assessment and Rating of Ataxia (SARA) was performed: 17.5. Electroneuromyography showed demyelinating sensory polyneuropathy. CGH array was normal. Magnetic Resonance Imaging (MRI) of the brain showed cerebellar atrophy, particularly of the vermis, diffuse and symmetrical hypomyelination of the cerebral hemispheres, and reduction of the corpus callosum. Spectroscopy was normal. Patient 2: I.U.F, male, 10 years old, brother of

patient 1. When he was 4 years old his gait worsened accompanied by mild ataxia. He presented with school difficulties, being unable to read or write, with complaint of academic lack of attention and aggressiveness at home and school. He was not able to mention the name or address of his school. Enamel of the teeth was not well formed. Joint hypermobility, fine tremor, SARA 3, and Tanner G1P1 were observed. Brain MRI showed discrete thinning of the corpus callosum, bilateral diffuse alteration of the white matter signal, without significant change in T1. Exoma was performed in both patients and mutation of the POLR3B gene was found.

**Discussion:** 4H leucodystrophy is an autosomal recessive disease caused by mutations in POLR3A, POLR3B, and POLR1C, resulting in a triad with hypomyelination, hypodontia, and hypogonadotropic hypogonadism. In the absence of these findings, brain MRI helps with the diagnosis showing diffuse hypomyelination associated to cerebellar atrophy, T2-weighted hypointensity of the ventrolateral thalamus and myelination of the pyramidal tracts, dentate nuclei and optic radiations.

**Final comments:** The interesting observation of this case report resides in the fact that we were able to demonstrate different phenotype presentations for the same gene mutation. One of the siblings showed predominantly ataxic manifestations whereas the other presented with neuropsychiatric symptom.

#### Code: PE110

##### **A novel splice-site SGCB mutation causing Limb-girdle muscular dystrophy type 2E in a Brazilian patient**

Fernanda Ferrão Antonio<sup>1</sup>, Alexandre Motta Mecê<sup>1</sup>, Paula Thais Bandeira Elias<sup>1</sup>, Maria Luiza Benevides<sup>1</sup>, Ana Carolina Piaulino Falcão<sup>1</sup>, Karine Couto Sarmiento Teixeira<sup>1</sup>, Felipe Franco Graça<sup>1</sup>, Anamarli Nucci<sup>1</sup>, Marcondes Cavalcante Franca<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas, SP, Brazil

**Case presentation:** An 8-year-old girl, born from consanguineous parents, was admitted with a history of difficulty getting up from the floor since the second year of life. Thereafter, she developed muscle pain, exercise intolerance (particularly walking long distances) and evident hyperlordosis. On neurological examination, there was flaccid proximal-predominant tetraparesis. There was no evidence of sensory or cardiac involvement. During the investigation, aldolase, creatine phosphokinase (CPK), lactate dehydrogenase (DHL), and alanine aminotransferase (ALT) were found to be remarkably elevated (up to 5x the upper limit of normal). Genetic testing revealed the likely pathogenic splice-site c.753+5G>A SGCB variant in homozygosis, which confirmed the hypothesis of limb-girdle muscular dystrophy (LGMD 2E).

**Discussion:** The SGCB gene encodes the  $\beta$  subunit of the sarcoglycan protein complex, which is important for maintenance of sarcolemmal integrity. The sarcoglycanopathies are caused by pathogenic variants in any of the genes related to the sarcoglycan complex. They are considered the most severe forms of autosomal recessive LGMDs (LGMD 2). Genetic epidemiology studies reveal that the most frequent form worldwide is LGMD 2D, followed by LGMD 2C, and then LGMD 2E and LGMD 2F. Approximately 50 mutations in the SGCB gene have been identified in people with LGMD 2E, which is characterized by muscle weakness and wasting, particularly in the shoulders, hips, and limbs. Dilated cardiomyopathy is a conspicuous finding later in disease course. Severe clinical DMD-like presentations tend to be more common among

sarcoglycanopathies patients, with onset early in childhood and confinement to a wheelchair before the age of sixteen; nevertheless, milder courses (including pseudometabolic phenotypes) have also been described in LGMD 2C, LGMD 2D, and LGMD 2E patients as well as intrafamilial variability. **Final comments:** This case describes a milder manifestation of LGMD 2E, a sarcoglycanopathy caused by biallelic SGCB loss-of-function variants. It has been associated with muscle weakness of pelvic and scapular girdle as well as cardiomyopathy. Proper recognition of this rare LGMD subtype in children enables adequate management and genetic counseling.

#### Code: PE111

##### **Aicardi syndrome: case report**

Isabel Cordeiro Cid Bastos<sup>1</sup>, Cristina Maria Pozzi<sup>1</sup>, Verônica Camila Lazzarotto<sup>1</sup>, Elis Estevam<sup>1</sup>, Gabriela Vequi<sup>1</sup>, Letícia Rothenburg<sup>1</sup>, Maria Júlia Soares Mussi<sup>1</sup>, Débora Xavier Branco<sup>1</sup>

<sup>1</sup>Universidade do Vale do Itajaí, Itajaí SC, Brazil

**Case presentation:** M. V. S. R, female, 10 months, post-term, Apgar 6/8, requiring resuscitation at birth, was referred to a pediatric neurologist due to delay in neuropsychomotor development, with difficulty in fixing the gaze since birth, hypotonia of lower limbs, repetitive movements, lack of cervical support and ankyloglossia. The patient also previously suffered two episodes of tonic-clonic seizures. On physical examination a frontal bone bulge, occipital flattening, unfixated convergent bilateral strabismus was noticed. Transfontanelar ultrasound showed corpus callosum dysgenesis and subsequent magnetic resonance imaging confirmed the complete agenesis of the corpus callosum with no other alterations. It was not possible to perform an electroencephalogram. At ophthalmologic consultation bilateral optic disc coloboma was signed. Aicardi Syndrome was suspected. The patient was referred to multidisciplinary follow-up, with physical, speech and psychological therapy showing improvement in neuropsychomotor development.

**Discussion:** Aicardi Syndrome was initially described as a typical triad of agenesis of the corpus callosum, typical chorioretinal lacunae and infantile spasms. With the study of new cases other clinical patterns were also identified: seizures, cognitive and language alterations, impairment in walking or sitting, optic disc abnormalities, costovertebral joint fusion and hypotonia. In the aforementioned case, the diagnostic hypothesis of Aicardi Syndrome is of high suspicion. The patient presented the classic triad of Aicardi Syndrome. It was also possible to observe other characteristic alterations, such as delay in neuropsychomotor development, hypotonia of the lower limbs and absence of cervical support. The case studied is in line with the treatment established to date which prioritize the management of clinical manifestations, such as multidisciplinary support for neuropsychomotor delay, antiepileptic drugs and ophthalmic follow up. In this case, improvement was seen with multidisciplinary intervention.

**Final comments:** The singularity of the reported case is emphasized as it brings to light the diagnostic hypothesis of Aicardi Syndrome, a rare genetic condition with neuroretinal affection, that requires a multidisciplinary approach and individualized support treatment to improve survival and quality of life.

**Code: PE112****Aromatic L-amino acids decarboxylase (AADC) deficiency: a case report**

João Victor Polegato Bernichi<sup>1</sup>, Robson Marques Figueiredo Rocha Teixeira<sup>1</sup>, Maria Stela Lessa Paganelli<sup>1</sup>

<sup>1</sup>Universidade Estadual de Londrina, Londrina PR, Brazil

**Case presentation:** IGSC, 1 year old, with no significant gestational and perinatal history, presented a delay in neuropsychomotor development from 6 months of age. With progressive worsening of the neurological condition, difficulty in swallowing and bronchopulmonary aspiration, he was transferred to Intensive Care Unit in the University Hospital of Londrina, requiring tracheostomy and gastrostomy. Assessed by the Pediatric Neurology department, he had a social smile and eye contact, but was unable to hold his head, trunk, and limbs, with axial and limb hypotonia and diminished myotatic reflexes. He had ocular deviations interpreted as epileptic seizures and therefore was medicated with phenobarbital. Exams: Cranial Magnetic Resonance with small volumetric reduction of the brain, muscle enzymes, Electroencephalogram, Electroneuromyography and Screening for Inborn Errors of Metabolism normal. In view of the normal tests, a genetic panel for neurodevelopmental and movement disorders was requested: alterations were found in the DDC gene chr7:50.476.625 and chr7:50:537.934. and dosage of Aromatic L-amino Acid Decarboxylase 2.59 9 enzyme (36.00–129.00) was decreased, confirming the diagnosis.

**Discussion:** AADC deficiency (aromatic L-amino acid decarboxylase deficiency) is a very rare disease caused by pathogenic mutations in the DDC gene, which encodes this enzyme for the synthesis of neurotransmitters such as Dopamine, Serotonin, Epinephrine and Norepinephrine. Decreased levels of this enzyme and low levels of these neurotransmitters increase their precursors, causing symptoms. These occur from the third month of life onwards and are variable: hypotonia, movement disorders, delay in neuropsychomotor development, and oculogyric seizures, often confused with epileptic seizures. There are also changes in mood, sleep, body temperature with excessive sweating, cardiovascular and endocrine function. For diagnosis, with the positivity of at least two tests of the three: increase in cerebrospinal fluid, dosage with decreased AADC enzymatic activity, molecular-genetic analysis with complete sequencing of the DDC gene, diagnosis with two or more pathogenic mutations.

**Final comments:** AADC deficiency is a very rare disease, little known and with different symptoms. The importance of this report is to draw attention to the need for genetic investigation in cases of hypotonia, developmental delay and movement disorders without a clarified etiology, allowing the patient to have an adequate diagnosis and treatment.

**Code: PE113****Atypical neuronal ceroid lipofuscinosis type 2 disease (CLN2): a case report**

Mariana Braga Valadão<sup>1</sup>, Juliana Gurgel Gianetti<sup>1</sup>, Beatriz Vilela Moraes de Azevedo<sup>1</sup>, Yuri Barcelos<sup>1</sup>, Laryssa da Silva Ribeiro<sup>1</sup>, Aline dos Passos Moraes<sup>1</sup>

<sup>1</sup>Universidade Federal de Minas Gerais, Hospital das Clínicas, Belo Horizonte MG, Brazil

**Case presentation:** Thirty-one-year-old female patient, born from a non-consanguineous couple. Presenting with a referred normal psychomotor development as an infant and no history of gestational or perinatal complications. As of eight years old, she developed cognitive impairment associated with gait disturbances. On her first neurological evaluation,

with thirteen years old, dysarthric speech, ataxia, dystonia and chorea were prominent. Epilepsy was evident by nineteen years old, with myoclonic jerks as the primary presentation, time at which the patient was aphasic. As the years progressed, there was significant worsening of the symptoms with loss of hand abilities and the deambulatory capability by twenty-three years old. On the latest follow-up, the patient had no eye contact and displayed spastic palsy, truncal hypotonia, ataxia and extrapyramidal symptoms. MRI with spectroscopy studies showed diffuse cerebral atrophy, white matter signal alterations, reduced N-acetyl aspartate peak and no lactate or choline peak variation. Electroretinogram was not feasible due to technical limitations. Molecular studies using next-generation sequencing (NGS) revealed two heterozygous mutations on the Tripeptidyl Peptidase 1 (TPP1) gene – c.899delG and c.1340G>A, being the latter previously described in association with CLN2.

**Discussion:** CLN2 is an autosomal recessive neurodegenerative disorder, caused by reduced or absent activity on the TPP1 enzyme. Typical phenotypes have symptom onset between 2 and 4 years old (late infantile) with a rapid progression, marked epilepsy, visual, motor and speech impairments, resulting on early death. The presented case exhibits an atypical form, with later onset, slower progression, seizures starting later in life, important ataxia and a more evident movement disorder, which corroborates with literature descriptions of atypical forms. Recent studies analyze the effectiveness of cerliponase alfa on both typical and atypical cases of CLN2 and are indicating potential benefits as to the stabilization of the disease progression.

**Final comments:** CLN2 implicates on high morbidity and mortality rates for patients' lives. Hence, early diagnosis is important to determine prognosis and to evaluate the possibility of treatment with cerliponase alfa. NGS facilitates the identification of atypical cases, allowing for a better understanding of the conditions' features and the patients' needs.

**Code: PE114****Canvan's disease: case report**

Ana Cristina Azevedo Leão<sup>1</sup>, Clarice Samião Coimbra<sup>1</sup>, Rafaela Fernandes Dantas<sup>1</sup>, Nicholas Dos Santos Barros<sup>1</sup>, Roberta Diniz de Almeida<sup>1</sup>, Renata Silva de Mendonça<sup>1</sup>, Daniel Shoji Hayashi<sup>1</sup>, Leticia Pereira de Brito Sampaio<sup>1</sup>, Fernando Kok<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Case presentation:** In the present work, we analyze the case of a child, daughter of consanguineous parents, without acquisition of developmental milestones and already at 4 months without cephalic control. With hypotonia in the first months of life, could sit with support, and lost this milestone at age three. There is no social interaction, severe delay language and significant dysphagia with the need for a Gastrostomy and an increase in the head circumference. At the age of four, started tonic-clonic at right and bilateral crises, usually in the presence of an infectious condition. On physical examination presented macrocephaly with a prominent forehead, ocular hypertelorism, and a low nasal bridge. Has spasticity and bilateral pyramidal release. No eye fixation, absent blink, with limited left eye abduction and upbeat nystagmus with bilaterally absent cochleopalpebral reflex. In a serial resonance examination in 2018 and 2021, there was evidence of a reduction in brain volume with the appearance of areas of diffusion restriction affecting the globus pallidus, pons and middle cerebellar peduncles, with a slight swelling effect, suggestive of disease progression and T2 signal changes in white matter and N-acetylaspartate peak in spectroscopy. Such clinical findings were sufficient for a diagnostic

hypothesis of Canavan Syndrome, with molecular examination demonstrating a mutation in the ASPA gene in homozygous splice c.526+1G>C.

**Discussion:** Canavan disease is caused by pathogenic variants in the ASPA gene, leading to N-acetylaspartic acid toxicity in the brain and other parts of the body<sup>1</sup>. The presentation is characterized as ataxia, hypotonia, and failure to acquire normal developmental milestones, often in association with macrocephaly and late seizures<sup>2</sup>, in which most common variants are missense such as p.Tyr231Ter, p.Glu285Ala, and p.Ala305Glu with pathogenic variants in the homozygous or compound heterozygous (with each other) state are associated with neonatal/infantile disease 3. The mutation found in the patient so far has not been described in the literature, this affects a donor splice site in intron 3 of the gene. It is expected to disrupt RNA splicing, leading to a loss of protein function<sup>3</sup>. **Final comments:** This splice mutation with pathogenic potential described first in this case is compatible with the patient's symptoms described by Blay et al<sup>2</sup>. It is necessary to provide genetic counseling and treatment for the symptoms presented, to this date, no treatment proved to be curative.

**Code:** PE115

**Case report: pontocerebellar hypoplasia type 1D**

Larissa Maria Soares Lyrio<sup>1</sup>, Rafael Guerra Cintra<sup>1</sup>, Vanessa Akemi Imaizumi<sup>1</sup>, Kleiton Rodolfo da Silveira Rufino<sup>1</sup>, Raquel Paiva Arruda<sup>1</sup>, Paulo Breinis<sup>1</sup>, Ana Elisa Ribeiro de Faria Almeida<sup>1</sup>, Lais Russo Carneiro Peruzzi<sup>1</sup>, Rubens Wajnsztejn<sup>1</sup>

<sup>1</sup>Centro de Saúde do ABC, Santo André SP, Brazil

**Case presentation:** This report aims to describe the case of a patient with a rare diagnosis of type 1D pontocerebellar hypoplasia (PCH1D), resulting from the alteration of the EXOSC9 gene. G. T. S. D. S., male, 1 year and 2 months old, fruit of unplanned pregnancy of non-consanguineous parents. Prenatal care was complete. The patient was born by vaginal delivery without complications, with 36 weeks and 6 days of gestational age, and with the following measurements: height = 44.5 cm; weight = 2,660 kg; head circumference = 33.8 cm.

**Discussion:** At the age of 2 months, the first change arose and was noticed: look evered up fixedly. When started investigation: electroencephalogram, computed tomography of the skull and magnetic resonance imaging of the skull. All with unchanged results. Then, they consulted a geneticist, who requested the following tests: screening tests for inborn errors of metabolism. All with unchanged results. From the age of 3 months, he started rehabilitation and he showed improvement: he still did not present cephalic support, but he was able to rotate her neck. At the age of 6 months, he started with spasms, several per day. When started with valproic acid, but adverse reactions of drowsiness caused it to be suspended before 1 month of use; vigabatrin was introduced and, after 1 month, spasms ceased completely. Currently, the patient remains under specialized follow-up, and makes use of: vigabatrin 500 mg a day. At this time, a new MRI was also performed, which showed pontocerebellar hypoplasia, and received the result by the complete exome sequencing test: a homozygous EXOSC9 gene variant (NM\_001034194.1: c.41T>C-p.Leu14Pro) From the age of 7 months, he stopped gaining weight, requiring follow-up with gastropediatrics and nutrology. Since then, he has needed gastrostomy to be able to receive a full diet.

**Final comments:** In addition to the present case, only 10 others were reported, with the same EXOSC9 gene variant

(NM\_001034194.1: c.41T>C-p.Leu14Pro), which represents 60% of the total reported cases of PCH1D. It is a severe autosomal recessive neurologic disorder characterized by severe hypotonia and a motor neuropathy apparent, and also includes severely delayed gross motor development. The patients may present poor overall growth, contractures, eye movement abnormalities, respiratory insufficiency and feeding difficulties and epilepsy. The case shows the importance of molecular study for predicting prognosis and family guidance.

**Code:** PE116

**Case series: array CGH as a tier 1 testing in diverse neurodevelopmental disorders evaluation**

Carlos Magno Leprevost<sup>1</sup>

<sup>1</sup>Instituto de Genética Médica Dr. Carlos Leprevost, São Paulo SP, Brazil

**Case presentation:** Comparative genomic hybridization based on microarrays (array CGH) is a reality in clinical practice in the neuropediatric population. It allows a high-resolution assessment of DNA copy number changes associated with chromosomal abnormalities. Objective: To highlight the importance of using the technique in the investigation of patients with diverse phenotypes. Methods: Series of case studies.

**Discussion:** Case 1: A 9-year-old boy with intellectual disability (ID), wide hypertelorism, wide philtrum of the nasal bridge, smooth nasolabial philtrum and shortening and fingers. CGH array showed chromosome 8 microdeletion, q23.3124.12, 2820Kb, containing 14 genes, including TRPS1, EXT1 and RAD21. Final diagnosis of Trichorhinophalangeal Syndrome type 2. Case 2: A 7-year-old boy with neurodevelopmental disorder disease (NDD), congenital clubfoot, sleep apnea, hypothyroidism and precocious pubarche. CGH with a pathogenic 4,9Mb 19p13.3p13.2 duplication. Other cases described in the literature with a similar phenotype in the same region. Case 3: A 2-year-old boy presenting with NDD and hypotonia. MRI showed agenesis of corpus callosum. CGH with a pathogenic 13q32.3 microdeletion. The older brother of the index case died with a severe form of holoprosencephaly and had the same microdeletion. Parents CGH were normal, with a suspicion of gonadal mosaicism in one of the parents causing both brothers to be affected by midline defects related to chromosome 13. Case 4: A 4-year-old boy with non-syndromic ASD. CGH evidenced duplication in the 2p25.3 region (366kb), probable pathogenic, containing MYT1L (\*613084), a gene associated with neurodevelopmental disorders (NDD). Case 5: A 12-year-old girl diagnosed as cerebral palsy (CP), severe ID, refractory seizures with neurodevelopmental regression. CGH reported with a pathogenic deletion of 7.3 Mb of chromosome 2 (2q24.1q24.2), containing important genes such as SLC4A10, GCG and TBR1 (OMIM \*604616) whose loss of function is associated with epilepsy and NDD.

**Final comments:** The use of the CGH-array is a fundamental part in the evaluation of children with ID, NDD and CP. The syndromes of microdeletions and microduplications can present with diverse phenotypes and it is up to the specialist physician to guide the family to the right diagnosis and genetic counseling.

Code: PE118

**Cornelia de Lange syndrome associated with ASD and epilepsy: a case report**

Ana Clara Kunz<sup>1</sup>, Naiara Bozza Pegoraro<sup>2</sup>, Júlia de Oliveira Barbosa<sup>3</sup>, Isabelle Caroline Fasolo Normandia Moreira<sup>3</sup>, Caroline Brandão Piai<sup>4</sup>, Aline Sauzem Milano<sup>3</sup>, Gabriela Esmanhoto Rodrigues<sup>2</sup>, Rie Tiba Maglioni<sup>3</sup>, Simone Carreiro Vieira Karuta<sup>1</sup>

<sup>1</sup>Faculdades Pequeno Príncipe, Curitiba PR, Brazil

<sup>2</sup>Hospital Universitário Evangélico Mackenzie, Curitiba PR, Brazil

<sup>3</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>4</sup>Pontifícia Universidade Católica do Paraná, Curitiba PR, Brazil

**Case presentation:** 4 year-old male, diagnosed with Cornelia de Lange syndrome (CdLS). Born preterm at 35 weeks of gestation, the baby weighted 1670 kg and remained in the ICU for 25 days. At 1 year of age he presented a cephalic perimeter of 44cm (microcephaly), horizontal nystagmus at the extreme lateral gaze, slow saccades, hypertonia and hyperreflexia on all four limbs and dysmorphic features (hypertelorism, wide nose base, thin lips, microcephaly and webbed neck). The patient has been diagnosed with 3rd degree Autism Spectrum Disorder (ASD) due to speech apraxia, low socialization, psychomotor agitation, low interest in playing activities, low self-regulation and repetitive behavior. The first convulsion happened in July 2022 with eye paralysis, 2 minute-long cyanosis and Todd's paresis postictal to the right. After 15 days he had a new tonic clonic seizure with central cyanosis, sialorrhea and ocular version, lasting less than 2 minutes. Presented postictal right upper limb paralysis for 15 minutes. Genetic examination identified SMC3 (10q25.2) alteration of unknown variant.

**Discussion:** CdLS is a rare genetic condition that presents with intrauterine growth restriction, intellectual disabilities, craniofacial and upper limbs abnormalities and hirsutism. GI tract or genitourinary malformations, pyloric stenosis, diaphragmatic hernia and cardiac defects may also happen. Etiology is mainly attributed to variants that affect coesin protein complex's functions. Variants at the NIPBL coesin regulator are responsible for 70% of cases. Other subunits/regulators of this complex (SMC1A, SMC3, RAD21 and HDAC8) are responsible for 10 to 15% of cases. Association between CdLS e ASD is rare. In comparison to patients with isolated ASD diagnosis, patients with CdLS can present lower intensity repetitive behavior, less difficulty in maintaining eye contact and bigger struggles with social interactions and anxiety. Epilepsy may be associated with CdLS at a 14–25% rate. It is also estimated that most cases are associated to SMC1A and NIPBL genes. A series of 14 CdLS and epilepsy case reports, showed that most patients had partial crisis, adequately solved with valproate monotherapy.

**Final comments:** CdLS in association with ASD and epilepsy is extremely rare. This case report shows the importance of early detection of these signs to ensure better treatment.

Code: PE119

**Developmental disorders associated with PTEN gene: case series report**

Gabrielle Gruppelli Good<sup>1</sup>, Maria Vitória Ruiz Fatuch<sup>1</sup>, Marina Massuchin Précoma<sup>1</sup>, Ana Luiza de Rezende e Cota<sup>1</sup>, Giulia Vilela Silva<sup>2</sup>, Daniel Almeida do Valle<sup>1</sup>, Lucas Procopiak Gugelmin<sup>1</sup>, Maria Fernanda Jara Maldonado<sup>1</sup>, Maria Vitória Correa<sup>1</sup>

<sup>1</sup>Universidade Positivo, Curitiba PR, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Case 1: A boy with developmental delay and congenital macrocephaly, evolving with dysphagia and airway hypotonia. Complete exome sequencing was performed with detection of pathogenic variant in the PTEN gene (c.737C>T). Case 2: Premature boy, with delayed development of departure, macrocephaly and ephelides in the foreskin. He developed nodular hyperplasia in ileum and painful amplification syndrome with pharmacoresistant pain. Sequencing of the PTEN gene detected an intragenic deletion. Case 3: Girl with autism spectrum disorder identified at 17 months. Neurological examination with central hypotonia and macrocephaly. Magnetic resonance imaging of the skull identified craniofacial disproportion and confluent foci of hypersignal in white matter, suggestive of mucopolysaccharidosis. The panel sequence for leukodystrophy, identific orpathogenic variant in the PTEN c.388 C>G gene.

**Discussion:** PTEN (phosphatase and tensin homologue) is a tumor suppressor gene, responsible for the production of a protein of the same name capable of regulating the cell cycle. Variants in the PTEN gene are associated with PTEN-hamartoma tumor syndrome (PHTS) characterized by a significant increase in the chance of developing neoplasms, as well as trixylemomas, hamartomas, lipomas, thyroid nodules, macrocephaly, cerebrovascular malformations, ephelides in foreskin, as well as developmental delay, intellectual disability, and autism spectrum disorder. Among neurodevelopmental disorders, non-tumor manifestations were extremely relevant in the diagnosis, and all patients had macrocephaly. The relevance of this diagnosis is also in genetic counseling, since it has autosomal dominant inheritance. It is essential that carriers of mutations in the PTEN gene be regularly monitored for the development of neoplasms and complications associated with PHTS.

**Final comments:** The reported cases illustrate the importance of clinical suspicion for the diagnosis of PTEN-related syndromes in the presence of a child with macrocephaly and neurodevelopmental disorder, regardless of the presence of tumor lesions. Once identified, affected patients and parents should be periodically screened for the development of tumors and oriented about the risk of recurrence in their offspring.

Code: PE122

**Early-onset hereditary spastic paraplegia: case report**

Luan Guanais<sup>1</sup>, Patrícia Pontes Cruz<sup>1</sup>, Aline Rocha Anibal<sup>1</sup>, Emília Katiane Embiruçu<sup>1</sup>

<sup>1</sup>Universidade Federal da Bahia, Hospital Universitário Professor Edgard Santos, Salvador BA, Brazil

**Case presentation:** Girl, 5 years old, she had not gestational and neonatal complications and her parents is consanguineous. She had neuropsychomotor developmental delay (NDD) and dysphagia for solids at 6 months. At 2 years old, she had cognitive impairment, motor delay with axial ataxia, appendicular hypotonia and dysmetria. Her symptoms progressively worsening associated with pyramidal signs. Cerebellar atrophy and increased arachnoid space in the posterior fossa were identified on her neuroimaging. Her whole genome sequencing identified a pathogenic variant c.395A>C.p. (Asp132Ala) in the EXOSC3 gene in homozygosity.

**Discussion:** The clinical features are compatible with Pontocerebellar hypoplasia (PCH) type 1B, autosomal recessive inheritance. Pathogenic variants in the EXOSC3 gene are responsible for 30% to 50% of patients with PHC. EXOSC3 gene associated PCH is characterized by abnormalities in the posterior fossa and degeneration of the anterior horn cells. At birth, the main clinical symptoms are hypotonia and poor feeding. Survival and symptom severity is variable and they



depend on genotype. In this case, the onset of symptoms was in the first months of life with axial and appendicular hypotonia, dysphagia, early pyramidal and cerebellar signs and her survival was after early childhood. This case is classified as mild PCH after phenotype-genotype correlation and according to the report of other authors. However, it is important to note that the progression of spastic paraplegia may not have a favorable outcome.

**Final comments:** The phenotype of hereditary early-onset spastic paraplegia associated with the EXOSC3 gene was described in this report. Genetic tests are important for performing differential diagnosis for suspected cerebral palsy when there are no risk factors, in addition to prognostic guidance and genetic counseling.

### Code: PE123

#### **A case report of neonatal PURA syndrome**

Letícia Pugim Ferreira<sup>1</sup>, Ana Chrystina Souza Crippa<sup>1</sup>, Liara Bohnert<sup>1</sup>, Maytza Mayndra Côrrea<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Hospital das Clínicas, Curitiba PR, Brazil

**Case presentation:** G.D.V.S, a male neonate, was admitted into the neonatal intensive care unit due to respiratory insufficiency. On his sixth day of life, the patient presented with a series of tonic movements and spasm in upper and inferior limbs, followed by an approximate five-minute duration, apnea and central cyanosis. He had a term and complication-free pregnancy. On admission, could be noted global hypotonia, difficulties for nourishing, hyperreflexia, facies with cleft palate and micrognathia. He later developed an excessive hyper startle responsiveness, oculogyric crises and persistent dyskinesia. Electroencephalography has no spikes. Cerebral magnetic resonance imaging visualizes a diffuse cerebral volumetric reduction and subdural hydroma. Genetic test shows deletion of 152Kb, on heterozygous, with a pathogenic variation involving the PURA gene. During hospitalization, movements had a positive response to the use of benzodiazepines (midazolam) and was discharged after treatment of several complications (infections, chyloperitoneum, panhypopituitarism), in addition to tracheostomy, gastrostomy and continuous use of oxygen.

**Discussion:** PURA syndrome is caused by the mutation of the purine rich binding element protein  $\alpha$  (PUR $\alpha$ ) gene in chromosome 5q31.2–q31.3. Neonatal patients exhibited hypotonia, feeding difficulties, apnea or primary hypoventilation, intrauterine excessive hiccupping and drowsiness. The pediatric patients demonstrated moderate to severe mental retardation, epilepsy, progressive hip dysplasia, scoliosis, dysphagia, salivation and constipation. Respiratory insufficiency, including central and obstructive sleep apnea and recurrent pulmonary aspiration, were frequently observed. Early-onset feeding difficulties with moderate dysphagia and evidence of tracheal aspiration often needed nasogastric or gastric-tube feeding. Moderate to severe neurodevelopmental delays might occur, with some developing later epilepsy and nonepileptic hyperkinetic movements (dystonia, dyskinesia, and eye movement abnormalities). Most patients showed a decreased volume of white matter, a slight enlargement of lateral ventricles, and subarachnoid cysts in cerebral magnetic resonance.

**Final comments:** In newborns with severe hypotonia associated with respiratory abnormalities or movement disorders, further evaluation is needed since early diagnosis and inter-

vention provides a better prognosis and allows genetic counseling.

### Code: PE127

#### **Infantile neuroaxonal dystrophy (INAD): a case report**

Fernanda Ferrão Antonio<sup>1</sup>, Maria Luiza Benevides<sup>1</sup>, Paula Thais Bandeira Elias<sup>1</sup>, Larisse Souza Somavilla<sup>1</sup>, Ana Carolina Piauilino Falcão<sup>1</sup>, Isabelle Salgado Castellano<sup>1</sup>, Katia Maria Ribeiro Schmutzler<sup>1</sup>, Ana Carolina Coan<sup>1</sup>, Karine Couto Sarmento Teixeira<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas SP, Brazil

**Case presentation:** A previously healthy 3-year-old girl was admitted with a history of loss of developmental milestones since 18 months of age. So far, only language delay had been noticed. It evolved from then on, with frequent falls, incoordination, and truncal hypotonia. Throughout the next year, she lost the ability to walk. During the same year, she began to have episodes of tonic seizures, with partial control after the introduction of levetiracetam. When examined, there was severe global hypotonia, with strabismus and nystagmus. During the investigation, it was identified diffuse cerebellar atrophy in the MRI. In addition, there was elevated aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ratio and elevated lactate dehydrogenase (DHL). At the moment of the initial investigation, there was no optic atrophy. The molecular genetic testing showed biallelic pathogenic variants in PLA2G6 in homozygosis.

**Discussion:** Phospholipase A2 group VI (PLA2G6)- associated neurodegeneration (PLAN) is associated with two childhood neurologic disorders: infantile neuroaxonal dystrophy (INAD) and atypical neuroaxonal dystrophy (atypical NAD). The most common presentation during the first years of life is infantile neuroaxonal dystrophy (INAD) which usually begins between the ages of six months and three years with psychomotor regression or delay, hypotonia, and progressive spastic tetraparesis. Commonly, there is strabismus, nystagmus, and optic atrophy. Disease progression is rapid, leading to loss of the ability to walk, progressive cognitive decline, and visual impairment. Typically, there is an elevated AST/ALT ratio and increased levels of DHL. The neuroimages can show cerebellar atrophy and a hypointense globus pallidus in T2 MRI, indicating iron accumulation. Before the onset of genetic testing, the establishment of the diagnosis was based on the clinical features and tissue biopsy, with the evidence of dystrophic axons. Nowadays, the use of molecular testing with the identification of biallelic pathogenic variants in PLA2G6 confirms the diagnosis.

**Final comments:** This case describes INAD, one of the phenotypes of PLAN. It has been associated with psychomotor regression, early truncal hypotonia, and visual abnormalities. The knowledge about its evolution contributes to the development of therapeutic possibilities in the future and the adequate management and orientation of the child and its family.

### Code: PE128

#### **Infantile neuroaxonal dystrophy associated with seizures in a patient from a teaching hospital in southern Brazil: case report**

Heloísa Augusta Castralli<sup>1</sup>, Bruna Gularte da Conceição<sup>2</sup>, Antônio Diniz da Rosa Pereira<sup>2</sup>

<sup>1</sup>Universidade Federal de Santa Maria, Santa Maria RS, Brazil

<sup>2</sup>Hospital Universitário de Santa Maria, Santa Maria RS, Brazil

**Case presentation:** Male, 6 years old, only child of healthy and non-consanguineous parents. Born at term, weighing 3960 g, by cesarean delivery. Under neurological follow-up since 1 year and 4 months of age due to delayed neuro psychomotor development with motor regression between 6–8 months of age. At that time, he had incomplete head support and could not sit or stand. At 3 years of age, he was referred to the Pediatric Neurology service for investigation of tonic seizures that had started 3 months ago, with gaze lateralization to the left, for around 5 minutes, without crying or cyanosis, followed by a period of drowsiness and hypotonia for ~10 minutes. The seizures occurred 1–2 times a day, and phenobarbital was prescribed in external care. On physical examination, epicanthus, spontaneous horizontal nystagmus, tongue fasciculation, hypotonia and global muscle hypertrophy, hyperreflexia in upper and lower limbs, absence of abdominal reflex, bilateral Babinski were identified. He had grade 1 strength in lower limbs and 2 in upper limbs. The child did not sit with support and did not speak. Laboratory tests showed LDH 784, AST 76, ALT 18. The EEG presented alterations due to basal rhythm disorganization with loss of the anteroposterior gradient, in addition to epileptiform activity in the left temporoparietal region. A year later, an extremely disorganized grassroots activity was observed; with severe multifocal irritative activity and intense diffuse ictal activity. The brain MRI showed marked global cerebellar atrophy, cerebellar cortex volumetric reduction, cerebellar sulci and fissures enlargement, bilateral volumetric reduction of the middle cerebellar peduncles and brainstem, in addition to secondary basal cisterns enlargement and IV ventricle prominence. Diagnosis of Infantile Neuroaxonal Dystrophy (INAD) confirmed after identification of variant c.437dup; p.Cys146TrpfsTer19 in exon 4 of the PLA2G6 gene, in homozygosity, causing loss of reading frame from amino acid 146. Currently, the child is bedridden and has no verbal communication. He uses gastrostomy and presents refractory seizures due to an irregular use of anticonvulsants.

**Discussion:** Generally, the development of babies with INAD starts to slow down between the ages of 6 months to 3 years. The first symptoms are slowing of motor and mental development, followed by loss or regression of previously acquired skills.

**Final comments:** INAD is a rare neurodegenerative disease which significantly shortens a child's life expectancy.

## Code: PE129

### A mutation in a one-year-old girl: a case report

Ana Clara Kunz<sup>1</sup>, Naiara Bozza Pegoraro<sup>2</sup>, Rie Tiba Maglioni<sup>3</sup>, Isabelle Caroline Fasolo Normandia Moreira<sup>3</sup>, Gabriela Esmanhoto Rodrigues<sup>4</sup>, Caroline Brandão Piai<sup>5</sup>, Aline Sauzem Milano<sup>3</sup>, Julia de Oliveira Barbosa<sup>3</sup>, Ana Chrystina de Souza Crippa<sup>3</sup>

<sup>1</sup>Faculdades Pequeno Príncipe, Curitiba PR, Brazil

<sup>2</sup>Hospital Universitário Evangélico Mackenzie, Curitiba PR, Brazil

<sup>3</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>4</sup>Faculdade Evangélica Mackenzie do Paraná, Curitiba PR, Brazil

<sup>5</sup>Pontifícia Universidade Católica do Paraná, Curitiba PR, Brazil

**Case presentation:** A one year and two months old girl, born at term with a birth weight of 2990 g with unremarkable prenatal history and non-consanguineous parents, presented with ocular deviation at four months of age. A retinography and brain MRI were performed, showing no abnormalities. At five months of age, she stopped making eye contact, and experienced delayed psychomotor development with sudden social, behavioral and language deterioration. At one year old, she presented dyskinesia affecting hands and feet and ataxia of head and trunk. A whole exome sequencing was requested,

which identified a likely pathogenic variant in heterozygosity in KIF1A (c.920G>A, p.Arg307Gln) on chromosome 2q37.3, compatible with NESCAV syndrome, and pathogenic variants on IQCB1 and POLG as secondary findings. Our patient is currently on physical and occupational therapy, and we will continue to follow up on the patient's condition and its clinical course.

**Discussion:** KIF1A stands for kinesin family member 1A, which is a molecular motor for membrane-bound cargo almost exclusively expressed in the brain and spinal cord. The improper functioning of KIF1A due to genetic variants may result in problems with synaptic plasticity and transmission, learning and memory, leading to the following disorders: (a) neuropathy, hereditary sensory, type IIC; (b) spastic paraplegia 30, autosomal recessive; (c) spastic paraplegia 30, autosomal dominant; and (d) neurodegeneration and spasticity with or without cerebellar atrophy or cortical visual impairment (NESCAV syndrome). The NESCAV syndrome may include moderate to severe intellectual disability, language and motor delay, hypotonia, spastic paraparesis, hyperreflexia, postnatal microcephaly, and peripheral neuropathy, and patients may show varying degrees of brain and optic nerve atrophy on MRI.

**Final comments:** This case further supports the association between KIF1A and NESCAV syndrome, highlighting the importance of genetic testing and screening for KIF1A variants in patients with early-onset ataxia and dyskinesia. By establishing a correct diagnosis, we thereby detect symptoms at an early stage in their evolution where treatment is facilitated, improving our patient's prognosis.

## Code: PE130

### Menkes disease spectrum: a case report

Rui Carlos Silva Júnior<sup>1</sup>, Shema El-Laden Hammoud<sup>2</sup>, Gabriel de Lima Cavassim<sup>2</sup>, João Victor Rodrigues Bubicz<sup>2</sup>, Jessica Moraes Jacomasso<sup>2</sup>, Mariana Brunetto<sup>2</sup>, Ana Luiza Masselari<sup>2</sup>, Giulia Vilela Silva<sup>3</sup>, Daniel Almeida do Valle<sup>3</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

<sup>2</sup>Universidade Positivo, Curitiba PR, Brazil

<sup>3</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Male patient, 11 years of age, referred to the service at 1 years old, due to developmental delay and hypotonia. At birth, presented with difficulty in feeding, and at 6 months hypotonia was identified. Sat at 1 years old and currently walks with assistance, is able to speak monosyllabic words and tonic syllables, and grabs objects with difficulty. Electroneuromyography, cranial magnetic resonance, auto-immune tests, and urine organic acid analysis were not compatible with the clinical findings. In addition, screening for Fabry disease was negative, and histological analysis of muscular tissue revealed only signs of vasculitis. Thus, genetic analysis was performed, which revealed hemizygous variant of uncertain significance in the ATP7A gene. The pathological significance of the finding was confirmed by the decreased levels of serum copper (<20 µg/dL) and ceruloplasmin (8 mg/dL) and by a segregation study in family members, which revealed the absence of said variant in the patient's brother and maternal cousin and the presence of the same variant in another maternal cousin affected by the same symptoms.

**Discussion:** Menkes syndrome is a rare disease associated with variations in the ATP7A gene, which is responsible for copper's metabolism within the body. Early signs, such as feeding difficulty and epileptic crisis, are often identified during the first weeks of life. Then, patients present with developmental delays, hypotonia, and short, sparse, twisted, and usually fair strands of hair. Patients with better motor

and cognitive development than what is seen in the classic form of Menkes disease were described as mild Menkes. They usually walk without support and are able to acquire formal language. Muscle weakness and ataxia are typical, and, when present, intellectual disability is mild. Connective tissue disorders may be more prominent than in the classic Menkes disease. Laboratory evidence of the disease includes low levels of serum copper and ceruloplasmin, however, diagnosis is only possible through genetic testing regarding mutations in the ATP7A gene, located in the X chromosome.

*Final comments:* Patients with mild forms of Menkes may present variable intellectual impairment, ataxia, and hypotonia. Furthermore, epileptic symptoms and skin and hair alterations, cardinal symptoms in the classic form, may not be present. This report corroborates with the broad spectrum of symptoms that can be seen related to this syndrome.

#### Code: PE131

##### **COL4A1-related disorders: a case report**

Bruna Torres Homem Fonseca<sup>1</sup>, Ana Luiza Almeida Carneiro<sup>1</sup>, Tânia Saad<sup>1</sup>, Ludimila Marins Almeida Moura<sup>1</sup>, Aline Fonseca Lima<sup>1</sup>, Alessandra Augusta Barroso Penna e Costa<sup>1</sup>, Fernanda Veiga Góes<sup>1</sup>, Marcela Rodrigues Freitas<sup>1</sup>, Talys Jason Pinheiro<sup>1</sup>  
<sup>1</sup>Instituto Fernandes Figueira, Rio de Janeiro RJ, Brazil

*Case presentation:* Young male, 17 years old, born in Rio de Janeiro, with a history of global developmental delay and neuroimaging with leukoencephalopathy. Basic screening for inborn errors of metabolism, ophthalmoscopy and electro-neuromyography did not show any changes. Specific enzyme measurements performed during diagnostic investigation excluded leukodystrophies and Tay-Sachs as possible etiologies. The presence of bilateral basal ganglia hyperdensity, compatible with calcifications, associated with a static clinical condition have pointed to the possibility of leukoencephalopathy due to congenital cytomegalovirus infection. From the age of 11, transient and recurring events of paresis and paresthesia were noted, from March 2016 to April 2022, consistent with stroke, predominantly of hemorrhagic etiology. The main cardiovascular, hematological, inflammatory and rheumatological causes were investigated and ruled out. At this time, genetic etiologies, such as Leukoencephalopathy with Calcifications and Cysts and the Small Brain Vessel Disease group, became the main hypotheses. A gene panel by next generation sequencing was performed identifying a heterozygous, probably pathogenic de novo variant in the COL4A1 c.2432G>T;p.Gly811Val gene, not previously reported.

*Discussion:* Variants in the COL4A1 gene, of autosomal dominant (AD) inheritance, are associated with a heterogeneous group of rare genetic conditions with endothelial dysfunction and fragility of variable phenotypic spectrum. One of the phenotypes related to COL4A1 variants is autosomal dominant brain small-vessel disease with hemorrhage. Clinical manifestations include brain hemorrhages in young, non-hypertensive patients, some degree of cognitive impairment, the possibility of ocular changes and, rarely, muscle and renal involvement. The radiological presentation includes leukoencephalopathy, lacunar infarcts, microhemorrhages, dilatation of the perivascular space, deep intracerebral hemorrhages, and calcifications.

*Final comments:* Cerebral small vessel disease represents a cluster of pathologies with heterogeneous etiology and mechanisms affecting elements of the vascular system, clas-

sified according to pathological, radiological and clinical criteria. The small vessel disease with COL4A1 mutation is included in the group of genetic etiology, with cerebral autosomal dominant arteriopathy with subcortical ischemic stroke and leukoencephalopathy (CADASIL) and Fabry's disease being the most well-described causes.

#### Code: PE132

##### **Mitochondrial disease in a heteroplasmic MT DNA mutation causing mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and Leigh syndrome phenotypes**

Rafaela Fernandes Dantas<sup>1</sup>, Joemir Jábson da Conceição Brito<sup>1</sup>, Clarice Semiao Coimbra<sup>1</sup>, Ana Cristina Azevedo Leão<sup>1</sup>, Nicholas dos Santos Barros<sup>1</sup>, Roberta Diniz de Almeida<sup>1</sup>, Cristiani Rocha Lima Cruz<sup>1</sup>, Clarissa Bueno<sup>1</sup>, Fernando Kok<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

*Case presentation:* A six year-old female child presented in a tertiary hospital with an acute stroke-like event after a week of cerebellar, bulbar and pyramidal syndromes. She had past history of failure to thrive, since young age, and another three stroke-like events since she was 2 years old. The course of the disease was chronic with acute exacerbation with some recovery in between. Milestones of motor development were adequate, but she present speech delay and learning disabilities. She is the third child of a non-consanguineous healthy couple. Mother's second gestation the child had unique multicystic kidney disease and died within five hours after being born. No family history of neurologic disease was reported. During investigation she was submitted to neuroimage with identification of stroke-like acute and past events, compared with previous images, and showed symmetrical hyperintense T2/FLAIR in striatum and putamen. Spectroscopy was normal. Cardiologic, auditory and visual investigations showed no additional findings. The cerebrospinal fluid showed slightly high lactate and cellularity and isolated herpes VI and VII-PCR. It was presumed that the infection was a trigger to the acute event, and therefore treated such, with ganciclovir. The acute event was treated with arginine and she had improvement mainly in bulbar symptoms.

*Discussion:* Genetic investigation showed mutation on MT ND 6 chr14.430 A>G, complex I in the respiratory chain, so far described once as a Leigh syndrome on a Chinese study. The percentage of heteroplasmic mutation on our patient was 78% on MT DNA on evaluated cells. We hereby describe a case of a recently described mutation on MT DNA but with a different phenotype, a patient with clinical stroke-like events, and neuroimage adding component of Leigh syndrome, despite the fact of the absence of movement disorders so far, neither epileptic events.

*Final comments:* Mitochondrial diseases has been a broad field for studies, with its different pattern of presentation, genetic mutations and mainly its treatment's challenges. So far, some evidence has shown categorization of mitochondrial diseases into syndromes and directed treatment accordingly. The previous idea of mitochondrial cocktail is no longer seen as no doubtful plan. Arginine has been promising as a useful tool for stroke-like events, but it's still more evidence required.

Code: PE133

**Mitochondrial disorder related to the AFG3L2 gene in a boy with neurodevelopmental delay, ataxia and refractory epilepsy**Mariah Pereira de Andrade Vallim<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Lorena Vilela Rezende<sup>1</sup>, Rui Carlos Silva Junior<sup>1</sup><sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** J.A.R, 2 years old, only child of a couple with no history of neurological diseases, born at term, pregnancy and delivery without complications, normal development in the first trimester of life. At 4 months, delayed neuromotor development was noticed, without cephalic support, did not follow objects or search for faces, presented tongue fasciculation, hypotonia and hyporeflexia. At 5 months he had strabismus and nystagmus; and at 10, he was diagnosed with West syndrome, started using vigabatrin but due to evolution with magnetic resonance imaging (MRI) uptake, it was suspended, he used other anticonvulsants without achieving optimal seizure control. Currently, he has refractory epilepsy, 12-hour VEEG showed moderately disorganized background activity, frequent polymorphic discharges either generalized or multifocal and generalized myoclonic seizures; significant delay in neuropsychomotor development, ataxia, dystonia, choreoathetosis and gastroesophageal reflux. In the exome, the mutation p.L772F:C>T in the AFG3L2 gene was identified in heterozygosity; changes in this gene are associated with autosomal dominant spinocerebellar ataxia type 28 and autosomal recessive spastic ataxia-neuropathy syndrome.

**Discussion:** The AFG3L2 gene encodes an ATP-dependent proteolytic complex of the mitochondrial membrane and is involved in several crucial pathways for mitochondrial function, including mitochondrial protein quality control and homeostasis. The impairment of this gene can lead to dysfunctions in mitochondrial protein synthesis, respiration, mitochondrial integrity and networking. Mutations in AFG3L2 have been associated with both autosomal dominant spinocerebellar ataxia type 28 (SCA28) and autosomal recessive spastic ataxia-neuropathy syndrome (SPAX5).

**Final comments:** Different forms of the disease, with different levels of severity and neuropathological correlations, were found in different mutations of the AFG3L2 gene in mice, indicating that these variants differently alter the structure and activity of the m-AAA protease. Possibly justifying the reason for the patient, who, although he has a heterozygous mutation, has a clinic more similar to the cases of homozygosity, with more severe symptoms and early onset.

Code: PE136

**Mutation in the TANGO2 gene in a pediatric patient**Paula Luísa Lopes Schell<sup>1</sup>, Isadora Cavalcante Olímpio de Melo<sup>1</sup>, Ana Carolina Jorge Fogolin<sup>1</sup>, Michelle Basso Couto Gouvêa<sup>1</sup>, Iris do Vale Miranda<sup>1</sup>, Helen Ramos Vasconcelos<sup>1</sup>, Rubens Wajnsztein<sup>1</sup>, Paulo Breinis<sup>1</sup>, Laís Russo Carneiro Peruzzi<sup>1</sup><sup>1</sup>Faculdade de Medicina do ABC, Santo André SP, Brazil

**Case presentation:** Patient A.S.P, male, two years old, started with fever on June 2021 associated with others viral symptoms. Three days after, he was admitted on the pediatric emergency room with hypotonia of the trunk and limbs. He also referred pain and paresis mainly in the lower limbs. Transferred to intensive care unit he evolved with dysphagia and worsening of the motor condition, maintaining only eye movement. He also required a nasogastric tube and did not need ventilatory support. On the eleventh day, he started with spontaneous and progressive improvement of the con-

dition. He was discharged on beginning of July with mild cervical hypotonia, sitting without support and receiving oral feeding. In December 2021 and March 2022, he sought the pediatric emergency room again with the same symptoms. After the first hospitalization, the follow-up and outpatient investigation began. He performed several laboratory tests, and the diagnosis was made through the DNA genetic test, which showed a mutation in the TANGO2 gene.

**Discussion:** The TANGO2 gene-related disease is an autosomal recessive disorder. Mutations in this gene have been identified as the cause of a pediatric disease with multiple organ involvement. The TANGO family of proteins plays a crucial role in the interaction of the Golgi apparatus and the endoplasmic reticulum. The manifestations usually occur between six months and nine years old. These include episodic rhabdomyolysis, severe metabolic crises, hypoglycemia, lactic acidemia, high CPK, increased ammonia and cardiac arrhythmias. Usually triggered by stress, such as illness or fasting.

**Final comments:** As it is a disease with few known cases, it is necessary to keep a close eye on patients who have episodes of rhabdomyolysis, severe metabolic crisis and significant increase in CPK, which appear in outbreaks. Thus, it becomes possible to carry out new diagnoses and, consequently, provide family genetic counseling.

Code: PE137

**Neurodegeneration with cerebral iron 5 accumulation associated with BPAN beta-helix protein: a case report**Victoria Faustino Silva Reis<sup>1</sup>, Bruna Freitas Souza<sup>1</sup>, Murilo Lopes Coelho<sup>2</sup>, Samantha Lopes Oliveira<sup>2</sup>, Iana Maciel Silva Souza<sup>2</sup>, Sâmara Pinto Vasconcelos<sup>2</sup>, Juliana Silva Almeida Magalhães<sup>2</sup>, Julia Monteiro Barros Pereira Carvalho<sup>2</sup>, Camilo Vieira Santos<sup>2</sup><sup>1</sup>Escola Bahiana de Medicina e Saúde Pública, Salvador BA, Brazil<sup>2</sup>Hospital Martagão Gesteira, Salvador BA, Brazil

**Case presentation:** K.D.S.P, male, 3 years old. The mother reports from the age of 6 months, the child began with seizures characterized as generalized tonic-clonic, with ocular eversion, lasting less than five minutes, at a frequency of 2 seizures/day. Associated to this, he presents with delayed neuropsychomotor development. Physical examination: the patient did not present cervical control and was unresponsive to stimulation, non-contactful, reflexes grade 3, with symmetrical appendicular hyperreflexia. Due to the clinical story, he was sent to the child neurology service, where a computed tomography of the skull and an electroencephalogram were done, which showed encephalic volumetric reduction, enlarging sulcus of the frontal convexity, bilateral parietal and anterior portions of the lateral ventricles and evidencing disorganization of the brain electrical activity, with presence of irritative activity in the left central parietal region, respectively. In addition, a genetic panel for Epilepsy was performed, which identified Neurodegeneration with brain iron accumulation 5 (NBIA5), associated with  $\beta$ -helix protein (BPAN), with the mutation caused to the WDR45 domain located in Xp11.23 of the X chromosome.

**Discussion:** NBIA5 is a disease that courses with accumulation of this substance mainly in the basal ganglia and substantia nigra, which can be seen on MRI. NBIA has overlapping phenotypes and is subdivided according to the associated genes. This genetic disease has a prevalence of 1:500,000 live births, and the most common phenotype is pantothenate kinase-associated neurodegeneration (PKAN), present in 50% of cases. The case subject has an early phenotype of BPAN, the only NBIA linked to X mutation, which includes neurodevelopmental delay, intellectual deficit, epilepsy, and sleep

problems. In addition, patients can develop movement disorders such as parkinsonism and dystonia.

*Final comments:* Although there is no specific treatment, the diagnosis of NBIA is important for genetic counseling and symptomatic treatment. In the patient's case, with anti-epileptic drugs and therapies such as physiotherapy and speech therapy. Furthermore, it is important to consider NBIA as a possible differential diagnosis, since the symptomatology can be confused with epileptic encephalopathy and/or atypical Rett syndrome.

#### Code: PE138

##### **Neurodevelopmental disorder associated with the DOCK7 gene**

Icaro Bertechini Soler Lopes<sup>1</sup>, Nadia Bertechini Soler Lopes<sup>1</sup>, Aluana Moraes<sup>1</sup>

<sup>1</sup>Universidade Estadual do Oeste do Paraná, Cascavel PR, Brazil

*Case presentation:* PHAPS, male, 9 years old, being followed up at the neuropediatric outpatient clinic for a history of seizures since 1 year and 6 months, focal epilepsy with seizures in type in the left side, eyelid myoclonus and drooling, with subsequent generalization. At seven years old, he started with behavioral changes and stereotypies. Delayed neuropsychomotor development: sustained cervical at 3 months, lallation at 1 year, articulation of first words at 3 years and 6 months, language with sentence formation only at 7 years. Past pathological history: born at term, normal delivery and without complications. Physical examination: patient with little contact, low implantation of ears and high-arched palate. Neurological examination without focal deficit, preserved reflexes, atypical gait, muscle strength grade 5, normal muscle tone, cranial nerves without alterations. Complementary exams: Cranial magnetic resonance imaging: right mesial temporal sclerosis. Video-electroencephalogram: epileptiform paroxysms with diffuse projection and hemispheric accentuation on the right, epileptiform paroxysms in the posterior regions occurring synchronously and asynchronously, predominantly on the left. CGH-ARRAY genomic comparison analysis: normal. Exome sequencing: heterozygosity mutation in the DOCK 7 gene (chr1:62.954.634 G>GA and chr1:63.091.022 G>A). Clinical significance: likely pathogenic mutation.

*Discussion:* Neurodevelopmental disorders are a group of heterogeneous disorders that predominantly encompass autism spectrum traits and cognitive impairment. The DOCK 7 gene plays a key role in neurogenesis, promoting glial cell differentiation and neuroblast migration. Abnormalities in the DOCK7 gene cause neurodevelopmental disorders and a specific type of encephalopathy with early-onset epilepsy and intellectual disability, causing varying degrees of cognitive, language, and behavioral impairments, and seizures contribute to neurodevelopmental impairment and regression. Predominant physical characteristics are described in the literature such as low ear implantation and brachycephaly.

*Final comments:* DOCK7 gene-associated neurodevelopmental disorder is part of a large and heterogeneous group of neurodevelopmental disorders and neurogenetic diseases.

#### Code: PE139

##### **Neurodevelopmental disorder related to the GABRB2 gene as a differential diagnosis of angelman syndrome: case report**

Mariah Pereira de Andrade Vallim<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Lorena Vilela Rezende<sup>1</sup>, Rui Carlos Silva Junior<sup>1</sup>, Daniel Almeida do Valle<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

*Case presentation:* D.H.S., male, 23 months, non-consanguineous parents, born at term, pregnancy and delivery without complications, healthy 7-year-old brother, and no cases of epilepsy or developmental delay in the family. From birth he had difficulty breastfeeding and hypotonia, at 3 months he started episodes of behavioral arrest, and at 9 months episodes of lip cyanosis, hypertonia of the four limbs lasting less than one minute and post-ictal with exacerbation of hypotonia. At the first hospital evaluation, at 18 months, D.H.S. had significant neuropsychomotor delay, global hypotonia, hypopigmentation of the skin and hair, difficulty in eating and sleeping, signs suggestive of autism spectrum disorder, choreoathetosis, dystonia and refractory epilepsy, Angelman Syndrome (AS) was one of the diagnostic hypotheses evaluated. In the diagnostic investigation, the video electroencephalogram showed a generalized electroclinical crisis with a rhythm starting in bilateral central parietal regions and in the midline, clinically classified as generalized tonic-clonic motor onset; what would be considered an atypical pattern in AS, the other tests performed were not elucidative at first for the case. In a genetic evaluation, the variant c.228A>T (p. Glu76Asp) was identified in the GABRB2 gene in heterozygosity; of uncertain meaning, but potentially deleterious, and may be the cause of all symptoms presented by the patient.

*Discussion:* The GABRB2 gene encodes a subunit of the gamma-aminobutyric acid (GABA) receptor, which is an ion channel involved in inhibitory neurotransmission. Heterozygous pathogenic variants in GABRB2 are associated with epileptic and developmental encephalopathy. Therefore, the clinic presented by the patient, refractory epilepsy, movement disorder and delay in neuromotor development, is consistent with the genetic alteration found. The variant found is of autosomal dominant inheritance, and although it is classified as a variant of uncertain significance (VUS), it is possible to consider that this rare variant is pathogenic.

*Final comments:* The recent increase in the availability of genetic tests has allowed the diagnosis of diseases that could previously have been clinically misdiagnosed. In the case of the patient reported here, in which the typical facial features of AS would not yet be observed due to age and the clinical picture was compatible, genetic testing was essential for the differential diagnosis.

#### Code: PE140

##### **Neurodevelopmental disorder with or without hyperkinetic movements and seizures: a rare genetic case**

João Garcia<sup>1</sup>, Carla Lenita Coelho Siqueira<sup>1</sup>, Vinícius Paulo Lima de Menezes<sup>1</sup>, Lisiane Seguti Ferreira<sup>1</sup>, Carlos de Almeida Dias Neto<sup>1</sup>

<sup>1</sup>Universidade de Brasília, Brasília DF, Brazil

*Case presentation:* Patient RSP, female, born full-term and without complications during pregnancy or perinatally. She presented her first episode of tonic-clonic episode at 5 months of age, evolving with recurrent seizures of variable frequency and intensity, neuropsychomotor development (NPMD), tremors in the upper limbs and precocious puberty. Brain MRI presented diffuse leukoencephalopathy associated

with volumetric reduction. Electroencephalogram (EEG) presented with multifocal epileptic activity and disorganized baseline rhythm. Genetic Panel of Epilepsies collected in 2021 showed pathogenic variant in heterozygosity in the GRIN1 gene, associated with Neurodevelopmental Disorder with or without Hyperkinetic Movements and Seizures (NDHMSD, OMIM: # 614254).

**Discussion:** NDHMSD is an autosomal dominant disorder caused by heterozygous mutation in the GRIN1 gene on chromosome 9q34. It presents significant delay in neurodevelopment, severe intellectual deficit with absence of speech, muscular hypotonia and hyperkinetic hyperkinetic movement changes, and may be associated with cortical blindness, brain atrophy, and seizures. This is a rare etiology of seizures associated with delayed NPMD, with only 72 cases reported as of 2019, and with pleomorphic presentation, ranging from milder cases with delayed in development associated with autistic spectrum disorder to complex ones with altered cortical visual, epilepsy, hyperkinetic disorders. **Final comments:** Developmental delays and intellectual disabilities are part of a large spectrum that encompasses numerous pathologies and etiologies, with little appreciation often given to genetic etiologies and their causal investigation with genetic panels. Such undervaluation implies delays in genetic diagnosis and counseling, with potentially significant consequences for the psychosocial context of the families involved, being a good multidisciplinary follow-up in these scenarios fundamental.

#### Code: PE142

##### **Neuronal ceroid lipofuscinosis: when to use right clues for a rare disease?**

Renata Beatriz Boechat Quadros<sup>1</sup>, Mariana Sathler Pereira Dantas<sup>1</sup>, Renata Jordão Pereira de Vasconcellos<sup>1</sup>, Manuella Pinto Pessanha Siqueira<sup>1</sup>, Gabriela Rochedo Villela<sup>1</sup>, Jessyca Thays Melo de Andrade Ramos<sup>1</sup>, Hanid Fontes Gomes<sup>1</sup>

<sup>1</sup>Hospital Municipal Jesus, Rio de Janeiro RJ, Brazil

**Case presentation:** We describe the case of a previously healthy girl who, at 6 years of age, initiates a difficult-to-control epilepsy associated with agitation and aggressiveness. At the age of 9, she already showed school difficulties, infantilization, dependence for daily activities and signs of dementia. The neuroimaging that was initially normal at the age of 11 showed cerebellar atrophy and small frontal to left subcortical focus with lateral ventricle asymmetry. EEG showed sharp waves and complex acute occipital tips on the right and slow and wide waves. Genetic panel of epilepsy and ataxia showed two variants in heterozygosity in the MFSD8 gene diagnosing neuronal ceroid lipofuscinosis 7.

**Discussion:** The lipofuscinoses are a group of inherited neurodegenerative lysosomal storage diseases characterized by intracellular accumulation of autofluorescent lipopigment. Collectively they are the most common cause of genetic neurodegenerative disease of childhood with an estimated incidence of 1.3 to 7/100,000 live births. LCN7 is a late onset variant of childhood, typically between two to seven years of age, with severe epilepsy and aggressive behavior, associated with developmental regression. It progresses rapidly with onset of myoclonus, ataxia, dementia, and blindness. It occurs by mutation in the MFSD8 gene that encodes a lysosomal transmembrane protein. Brain MRI shows cerebral and cerebellar atrophy with signal hyperintensity in the white matter. EEG usually shows slow baseline activity and multifocal, occipital epileptiform discharges. Ophthalmologic examination may reveal retinopathy and optic atrophy. Currently genetic testing is the diagnostic method of choice through epilepsy gene panel or exome sequencing.

**Final comments:** Treatment in this subtype is supportive only with a reserved prognosis. However, it is important to research LCN in the context of children with behavioral regression, refractory epilepsy, visual loss and progressive ataxia with cerebellar atrophy since we have a disease-modifying therapy in the LCN 2 subtype through enzyme replacement with intrathecal application of recombinant human cerliponase alfa in those older than three years.

#### Code: PE143

##### **Leukoencephalopathy with cerebral calcifications and cysts: a case report**

Gabriel De Lellis Neto<sup>1</sup>, Ana Clara Bernardi<sup>1</sup>, Renata Yasmin Cardoso Sousa<sup>1</sup>, Hugo Leonardo Justo Horácio<sup>1</sup>, Dayana Lima Mariano<sup>1</sup>, Michele Michelin Becker<sup>1</sup>, Lygia Ohlweiler<sup>1</sup>, Maria Isabel Bragatti Winckler<sup>1</sup>, Rudimar Santos Riesgo<sup>1</sup>

<sup>1</sup>Hospital de Clínicas de Porto Alegre, Porto Alegre RS, Brazil

**Case presentation:** A 5-year-old girl initially suspected of having neurofibromatosis type 1 (NF1) due to developmental delay and café au lait spots. In March 2022, evolved with neurodevelopmental regression, progressive loss of strength and gait ataxia. Three months later she had an afebrile epileptic seizure, a computed tomography (CT) scan of the brain was performed, which showed leukoencephalopathy with microcalcifications and cysts, the largest in the right semi-oval center. Upon admission, she could no longer stand without support, presenting a divergent deviation of the right eye, worsening of speech but without impairment of swallowing or cognition. On physical examination, obeyed commands, had isochoric and photoreactive pupils, right divergent strabismus, decreased trophism, axial hypotonia, partial cephalic support, right appendicular hypotonia, left distal hypertonia with strength alteration, asymmetrical phasic myotatic reflexes, several café au lait spots in trunk and arms. A new brain CT, cranial and neuraxial magnetic resonance imaging was performed, which ruled out lesions suggestive of NF1. The patient was evaluated by the ophthalmology team that ruled out retinal lesions. Neurosurgery chose not to intervene given the location of the cyst. Genetic testing for Labrune Syndrome was performed, still without result.

**Discussion:** Leukoencephalopathy with cerebral calcifications and cysts, Labrune Syndrome, was recently described, in 1996. The radiological manifestations had already been described in 1988, as part of Coats plus Syndrome or Cerebroretinal Microangiopathy with calcifications and cysts. The microangiopathy of Labrune Syndrome is characterized only by the involvement of the CNS. In Coats plus Syndrome, this is more widespread, with retinal telangiectasia and osteopenia, anemia, portal hypertension, liver, nail and capillary changes and, in rare cases, café au lait spots. This patient has only CNS involvement and café au lait spots. Deficits on physical examination appear to be due to the cyst in the semi-oval center on the right.

**Final comments:** This case confirms the difficulty in making the differential diagnosis, since the brain lesions are identical in both diseases. In the specific case, a further complicating factor emerged, which was the presence of café au lait spots. Thus, there is a need for diagnostic confirmation through genetic tests.

Code: PE144

**Microcephaly with pontine and cerebellar hypoplasia (MICPCH): atypical presentation in female**Carla Lenita Coelho Siqueira<sup>1</sup>, Carlos de Almeida Dias Neto<sup>1</sup>, Jeanne Alves de Souza Mazza<sup>1</sup>, José Ribamar Pereira Neto<sup>1</sup>, João Garcia<sup>1</sup>, Vinicius Paulo Lima de Menezes<sup>1</sup><sup>1</sup>Universidade de Brasília, Brasília DF, Brazil

**Case presentation:** LSLLMRG, female, 7 years old, presented with microcephaly and global hypotonia at birth, evolving to spastic tetraparesis. He started difficult-to-control epileptic seizures at 3 years of age. Skull MRI showed pontocerebellar hypoplasia. Mother with a history of two previous miscarriages, with pregnancy complicated by bleeding. She was born at term, Apgar 9/10, evolving with difficulty in sucking and low weight gain in the first month, in addition to significant delay in developmental milestones. Exome collected in 2020 showed a variant of uncertain significance in heterozygosity in the CASK gene (Microcephaly with pontine and cerebellar hypoplasia - MICPCH - OMIM #300749), associated with very rare variants identified in the ARID1A and TBX1 genes, related to phenotypes partially overlapping with the one described in the case index. Genetic evaluation of the parents did not point to similar pathogenic variants.

**Discussion:** Microcephaly with pontine and cerebellar hypoplasia (MICPCH) is a condition generally associated with pathogenic loss-of-function variants in CASK gene. CASK pathogenic variants MICPCH is typically seen in females with moderate-to-severe intellectual disability, progressive microcephaly with or without ophthalmologic anomalies, and sensorineural hearing loss. Most are able to sit independently; 20–25% attain the ability to walk; language is nearly absent in most. Neurologic features may include axial hypotonia, hypertonia/spasticity of the extremities, and dystonia or other movement disorders. Nearly 40% have seizures by age ten years. Behaviors may include sleep disturbances, hand stereotypies, and self-biting. MICPCH in males may occur with or without severe epileptic encephalopathy in addition to severe-to-profound developmental delay. When seizures are present, they occur early and may be intractable. Dysmorphic features include overall poor growth, severe microcephaly, broad nasal bridge and tip, large ears, long philtrum, micrognathia, and hypertelorism. At 2013, a total of 130 individuals (45 males and 85 females) with MICPCH have been reported to date, the eldest of whom is age 25 years.

**Final comments:** This is a rare case of a de novo mutation in a female patient with an unusual presentation, evolving with early epileptic encephalopathy and more commonly seen in males. The mother's gestational history is remarkable. Parental screening and genetic counseling are of great importance in these cases.

Code: PE145

**Niemann Pick Type C1: a rare disease and a race against time**Hanid Fontes Gomes<sup>1</sup>, Victoria Holcman de Marsillac<sup>1</sup>, Carolina Sanches Alvim de Oliveira<sup>1</sup>, Renata Beatriz Boechat Quadros<sup>1</sup>, Carolina Paixão Santos<sup>1</sup>, Gabriela Rochedo Villela<sup>1</sup>, Ana Clara Fandinho Montes<sup>2</sup>, Thais Siqueira Fernandes<sup>2</sup>, Manuella Pinto Pessanha Siqueira<sup>1</sup><sup>1</sup>Hospital Municipal Jesus, Rio de Janeiro RJ, Brazil<sup>2</sup>Instituto Fernandes Figueira, Rio de Janeiro RJ, Brazil

**Case presentation:** This is a report of a female patient from Hospital Municipal Jesus, seven years old, born in Rio de Janeiro, without gestational and perinatal history abnormalities, that at six months years old after persistent abdominal distension, was diagnosed with splenomegaly with sponta-

neous regression. When two years old, began with gait disturbances, and later with paresis on the right inferior limb, recurrent loss of balance, with stumbles. In few months, developed a total loss of strength of inferior and superior limbs and body trunk. At five years old, experienced dysphagia, complete aphasia, loss of interaction, cataplexy, ocular paralysis, leading her to several hospitalizations, later needing tracheostomy and gastrostomy. During the last hospitalization, a genetic molecular test was collected confirming Niemann Pick type C1 (NPC).

**Discussion:** Niemann Pick type C1 is a rare autosomal recessive genetic disease, consisting of mutations in the NPC1 gene, and to a lesser extent in NPC2. Gene that is responsible for intracellular transport, especially cholesterol, and its mutation is responsible for the defect in this transport, causing a complex lysosomal lipidosis. It is subdivided by clinical manifestations, according to age group. In children under two years of age, symptoms may be intrauterine or neonatal stage, commonly with ascites, hepatomegaly or hepatosplenomegaly, prolonged icterus, and infiltrative lung disease, and can even lead to multiple failure and death in a few days. Between two and six years of age, the manifestations are usually noticed with gait alteration, presenting stumbling and imbalances, ataxias, generalized hypotonia with dysphagia and dysarthria, and vertical ocular paralysis, in addition to learning difficulties that progressively intensify with cognitive alterations and regression, even dystonia and cataplexy. In some cases, they associate seizures. After diagnosis, multidisciplinary support is recommended, and currently Miglustat, a molecule that reversibly inhibits glucosylceramide synthase, proves to increase life expectancy from five to 10 years.

**Final comments:** The patient had manifestations compatible within her age group, although, her diagnosis was made at an advanced age and in the face of extensive commitment, through genetic molecular testing at six years of age. A present, an earlier diagnosis allows to slow down neurodegeneration with Miglustat, and improves life quality.

Code: PE146

**Pathological EXOSC3 mutation and its neurological manifestations: a case report**Ana Clara Kunz<sup>1</sup>, Naiara Bozza Pegoraro<sup>2</sup>, Rie Tiba Magliani<sup>3</sup>, Isabelle Caroline Fasolo Normandia Moreira<sup>3</sup>, Gabriela Esmanhoto Rodrigues<sup>2</sup>, Caroline Brandão Piai<sup>4</sup>, Aline Sauzem Milano<sup>3</sup>, Julia de Oliveira Barbosa<sup>3</sup>, Ana Chrystina de Souza Crippa<sup>3</sup><sup>1</sup>Faculdades Pequeno Príncipe, Curitiba PR, Brazil<sup>2</sup>Faculdade Evangélica Mackenzie do Paraná, Curitiba PR, Brazil<sup>3</sup>Universidade Federal do Paraná, Curitiba PR, Brazil<sup>4</sup>Pontifícia Universidade Católica do Paraná, Curitiba PR, Brazil

**Case presentation:** AMD, 12 year-old male presented with developmental delay starting at 4 months-old, with motor difficulties, hypotonia, significant weight gain and 2 episodes of febrile convulsion. Unplanned pregnancy of a non-consanguineous marriage. Delivery at 7 months of pregnancy, APGAR 9/10, no further complications presented. Physical examination showed more pronounced hypotonia on upper limbs in comparison to lower limbs, but normal reflexes on the latter, currently walking with support. Skull and spine MR showed moderate to severe atrophy of cerebellar hemispheres and superior vermis; inferior vermis agenesis, discrete pontine atrophy, arachnoid cyst, sulcal widening and an increase in the supratentorial ventricular system's amplitude. The spine presented a slight dorsal scoliosis and bilateral posterior paravertebral hypotrophy in the lumbar region. An increase in triglycerides, cholesterol and glucose was also

identified. Array-CGH examination showed a heterozygotic duplication of around 228Kb of the short arm of the X chromosome, including the PPP2R3B gene - of uncertain significance. A complete exome sequencing showed a pathogenic EXOSC3 mutation.

**Discussion:** EXOSC3 mutations have been recently defined as one of the main causes of pontocerebellar hypoplasia subtype 1, which is characterized by cerebellar atrophy and hypoplasia, variable pontine atrophy, as well as severe motor and mental disorders. This case report shows the importance and complexity of the genotype-phenotype correlations. The exosome complex is involved in the processing and synthesis of RNA. Hence, an alteration of this functional axis can lead to mutations of this process. It is suggested that the EXOSC3 unit is essential to the survival of cerebellar and spinal neurons' motor function. Therefore, an anomaly of this subunit could cause a deregulation of RNA's metabolism, leading to developmental delay, pyramidal, extrapyramidal and/or cerebellar damage.

**Final comments:** EXOSC3 gene mutations are directly correlated to pontocerebellar hypoplasia subtype 1, presenting itself on patients with ataxia and motor disorders. This case report promotes attention to premature patients with abnormal neurological examination with no other reasonable cause for alterations, which is relevant to the investigation of a genetic cause, to find an etiological conclusion for symptoms, correct diagnosis and patient treatment.

#### Code: PE147

##### **Patients with mitochondrial diseases followed up at an outpatient clinic in Belo Horizonte: a case series**

Renan Guimarães Santana<sup>1</sup>, Fernando Nascimento Dias Carneiro<sup>2</sup>, Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, André Vinícius Soares Barbosa<sup>1</sup>, Nathalia Jamille Moreira Nascimento David<sup>1</sup>, Laura Maria Silva Thiersch<sup>1</sup>, Thais de Almeida Oliveira Fonseca<sup>1</sup>, Luiz Fernando Fonseca<sup>1</sup>, Christovão de Castro Xavier<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

<sup>2</sup>Universidade de Itaúna, Itaúna MG, Brazil

**Case presentation:** In a referral hospital for rare diseases in Belo Horizonte, Minas Gerais, we followed up five patients with a molecular diagnosis of mitochondrialriopathies. A.E.S.V, 3 years and 11 months, diagnosed with Leigh Syndrome due to a homozygous point mutation in the NDUFAF5 gene, presented delayed onset of neuropsychomotor development associated with central characteristic hypotonia, difficult-to-control epilepsy and brain MRI with multiple nodular lesions in T2/FLAIR affecting brain parenchyma. M.R.M.R, 2 years and 2 months old, has a mutation in the POLG gene, and had as clinical presentation regression in neurodevelopmental milestones, difficult-to-control epilepsy, and orofacial dyskinesias, with unaltered brain MRI. H.R.R, 2 years old, with a point mutation in the NDUF51 gene, presented at 9 months, regression in the neurodevelopmental milestones associated with spasticity and brain MRI showed an extensive area of signal hyperintensity in T2/Flair compromising subcortical and periventricular white matter bilaterally and symmetrically, with some areas of periventricular cystic degeneration. A.B.T.G, 11 years old, diagnosed with Leigh Syndrome due to a homozygous pathogenic mutation in the SURF1 gene (mitochondrial respiratory chain IV complex deficiency), presented dystonia and development regression at 1 year and 6 months. E.S.S, 15 years old, diagnosed with Leigh Syndrome due to a point mutation in the MT-ATP6 gene (respiratory chain V complex deficiency), presented with a lowered level of consciousness, ataxia and vomiting at 8 years

old. Both with brain MRI with symmetrical hypersignal of the basal ganglia on T2/FLAIR.

**Discussion:** Mitochondrial diseases are the most common hereditary metabolic diseases, with an approximate prevalence of 1:5000 births, the presentation can start at any age group, can affect a single organ or be multisystemic, affecting organs that demand more energy, such as the brain, skeletal muscle, eyes and heart. The clinical presentation is varied even in mutations within the same complex of the respiratory chain. In our sample, we observed that patients with the NDUFAF5 and NDUF51 mutations have mitochondrial complex 1 deficiency, and the clinic between them was not similar.

**Final comments:** The clinical presentation of mitochondrial diseases is greatly varied. In the face of clinical suspicion, one should proceed with genetic investigation and start with vitamin cocktails.

#### Code: PE148

##### **Neurodegenerative disease caused by the TRAPPC4 gene**

Aline Fonseca Lima<sup>1</sup>, Ana Luiza Almeida Carneiro<sup>1</sup>, Bruna Torres Homem Fonseca<sup>1</sup>, Alessandra Augusta Barroso Penna e Costa<sup>1</sup>, Fernanda Veiga Góes<sup>1</sup>, Marcela Rodriguez de Freitas<sup>1</sup>, Talys Jason Pinheiro<sup>1</sup>, Tania Regina Dias Saad Salles<sup>1</sup>, Ludimila Marins de Almeida Moura<sup>1</sup>

<sup>1</sup>Instituto Fernandes Figueira, Rio de Janeiro RJ, Brazil

**Case presentation:** Female, 5 years old, daughter of a non-consanguineous couple, with pregnancy history of toxoplasmosis seroconversion but no perinatal complications and negative newborn screening tests. She had adequate neuro-psychomotor development up to three months of age, when she began to experience milestones regression and acquired microcephaly, accompanied by hearing loss and movement disorders. At first evaluation, she had microcephaly, poor eye fixation, axial hypotonia and appendicular hypertonia, global hyperreflexia, myoclonus and generalized dystonias. No dysmorphisms were noted. She has undergone extensive diagnostic investigation, with metabolic acidosis, hyperlactatemia, plasma amino acid chromatography with increased glycine. Toxoplasmosis serology was non-reactive and the results of ammonia, urinary organic acids and mucopolysaccharides, enzyme assays (arylsulfatase A,  $\beta$ -galactosidase and palmitoyl-protein thioesterase 1), lymphocytes inclusions research and molecular panel for epilepsies were all normal. Electro-neuromyography was normal and electroencephalogram showed low-amplitude tracing. Cranial MRI (2018) presented important diffuse reduction of brain parenchyma, hypersignal on T2 and FLAIR in the remaining parenchyma with thinning of the corpus callosum; Cranial MRI (2021) showed progressive worsening of cerebral parenchyma atrophy and T2 hypersignal in bilateral subcapsular thalamic region, trunk and cerebellum. The diagnosis was confirmed by exome sequencing with the homozygous pathogenic variant in the TRAPPC4 c.454+3A>G; p(?) gene. Our patient showed improvement of abnormal movements after using levetiracetam.

**Discussion:** The TRAPPC4 gene synthesizes one of the proteins that form the TRAPP complex, which has the function of regulating the transport of vesicles between endoplasmic reticulum and Golgi complex, besides secretion and cellular autophagy. Pathogenic variants in the TRAPPC4 gene cause an autosomal recessive developmental disorder with epilepsy, spasticity and cerebral atrophy. Epilepsy has an early onset, associated with microcephaly, dysmorphisms, hearing loss, visual alteration and movement disorders. Skull MRI shows cerebral atrophy, reduced white matter and cerebellar atrophy.



*Final comments:* This entity is rare, with few cases described in recent literature. Next-generation sequencing is critical for diagnosis and enables genetic counseling.

#### Code: PE149

##### **Pelizaeus-Merzbacher disease (PMD): case report**

Sofia Russi<sup>1</sup>, Amanda Regina Farias Teixeira<sup>1</sup>, Caroline Sccantamburlo Martins<sup>1</sup>, Jéssica Kayene Souza Ferreira<sup>1</sup>, Lana Correa Paschoal<sup>1</sup>, Maria Lina Giacomino de Almeida Passos<sup>1</sup>, Marlos Melo Martins<sup>1</sup>, Mariana Horst Mendes<sup>2</sup>, Nilson Russi Neto<sup>3</sup>

<sup>1</sup>Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil

<sup>2</sup>Santa Casa de Misericórdia de Juiz de Fora, Juiz de Fora MG, Brazil

<sup>3</sup>Autonomo, Cataguases MG, Brazil

*Case presentation:* FHTA, male, 12 years old, child of a non-consanguineous couple, history of fetal distress, born at term, Apgar 7/8. Reported nystagmus since birth, difficulty controlling the head and hypotonia, despite maintaining eye contact, recognizing voices and smiling. First evaluation with a Pediatric Neurologist was at 5 months with clinical features of horizontal and vertical nystagmus, head circumference of 43.5 cm, axial hypotonia, poor cervical support, airway clearance without shoulder elevation, strength 1/5 in all four limbs, present, increased and symmetrical deep reflexes and, anthropometric assessment below the P3 percentile, without stagnation. At 12 months on Magnetic Resonance Imaging (MRI), there was a delay in CNS myelination. Neuroimaging was repeated at 3 years and 8 months with the same pattern of hypomyelination. At 4 years old, a molecular test was performed confirming the disease (Pelizaeus Merzbacher Syndrome) by the presence of duplication in the PLP1 gene, which encodes the myelin proteolytic protein, of X-linked recessive inheritance. Patient evolved with delayed developmental milestones, currently walks with some difficulty, short stature and weight, head circumference at the lower limit, mild/moderate intellectual deficit, remains with vertical and horizontal nystagmus and is more dependent for his daily activities than expected.

*Discussion:* Pelizaeus-Merzbacher disease is a progressive X-linked recessive hypomyelinating leukodystrophy (HLD1) in which myelin is not properly formed in the central nervous system, thus permanently reducing its amount in the body. PLP1 is a transmembrane protein highly expressed in oligodendrocytes, responsible for myelin compaction and formation of intraperiodic lines of the myelin sheath. Diseases related to the PLP1 gene mainly comprise the classical (HLD1), connatal (HLD3) and transitional PMD forms. The patient presented has the classic form, which is characterized by starting in the first year of life, with a slow and progressive course.

*Final comments:* Because it is a rare disease of genetic origin and presents nonspecific and progressive characteristics, the diagnosis must be suspected by the clinic and imaging tests, being confirmed with genetic tests. Treatment is still based on support depending on the needs of each patient; thus, better knowledge of this pathology increases the number of diagnoses and genetic evaluation has relevant implications for the prognosis and genetic counseling of the family.

#### Code: PE150

##### **Pigmentary incontinence (or Bloch-Sulzberger syndrome): a case report in a female infant with epilepsy**

Anna Rita Barcelos Martin<sup>1</sup>, Orlando Oliveira Silva Junior<sup>1</sup>, Bárbara Souza Dias<sup>1</sup>, Meire Soares Ataíde<sup>1</sup>, João Carlos Saldanha<sup>1</sup>, Lucinda Calheiros Guimarães Calheiros Guimarães<sup>1</sup>

<sup>1</sup>Universidade Federal do Triângulo Mineiro, Uberaba MG, Brazil

*Case presentation:* Patient L.V.M.B., female, 3 months old, born and resident in Frutal-MG. She was admitted to the Pediatric Emergency Room of the Hospital de Clínicas da UFTM, referred from the Hospital in the city of origin, due to an unprecedented convulsive crisis 1 day ago, which was characterized by spastic movements in the topography of the hemiface on the right (right eye and traction of the labial commissure) and which was preceded by hyporexia and irritability, according to the mother's report on admission. The patient underwent physical examination of all segments, but changes were only observed in the dermatological examination. According to the mother's report, the child had skin changes since birth, but initially it was a mild condition composed of small hyperchromic papules and vesicles located on the upper limbs. However, there was a progressive worsening of the lesions, mainly on the 7th day after birth, with the appearance of bubbles and grouped vesicles with an erythematous base and a yellowish center, in the upper and lower limbs, face and scalp, predominantly in the left hemibody (see images 1- 4). At that moment, the patient was admitted to the Hospital of the city of origin with suspicion of Impetigo, having been treated with antibiotic therapy and after 4 days, the blisters ruptured spontaneously and the patient was discharged with antibiotic therapy at home. However, the mother reports that the patient showed a worsening in the number and extent of the lesions and they progressed to the stage presented at admission. Pathological examination then revealed spongiotic dermatitis with eosinophilic exocytosis and melanophages in the superficial dermis, which is characteristic of Incontinence Pigmenti. Histopathological findings can be seen on image 12 (hematoxylin-eosin stain, 40X magnification) and on images 13 and 14 (hematoxylin-eosin stain, 100X magnification).

*Discussion:* The reported case brings to light the discussion about Pigmentary Incontinence (or Bloch-Sulzberger Syndrome) which is an X-linked dominant genodermatosis. Therefore, the objective of this case was to show that the general pediatrician or general practitioner are usually the first professionals to come across this patient. Therefore, these professionals need to know the IP to include it among the differential diagnoses of vesicobullous lesions in childhood and differential diagnoses of epilepsy.

*Final comments:* multisystem involvement, the management is multidisciplinary.

#### Code: PE151

##### **Presence of point mutation in APC2 gene in patient presenting Sotos'-like phenotype: a case report**

Hanid Fontes Gomes<sup>1</sup>, Carolina Paixão Santos<sup>1</sup>, Ana Clara Fandinho Montes<sup>2</sup>, Thaís Siqueira Fernandes<sup>2</sup>, Renata Beatriz Boechat Quadros<sup>1</sup>, Carolina Sanches Alvim de Oliveira<sup>1</sup>, Victoria Holcman de Marsillac<sup>1</sup>

<sup>1</sup>Hospital Municipal Jesus, Rio de Janeiro RJ, Brazil

<sup>2</sup>Instituto Fernandes Figueira, Rio de Janeiro RJ, Brazil

*Case presentation:* Six-year-old, female, daughter of nonconsanguineous parents, with normal neuropsychomotor development until her first year, with posterior developmental regression. At the age of 2, she started having absence

seizures, evolving to generalized tonic-clonic seizures. Her phenotype exhibits a triangular face, prognathism, hypertrophic gums, and accelerated growth. Additional tests: elevated FSH, IGF-1, and IGFBP-3, bone age advancement (+3 years), cerebellar vermis hypoplasia, prominent 4th ventricle communicating with the cisterna magna on MRI, diffuse bilateral point-wave complexes on EEG. GTG karyotype 46, XX, CGH Array and panel for epilepsy and inborn errors without alterations. Complete exome sequencing showing variant of uncertain significance (VUS). Due to the suspicion of hypergrowth syndrome, an exome test was requested, identifying a variant of uncertain in heterozygosity in APC2 gene c.5859\_5888del; p.(Gly1952\_Ala1961del). Although the causal relationship between such gene and Sotos syndrome, similar phenotypes with APC2 mutations have already been reported in the literature.

**Discussion:** In one of the reports, the patient presented difficulty in controlling seizures, his EKG demonstrated a wave-pointed pattern. Genome sequencing showed 2 distinct missense mutations in different alleles for APC2 (compound heterozygote). In another paper, a frameshift mutation in two siblings of consanguineous parents was presented, both showing intellectual disability, macrocephaly and prognathism.

**Final comments:** The APC2 gene has been described as fundamental to neurodevelopment. Although mutations in this gene have been associated with signs and symptoms that resemble Sotos syndrome, variations in it are still of uncertain significance. Therefore, the reporting of similar cases is necessary to elucidate a causal relationship between phenotype and genotype.

#### Code: PE152

##### Neuronal ceroid lipofuscinosis type 1: a case report

Victoria Faustino da Silva Reis<sup>1</sup>, Laís Fé Matos Galvão<sup>1</sup>, Murilo Lopes Coelho<sup>2</sup>, Samantha Lopes Oliveira<sup>2</sup>, Iana Maciel Silva Souza<sup>2</sup>, Sâmara Pinto Vasconcelos<sup>2</sup>, Juliana Silva Almeida Magalhães<sup>2</sup>, Julia Monteiro Barros Pereira Carvalho<sup>2</sup>, Camilo Vieira Santos<sup>2</sup>

<sup>1</sup>Escola Bahiana de Medicina e Saúde Pública, Salvador BA, Brazil

<sup>2</sup>Hospital Martagão Gesteira, Salvador BA, Brazil

**Case presentation:** M.I.L.S, female, 7 years old, daughter of consanguineous parents. The mother reports that the child was healthy until she was 5 years old, when she started having episodes of frequent falls and myoclonic crises, lasting less than 1 minute, without loss of consciousness, cyanosis or sphincter release. After these episodes, there was regression in neuropsychomotor development, progressive weakness in lower limb, reduced speech, and dysphagia. She was sent to a child neurologist for investigation. On physical examination, cognitive loss (does not form sentences and does not understand commands), proximal weakness, patellar reflex: +3, radial reflex: +2, positive Babinski and absence of cutaneous-abdominal reflex were evidenced. In the service, an MRI of the skull was done, which showed encephalic volumetric reduction. Accordingly, a genetic panel for epilepsy was conducted, which confirmed the diagnosis of neuronal ceroid lipofuscinosis (NCL) type 1.

**Discussion:** Neuronal ceroid lipofuscinosis constitutes a group of neurodegenerative diseases with autosomal recessive inheritance, characterized by abnormal accumulation of autofluorescent lipopigment substance within the lysosomes of neurons and other cells, being the leading cause of dementia in childhood. The diagnosis of NCL can be challenging due to the variety of described phenotypes of the disease, which

differ according to genetic involvement (NCL1- NCL14). The patient in the case reported has NCL1. The genetic investigation was done aiming the diagnosis as a treatment definer, because there is a treatment available for NCL2 with the enzyme replacement of cerliponase  $\alpha$ . In addition, there are studies in clinical phase of treatment, such as enzyme replacement therapy (NCL1 and NCL2), stem cell therapy (NCL1, NCL2, and NCL8), gene therapy (NCL1, CLN2, NCL3, NCL5, NCL6, NCL7, NCL10, and NCL11), and pharmacological treatment (NCL1, NCL2, NCL3, and NCL6).

**Final comments:** Due to the clinical picture, a genetic panel for epilepsy was performed, aiming to confirm the diagnosis of type 2 NCL and initiate treatment. However, the test revealed type 1 NCL. Although this disease has no specific treatment, the diagnosis elucidated the patient's prognosis and aided genetic counseling of her parents, as well as ensuring palliative care.

#### Code: PE153

##### Neuronal Ceroid Lipofuscinosis Type 2- Early Diagnosis Importance for Treatment Start with Cerliponase Alfa: A Case Report

Melissa Pereira de Oliveira<sup>1</sup>, Milena de Souza Alvarenga Schaffelu<sup>1</sup>, Elisa Victoria Costa Caetano Funk<sup>1</sup>, Natalia Josiele Cerqueira Checon<sup>1</sup>

<sup>1</sup>Hospital Infantil Nossa Senhora da Glória, Vitória ES, Brazil

**Case presentation:** Female patient, 4 years old, cousin parents. Normal development up to 3 years old, when seizures started as cephalic and ocular versions, labial commissure myoclonus, left upper limb flexion and left lower limb extension, lasting 5–6 minutes, in addition to atonic crises. An electroencephalogram showed paroxysms in the right temporal region, and a brain magnetic resonance imaging showed cerebellar atrophy. Treatment started with levetiracetam and valproic acid. Progressed with an increase in the frequency and duration of seizures, in addition to global ataxia. After the condition worsened, she was referred to our service for investigation. A genetic panel of epilepsies and ataxias was requested, which showed an alteration in homozygosity in the TPP1 gene, confirming the diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2). At the time of diagnosis, she scored 8/12 on the Hamburg Scale, 10/12 on the Weill Cornell scale, and 4/6 on the motor-language CLN2 scale. A court order was made the treatment with cerliponase alfa possible. This is the first patient in the Espírito Santo state who will undergo the treatment.

**Discussion:** CLN2 is a neurodegenerative disease of autosomal recessive inheritance, in which there is a deficiency of the enzyme tripeptidyl peptidase (TPP1), generating lysosomal accumulation of ceroid lipofuscin. It manifests between 2 and 4 years of age, a period of peak expression of TPP1. The main symptoms are visual loss, seizures, ataxia, movement and language disorders. The natural course is a progressive neurological decline, with death by early adolescence. Findings such as cerebellar atrophy on neuroimaging are seen in the early stages. The gold standard for diagnosis is genetic confirmation of a mutation in the TPP1 gene or evidence of reduced or absent TPP1 activity. Treatments proposed until then were palliative, but the development of cerliponase alfa, a recombinant TPP1 used as a proenzyme, brought new perspectives. A multicenter study published in 2018 showed a delay in the loss of motor and language functions after intraventricular administration, every 2 weeks, thus making it a promising proposal for the disease treatment.

*Final comments:* Cerliponase  $\alpha$  emerged as a possibility to modify the course of a serious and fatal disease. Therefore, the importance of early CLN2 diagnosis and quick access to medication is explicit. The patient in the case is eligible for treatment and the first in the state to start using the medication.

#### Code: PE154

##### **p.Arg499His mutation in SPAST associated with infantile-onset complicated spastic paraplegia in a child with bilateral retinoblastoma: association or coincidence?**

Louise Scridelli Tavares<sup>1</sup>, Bryan da Silva Marques Cajado<sup>1</sup>, Mateus Oliveira Torres<sup>1</sup>, Lorena Raulik Cyrino<sup>1</sup>, Caroline Corrêa Maranhão<sup>1</sup>, José Marcos Vieira Albuquerque<sup>1</sup>, Alulin Tácio Quadro Monteiro Fonseca<sup>1</sup>, Ricardo Silva Pinho<sup>1</sup>, Marcelo Aragão Moraes<sup>1</sup>

<sup>1</sup>Universidade Federal de São Paulo, São Paulo SP, Brazil

*Case presentation:* Patient was the first child of non-consanguineous parents whose father was healthy, but mother had mild intellectual deficiency and spastic paraparethic gait that had been attributed to cerebral palsy. At birth he presented congenital talipes equinovarus. He began to crawl at 1yo but was never able to walk independently despite orthopedic feet correction. At 1yo, leukocoria in the left eye was noticed. Bilateral retinoblastoma was diagnosed by the age of 2y 9m. He was submitted to primary bilateral enucleation that confirmed extra-ocular bilateral undifferentiated retinoblastoma. At 3yo it was noticed prominent forehead, underdeveloped supraorbital ridges, low set ears, triangular shaped face, tongue protrusion, long hand and feet fingers, axial hypotonia, upper limb hypotonia, lower limb hypertonia, oral hypotonia and tendon reflexes were 4+ globally, with unsustained knee clonus and bilateral extension of hallux. He emitted guttural sounds and only partially obey commands. His MRI showed post-surgical manipulation status in both orbits and bilateral hippocampal rotation. A genetic panel revealed a heterozygous pathogenic missense variant, c.1496G>A (p.Arg499His), confirming the autosomal dominant hereditary spastic paraplegia 4 (SPG4) diagnostic.

*Discussion:* Hereditary Spastic Paraplegia (HSP) is a group of neurodegenerative disorders with wide range of different genetics and phenotypes. SPG4, caused by a pathogenic variant in gene SPAST, is the most frequent type and in most cases is considered a pure HSP, rarely associated with additional neurological signs. Exceptionally, patients with p.Arg499His mutations are associated with complicated phenotypes and also suffered from a more severe type of spastic paraplegia with onset within 2 year of life. Retinoblastoma cells contain a mutation or deletion of the retinoblastoma gene (RB1 gene), a tumor-suppressor gene, located on chromosome 13q. In literature, cases of SPG and retinoblastoma has not been described.

*Final comments:* We have not found sufficient evidence to support a causal association between the presence of bilateral retinoblastoma and SPG4. SPG 4 usually presents in motor pure HSP. This rare report case aims to describe a infantile-onset complicated spastic paraplegia due to p.Arg499His mutation in SPAST, presenting with language and cognitive delay in a child with bilateral retinoblastoma. This rare association represents a challenging case and aims to raise awareness for cerebral palsy mimics.

#### Code: PE155

##### **Pearson's syndrome: a case report**

Lorena Vilela Rezende<sup>1</sup>, Julia Vilela Rezende<sup>2</sup>, Michelle Silva Zeny<sup>1</sup>, Rui Carlos Silva Júnior<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Mariah Pereira de Andrade Vallim<sup>1</sup>, Elisabete Coelho Auersvald<sup>1</sup>, Mara Lucia Schmitz Ferreira Santos<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

<sup>2</sup>Centro Universitário de Mineiros, Mineiros GO, Brazil

*Case presentation:* VTG, 2 years old, daughter of non-consanguineous parents, born by cesarean section at 35 weeks. At birth, he had neonatal sepsis and hypoglycemia. At 3 months, he started generalized tonic-clonic seizures associated with behavioral arrest seizures and ocular version, refractory to treatment and optimization of antiepileptic drugs. In addition to neuropsychomotor developmental regression, sleep disturbance, behavioral changes, severe malabsorptive syndrome, dystonia, hepatitis with aspartate aminotransferase transaminase levels: 207 alanine aminotransferases: 186, severe pancreatitis and clotting disorder with epistaxis, gingival bleeding, and melena. During the investigation, he had a magnetic resonance imaging of the skull with a slight reduction in brain volume and spectroscopy without alterations. Video electroencephalogram with slowed background activity, slightly disorganized for age. Rare irregular epileptiform discharges of focal projection in the right frontal region, isolated. And complete exome sequencing with double mutation in cis of the POLG gene – Haplotype. Mutation in the POLG Gene in heterozygosity - double mutation. A segregation study was performed for parents who do not have the described mutation. And so, the reclassification of the mutation as pathogenic. Closing diagnosis of Pearson Syndrome (OMIM 557000), Gene MT-CO2: Chr12(GRCh37) NC\_012920.1:m.8480\_13440del. He progressed to total parenteral nutrition, requiring regular vitamin K replacement, and using levetiracetam, phenobarbital, midazolam, chlorpromazine, B complex, folic acid, haldol, trihexyphenidyl and cannabidiol, with partial control of myoclonic seizures and behavioral arrests.

*Discussion:* Pearson Syndrome (PS) is a multisystem disease caused by a deletion in mitochondrial DNA that ranges from 2 to 10 kilobases in size. The hallmarks are sideroblastic anemia and pancreatic insufficiency. In addition to hematologic and pancreatic symptoms, SP can harm the heart, kidneys, eyes, ears, and brain. Since its discovery in 1979 by Howard Pearson, there have been only ~100 cases reported in the medical literature. The syndrome is usually fatal in childhood. Those who survive beyond childhood develop signs and symptoms of Kearns-Sayre Syndrome or Progressive External Ophthalmoplegia.

*Final comments:* There is still no cure, there is ongoing research in general with gene therapies among others for mitochondrial diseases. Preventive measures aim to avoid secondary physiological stressors.

#### Code: PE157

##### **SCA 5: a Differential Diagnosis of Ataxic Cerebral Palsy**

Maria Luiza Benevides<sup>1</sup>, Paula Thaís Bandeira Elias<sup>1</sup>, Fernando Ferrão Antônio<sup>1</sup>, Larisse Souza de Moraes Somavilla<sup>1</sup>, Ana Carolina Piauilino Santos Falcão<sup>1</sup>, Isabelle Salgado Castellano<sup>1</sup>, Marcondes Cavalcante França Júnior<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas SP, Brazil

*Case presentation:* A 2.5-year-old girl presented to the Outpatient Neurogenetic Clinics of tertiary reference center, with motor delay since birth. At 2.5 years, she does not crawl, stands or walk. Perinatal history was unremarkable, there

was no history of consanguinity, neither family history of neurological diseases. Neurological exam showed a cognitive and speech delay. Her speech was dysarthric. Cranial nerves were intact with normal extraocular movements and without nystagmus. Muscle tone was globally reduced and ankle joints had limited range of movement. Muscle strength was normal. Deep tendon reflexes were globally attenuated. She presented with predominant axial ataxia and mild appendicular ataxia. She was able to stand with the support of knee-ankle-foot orthoses. Electromyography and nerve conduction were normal. Brain MRI showed reduced volume of the cerebellar vermis and hemispheres associated with mild prominence of the inferior olive nucleus. Standard laboratory tests were normal. Whole exome sequencing (WES) showed a de novo heterozygous likely-pathogenic missense variant in SPTBN2 (NM\_006946.3: c.1052G>C, p.Arg351Pro), previously associated with Spinocerebellar ataxia type 5 (SCA5).

**Discussion:** The spinocerebellar ataxias (SCAs) are genetic disorders characterized by incoordination, cerebellar ataxia, dysarthria, and swallowing difficulties. SCA5 is a rare subtype of SCA caused by heterozygous variants in the Spectrin  $\beta$  nonerythrocytic 2 (SPTBN2) gene, and it usually affects adults. It has been recently reported in children in Europe, North America, China, and Brazil.

**Final comments:** SCA5 is a relevant clinical and genetic entity for neurologists, pediatric neurologists, pediatricians, and geneticists, particularly considering the differential diagnosis of ataxic cerebral palsy and the autosomal recessive cerebellar ataxias.

#### Code: PE162

##### **Tay-Sachs disease without cherry-red spot: a case report**

Isadora Cristina Barbosa Lopes<sup>1</sup>, Mariane Wehmuth Furlan Eulalio<sup>1</sup>, Ana Clarice Bartosiewicz Prestes<sup>1</sup>, Melanie Scarlet Diaz Solano<sup>1</sup>, Eduarda de Boer Fursgtenberger<sup>1</sup>, Carolina Oliveira de Paulo<sup>1</sup>, José Antonio Coba Lacle<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>

<sup>1</sup>Hospital Universitario Evangelico Mackenzie, Curitiba PR, Brazil

**Case presentation:** Boy, 4 years old. Born term, cesarean for oligohydramnios, without consanguinity. Mother with hypothyroidism, maternal uncle with autism, maternal cousin with epilepsy and paternal cousin with cerebral palsy. Adequate neuropsychomotor up to 2 years of age. At this age, started with ataxic gait, refractory epilepsy, spasticity, language loss and dysphagia. Multiple hospitalizations due to bronchoaspiration pneumonia. Gastrostomy and tracheostomy were performed at 4 years of age. He used levetiracetam, clobazam, valproic acid, nitrazepam and phenytoin at optimized doses, still with bad control of epilepsy. Followed up by palliative care. Cranial MRI showed hyperintensity on T2/FLAIR in the white matter (subinsular, periventricular, thalamus, internal capsule's posterior arm and dentate nucleus). Genetic exam with two heterozygous variants in HexA. Fundoscopic exam was normal. Death at 4 years and 11 months due to status epilepticus.

**Discussion:** Tay-Sachs disease is a lysosomal maintenance disorder with autosomal  $\beta$  deficiency in the HexA gene. It results in progressive accumulation of GM2 gangliosides in the lysosomes of nerve cells, causing neurodegeneration in childhood (infant form). In adolescents and young adults, it's rare (juvenile form). The patient had typical symptoms of the infant form. In a retrospective study, 90% of patients with GM2 gangliosidosis exhibited cherry-red spots. In another study, 88% of patients had this same change. In the case

described, there aren't typical retinal problems, which is uncommon. Treatment is based on epilepsy control, nutrition and rehabilitation, especially in the infant form, which has a life expectancy of ~5 years. The treatment in this case was focused on combined anticonvulsant therapy as well as nutritional support and palliative care therapy. The patient died at an age close to the average observed in the literature. **Final comments:** Absence of ophthalmological alterations in a patient with neurodevelopmental regression doesn't exclude Tay-Sachs disease, given that the cherry-red spot isn't mandatory for this diagnosis.

#### Code: PE163

##### **Unilateral retinoblastoma, autism spectrum disorder and macrocrania in 13q deletion syndrome: a case report**

Vinicius Alves Lima<sup>1</sup>, Louise Scridelli Tavares<sup>1</sup>, Felipe Arthur Almeida Jorge<sup>1</sup>, Bryan da Silva Marques Cajado<sup>1</sup>, Katrine de Freitas Valeriano<sup>1</sup>, José Marcos Vieira Albuquerque Filho<sup>1</sup>, Alulin Tácio Quadro Monteiro Fonseca<sup>1</sup>, Marcelo Aragão Moraes<sup>1</sup>, Ricardo Silva Pinho<sup>1</sup>

<sup>1</sup>Universidade Federal de São Paulo, São Paulo SP, Brazil

**Case presentation:** The patient was the first child of healthy non-consanguineous parents. She was a late preterm, infant of a diabetic mother and born in cesarean due to polyhydramnios. By the age of one year old, the family noticed leukocoria in the right eye and she was diagnosed with unilateral retinoblastoma. Histopathological analysis was compatible with unilateral differentiated group D retinoblastoma. She was successfully treated with primary enucleation and chemotherapy with vincristine, carboplatin and etoposide. At the age of 2 years old, she was submitted to neurological consult due to language delay and impairment in communication skills. Primary consult revealed macrocrania (>2 SD Nellhaus), poor eye contact, poor nonverbal conversation skills, hand stereotypies. She could only emit disyllables, had difficulty interacting with other children, would only engage in parallel and showed tactile hypersensitivity. She had normal motor development and presented with lower limb areflexia with normal force due to chemotherapy-induced peripheral neuropathy. Her exam showed a prominent forehead, sharp face, big and low set ears, smooth philtrum and long fingers. Also, she met autism spectrum disorder (ASD) criteria. Her MRI only showed the post-surgical site manipulation. A karyotype was performed and revealed 46, XX, del(13)(q12q14).

**Discussion:** Retinoblastoma is a pediatric ocular tumor caused by biallelic inactivation of the RB1 gene, located in 13q14.2. In 10% of those patients, this deletion also involves additional genes surrounding the RB1 genome, causing a rare contiguous gene deletion condition defined as 13q deletion syndrome. These patients manifest with heterogeneous phenotypes that correlates with the size and location of the deletion. Usually presents with increased risk of retinoblastoma, development disorders, including autism spectrum disorder (ASD) and craniofacial dysmorphism.

**Final comments:** We report a case of contiguous gene deletion condition defined as 13q deletion syndrome, characterized by unilateral retinoblastoma, macrocrania, facial dysmorphism and autism spectrum disorder criteria. Throughout this data, we aim to raise awareness to this genotype-phenotype and advocate periodic screening for retinoblastoma to patients with 13q deletion syndrome aiming to reduce the morbimortality related to this entity.

## Neuroimagem

Code: PE164

### Gomez Lopez Hernandez syndrome: a case report

Nicholas Santos Barros<sup>1</sup>, Clarice Semiao Coimbra<sup>1</sup>, Ana Beatriz Arruda Carvalho Oliveira<sup>1</sup>, Cristiani Rocha Lima Cruz<sup>1</sup>, Daniel Shoji Hayahi<sup>1</sup>, Joemir Jabson Conceição<sup>1</sup>, Renata Silva Mendonça<sup>1</sup>, Marco Antonio Veloso Albuquerque<sup>1</sup>, Clarissa Bueno<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, São Paulo SP, Brazil

**Case presentation:** Female patient, 8 years old, born in Itanhaem, from São Paulo, with a previous context of hypotonic infant syndrome, repetitive head nodding movements, convergent strabismus, alopecia, low implantation of the ears and short stature. On evaluation, he was alert, without language alterations, low threshold for fructation, difficulty concentrating, hyperactivity, but without evidence of intellectual disability. Alopecia on the left forehead, low ear implantation, global grade 5 muscle strength, normoactive osteotendinous reflexes, no clonus, no fasciculations, adequate tone and trophism. Abnormal “no-no” head movements, with inhibition by eye fixation for up to two seconds, mild dysmetria and intention tremor. Broad-based gait, imbalance and fall without a preferred side to the tandem, with trunk instability. She assumed the nine gaze positions without diplopia, had limited saccades with cervical correction. Hypoesthesia on the left face, absent left palpebral corneal reflex, with balaclava pattern, normal jaw movement. Cranial MRI showed partial rhombencephalosynapse and hypoplasia of the left trigeminal nerve.

**Discussion:** The clinical picture allowed the clinical diagnosis of Gomez Lopez Hernandez syndrome, also known as Cerebellotrigeminal Dermal Dysplasia, characterized by the triad rhombencephalosynapse, trigeminal anesthesia and alopecia, in addition to other heterogeneous clinical features that vary from case to case, such as midface hypoplasia, turricephaly, prognathism, hypertelorism, low implantation of the ears, short stature, corneal opacity, ataxia, intellectual disability and delayed neuropsychomotor development. The pathophysiology involved is still not fully understood, the most accepted theory is the failure of migration of ectoderm cells around the 4th month of gestation, with no confirmed evidence of genetic influence. Differential diagnosis must be considered between CEBALID (autosomal dominant mutation in the MN1 protooncogene) and VACTERL syndromes. Treatment involves a multidisciplinary team for rehabilitation, important to emphasize the risk of corneal injuries.

**Final comments:** In conclusion, despite being rare, the condition described must be known and differentiated from the others, to ensure correct management and better quality of life for patients.

## Neuroimunologia, esclerose múltipla e outras doenças desmielinizantes

Code: PE165

### Acute disseminated encephalomyelitis (ADEM) in children: a case report

Nicole Zanardo Tagliari<sup>1</sup>, Felipe Neto Kalil<sup>1</sup>, Silvana Palmeiro Marcantonio<sup>1</sup>, João Ronaldo Mafalda Krauzer<sup>1</sup>, Mariana Menengon de Souza<sup>1</sup>, Mariane Cibelle Barreto da Silva Barros<sup>1</sup>, Débora Dettmer<sup>1</sup>, Cristina Detoni Trentin<sup>1</sup>, Fernanda Chaves Barcellos Carvalho<sup>1</sup>

<sup>1</sup>Hospital Moinhos de Vento, Porto Alegre RS, Brazil

**Case presentation:** Female, 2 years old, admitted in emergency with fever and backache, evolving with abnormal sleepiness. At hospital admission, disoriented, ataxic and sleepiness, without signs of meningeal irritation. Encephalitis is suspected and a lumbar puncture was performed. Analysis of cerebrospinal fluid (CSF) excluded infectious causes of central nervous system. Brain magnetic resonance (MRI) shows hypersignal on T2/FLAIR in the pontine tegmentum, extending to the medial aspect of the middle cerebellar peduncles and dentate nuclei. Spine MRI shows alterations suggestive of extensive longitudinal myelitis, with signal alteration at the pons and medulla. Acute disseminated encephalomyelitis (ADEM) is suspected. Treatment with methylprednisolone 30mg/kg/day was performed, showing progressive improvement. Discharged for outpatient follow-up with neuropsychiatric, physical therapy and prednisolone 1mg/kg/day for 30 days.

**Discussion:** ADEM is an inflammatory demyelinating disease of the central nervous system (CNS) present in childhood, characterized by encephalopathy and multifocal brain lesions with involvement of the cerebral white matter and spinal cord. It has annual incidence of 5:10.000 children, with a mean age of onset of 3 to 7 years. It is a disease that manifests in a genetically susceptible individual, with sudden onset and polysymptomatic presentation, including meningeal signs, fever and encephalopathy, usually preceded by viral infection or recent vaccination. Involves the cortex, as well as lesions in the deep portions of the brain, including the basal ganglia region, brainstem region and cerebellum. ADEM is considered a diagnosis of exclusion, requiring neuroimaging and laboratory studies to exclude other potential diagnosis. MRI is the exam of choice for evaluation. Almost all patients have multiple subcortical lesions, typically bilateral and asymmetrical, characteristic of demyelination. The CSF analysis can be normal, but usually shows inflammatory evidence with pleocytosis and increased protein. Acute therapies include high-dose corticosteroids, plasmapheresis and immunoglobulin. The long-term prognosis is usually favorable, with a recovery over 4 to 6 weeks.

**Final comments:** ADEM is a demyelinating disease of the CNS, usually presenting itself as a monophasic disorder associated with multifocal neurological symptoms and encephalopathy, preceded by infectious events and can simulate other autoimmune and infectious disorders. Requires early diagnosis and treatment for a good prognosis.

Code: PE166

### An atypical phenotype of myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD)

Eduardo Ferraz Troijo<sup>1</sup>, Manoel Jacinto de Abreu Neto<sup>1</sup>, Ingrid Lacerda Pessoa<sup>1</sup>, Marcela Gonçalves de Souza Machado<sup>1</sup>, Rafael Paternò Castello Dias-Carneiro<sup>1</sup>, Érico Induzzi Borges<sup>1</sup>, Luiza Oliveira Prata Silveira<sup>1</sup>, Anna Carollina Eulalio Amorim Baratta<sup>1</sup>, Debora Carinhato Thomaz<sup>1</sup>

<sup>1</sup>Santa Casa de São Paulo, São Paulo SP, Brazil

**Case presentation:** A previously healthy boy, aged 3 years and 2 months, with no relevant perinatal or personal history and with normal neuropsychomotor development, started with monoparesis of the right lower limb that evolved in 4 days to hemiparesis without change in level of consciousness or behavior. Neurological examination showing hemiparetic gait. Hyperreflexia, more evident in right hemibody members. Absence of Babinski sign. Screening laboratory tests were normal. Brain MRI showed diffuse hyperintensity on T2/FLAIR white matter, extending through the temporal, occipital and bilateral parietal regions, more markedly on the left, with bilateral punctate areas of contrast medium uptake. In

view of the initial condition, corticosteroid therapy was initiated with complete remission of hemiparesis in 3 days. It was then decided to maintain corticosteroid therapy and complement the investigation with an anti-MOG antibody test whose result was positive. He maintained a normal neurological exam in the outpatient visits and control MRI showed improvement in the lesions.

**Discussion:** Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease (MOGAD) represents 34% of pediatric acquired demyelinating disease cases. The phenotypes vary according to the age of presentation, with optic neuritis (in all age), ADEM (in children) and myelitis (in adolescents) being more common. Other less frequent phenotypes were described, including a phenotype supported by bilateral and relatively symmetrical white matter commonly described as Leucodystrophy-like phenotype. Although the imaging exam and the patient's age corroborate the picture of this type, the dystrophy-like phenotype is a recurrent condition characterized by encephalopathy, ataxia, optic neuritis and seizures, with long-term behavioral impairment and intellectual deficit. About 50% of children with MOGAD will have a recurrence, so do not rule out the possibility of developing this phenotype in the future.

**Final comments:** The phenotypic description of MOGAD cases is important to the determination of patient's prognosis. A better understanding and prediction of outcome is essential to guide treatment decisions.

**Code: PE167**

**Anti-N-Methyl-D-Aspartate receptor encephalitis by prior Epstein barr infection**

Caroline Razera<sup>1</sup>, Dayane Danieli<sup>1</sup>

<sup>1</sup>Universidade Federal do Mato Grosso do Sul, Campo Grande MS, Brazil

**Case presentation:** Female, 8 years old, previously healthy, referred to our service due to 10 days of agitation and excessive crying associated with a fever peak. Evolved with seizures, self-harm behavioral changes, dysarthria, visual hallucinations, and movement disorders. On admission, presence of drowsiness, mental confusion, and dyskinetic appendicular orofacial movements. General laboratory tests, cultures, and brain magnetic resonance imaging (MRI) without changes. Initial cerebrospinal fluid (CSF) analysis with lympho-monocytic pleocytosis without serology results. Treatment with an antiviral (acyclovir) was started due to the initial hypothesis of infectious encephalitis. Child with worsening symptoms, new seizures, lowered level of consciousness, and intubation need. Electroencephalogram (EEG) with moderate disorganization of background rhythm without epileptiform paroxysms. Given the patient's clinical deterioration over the days, a hypothesis of autoimmune encephalitis (AE) was made. Presence of IgM reagent for Epstein-Barr Virus (EBV) in the serum with remaining serologies negative. Herpes simplex virus-1 search on negative LQR. The patient received pulse therapy with methylprednisolone and intravenous immunoglobulin (IVIG). Encephalitis was confirmed by the positive presence of anti-NMDA receptor (anti-NMDAR) on LQR (1:16) and in the blood (1:800). Associated tumors were ruled out. 15 days past IVIG, there was a significant clinical improvement. Currently asymptomatic.

**Discussion:** Anti-NMDAR encephalitis is the second most frequent cause of encephalitis. The first stage with a prodromal phase both respiratory and gastrointestinal symptoms

are around 70%, although systemic infections are not associated. Behavioral changes and epileptic seizures are the most frequent initial symptoms in children. In this case, we had the occurrence of AE after primary EBV infection. It is believed in viral DNA reactivation during an autoimmune condition, and it cannot be ruled out that neurotropic viruses are responsible for triggering the various cellular immune mechanisms that cause AE. Our patient evolved with complete recovery after ~1 month and normal MRI, thus suggesting that the AE resulted from a post-infectious autoimmune response.

**Final comments:** Anti-NMDAR encephalitis is still a challenging diagnosis, and may evolve after viral infections and with a wide range of symptoms and easily confused with other encephalitis or psychiatric conditions.

**Code: PE168**

**Challenging diagnosis of myelin oligodendrocyte glycoprotein (MOG) antibody: positive optic neuritis**

Nathalia Jamille Moreira Nascimento David<sup>1</sup>, Bruna Campos Cardoso Vilela<sup>1</sup>, Sanny Kemelly Miquelante Yoshida<sup>1</sup>, Laura Maria Silva Thiersh<sup>1</sup>, Thais de Almeida Fonseca Oliveira<sup>1</sup>, Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, Renan Guimarães Santana<sup>1</sup>, André Vinícius Soares Barbosa<sup>1</sup>, Karina Soares Louf<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

**Case presentation:** Ten year-old female presented whit visual loss and ocular pain with extraocular movements in the left eye and papilledema. After 15 days, it progressed to the right eye. No other neurological symptoms were observed. The case was investigated with optical nerve magnetic resonance imaging (MRI), which evidenced enhancement of the optical nerve with perineural involvement, and brain and spinal cord MRI without demyelination. Cerebrospinal fluid demonstrated pleocytosis (31 cells) and gammaglobulin increase (19%), without oligoclonal immunoglobulin G bands elevation. Anti-aquaporin-4 (AQP4) IgG, by Cell Based Assay, presented negative. Treatment with methylprednisolone was initiated, with adequate response. After 1 and 3 years, there were relapses, with similar symptoms of neuritis. Imaging in MRI (brain, optic nerve and spinal cord) was maintained, and no other neurological alterations were observed. After the last attack, testing for MOG-IgG became available, which presented positive results. Treatment with steroids and azathioprine was sustained, without new acute attack until this moment.

**Discussion:** The presentation of MOG-IgG-positive optic neuritis is diverse. In most cases it is recurrent and may occur with or without other neurological symptoms. It should be suspected when severe optic disc edema and optic nerve sheath involvement in MRI are observed and AQP4-IgG is negative. Compared with AQP4-IgG-positive patients better outcomes for visual recovery are expected, despite recurrence and severe visual loss during attacks.

**Final comments:** MOG-IgG antibody testing has become more available, and it provides the correct diagnosis and differentiate it from multiple sclerosis. Therefore, this diagnostic test is important to predict the prognosis and to guide the treatment.

Code: PE169

**COVID-19 infection as trigger of chronic inflammatory demyelinating polyneuropathy (CIDP)**

Rafaela Fernandes Dantas<sup>1</sup>, José Albino da Paz<sup>1</sup>, Ana Lucila Moreira<sup>1</sup>, Ana Cristina Azevedo Leão<sup>1</sup>, Roberta Diniz de Almeida<sup>1</sup>, Nicholas dos Santos Barros<sup>1</sup>, Eric Oneda Sakai<sup>1</sup>, Cristiani Rocha Lima Cruz<sup>1</sup>, Ana Beatriz Arruda Carvalho de Oliveira<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Case presentation:** In March 2020, during the first outbreak of COVID-19 pandemic, a seven years-old boy, presented flu-like symptoms with anosmia. The parents presented the same symptoms but did not search medical service. Around 8 weeks later, he presented an acute progressive symmetric ascending flaccid tetraparesis, evolving 28 days after to the worst weakness in lower limbs, being at this moment unable to walk without support. The cerebrospinal fluid (CSF) showed albuminocytologic dissociation; electroneurography demonstrated demyelinating sensory and motor polyneuropathy. Serological test for SARS-CoV-2 IgG result was positive. Patient was diagnosed with Guillain Barré Syndrome (GBS). On follow up he showed neurological improvement.

**Discussion:** In January 2022, he presented the same clinical picture of the initial event, preceded by flu-like symptoms 4 weeks before. At the hospital admission RT-PCR of nasal swab for SARS-CoV-2 was positive. CSF showed albuminocytologic dissociation, and electroneurography demonstrate peripheral motor sensory demyelinating polyneuropathy with secondary motor axonal degeneration, evidencing another demyelinating event. Intravenous immunoglobulin pulse was initiated with improvement and discharge after 8 days. Nerve ultrasound in right upper limb and cervical region, identified enlarged proximal median and ulnar nerves, and bilateral C6-C7 root nerve enlargement, hence, differential diagnostic as CIDP was made.

**Final comments:** CIDP is a rare autoimmune disorder in the spectrum of GBS, a chronic/progressive disorder. During the outbreak of COVID-19, several autoimmune neurological diseases have been reported associated. We present a challenging pediatric case of COVID-19 as trigger of CIDP.

Code: PE171

**First demyelinating event with atypical evolution after vaccination in a pediatric patient: a case report**

Isadora Cristina Barbosa Lopes<sup>1</sup>, Mariane Wehmuth Furlan Eulalio<sup>1</sup>, Ana Clarice Bartosiewicz Prestes<sup>1</sup>, Melanie Scarlet Díaz Solano<sup>1</sup>, Eduarda de Boer Furstenberger<sup>1</sup>, Carolina Oliveira de Paulo<sup>1</sup>, José Antônio Coba Lacle<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>

<sup>1</sup>Hospital Universitario Evangelico Mackenzie, Curitiba PR, Brazil

**Case presentation:** Girl, 4 years old, healthy. Admitted with right hemiplegia, right central facial paralysis and aphasia over 15 days. Vaccines for triple viral and influenza given in the previous month. No recent infection. Magnetic Resonance Imaging (MRI) with angiography showed hypersignal on T2/FLAIR in the nucleus-thalamo-capsular region, corona radiata and external capsule on the left, without vasculopathy. Negative serology for anti-NMDAR, cultures also negative. Normal ocular funduscopy. Partial improvement after pulse therapy. Evolved with progressive worsening of symptoms over two weeks, encephalopathy and seizures requiring new hospitalization. Human immunoglobulin 2 g/kg was infused, but patient persisted with global deficits. Serology for human immunodeficiency virus and rheumatological tests negative.

New MRI showed extensive lesion on the left of frontotemporal region, corpus callosum and thalamus on the right, compatible with demyelination. After 1 week of immunoglobulin a new pulse therapy was performed. Discharged with residual symptoms of right hemiplegia, mild dysphagia and motor aphasia.

**Discussion:** Acute Disseminated Encephalomyelitis (ADEM) is defined as the first episode of demyelization with multifocal deficits and encephalopathy. Typically occurs after infection or immunization. Symptoms improve in a few days, usually recovery in a month and with good response to immunotherapy. MRI shows in the most cases generalized injuries, especially in the basal ganglia and thalamus bilaterally. The patient described started with a single unilateral lesion that evolved in more than a month with bilateral injuries and encephalopathy. She has a recent vaccination history and lesions in a topography compatible with ADEM. She showed limited response to immunotherapy, maintaining residual symptoms. 32 to 50% of children and adolescents with a first acquired demyelination event evolve to multiple sclerosis in 5 years. Tests for diagnosis of multiple sclerosis, anti-MOG and neuromyelitis spectrum are requested, considering that atypical cases of these pathologies have already been reported and treatment is individualized.

**Final comments:** An initial presentation with localized symptoms and a single lesion on imaging don't exclude demyelinating events. Long-term follow-up and specific serologies will define chronic causes.

Code: PE172

**Guillain-Barre Syndrome: Case Series**

Layanna Bezerra Maciel Pereira<sup>1</sup>, Renata Yasmin Cardoso Sousa<sup>1</sup>, Lygia Ohlweiler<sup>1</sup>, Dayana de Lima Mariano<sup>1</sup>, Michele Michelin Becker<sup>1</sup>, Maria Isabel Bragatti Winckler<sup>1</sup>, Gabriel de Lellis Neto<sup>1</sup>, Hugo Leonardo Justo Horácio<sup>1</sup>, Josiane Ranzan<sup>1</sup>

<sup>1</sup>Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil

**Case presentation:** Guillain-Barré Syndrome (GBS) is an acute polyradiculopathy that occurs frequently following infectious diseases, which can lead to an immune response to nerve antigens, resulting in demyelination and/or axonal damage. Below, we will report 4 clinical cases of GBS associated with previous SARS-Cov-2 in pediatric patients. One patient was diagnosed with COVID by PCR testing and three with serology testing. Two patients had previous comorbidities – one had Cantu Syndrome and another had Glycogenosis type Ib. The diagnosis of GBS was confirmed by albuminocytologic dissociation in the cerebrospinal fluid in 3 cases, electroneuro-miography with demyelination pattern in all 4 cases, and one patient had brain magnetic resonance imaging showing contrast enhancement in the cauda equina e medullary cone, compatible with inflammatory process. The patients with previous comorbidities evolved with respiratory failure and required mechanical ventilation. 3 patients received intravenous immunoglobulin (IVIg), with adequate response. One of them required two IVIg cycles.

**Discussion:** The association between GBS and coronaviruses has been previously reported following such infections, including MERS-Cov (KIM et al., 2017) and, more recently, SARS-CoV-2. COVID-19 causes an exaggerated immune response with persistent fever, elevated inflammatory markers and pro-inflammatory cytokines. It is likely an immune dysregulation caused by COVID-19 that increases the risk of immune mediated conditions, such as GBS. It can occur as classic post-infectious disease or as part of the already reported Long COVID-19 Syndrome. The majority of reported cases begin acutely a few days after the viral infection.

**Final comments:** In neurologic presentations compatible with GBS in pediatric patients, we must consider previous or acute SARS-CoV-2 infection as the possible etiology.

**Code:** PE173

**Miller Fisher syndrome after COVID-19 vaccination: a case report**

Melanie Scarlet Diaz Solano<sup>1</sup>, Mariane Wehmuth<sup>1</sup>, Ana Clarice Prestes<sup>1</sup>, Isadora Cristina Barbosa Lopes<sup>1</sup>, Jose Antonio Coba Lacle<sup>1</sup>, Carolina Oliveira de Paulo<sup>1</sup>, Eduarda Furstenberger<sup>1</sup>, Danuta Iatchuk Gomes<sup>1</sup>

<sup>1</sup>Hospital Universitario Evangelico Mackenzie, Curitiba PR, Brazil

**Case presentation:** 17-year-old male patient, previously healthy. Two weeks prior to symptoms reports immunization against COVID-19. Admitted presenting asthenia, limb paresthesia, ophthalmoparesis, diplopia, ataxia, decreased muscle strength with ascending progression, urinary and fecal incontinence, peripheral facial paralysis, dysphagia, dysphonia and mental confusion. The neurological examination showed global areflexia, grade IV strength in upper limbs and grade III strength in lower limbs. During hospitalization evolved with respiratory failure and need for orotracheal intubation. Cranial MRI showed neuritis of the facial nerves and spinal MRI showed enhancement of the roots of the cauda equina. CSF with cytological protein dissociation, suggestive of Guillain-Barré Syndrome Variant of Miller Fisher. He was treated with intravenous human immunoglobulin 400 mg/kg/day for 7 days with partial improvement of symptoms. He needed a mature tracheostomy due to difficulty in extubation. After 23 days, he was discharged to a rehabilitation hospital.

**Discussion:** Miller Fisher syndrome (MFS) is a multifocal neuropathy that presents with ataxia, ophthalmoplegia and areflexia. Cranial nerves may be involved, especially the facial nerve. It is a rare variant of Guillain-Barré Syndrome. Associated with viral infection of the gastrointestinal or respiratory tract, or Campylobacter infection. Few cases are reported associated with COVID vaccination, and pediatric cases are rare. After COVID-19 peripheral nerve immunity response, means of molecular mimids against ganglia. In SMF, there is formation of anti-GQ1b (Anti-GQ1b), but due to its high cost, a protein-cytological dissociation in the CSF should be sought. The time interval between vaccination and the onset of MFS was 15 days similar to previous case reports in the adult population. The prognosis is generally favorable as it is a self-limiting disease that responds to immunoglobulin treatment.

**Final comments:** Recent vaccination and absence of any other signs or laboratory findings suggest that the vaccine is the trigger. Additional research is needed to establish an association between SMF and COVID-19 vaccination. The risk is low and the benefits of vaccination outweigh any potential risks or side effects.

**Code:** PE174

**Pediatric multiple sclerosis post covid: a case report**

Pietra Giovana Polisel<sup>1</sup>, Gilberto Hishinuma<sup>1</sup>, Greice Woloszin<sup>1</sup>, Rafaela dos Santos Pinheiro<sup>1</sup>, Tainara Carfane Gomes<sup>1</sup>

<sup>1</sup>Unicesumar, Maringá PR, Brazil

**Case presentation:** Female adolescent, 15 years old, complains that for 6 months she has felt generalized muscle weakness and that has increased in recent days associated with changes in muscle sensitivity in left dimidium, evolving in 1 week to the right and ~15 days after, culminates with bilaterally lower limb plegia. She denies fever and use of medication for continuous use. Her relevant personal history is: tested positive for SARS-CoV-2 6 months before neurolog-

ical symptoms. In the neurological evaluation, the muscular strength of the lower limbs was symmetrical of IV and V in the upper limbs, sensory level close to the thoracoabdominal transition (T9-T10) (with impairment of tactile, pain, vibratory and proprioceptive sensitivity), abolished Aquileus reflex, flaccid paraparesis of lower limbs with exaltation of patellar reflexes. Patient, in the absence of infectious signs, was hospitalized and conducted to methylprednisolone pulsotherapy associated with Omeprazole and Albendazole. The patient was initially classified as Clinically Isolated Syndrome (CIS) and the diagnosis of the disease was later closed with the result of the liquoric puncture with oligoclonal bands present and thus, the transition was made to the therapy with Glathyromer Acetate, Gabapentin and Vitamin D.

**Discussion:** Although the pathophysiological mechanisms of SARS-CoV-2 are not completely elucidated, its neuroinvasive capacity is already known for the emergence of post-infectious neurological complications. In the case described, the patient had acute neurological symptoms of paresis, plegia and loss of muscle sensitivity ~6 months after infection with COVID-19. As it is a viral infection with complications in multiple systems and, among them, the central nervous system by neurotropism, it is likely that COVID-19 has played a trigger role for the development of MS. The subsequent liquoric puncture with the presence of oligoclonal bands made it possible to confirm the DM picture by applying the diagnostic criteria of McDonald 2017.

**Final comments:** Although there is little scientific evidence available on this subject, we believe that there is a late stage of multiple sclerosis, probably associated with SARS-CoV-2 infection. Thus, we expect that the exposure and discussion of this clinical case might collaborate - as a form of evidence-, with the knowledge at the disposal of this pathology in pediatrics.

**Code:** PE175

**Post-vaccination Guillain-Barre syndrome: a case report**

Nicholas dos Santos Barros<sup>1</sup>, José Albino da Paz<sup>1</sup>, Renata Barbosa Paolilo<sup>1</sup>, Clarice Semião Coimbra<sup>1</sup>, Roberta Diniz de Almeida<sup>1</sup>, Rafaela Fernandes Dantas<sup>1</sup>, Ana Cristina Azevedo Leão<sup>1</sup>, Renata Silva de Mendonça<sup>1</sup>, Daniel Shoji Hayashi<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Case presentation:** Girl, 9 years old, started weakness in lower limbs, frequent falls with progressive worsening of ascending weakness and later distal involvement of upper limbs, in addition to burning pain in the calves. About eight days before the condition, she received vaccination with the 2nd dose of coronavac. At the initial evaluation, the patient had normal cognitive examination, incomplete tetraparesis with symmetrical crural predominance, on the MRC scale in lower limbs grade II and in upper limbs grade IV, absent osteotendinous reflexes, preserved superficial and deep sensitivity, cranial nerves without alterations. Normal sphincter function. Analysis of cerebrospinal fluid on the 3rd day of symptoms without alterations, however, in an electroneuromyographic study, non-length dependent multifocal motor axonal polyneuropathy was evidenced compatible with Guillain-Barré syndrome (AMAN variant). The patient was treated with intravenous human immunoglobulin for five days, in view of the evidence of clinical worsening over the five days due to the appearance of new superficial hypoesthesia and electroneuromyographic worsening that showed multifocal and non-length-dependent sensory and motor axonal polyneuropathy (AMSAN), performed five sessions of plasmapheresis, with partial improvement.



**Discussion:** Guillain-Barré syndrome is characterized by post-trigger autoimmune peripheral nerve involvement, in most cases infectious, either of the myelin sheath or of the axon itself, which classically courses with acute/subacute ascending a reflex weakness, with symptoms peaking at around 2 to 3 weeks. Typically, a cytological protein dissociation is observed in the CSF, but many patients may not experience dissociation in the first three weeks. Another useful test, especially for classifying the pattern of involvement, is electroneuromyography. Acute treatment involves intravenous human immunoglobulin and/or plasmapheresis, in addition to symptomatic treatment and clinical support. Chronic treatment involves a multidisciplinary team to ensure rehabilitation.

**Final comments:** We considered the case of interest for exposure, in view of the temporal report of vaccination with the coronavac vaccine, without other possible triggers associated with the outbreak of the condition. It is important to know the syndrome for the correct diagnosis and follow-up of these patients.

**Code: PE176**

#### **Tourettism secondary to multiple sclerosis**

Roberta Diniz de Almeida<sup>1</sup>, José Albino da Paz<sup>1</sup>, Renata Barbosa Paolilo<sup>1</sup>, Clarice Semião Coimbra<sup>1</sup>, Rafaela Fernandes Dantas<sup>1</sup>, Nicholas dos Santos Barros<sup>1</sup>, Ana Cristina Azevedo Leão<sup>1</sup>, Daniel Shoji Hayashi<sup>1</sup>, Joemir Jabson da Conceição Brito<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil

**Case presentation:** Previously healthy adolescent, started at age 15 with limitation of abduction of the right eye, with spontaneous improvement after two months. A brain magnetic resonance imaging was performed, which showed multiple supratentorial and infratentorial demyelinating lesions, without gadolinium enhancement, and prednisone 60 mg/day was started. After 6 months, she was admitted to the service, due to suppressable involuntary cervical hyperkinetic movements, with an increase in frequency for 3 days. Neurological examination showed hemiparesis predominantly crural, with suppressable tics in the neck, simple vocal tics, incomplete hemihypoesthesia on the right and horizontal diplopia on the right. A pulse with methylprednisolone 1 g/day was performed for 5 days, with no improvement in the tics.

**Discussion:** The term Tourettism refers to symptoms similar to Tourette Syndrome (TS) that appear secondary to the effects of a substance or a general medical condition. Tourettism is rarely associated with Multiple Sclerosis, with few reports in the literature. The patient in question does not meet the DSM V criteria for ST because she has symptoms secondary to an underlying medical condition, and at age 15 she started experiencing motor and vocal tics after a multiple sclerosis outbreak. There are hypotheses that Tourettism and Multiple Sclerosis may be related due to diffuse white matter, irreversible axonal loss, and progressive atrophy can impair the cortico-striatal-thalamo-cortical circuits at various levels, consistently implicated in the pathogenesis of TS.

**Final comments:** Tourettism in multiple sclerosis is a rare event, but the correlation must be remembered.

## **Neuroinfecções**

**Code: PE177**

#### **Acute cerebellar ataxia due to varicella zoster**

Murilo Possani Souza<sup>1</sup>, Fernanda Magalhães Bastos Ribeiro<sup>1</sup>, Margareth Santos Ramires Sigilião<sup>1</sup>, Fernanda Aparecida Costa Souza<sup>1</sup>, Thais Pereira Moreira<sup>1</sup>, Roberta Mariuzzo Ferreira<sup>1</sup>, Yanna Silva Guimarães<sup>1</sup>, Juliana Bento Rodrigues Gomes Nogueira<sup>1</sup>, Gabriela Franco Vandermas<sup>1</sup>

<sup>1</sup>Casa de Caridade de Muriaé Hospital São Paulo, Muriaé MG, Brazil

**Case presentation:** A 12-year-old child with a history of varicella infection for 7 days. On the seventh day, the patient presented prostration, inappetence, gait ataxia, dysdiadochokinesia, bilateral eye movement decomposition, pupils equal, round and reactive to light, with no focal deficit and absence of fever. Clinical support, laboratory tests, CSF analysis, and imaging exams were initiated. CSF test and hemogram normal; C-reactive protein test negative; electrolytes, and renal and hepatic function also normal. A neurological consult was requested, and dexamethasone and acyclovir were administered in intravenous infusion. The patient evolved favorably showing significant improvement in neurological deficits. Acyclovir was maintained for 14 days and dexamethasone for 07 days. The patient was discharged and referred to an outpatient neurology service.

**Discussion:** Varicella is highly contagious. Transmission occurs via contact with aerosolized droplets from nasopharyngeal secretions or by direct contact with fluid from skin lesions. The average incubation period is 14–16 days. The period of communicability of patients with varicella is estimated to begin 48 hours before the onset of rash and ends when all lesions are crusted. Mild varicella cases usually include a prodrome of fever, malaise or pharyngitis, and loss of appetite, following the development of generalized vesicular eruptions. After the introduction of the vaccine, the number of complications in children has decreased dramatically, the most common complication is bacterial superinfections. Encephalitis and Reye's syndrome are the most serious complications of varicella. Encephalitis accounts for 20% of pediatric hospital admissions due to varicella, manifesting in two different ways: acute cerebellar ataxia and acute encephalitis. These neurological disorders occur by the end of the first week of the rash. However, in some cases, the neurological manifestations may precede the rash. Acute cerebellar ataxia is more common in children, occurring in ~1 in 4000 varicella infections in children under 15. It has a limited course and is usually followed by complete recovery. Diffuse encephalitis is more common in adults and clinical manifestations include delirium, seizures, and focal neurological signs.

**Final comments:** This case report highlights the importance of informing about and promoting the encouragement of childhood vaccination so that we can reduce the risk of serious complications of vaccine-preventable diseases.

**Code: PE178**

#### **Adenovirus encephalitis associated with acute hepatitis: case report**

Dayana de Lima Mariano<sup>1</sup>, Layanna Bezerra Maciel Pereira<sup>1</sup>, Ana Clara Bernardi Saul<sup>1</sup>, Gabriel de Lellis Neto<sup>1</sup>, Renata Yasmim Cardoso Sousa<sup>1</sup>, Lygia Ohlweiler<sup>1</sup>, Josiane Ranzan<sup>1</sup>, Rudimar dos Santos Riesgo<sup>1</sup>, Maria Isabel Bragatti Winckler<sup>1</sup>

<sup>1</sup>Hospital de Clínicas de Porto Alegre, Porto Alegre RS, Brazil

**Case presentation:** Male, 6 years old, admitted to the hospital due to altered mental status (Glasgow Coma Scale = 3)

preceded by fever, vomiting, fatigue, hypothermia and seizures. The patient presented with refractory hypoglycemia and jaundice at physical examination. Blood tests showed altered hepatic function (AST 548UI/L, ALT 2833UI/L, total bilirubin 5,81mg/dL, INR 5,2, albumin 2,4 g/dL), and serologies for viral hepatitis were negative. Acyclovir was started due to the possibility of viral encephalitis. Evaluation included electroencephalogram with signs of accentuated diffuse encephalopathy, with moderate irritative activity in the left temporal lobe; brain magnetic resonance imaging showed hyperintensity in T2/FLAIR in the periventricular and deep white matter; viral culture in the cerebrospinal fluid was positive for adenovirus. It was opted to discontinue acyclovir. He presented with improvement of lethargy and hepatic function after 5 days but evolved with irritability and ataxia. Brain magnetic resonance imaging was repeated, showing discretely larger white matter lesions, spreading to the semi-oval centers and corona radiata. Supportive care was continued and the patient showed normal gait and behavior after 5 days, being released with no complementary treatment. Electroencephalogram before hospital discharge showed focal paroxysms in the left parieto-occipital region, but the patient did not have new seizures.

**Discussion:** The adenovirus family is an important cause of infection in children, with over 60 serotypes, causing more commonly respiratory and gastrointestinal infections, usually self-limited. Rarely, they can cause other types of infection, such as encephalitis, and in such cases can either cause mild or potentially fatal disease. Seizures are associated with worse prognosis. In the case above, the patient presented with associated acute hepatitis, compatible with the outbreak of adenovirus hepatitis of April of 2022. Thus, this is an unusual case characterized by systemic disease due to a common virus in childhood. There is no electroencephalogram specific or imaging findings. Treatment consists of supportive care.

**Final comments:** Adenovirus encephalitis is a rare disease in childhood, but can cause severe neurologic complications. It must be investigated in patients with evidence of central nervous system infection, especially susceptible groups, such as immunosuppressed individuals.

#### Code: PE179

##### **Basal ganglia ischemia associated with sars-cov infection in infant: a case report**

Isabelle Salgado Castellano<sup>1</sup>, Maria Luiza Benevides<sup>1</sup>, Paula Thais Bandeira Elias<sup>1</sup>, Fernanda Ferrão Antônio<sup>1</sup>, Larisse Souza de Moraes Somavilla<sup>1</sup>, Ana Carolina Piauilino Santos Falcão<sup>1</sup>, Karine Couto Sarmiento Teixeira<sup>1</sup>, Kátia Maria Ribeiro da Silva Schmutzler<sup>1</sup>, Ana Carolina Coan<sup>1</sup>

<sup>1</sup>Universidade Estadual de Campinas, Campinas SP, Brazil

**Case presentation:** A one-month-old male presented with fever, flu-like symptoms, decreased level of consciousness and seizures. He tested positive for SARS-CoV-2. Cerebrospinal fluid (CSF) analysis revealed pleocytosis and elevated protein, and the viral panel for herpes simplex virus (HSV) types 1 and 2, human herpesvirus (HHV) type 6, cytomegalovirus (CMV), Influenza A, B, Parechovirus e Enterovirus and COVID tested negative. Brain magnetic resonance imaging (MRI) showed tumefactive lesions in the basal ganglia, mostly thalamus, with increased signal in diffusion-weighted imaging (DWI) and evidence of necrosis and anaerobiosis in spectroscopy. The patient was treated with intravenous immunoglobulin at the time, with no significant response. On the follow-up, he presented with epileptic spasms and

hypersarrhythmia demonstrated by electroencephalography. Despite the early introduction of Vigabatrin and high dose prednisolone, the response to treatment was poor.

**Discussion:** Central nervous system involvement in COVID-19 infection is frequent, and range from mild symptoms to life-threatening conditions, namely meningitis, encephalitis and stroke, which are often associated with multisystem inflammatory syndrome. Since the CSF analysis for SARS-CoV-2 is not always available, most studies consider the presumed diagnosis when patients present with clinical findings and serological positivity for COVID-19. MRI abnormalities include acute disseminated encephalomyelitis (ADEM)-like pattern, myelitis, cranial nerve enhancement and hemorrhagic encephalitis. Basal ganglia hemorrhage and ischemia was found mostly in adults and was related to both altered mental status and movement disorders.

**Final comments:** Despite severe neurological manifestations being rare in children, there are cases of life-threatening neurologic conditions associated with COVID-19. Even though there are no specific MRI findings related to the SARS-CoV-2 infection, basal ganglia ischemia has been reported. The potential effects of COVID-19 on brain development are still to be appreciated and studied.

#### Code: PE180

##### **Brain abscess in adolescent caused by complicated sinusitis: a case report**

Sayonara Sousa Milhomens Marquez<sup>1</sup>, Vanessa Cristina Guedes Silveira<sup>1</sup>, Letícia Valadares de Oliveira<sup>1</sup>, Andressa Farias Vilela Ferreira<sup>1</sup>

<sup>1</sup>Universidade Federal do Tocantins, Palmas TO, Brazil

**Case presentation:** A 11-year-old girl, weighing 39 kg, evolved with severe headache, fever, and vomiting. Her computed tomography (CT) brain was normal, but sinus CT evidenced lesions in the right maxillary, ethmoid, and frontal sinuses. Antibiotics were administered for sinusitis intra-hospital for 6 days, and amoxicillin/clavulanate was prescribed for the ambulatorial treatment for 10 days. However, after 9-day, the patient developed seizures. Due to worsening symptoms and evidence in a new brain CT of brain abscess in the frontal lobe, she was referred to our hospital taking ceftriaxone, clindamycin, and phenytoin for evaluation of neurosurgery 40 days after symptom onset. Laboratory results: WBC of 19,100; CRP of 98; hemoculture and pharyngeal swab negatives. An intravenous combination of clindamycin, vancomycin, cefepime, and carbamazepine was given. Surgical drainage with Porto-Vac was done and referred to ICU. She did well without continued seizure activity.

**Discussion:** Acute sinusitis is prevalent in children, but it rarely may evaluate intracranial complications as brain abscesses may introduce symptoms such as progressively worsening headache, pyrexia, vomiting, and seizure. The literature describes intracranial complications of pediatric sinusitis most frequently in mean age 11.9–13.3 years and male. They most commonly involving the epidural space and often require neurosurgical intervention such as craniotomy. Cultures rarely are negative, unlike our case report. Unfortunately, a CT scan, initially may not reveal findings in the parenchymal brain as reported, resulting in complicated sinusitis due to late diagnosis. Prolonged intravenous antibiotic treatment and a greater overall hospital length of stay are required. Intracranial abscess recurrence was associated with involvement of brain parenchyma as occurred with this patient.

*Final comments:* Parenchymal abscesses from complicated sinusitis are uncommon, but it's important to recognize warning signs, give attention to persistent symptoms, and earlier diagnoses, and improve imaging techniques and culturing techniques. Successful management consists of antibiotic therapy combined with surgical drainage of loculated infection.

Code: PE181

**Central nervous system complications secondary to rhinosinusitis: a case report**

Daniela Fernanda de Almeida Santos<sup>1</sup>, Guilherme Cordaro Buckler Furini<sup>1</sup>, Laila Prazeres Schulz Moreira<sup>1</sup>, Maria Avanise Yumi Minami<sup>1</sup>, Rafaela Pichini de Oliveira<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup>, Isabela Bartholomeu Ferreira da Costa<sup>1</sup>, Rodrigo Santana Arruda<sup>1</sup>, Matheus de Souza Rosa<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Hospital das Clínicas, Ribeirão Preto SP, Brazil

*Case presentation:* A previously healthy 12 year-old male presented to our tertiary emergency care with classic meningoencephalitis symptoms and paraparesis, urinary retention, facial nerve palsy, lagophthalmos, abducens nerve palsy, oculomotor nerve palsy and hypoesthesia secondary to sinusitis complications. These were intracranial lesions, multiple ischemic subcortical areas and myelitis. The diagnosis was made through clinical examination, imaging tests and laboratory tests of blood and cerebrospinal fluid, including serology and cultures. Treatment was intravenous antibiotic, steroids, anticoagulants, nasoendoscopic surgery and rehabilitation therapies.

*Discussion:* Central Nervous System involvement in complicated acute rhinosinusitis is rare. That includes meningitis, sinus thrombosis and cerebral abscesses. Despite the improvement in the treatment of sinusitis due to the greater availability of antibiotics and the consequent lower incidence of complications, the mortality of these cases can reach 10–20% and patients may have long term neurologic sequels. The database about ischemic strokes secondary to acute sinusitis in the childhood are rare. The CNS complications of sinusitis are due to the sinus inflammation and pathophysiological mechanisms which can cause dehiscence and erosion of sinus wall and by progression of septic thrombi or transmission of septic emboli through the valveless diploic veins of the skull base that penetrates dura. In the patient case, there were clinical and imaging changes consistent with intracranial (meningitis with areas of infarction and superior sagittal sinus thrombosis) and medullary (meningoradiculitis with foci of cervicothoracic myelitis) involvement, suspicious findings for an infectious and inflammatory process.

*Final comments:* Mortality by intracranial complications of sinusitis have been decreasing, but they still carry a high risk of long-term morbidity like epilepsy, permanent visual changes, and focal paresis. And our best chance to improve the outcome is through early diagnosis and treatment with a multidisciplinary approach.

Code: PE182

**Central nervous system histoplasmosis in an immunocompetent 5-year-old patient: a case report**

Sara Julia Zorzi de Brum<sup>1</sup>, Augusto Nicaretta<sup>1</sup>, Letícia Moreira Cunha<sup>1</sup>, Vinicius Estanislau Albergaria<sup>1</sup>, Carolina Baptista dos Santos<sup>1</sup>

<sup>1</sup>Universidade Federal da Fronteira Sul, Passo Fundo RS, Brazil

*Case presentation:* IL, 5 years old, female, weighing 28,5kg, previously healthy. Sought medical attention due to intense

and progressive headache for a year, worsening in the previous 90 days, followed by vomiting. Cranial magnetic resonance showed an intraparenchymal lesion in the optic chiasm suggestive of inflammatory injury by infection or cancer, raising the hypothesis of tuberculosis and optic pathway glioma. Cerebrospinal fluid analysis was negative for tumor cells and Mycobacterium tuberculosis. Tuberculin tests and screening for HIV, hepatitis, cytomegalovirus, and syphilis were non-reactive. During hospitalization, presented with seizure, followed by persistent hyporesponsiveness, Glasgow Coma Scale (GCS) of 9. New neuroimaging showed an increase in the number of lesions diffusely in both hemispheres and in the meninges. In the third month of hospitalization, the patient evolved with complications, such as new seizures, repetitive respiratory infections, and a decrease in neurological state, GCS of 6–7. A biopsy of cerebral tissue showed the presence of Histoplasma capsulatum, giving the diagnosis of central nervous system histoplasmosis (CNS). Treatment with amphotericin B and itraconazole was established, both without improvement. The latest neuroimaging showed severe neurological sequelae, with lesions suggestive of granulomatous disease, ischemia, and gliosis/encephalomalacia. As the patient was stable, she was released for ambulatory treatment with itraconazole for a year. The family agreed to prioritize comfort above invasive measures, which would not bring benefits to the patient.

*Discussion:* Exposure to H. capsulatum is common for people in endemic areas, however, most are asymptomatic or exhibit few pulmonary symptoms. CNS involvement is uncommon in immunocompetent patients and its occurrence as the only manifestation is even rarer. CNS involvement occurs by hematogenous spread to the meninges or brain, with chronic meningitis being the most common manifestation. Treatment is difficult, and amphotericin B should be used as initial therapy in all patients, followed by an azole agent administered orally for an indefinite period.

*Final comments:* The clinical case reports an episode of histoplasmosis showing CNS involvement as the only manifestation of the disease in an immunocompetent pediatric patient. This type of manifestation is uncommon, making the diagnosis of the pathology and its early treatment even more challenging.

Code: PE183

**Childhood encephalitis: a challenging diagnosis**

Nicole Zanardo Tagliari<sup>1</sup>, Elisa Pacheco Estima Correia<sup>1</sup>, Glória Maria Wenzel Brodacz<sup>1</sup>, Evandro Freddy Mulinari<sup>1</sup>, Cristina Detoni Trentin<sup>1</sup>, Mariana Menegon de Souza<sup>1</sup>, Priscila Zabala Amorim<sup>1</sup>, Victória Bernardes Guimarães<sup>1</sup>, Gabriela Maycá Sanfelice<sup>1</sup>

<sup>1</sup>Hospital Moinhos de Vento, Porto Alegre RS, Brazil

*Case presentation:* A 16-year-old male patient, residing in the United States, on vacation to Brazil, with a history of attention deficit hyperactivity disorder, without other comorbidities, seeks the emergency with headache and vomiting for 3 days, evolving with headache worsening, sensorium and speech alteration. In the initial evaluation, he had labial commissure deviation and altered level of consciousness (Glasgow 14). Cranial CT was performed for suspected stroke, which was normal. Investigation progressed with lumbar puncture and laboratory tests, and CSF showed pleocytosis (142 leukocytes/mm<sup>3</sup>, lymphocytes 86% and monocytes 14%) and increased protein (134 mg/dl). The patient evolved with sensorium oscillation and was referred to the ICU for monitoring. The electroencephalogram showed severe diffuse encephalopathy with greater involvement of both temporal regions. A diagnostic hypothesis of viral encephalitis was

made, and acyclovir was started empirically. An extensive etiological investigation was performed, with collection of serology and molecular panel, which were negative for herpesvirus in cerebral spine fluid and serology. However, the search for neutralizing antibodies for Coxsackie virus B type 4 and 5 was positive at high titers (1/512 and 1/128), indicating active infection, thus confirming the hypothesis of Coxsackie meningoencephalitis.

**Discussion:** Enteroviruses are one of the main etiologic agents of acute encephalitis in children, accounting for ~5% of cases. Among the enteroviruses, coxsackievirus types A9, B2 and B5 and echovirus types 6 and 9 are the most frequently reported serotypes. Clinical manifestations are indistinguishable from other causes of acute encephalitis, although enterovirus encephalitis is associated with less severe illness, shorter hospitalization, and better outcomes compared with other viral agents. In our country, the identification of this etiologic agent is uncommon in view of the difficulty in accessing diagnostic tests.

**Final comments:** Viral encephalitis is a prevalent disease and an important cause of acute sensorium alteration. In most cases, the etiology remains unknown despite extensive evaluation. In cases where it is possible to identify the agent, enteroviruses, especially coxsackievirus, stand out as an important agent. In this case described, the patient did not present other clinical manifestations of infectious coxsackie disease, and the etiological identification was possible based on the search for neutralizing antibodies.

**Code: PE184**

**Disseminated tuberculosis in a three month old infant: effects on the central nervous system**

Laura Defensor Ribeiro de Melo<sup>1</sup>, Ana Paula Faria Ribeiro<sup>1</sup>, Vanessa Limeira Pontes de Lucena<sup>1</sup>, Amanda Pova de Paiva<sup>1</sup>, Maria Avanise Yumi Minami<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Hospital das Clínicas, Ribeirão Preto SP, Brazil

**Case presentation:** A 3 month-old boy with fever and new episodes of seizures was admitted from another institution in an ongoing tuberculosis investigation substantiated by central nervous system imaging. The patient evolved with seizures recurrence and fluctuating consciousness. Ophthalmology exam revealed chorioretinitis. Neural axis abnormalities on magnetic resonance imaging were described with signs of diffuse meningoencephalitis complicated with vasculitis and subacute infarctions in the territories of the anterior cerebral arteries bilaterally and nucleocapsular, hemoventricle and subarachnoid hemorrhage. Moreover, a nodular lesion in the medullary transition to the left and tenuous diffuse enhancement of the cauda equina roots. These evidences were relevant to guide the initial therapeutic strategy, until the patient's clinical stability allowed additional diagnostic measures performed in our service.

**Discussion:** Young children are especially susceptible to tuberculosis and its severe forms when exposed to *Mycobacterium tuberculosis*. Disseminated form of this disease reverberates with high morbidity and mortality in individuals with immature immune responses<sup>1</sup>. The infection and development of the disease is also related to the recurrence and intensity of exposure<sup>2</sup>. The most prevalent alterations in neuroimaging are hydrocephalus, tubercular meningitis, infarcts and basal exudates; in addition, coexisting tuberculomas may be found<sup>3</sup>. In this case report, important lesions

triggered seizures and consciousness oscillations. Neuroimaging findings corroborate diagnosis, help in timely therapeutic strategy and patient's outcome, especially in neurodevelopment perspective for this young children<sup>4</sup>.

**Final comments:** Disseminated tuberculosis is a threatening disease for children, especially with multiple neurological lesions that predicts unfavorable neurodevelopment. The mean of this case is to reinforce the importance of correlating clinical findings and timely complementary exams to guide the therapeutic choice and establish differential diagnosis.

**Code: PE185**

**Encephalomyelitis by adenovirus**

Izabela Cristina Macedo Marques<sup>1</sup>, Rui Carlos Silva Junior<sup>2</sup>, Giulia Vilela Silva<sup>2</sup>, Nildo Vilacorte de Araújo Júnior<sup>2</sup>, Daniel Almeida do Valle<sup>2</sup>, Michelle Silva Zeny<sup>2</sup>, Monica Jaques Spinosa<sup>2</sup>, Elisabete Coelho Coelho Auerswald<sup>2</sup>, Alfredo Lohr<sup>2</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Boa Vista PR, Brazil

<sup>2</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Three-year-old male admitted with aphasia and mental confusion that last 48 hours. Report a fever peak of 38°C. Vomiting and hyaline rhinorrhea resolved four days ago. Plus diarrheal symptoms three weeks prior to hospitalization. He did not recognize his mother and other family members, he was frightened by environmental stimuli, he could not walk, he fell if placed standing and did not sit without support. Previously healthy. History of febrile seizures at 1 year of age on sodium valproate. Proper motor development, but with speech delay. Son of a healthy couple non-consanguineous from Manaus, attended day care with good socialization. On examination he was awake but disoriented, cranial nerves unaltered. He presented traction of the lower limbs with flexion of the thigh to painful stimuli and spontaneous elevation of the lower limbs against gravity, without signs of pyramidal release with bilateral patellar areflexia. Lumbar puncture showed cellularity of 27 and predominance of lymphocytes, protein 19, glucose 51 and lactate 1.4. Normal metabolic tests and cranial tomography. Started acyclovir and requested panel for viral meningitis in the cerebrospinal fluid (CSF). The following day, he progressed with worsening, dysphagia and loss of head support, he maintained the lower limb areflexia, being referred to the ICU where he received immunoglobulin. He was discharged from the ICU after 48 hours with improvement. Ophthalmologic evaluation and EEG were normal. Neuroaxis MRI showed bilateral and symmetrical signal alteration in the posterior region of the brainstem, more evident in the bulb pontine region with insinuation to the dentate nucleus of the cerebellar hemispheres, without anomalous contrast impregnation, suggesting viral or autoimmune etiology. Therefore, it was chosen to repeat the lumbar puncture with normal CSF (4 cells). The patient evolved with recovery of consciousness and neurotendinous reflexes. The CSF panel showed positive PCR for adenovirus. The patient was discharged asymptomatic, and acyclovir was discontinued.

**Discussion:** Adenovirus infection is a rare cause of viral meningoencephalitis. Involvement ranges from reversible meningitis to fatal necrotizing encephalopathy.

**Final comments:** Isolation of the agent in CSF or other body fluids is essential and avoids unnecessary treatments and tests as well as favors the possibility of specific antiviral therapy.

**Code: PE186****Follow-up younger patient with anti-NMDA-R encephalitis**

Lisandra Coneglian Farias Rigoldi<sup>1</sup>, Rui Carlos Silva Junior<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Lorena Vilela Rezende<sup>1</sup>, Ana Paula Resende Silva<sup>1</sup>, Izabela Cristina Macedo Marques<sup>1</sup>, Mariah Pereira de Andrade Vallim<sup>1</sup>, Michelle Zeny<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** Male, 8 months old, previously healthy, initiated with fever, inappetence, dystonia and axial hypotonia. Initial examination presented cerebrospinal fluid (CSF) with lymphomononuclear leukocytosis and proteinorrachia. Electroencephalogram (EEG) with slowed base activity. Other infectious screening tests with viral serology, rheumatological, neoplastic diseases, nuclear magnetic resonance (NMR) imaging of the brain were standard. After exclusion of main causes of encephalitis, antibodies against N-methyl-D-aspartate receptor (NMDA-R) were identified in the CSF. It evolved with worsening motor and respiratory, and regression of neuropsychomotor development (NPMD), he needed tracheostomy (TQT) and gastrostomy (G-tube). Treatment, besides a front line with steroids and Human Immunoglobulin, were six cyclophosphamide cycles and starting azathioprine, remaining hospitalized for four months. Following up, at five years of age, he is still using azathioprine, in weaning. He presents NPMD milestones appropriate for his chronological age. There is no need for tracheostomy (TQT) and gastrostomy (G-tube).

**Discussion:** This case report exposes a younger patient with anti-NMDA-R encephalitis among those reported in the literature. It is an immune-mediated syndrome with antibodies in serum and/or CSF against an epitope located in extracellular domain of NMDA-R. It is the second most common cause of autoimmune encephalitis. Clinical signs include seizures, behavior, speech, and movement disorders. The diagnosis is based on CSF analysis—showing lymphocytic pleocytosis, EEG, and the detection of autoantibodies. The differential diagnosis includes psychiatric disorders and other viral encephalitis. Several reports of anti-NMDA-R encephalitis in patients with current or recent Severe Acute Respiratory Syndrome of SARS-CoV-2. First-line immunotherapy treatments are steroids. In refractory cases, cyclophosphamide, rituximab, or azathioprine might be added, with a slow recovery time. The mortality rate is 4% associated with secondary comorbidities acquired in the intensive care unit (ICU).

**Final comments:** Anti-NMDA-R encephalitis should be suspected in children with acute behavioral change, seizures, movement disorders, associated with CSF pleocytosis lymphocytic and/or EEG with slow and disorganized activity and/or normal brain NMR. The autoimmune picture identification and aggressive management at its first stages lead to a more favorable outcome in the follow-up, as presented in this report.

**Code: PE190****Post-covid Guillain-Barre syndrome with atypical clinical presentation**

Lorena Vilela Rezende<sup>1</sup>, Julia Vilela Rezende<sup>2</sup>, Michelle Silva Zeny<sup>1</sup>, Mariah Pereira de Andrade Vallim<sup>1</sup>, Guilherme Siqueira Gaede<sup>1</sup>, Izabela Cristina Macedo Marques<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Rui Carlos Silva Junior<sup>1</sup>, Lisandra Coneglian de Farias Rigoldi<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

<sup>2</sup>Centro Universitario de Mineiros, Mineiros GO, Brazil

**Case presentation:** EVMS, 7 years and 4 months old, started after symptoms of airway infection by the Sars Cov 2 virus

with paresthesia and pain in the lower limbs. The condition persisted for more than 20 days with progressive worsening, evolving to tactile, thermal, and painful hypoesthesia from the waist down. During the entire evolution, the patient maintained a preserved gait and associated symptoms of pruritus and anal paresthesia. On physical examination, he presented alteration in exteroceptive sensitivity with anesthesia in the boot, absence of tactile, kinesthetic and artistic sensitivity in the lower limbs, sensory level L5-S1, osteotendinous reflexes (ORT) 1+/4+ overall. Complementary Examinations: Magnetic Resonance of the skull, neuraxis and normal Electroneuromyography. Serology for COVID 19 reagent and Herpes I and II IgG: 28.4 reagent IgM: 0.9 undetermined. Cerebrospinal fluid CSF: Red cells: 0.31 Leukocytes: 2.18 Protein: 22 Cl: 126 Glucose: 52, viral meningitis panel negative. In view of the clinical findings and diagnosis of Guillain-Barré Syndrome (GBS) with a purely sensory presentation, treatment with Human Immunoglobulin was performed with complete resolution of signs and symptoms.

**Discussion:** Infection with the SARS-CoV-2 virus in the central nervous system causes neuroinflammation and evolves with the cytokine storm. There are frequent reports of neurological syndromes secondary to infection, such as GBS, meningitis, encephalitis, encephalopathy, cerebrovascular accident (CVA), in addition to signs and symptoms such as headache, dizziness, reduced level of consciousness, hypsomnia, and hypogeusia. The Guillain-Barré syndrome caused by the new coronavirus theoretically presents itself in a similar way to the pathology caused by other agents. The interval between the onset of symptoms of Covid 19 and the first symptoms of the syndrome varies from 5 to 12 days, with the classic sensorimotor form being the most prevalent manifestation in 75%, as shown in the review by P Zuberbühler et al, 2021. The purely sensitive and late-onset form, such as the one presented in this case, is rarer.

**Final comments:** It is concluded that the neurological evolution of GBS after COVID showed a good response to treatment with immunoglobulin, and few had respiratory failure.

**Code: PE191****Recurrent infectious encephalitis in adolescent: a case report and its differential diagnoses**

Jordana Dias Paes Possani de Sousa<sup>1</sup>, Vinicius Spazzapan Martins<sup>1</sup>

<sup>1</sup>Hospital Municipal Infantil Menino Jesus, São Paulo SP, Brazil

**Case presentation:** JASB, male, 11 years, complaining of headache, dizziness, diplopia, and dysarthria for 3 weeks, denying flu syndrome, trauma, or substance use. On physical examination: hypotonia, dysdiadochokinesia, paresis of cranial nerves III and IV, drunken gait, and positive Romberg test. A cranial tomography was performed as an initial imaging test, with no changes. Due to the severity of the case, pulse therapy was started empirically. Magnetic resonance imaging (MRI), 7 days after admission, shows hypersignal in basal ganglia, trunk, pons, peduncle, and cerebellum (T2 and FLAIR). Chemocytology and culture of cerebrospinal fluid were normal. After 13 days of admission, serology was positive IgG for Epstein Barr Virus (EBV) and Herpesvirus, negative IgM. After pulse therapy, prednisolone and acyclovir were prescribed. The patient was discharged after 32 days, with gradual weaning from corticoids and resolution of the condition. However, after 3 months, he was readmitted for diplopia and strabismus; MRI maintained the previous pattern, and new pulse therapy was performed.

**Discussion:** The child presented an unknown etiology condition; however, considering the MRI and age group, the scenario is similar to cerebellar ataxia due to viral encephalitis with an etiological focus on EBV. To reach a conclusion, must consider the differential diagnoses. Acute cerebellar ataxia is usually linked to viral encephalitis and 90% of cases resolve within 4 months. Recurrence is rare. The investigation of viral PCR in the cerebrospinal fluid is of great value for the etiology. Despite herpesvirus's leading viral agent, on MRI, affects the temporal lobes, cingulate gyrus, orbitofrontal cortex, and insula, which is not consistent with the case. EBV is a significant cause of encephalitis in adolescence, and there is usually no history of mononucleosis. Its tropism is in the basal ganglia, cerebellum, trunk, and thalamus, which agrees with our findings. Finally, acute disseminated encephalomyelitis, a demyelinating disease whose MRI suggests hypersign on T2 and FLAIR, asymmetrical, < 5 cm, usually confluent, must be excluded.

**Final comments:** The case describes a rare evolution for presenting recurrence, and despite the lack of viral screening, the clinic and image refer to EBV, which is not the main etiologic agent of viral encephalitis. Furthermore, the pediatric community should be aware of the differential diagnoses of neuroinfections and early ordering of tests.

#### Code: PE192

##### **Scholar patient with autoimmune encephalitis after being infected with SARS-CoV2**

Rui Carlos Silva Júnior<sup>1</sup>, Giulia Vilela Silva<sup>1</sup>, Lorena Vilela Rezende<sup>1</sup>, Mariah Pereira de Andrade Vallim<sup>1</sup>, Izabela Cristina Macedo Marques<sup>1</sup>, Shema El-Laden Hammoud<sup>1</sup>, Ana Paula Resende Silva<sup>1</sup>, Michelle Silva Zeny<sup>1</sup>, Daniel Almeida do Valle<sup>1</sup>  
<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** B,F,D, 6 years, female, previously healthy, initiated SARS-CoV2 symptoms with infection, fever, asthenia and recurrent vomiting, signals of extrapyramidal release, ataxia, dysarthria and paraplegia. These symptoms evolved to metabolic acidosis, flaccid quadriplegia and hospitalization at intensive care unit (ICU). When investigating, serology's and CSF with no alteration. Electrophysiological studies were made with EEG and electroneuromyography, and the results were normal. Nuclear magnetic resonance (NMR) image and angio-NMR of normal cranium. NMR from vertebral column without significantly changes. Received methylprednisolone 30(mg/kg/day) for 5 and 7 days of human immunoglobulin (IgH), gradually recovering from lower members and cervical tone. Keeping Broca's aphasia and PCR positive SARS-CoV2 for seven more days. Was discharged and initially following: Recovering from member's mobilization, strength and cognition. Dystonia got worse after three months and new development regression. With good recovering from the signals and symptoms after IgH, fulfilling criteria for autoimmune encephalitis possibility. Being opted for monthly replacement from IgH with gain maintenance from neuropsychomotor development.

**Discussion:** The disease caused by the new Coronavirus (COVID-19) mainly affects the respiratory system, with symptoms as: fever, dry cough, dyspnea and pneumonia, in addition to affect the gastrointestinal tract, the neurological system is one of the main affected by the disease. About one third of the patients have: feverish convulsions, convulsions and encephalitis, which can occur during the acute phase or after the infection. The virus can invade the Central Nervous System (CNS) through the olfactory bulb causing inflammation and demyelination of neurons.

**Final comments:** Encephalopathy is one of the main manifestations from (CNS) in patients with severe conditions of COVID-19. The diagnosis of encephalopathy has been done clinically way since there are prodromal symptoms. The clinical support associated to the corticosteroid immune modulating therapy with high doses and human immunoglobulin, shows benefits when limiting the systemic inflammatory answer caused by the virus, as in this related case, whereas observes an important recovery after those therapies.

#### Code: PE193

##### **Septic thrombosis of the cavernous sinus secondary to meningitis: case report from a referral hospital in Espírito Santo**

Natalia Josiele Cerqueira Checon<sup>1</sup>, Elisa Victoria Costa Caetano Funk<sup>1</sup>, Melissa Pereira de Oliveira<sup>1</sup>, Milena de Souza Alvarenga Schaffel<sup>1</sup>

<sup>1</sup>Hospital Estadual Infantil Nossa Senhora da Glória, Vitória ES, Brazil

**Case presentation:** Female patient, 1 year and 7 months old, previously healthy, presented cervical adenomegaly, fever, and periorbital edema after receiving MMR vaccine. She evolved with a deviation of the labial commissure to the right, neck stiffness, and bilateral periorbital edema. On hospital admission, she presented normal cranial tomography and infectious cerebrospinal fluid with negative culture. She had a generalized onset of a tonic-clonic motor crisis and evolved with anisocoria (L>R), left hemiparesis and left side hypotonia, ptosis, and left ophthalmoplegia. The blood culture was positive for *Staphylococcus aureus*. MRI of the brain was performed, with findings compatible with thrombophlebitis of the cavernous sinuses, associated with thrombosis of the superior ophthalmic veins, right sigmoid sinus, and right internal jugular vein, with areas of ischemic vascular injury predominantly in the parietal lobes bilaterally and epidural collection at the anteromedial margin of the right middle cranial fossa, suggestive of empyema. Anticoagulation was not performed due to the infectious etiology of the condition. An angioresonance of the brain was performed after 20 days of antibiotic therapy and showed signs of thrombosis partially recanalized along the sigmoid sinus and in the bulb of the right internal jugular vein and absence of thrombophlebitis and empyema. She was discharged from the hospital using anticonvulsants. Currently, she is being followed up at the neurology outpatient clinic, with progressive clinical improvement of the left peripheral facial nerve palsy, complete left third cranial nerve palsy, and ophthalmoparesis, in addition to left hemiparesis.

**Discussion:** Cavernous sinus thrombosis can occur for a variety of causes. When generated by infectious conditions, it is called cavernous sinus septic thrombosis. This is a serious and secondary complication, mainly, to facial infections, sinusopathy, and mastoiditis. *Staphylococcus aureus* is the main etiologic agent. Headache is the most common initial symptom, in addition to fever, edema and periorbital pain, chemosis, proptosis, eyelid ptosis, visual changes, restriction, and pain in eye movement, among others. Early diagnosis and treatment are extremely important in reducing morbidity and mortality and improving prognosis.

**Final comments:** Septic cavernous sinus thrombosis is a rare complication of meningitis. It is important to pay attention to the possibility of this situation so that it can be addressed promptly.

## Neurologia neonatal

Code: PE198

### Therapeutic hypothermia initiated after 6 hours of age and benefits in the treatment of hypoxic ischemic encephalopathy

Anna Rita Barcelos Martin<sup>1</sup>, Ana Paula Oliveira Bóscolo<sup>1</sup>, Bárbara Rocha Rodrigues<sup>1</sup>, Pávila Virginia De Oliveira Nabuco<sup>1</sup>, Fabiana Jorge Bueno Galdino Barsam<sup>1</sup>

<sup>1</sup>Universidade Federal do Triângulo Mineiro, Uberaba MG, Brazil

**Case presentation:** Term newborn, born by cesarean section after 3 days of induction, with urgent interruption indicated due to unfavorable cardiocography. At birth, the patient was hypotonic, without crying, was taken to a warm crib, suction of the airways was performed, with a large amount of meconium coming out. Performed 3 cycles of PPV (Positive Pressure Ventilation), proceeded with OTI (Orotracheal Intubation). Apgar 1/5. Referred to the Neonatal Intensive Care Unit (NICU). Tension pneumothorax was identified on the left, a relief puncture was performed, and a drain was left for drainage. He evolved with seizures in the first hours of life, with a loading dose of phenobarbital (20mg/kg/dose) and a maintenance dose (5mg/kg/dose). Evolved with distributive shock, requiring vasoactive drug. The SARNAT scale was applied, which showed moderate Hypoxic Ischemic Encephalopathy (EIH). Therefore, he was submitted to therapeutic hypothermia at 16 hours of life, with temperature maintained between 33.5°C and 34°C for 96 hours, with monitoring of vital signs and electroencephalographic monitoring. Evolved with improvement of seizures and neurological pattern observed daily through the SARNAT scale. It tolerated well the progression of the diet. Transfontanelar ultrasound and magnetic resonance imaging of the brain region were performed without alterations. After 21 days of hospitalization in a NICU bed, she was referred to the hemodynamically stable ward. Evolved with good acceptance of the oral diet, being discharged with multivitamins, phenobarbital 3mg/kg/dose and outpatient follow-up with neuropediatrics, general pediatrics and early stimulation.

**Discussion:** A randomized multicenter trial conducted at 21 centers of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Neonatal Research Network located in the United States over 8 years in infants with moderate and severe HIE treated with hypothermia resulted in a 76% probability of reduction in death or disability. While the probability of death or disability was less than 2% lower in hypothermia compared with non-cold babies it was 64%. In this case report, we present two cases of newborns who presented neonatal asphyxia and who underwent late therapeutic hypothermia in the neonatal ICU of the Hospital de Clínicas, Universidade Federal do Triângulo Mineiro, with good neurological evolution after the introduction of therapeutic hypothermia, although late.

**Final comments:** Protective late therapeutic hypothermia as an alternative.

## Outros

Code: PE199

### Case report: evaluation of intracranial compliance in a child with subdural empyema

Simone Carreiro Vieira Karuta<sup>1</sup>, Caroline Mensor Folchini<sup>1</sup>, Marinei Campos Ricieri<sup>1</sup>, Fabio Araujo Motta<sup>1</sup>, Guilherme de Rosso Manços<sup>2</sup>, Adriano Keijiro Maeda<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

<sup>2</sup>Complexo Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** A 12-year-old female patient presents a 5-day history of fever and severe frontal and occipital headache associated with vomiting, nocturnal awakenings, vertigo, and phonophobia. She evolved with dysarthria, decreased level of consciousness, left hemiparesis followed by systemic arterial hypertension, bradycardia and 8 episodes of focal seizures. On neurological examination, she was alert, lucid, oriented, and without focal points. An ophthalmoscopic examination revealed the, she had papilledema in both eyes. Cranial resonance (MR) showed suggestive signs of acute inflammatory maxillary and left frontal sinus disease related to subdural empyema with suggestive signs of intracranial hypertension (IH). The assessment of intracranial compliance (IC) with a non-invasive device, Brain4care, was performed in the lying and sitting position, with a mean p2/p1 ratio of 1.43 and 1.39, respectively. After the diagnosis, the patient was submitted to empyema drainage and antibiotic therapy. On the 13th postoperative day, with an improvement of the clinical condition, a new IC monitoring was made and revealed a p2/p1 lying down ratio of 1.01 and a sitting position of 1.07.

**Discussion:** IH is a secondary condition due to the loss of brain compensatory mechanisms related to different etiologies. In the clinical case, the presence of empyema caused classic signs of IH found on MR: the empty sella turcica sign, optic nerve tortuosity, changes in optic nerve intensity, and changes in the visualization of the adeno/neurohypophysis. Besides that, neuroimaging findings are not always as characteristic. Ophthalmological examination revealed papilledema, but absence of papilledema does not rule out IH. Most of the exams used for the diagnosis of IH reveal indirect data and because of that invasive exams are often used to prove the brain alterations, one of the reasons that justify the creation of a non-invasive device to monitor IC. Brain4care monitoring was consistent with the exams and patient's evaluation, showing acute changes in IC. And, sequentially demonstrated compliance improvement that was concomitant with clinical and imaging tests.

**Final comments:** Due to the life-threatening risk, IH and its causes could be accurately and quickly investigated and diagnosed. Thus, brain4care seems to be an easy-to-handle, non-invasive device that can measure IC, which can assist the treatment and clinical follow-up of the patients.

Code: PE200

### Case report: scurvy in a child with autistic spectrum disorder due to food selectivity

Jamile Bonini Hadaya<sup>1</sup>, Ana Chrystina Crippa<sup>1</sup>, Christina Palajo<sup>1</sup>, Maria Augusta Kormann<sup>1</sup>, Angela Nazari dos Santos<sup>1</sup>, Ana Carolina Pecoraro Fiovaranti<sup>1</sup>, Melissa Paes Camargo<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Hospital das Clínicas, Curitiba PR, Brazil

**Case presentation:** O.R, male, 2 years and 6 months, language and social delay. The diet was based on bread, rice, beans and yogurt. Petechiae and gingival bleeding were noted 55 days ago. After 15 days, progressive pain in the lower limbs prevented the child to sit or walk. The clinical examination showed edema, pseudofolliculitis, petechiae and intense pain on palpation and mobilization of the lower limbs, bleeding spots and hypertrophy in the gingivae. Blood count and cerebral spinal fluid analysis were performed, with results within the normal range. Bone marrow biopsy ruled out acute leukemia. A limb MRI presented marked bone marrow edema of the metaphyseal region of both femurs, tibias and fibulas, with signs of periostitis and edema of the adjacent muscle groups. The child was given analgesics and ascorbic acid supplementation (300mg/day orally), showing in 2 days

progressive improved lower limb pain and partial motor recovery. The M-Chat scale was applied and positive for autism spectrum disorder.

**Discussion:** Around 46% to 89% of patients with autism spectrum disorder show food selectivity, depending on shape, color and texture. The selective and repetitive intake of foods, especially those with high-calorie content, can contribute to obesity and nutritional deficit, resulting in significant morbidity. Scurvy diagnosis is rare in the literature, and there are few published studies on the frequency of nutritional deficiencies in the pediatric population with autism spectrum disorder. However, in the United States, vitamin C deficiency represents less than 2% of the nutritional deficits in children aged 6 to 11 years and less than 4% in adolescents. Bone and soft tissue manifestations secondary to scurvy can mimic other osteoarticular disorders, including osteomyelitis.

**Final comments:** In this case, clinical signs suggestive of scurvy and behavioral inflexibility led to the diagnosis of Autism Spectrum Disorder, in addition to vitamin D and iron deficiency. The complete analysis of clinical history provided shortcuts to the correct diagnosis. In the context of a restricted diet and osteoarticular manifestation, the possibility of micro and macronutrient deficiencies, including vitamin C, must be raised. Proper recognition of the condition avoids unnecessary investigations and treatments

#### Code: PE204

##### **Callosotomy: should it be indicated earlier?**

Vinícius Paulo Lima de Menezes<sup>1</sup>, João Garcia<sup>1</sup>, Carla Lenita Coelho Siqueira<sup>1</sup>, Carlos de Almeida Dias Neto<sup>1</sup>, Paulo Emídio Lobão Cunha<sup>1</sup>, Lisiane Seguti Ferreira<sup>1</sup>

<sup>1</sup>Universidade de Brasília, Brasília DF, Brazil

**Case presentation:** Male 9 years and 9 months old patient with cerebral palsy (GMFCS5) and refractory epilepsy secondary to extensive and bilateral hypoxic ischemic encephalopathy started epileptic seizures in the first hours of life and after evolved with persistent and countless daily polymorphic seizures. He was diagnosed with West syndrome (WS) followed by Lennox-Gastaut syndrome (LGS). He got many treatments, with a total of more than 10 anti-crisis drugs (ACD), including rufinamide, explored in single or polytherapy and in the maximum tolerated doses. He also underwent alternative treatments with acetazolamide, corticosteroids, cannabidiol, and ketogenic diet. No therapeutic measure showed efficacy above 50%. At 9 years old, he was evaluated by the neurosurgery team after a video electroencephalography (EEG) showed an increase in interhemispheric synchronization and many spindle-like segments of rapid and rhythmic activity with record of countless tonic-type epileptic seizures and spasms in cluster. A total callosotomy was performed 4 months later. Two months after the surgery, the patient's mother reported an 80% reduction in the number of attacks and a decrease in their duration. In the last performed EEG, no burst-suppression pattern was detected as in the EEG before surgery. There was persistence of multifocal epileptiform activity, with a left occipital and right frontocentral predominance.

**Discussion:** Callosotomy is an option for drug resistant epilepsies not amenable to focal resection. It best suits drop attacks cases, but is also relevant regarding WS, LGS and frontal epilepsy. Its rationale is based on the role of the fibers of corpus callosum on spreading the epileptic activity in both cerebral hemispheres. It is an invasive but effective interven-

tion with low morbimortality. Possible complications are usually transient, such as aphasia, memory losses, or infections. In the palliative management of LGS, callosotomy is associated with a 50–90% reduction in the number of crises, better quality of life and high rates of family satisfaction.

**Final comments:** Our patient has had seizures since the first hours of life and went through an exhausting range of therapies with efficacy always below 50%. After callosotomy, there was a significant clinical improvement with corresponding EEG changes. Although it is a palliative, invasive and irreversible procedure, a discussion should be raised on the earlier indication of callosotomy in selected cases.

#### Code: PE206

##### **Iphosphamide-induced encephalopathy treated with Methylene Blue: a pediatric case report**

Luiza Fernandes Fonseca Sandes<sup>1</sup>, Paulyane Thalita Miranda Gomes<sup>1</sup>, Thamis Nader Mota<sup>1</sup>, Patricia Semino Tavares<sup>1</sup>, Halisson Mesquita Braga<sup>1</sup>, André Vinícius Soares Barbosa<sup>1</sup>

<sup>1</sup>Santa Casa de Misericórdia de Belo Horizonte, Belo Horizonte, MG, Brazil

**Case presentation:** This is a 12-year-old female patient hospitalized for chemotherapy due to Acute Lymphoblastic Leukemia. She was on the fifth day of treatment, receiving iphosphamide, dexamethasone and daunorubicin. Suddenly, she developed hyporesponsiveness and focal seizure, which improved after Midazolam. A few hours later, there was another generalized seizure and she presented irritability afterwards. She was referred for pediatric ICU monitoring, admitted sleepy and hyperreactive. Methylene Blue at 1 mg/kg dose was started due to suspected neuro-intoxication by iphosphamide, maintained for 3 days total. Brain MRI showed multiple lesions with cortical and subcortical involvement. The patient showed clinical improvement after 24 hours of symptoms' onset. There was no neurological sequel afterwards. Control MRI after two months had no parenchymal lesions. Due to clinical and radiological improvement, the diagnosis of iphosphamide encephalopathy was maintained.

**Discussion:** Iphosphamide is an alkylating chemotherapy drug used in treatment of different tumors such as ovarian and testicular cancer, lymphomas and sarcomas. The neurotoxicity side effect of iphosphamide can affect 10 to 15% of patients, which may occur within 12 hours to 6 days after starting treatment and usually improves within 48 to 72 hours after discontinuation of the drug. Predisposing factors for iphosphamide encephalopathy include higher doses, poor initial treatment response, association with cisplatin, renal or liver failure and hypoalbuminemia. The mechanisms involved at iphosphamide-induced encephalopathy are still unknown. However, it is known that precipitation of chloroacetaldehyde, its toxic metabolite, in the central nervous system (CNS) is the main cause of its neurotoxicity. Patient's symptoms can range from drowsiness, confusion, hallucinations, seizures to status epilepticus and coma. In addition, several patterns of electroencephalogram have been described. To date, there is no specific treatment for reversing the iphosphamide's encephalopathy, however, Methylene Blue and Thiamine have been used, with variable efficacy.

**Final comments:** Iphosphamide-induced encephalopathy is a severe complication of some chemotherapy in children. All of its neurotoxicity mechanisms are still unclear, and it is necessary to study and describe more cases to establish an effective and rapid treatment to minimize short and long-term neurological outcomes.



Code: PE208

**Miller Fisher syndrome with idiopathic intracranial hypertension: a case report**

Laura Maria Silva Thiersch<sup>1</sup>, Leonardo Mendonça Monteiro de Castro<sup>1</sup>, Thais de Almeida Fonseca Oliveira<sup>1</sup>, Nathalia Jamille Moreira Nascimento David<sup>1</sup>, Renan Guimarães Santana<sup>1</sup>, Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, Ana Carolina Cardoso Diniz<sup>1</sup>, Karina Soares Loutfi<sup>1</sup>, Sílvia Santiago Cordeiro<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

**Case presentation:** A 11-years-old girl, previously healthy, presented with a respiratory infection. Few weeks later, developed myalgia and proximal weakness. Her symptoms worsened promptly and, in a week, she lost the ability to walk. She was admitted to our hospital presenting confusion, ataxia, dysmetria, facial paralysis, nuchal rigidity, gaze palsy and hyporeflexia. Cerebrospinal fluid (CSF) showed albuminocytological dissociation and an opening pressure of 330 mmH<sub>2</sub>O with a normal brain MRI and fundus examination. Electromyoneurography indicated a recent sensorimotor axonal polyradiculoneuropathy. Based on these clinical and neurophysiological data, the diagnosis of Miller Fisher syndrome (MFS) was established and she received intravenous immunoglobulin for 4 days. Two weeks later, she complained of visual acuity worsening and bilateral optic disc swelling was noticed. A new brain and orbital MRI showed dilation of both optic nerve sheath and flattening of the posterior sclera. An idiopathic intracranial hypertension (IIH) was diagnosed and acetazolamide started, followed by a significant clinical improvement.

**Discussion:** MFS is an acute demyelinating disease of the peripheral nervous system. It is considered a variant of Guillain-Barré syndrome (GBS), and is characterized by: ophthalmoplegia, ataxia and hyporeflexia. IIH is rare among patients with GBS. Among children with GBS in a pediatric survey, only 4% presented with papilledema, usually developing days to weeks after the onset of symptoms. IIH is characterized by raised intracranial pressure without an obvious cerebral pathology. CSF is normal and shows a raised opening pressure. The explanation for the occurrence of both syndromes is not yet explained, but it might be caused by high CSF protein in GBS, that blocks CSF path at the arachnoid granulations.

**Final comments:** Although rare, raised intracranial pressure (with or without papilledema), might be a feature of GBS and its variants. Early diagnosis of IIH in these cases is important, since it allows symptomatic management and can prevent permanent visual loss associated with papilledema. Therefore, we propose that every patient with GBS suspected should have the CSF opening pressure monitored in every lumbar puncture performed. The timing of fundus examination is also important, since papilledema may be missed if examination is performed early in the course of the disease.

Code: PE209

**Neurocutaneous Melanocytosis: Case Report of a Catastrophic Evolution**

Vanessa Limeira Pontes de Lucena<sup>1</sup>, Bruna Ramos Velani<sup>1</sup>, Amanda Póvoa Paiva<sup>1</sup>, Carolina Augusta Arantes Portugal<sup>1</sup>, Maria Avânise Yumi Minami<sup>1</sup>, Laura Defensor Ribeiro de Melo<sup>1</sup>, Ana Paula Faria Faria Ribeiro<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup>

<sup>1</sup>Universidade de São Paulo, Ribeirão Preto SP, Brazil

**Case presentation:** A 2-year-old boy with Dandy-Walker syndrome diagnosed by obstetric ultrasound, presented diffuse and large nevi at birth. He was submitted to endoscopic

third ventriculostomy at 15 days old due to obstructive hydrocephalus. Spinal fluid was then sent for analysis but showed no melanocytes. MRI of the brain showed no additional findings and mutation analysis could not be performed. After 1 month he needed a ventriculoperitoneal shunt. During the COVID-19 pandemic, he lost follow-up care until presenting at the emergency room with decreased level of consciousness, respiratory distress and flaccid paraparesis at 21 months of age. A new MRI revealed a hyperintense signal which characterized an expansive lesion embracing the bulb and obliterating the great cistern on T2 weighted images. A biopsy was performed showing leptomeningeal melanoma, therefore, confirming the diagnosis of neurocutaneous melanocytosis (NCM). As there were no available curative options, a palliative extubation was performed.

**Discussion:** Described in 1861 by Rokitsansky and named by Van Bogaert in 1948, NCM is a rare sporadic congenital syndrome with only around 300 cases reported in literature. It is characterized by large ( $\geq 20$  cm in adults,  $\geq 9$  cm on an infants' head, or  $\geq 6$  cm on an infants' body) or multiple ( $\geq 3$ ) congenital melanocytic nevi in association with melanocytes proliferation in the leptomeninges and brain parenchyma. Approximately 80% of NCM have a single mutation in codon 61 of NRAS. It has an elevated morbimortality due to increased risk of intracranial hypertension secondary to obstruction and malignization of melanocytes lesions. Association with CNS malformations is common, particularly the Dandy-Walker complex. Until now, there is no specific treatment for this disease, although early diagnosis assures a better multidisciplinary approach and prompt treatment of complications.

**Final comments:** Our case illustrates a fast and tragic evolution of NCM. It sheds light on the need of a high level of surveillance for complications, therefore demanding serial neuroimages. Despite the severity, we now have reached a better rate of survival when compared with older series reports that showed mortality as high as 98 per cent. Advances in oncology and surgical fields are cardinal for this paradigm shift. Therefore, early diagnosis and multidisciplinary approach are essential.

Code: PE210

**Posterior reversible encephalopathy syndrome (PRES) in pediatrics: 2 report cases and literature review**

Milena de Souza Alvarenga Schaffellu<sup>1</sup>, Melissa Pereira De Oliveira<sup>1</sup>, Natalia Josiele Cerqueira Checon<sup>1</sup>, Elisa Victoria Costa Caetano Funk<sup>1</sup>

<sup>1</sup>Hospital Estadual Infantil Nossa Senhora da Glória, Vitória ES, Brazil

**Case presentation:** A 9-year-old female patient undergoing treatment for type B acute lymphoblastic leukemia, without central nervous system involvement. She was undergoing chemotherapy treatment. Two weeks after the methotrexate (MTX) infusion, she developed an episode of amaurosis, followed by a lowered level of consciousness and generalized tonic-clonic motor seizures. During the diagnostic investigation, an MRI was performed showing extensive areas of hypersignal on T2/FLAIR asymmetrically affecting the parieto-occipital cortico-subcortical regions, as well as the left temporal lobe and the middle frontal gyri and part of the superior frontal gyri, in the central aspect of the pons, in the right frontal periventricular region and on the posterior aspect of the splenium of the corpus callosum. Small foci of hemosiderin deposits - subcortical corticoid microhemorrhages sparse across the above-described signal alteration zones. The set of changes confirmed posterior reversible encephalopathy (PRES). A 15-year-old male patient was hospitalized due to status epilepticus associated with arterial

hypertension. Under investigation, severe chronic kidney disease was diagnosed, requiring hemodialysis. He evolved with severe hypertension that was difficult to control, seizures, and bilateral visual deficits. The MRI exam also showed a pattern compatible with PRES.

**Discussion:** Posterior reversible encephalopathy syndrome (PRES) is an acute neuroradiologic diagnosis that presents headache, vomiting, seizures, mental confusion, visual disturbances, ataxia, encephalopathy, and other neurologic abnormalities. It is associated with some etiologies, of which the use of immunosuppressive drugs and arterial hypertension are the most frequent. Although PRES is usually reversible and most patients recover fully with the resolution of the imaging findings, its early diagnosis and prompt treatment are essential for the reduction of morbidity and mortality in these patients.

**Final comments:** It is very important for pediatric intensivists and neurologists to consider PRES syndrome in patients with risk factors for the development of the condition. This allows for an early diagnosis and approach, reducing the morbidity and mortality rates of these patients.

## Reabilitação

Code: PE217

### **Diffusion tensor tractography, motor, cognitive and behavior scales in a rehabilitation outcome following a pediatric traumatic brain injury: a case report**

Eliane Cespedes Paes Huard<sup>1</sup>, Marcus Vinicius Teles Rodrigues<sup>1</sup>, Bernardo Jose Alves Ferreira Martins<sup>1</sup>, Ana Luisa Lourenço Moretto<sup>1</sup>

<sup>1</sup>Associação das Pioneiras Sociais, Rede Sarah de Hospitais de Reabilitação, Brasília DF, Brazil

**Case presentation:** A 7-year-old boy who has been severely brain-injured in a car accident in February 2016. Initially, Glasgow coma scale was 7. He needed decompressive craniectomy and a ventriculoperitoneal shunt. At first, he was tetraplegic, without ability for locomotion. His initial MRI including DW, CSD tractography and spectroscopy showed frontal and parietal hemorrhage, parenchymal contusions, areas of reduced levels of Naa and less fibers of right corticospinal tract and of the corpus callosum. We used Gross Motor Function Scales (GMFM; Functional skills: mobility, self-care and social function (Pediatric Evaluation of Disability Inventory- PEDI); Manual function - PEGBOARD); Cognitive (Wechsler Intelligence Scale Cognitive IV); Vineland Adaptive Behavior Scales-Second Edition (VINELAND-II), which evaluates communication, daily living skills, socialization and motor skills. We decided for an internal and intensive 8-week rehabilitation program with an experienced transdisciplinary team, followed by an external program, 3 times a week.

**Discussion:** Radiological Images collected three months after the initial (Pictures 3,4, 5) showed that there was almost no more parenchymal hemorrhage; there was reduction on the ventriculomegaly and partial increasing of the number of fibers of the corpus callosum. GMFM scale shows that now he has the abilities of rolling, sitting, crawling and uses a walker for limited distance locomotion. PEDI scale shows that he has gained important progresses at daily life activities, being partially dependent: Manual Function- PEGBOARD: Initially, he was unable to execute the test; now, he is able to perform it, still slow, because of movements incoordination, mainly using his left hand, but now he is already able to do bimanual

activities. Cognitive and behavioral evolution: the results for total Scores, in both moments, have compatible classifications, although his performance was better at the second. Mild differences at the results show global improvement, specially at the processing speed; worsen at perceptual organization, which may be related to changes at his behavior. VINELAND II shows that after the rehabilitation period the patient had gains considering socialization and adaptive behavior.

**Final comments:** Comparative evaluation showed a positive correlation between motor, cognitive and behavioral improvement, compared with a resolution of an intracranial hemorrhage, on MRI, and an increase at the fibers of corpus callosum on tractography.

## Transtornos do movimento

Code: PE219

### **Atypical presentation of opsoclonus-myoclonus-ataxia syndrome in a newborn: a case report**

Luiza Fernandes Fonseca Sandes<sup>1</sup>, André Vinicius Soares Barbosa<sup>1</sup>

<sup>1</sup>Santa Casa de Misericórdia de Belo Horizonte, Belo Horizonte MG, Brazil

**Case presentation:** This is a newborn patient, male. Vaginal delivery with no complications, preterm birth. The initial physical examination of the newborn (NB) identified a hard and painful mass in the left flank. The patient was transferred to Neonatal Intensive Care Unit (NICU) for extended workup and monitoring. In the first neurological examination, opsoclonus, myoclonus and ataxia of limbs and trunk were identified. During hospitalization, the NB developed systemic arterial hypertension. In Magnetic Resonance (MRI) an expansive formation was identified in upper and middle thirds of the left kidney. The newborn underwent total left nephrectomy and is being followed up by pediatric neonatology, neurology and oncology outpatients clinics.

**Discussion:** Opsoclonus-Myoclonus-Ataxia Syndrome, or Kinsbourne Syndrome, is a rare neurological pathology, prevalent in children, caused by autoimmune reactions and/or inflammation in the cerebellum or brain. Clinically, there is muscle incoordination of the trunk (ataxia), rapid eye movements (opsoclonus) and irregular spasms (myoclonus). Kinsbourne Syndrome (KS) is a neuroimmune pathology frequently associated with post-infectious or paraneoplastic conditions. Post-infectious KS is associated with infections by Enterovirus, Epstein-Barr, Chikungunya, Flavivirus, among others. Neoplastic KS requires screening for primary tumors, especially neuroblastomas. Often noticed before cancer suspicion, the case described is an early and atypical presentation of KS. After excluding infectious causes, patients with KS should be evaluated with radiologic screening of thorax, abdomen and pelvis. The treatment of neurological symptoms of KS includes immunoglobulin and/or corticosteroids. In paraneoplastic cases, the immunomodulators are complemented with resection of primary tumor.

**Final comments:** In children with ataxia, opsoclonus and myoclonus symptoms it is mandatory to investigate possible causes for Kinsbourne Syndrome, such as infectious or neoplastic origin. The neurological and oncologic prognosis of patients is affected by time of diagnosis and treatment of primary cause.

**Code: PE220****Case report of two brothers with infantile Parkinsonism-dystonia (OMIM #613135)**

Ana Paula Resende Silva<sup>1</sup>, Josiane de Souza<sup>1</sup>, Daniel Almeida Valle<sup>1</sup>, Michelle Silva Zeny<sup>1</sup>, Izabela Cristina Marques<sup>1</sup>, Rui Junior<sup>1</sup>, Monica Jaques Spinosa<sup>1</sup>, Elisabete Coelho Auersvald<sup>1</sup>, Berkmis Viana Santos<sup>1</sup>

<sup>1</sup>Hospital Pequeno Príncipe, Curitiba PR, Brazil

**Case presentation:** V.H.P.S, male, 7 years old, son of consanguineous parents, born at term, without complications. According to a family report, the patient had reduced movement, abnormal postures in the first year of life, and started follow-up with speech therapy and physical therapy. He had infantile spasms at the age of 1 year and has been using anti-seizure drugs since then. Patient evolved with severe dystonia, protein-calorie malnutrition. Previous exams – 2016 skull MRI without changes. Extended screening for normal EIM. Unchanged eye bottom. Audiometry without alterations. Patient admitted to our service referred for genetics in November 2021. Molecular analysis by complete exome sequencing identified a heterozygous mutation in the SLC6A3 gene - position chr5:1,404,016–1,411,358. Deletion of exons 9 to 11 ENST00000270349. J.M.P.S, male 2 years old, brother of the aforementioned patient, born at term, prenatal and delivery without complications. Family report of sibling-like symptoms with reduced movement since birth, evolving with dystonic postures. Patient started seizures at 2 years of age. Currently using anti-crisis drugs with good control. Patient with severe dystonia and protein-calorie malnutrition.

**Discussion:** Infantile Parkinsonism is caused by homozygous or compound heterozygous mutations in the SLC6A3 gene. The gene is responsible for encoding a dopamine transporter (DAT1) on chromosome 5p15. The pathophysiology described so far justifies that the loss of presynaptic dopamine transporter function leads to defective dopamine reuptake and progressive accumulation of this neurotransmitter in the synapse, leading to its catabolism. Poor dopamine reuptake leads to depletion of presynaptic stores. Excess extraneuronal dopamine can lead to reduced dopamine production and lead to downregulation of dopaminergic receptors mimicking the symptoms of dopamine deficiency. Affected individuals present with hyperkinesia with orolingual and limb dyskinesia, dystonia and chorea, or hypokinesia with parkinsonian features such as bradykinesia, rigidity, and tremor. Other features may include axial hypotonia, signs of pyramidal release, and abnormal eye movements. Often these patients are initially diagnosed as having cerebral palsy.

**Final comments:** Life expectancy is short, most cases described died in adolescence. To date, no disease-modifying treatment has been described.

**Code: PE221****Case report: hyperkinetic movement disorder in a patient with heterozygous mutation in the GNAO1 gene**

Laura Comeli Ordonho<sup>1</sup>, Benaia Silva<sup>2</sup>, Luís Paulo Ferreira de Souza Dutra<sup>3</sup>, Petrus Davi Pinheiro Freire<sup>4</sup>, Sérgio Antônio Antoniuk<sup>3</sup>, Edilici Ribeiro dos Santos Malucelli<sup>3</sup>

<sup>1</sup>Pontifícia Universidade Católica de Campinas, Campinas SP, Brazil

<sup>2</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>3</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>4</sup>Universidade Federal de São Paulo, São Paulo SP, Brazil

**Case presentation:** A male infant, cesarean term delivery. His mother had an unremarkable pregnancy. Apgar score of 8/10 and weight of 2,945 g. Newborn screening tests were normal.

At 8 days of age, he presented with episodes of impaired awareness, unresponsiveness and clonus of the limbs, lasting for up to one minute. Phenobarbital was initiated, attaining full seizure control. At 6 months of age, he developed dystonia and chorea. Whole exome sequencing test was performed, which identified a heterozygous mutation in the GNAO1 gene, with substitution of Guanine to Adenine in the position chr 16:56.370.656. At 2 years of age, he presented with sporadic nocturnal dystonia episodes, preceded by nausea and vomiting. Videofluoroscopic swallowing study showed velopharyngeal insufficiency and tracheal micro-aspiration. Electroencephalogram showed spike-and-wave paroxysms and slow-wave activity in both temporo-occipital regions alternating between cerebral hemispheres. Neurological exam alterations included convergent strabismus, dystonia, chorea, hypotonia and hyporeflexia. At 4 years of age, he was admitted with status dystonicus associated with hypovolemic shock, with subsequent orotracheal intubation, sedation and transfer to a intensive care unit, where he was started on trihexyphenidyl and clobazam, with improvement and discharge after 21 days of hospitalization. Neurological exam at 6 years included global development delay, paroxysmic dystonia, global hypotonia, areflexia and hypotrophy. He maintains follow-up with a multiprofessional team, using topiramate, baclofen, trihexyphenidyl and clobazam.

**Discussion:** The GNAO1 mutation was first described in 4 patients and was associated with early onset severe epileptic encephalopathy, although at the time there was no knowledge about other possible phenotypes. Currently, GNAO1 mutation is known to be related to a myriad of clinical presentations, which include epilepsy, neurodevelopmental delay and hyperkinetic movement disorder. The reported case exemplifies the variety of manifestations that such mutation may be correlated to. Some of its complications, such as status dystonicus, are life-threatening occurrences that require prompt recognition and treatment.

**Final comments:** The GNAO1 gene mutation is responsible for multiple clinical presentations. As such, it would be well advised to consider it as a differential diagnosis in patients presenting with neurodevelopmental delay, epileptic seizures and hyperkinetic movement disorders in the first year of life.

**Code: PE222****DNM1L mutation presenting as progressive myoclonic epilepsy associated with acute febrile infection-related epilepsy syndrome**

Ana Chrystina de Souza Crippa<sup>1</sup>, Gustavo Leite Franklin<sup>2</sup>, Bruno Toshio Takeshita<sup>3</sup>, Hélio Afonso Ghizoni Teive<sup>1</sup>

<sup>1</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

<sup>2</sup>Pontifícia Universidade Católica do Paraná, Curitiba PR, Brazil

<sup>3</sup>Instituto de Neurologia e Cardiologia de Curitiba, Curitiba PR, Brazil

**Case presentation:** A 12-year-old girl presented with recurrent tonic-clonic seizures, alternating with interictal sleepiness and confusion, after an initial picture of two days of fever and flu-like symptoms. The patient developed a refractory status epilepticus and was intubated and remained in coma for 30 days. The patient had a previous history of mild neurodevelopmental delay and a diagnosis of mild mental retardation. At seven years old, the patient started to present tonic-clonic seizures, and later, the patient developed behavioral changes, an unbalanced gait, and sudden and brief jerks, consistent with eyelids myoclonus, multifocal erratic myoclonus and generalized myoclonus, that worsened with anxiety and with sound. At the examination the patient presented an ataxic gait, and mild dysmetria. During the investigation, an initial electroencephalogram showed generalized

polyspikes and wave discharges, with bifrontal predominance. The brain magnetic resonance image showed cortical atrophy, subcortical vacuolar lesions in both cerebral hemispheres, and laminar cortical necrosis with underlying cortical thinning. Hematologic and then, anti-neuronal antibodies in cerebrospinal fluid (CSF) were normal. Thus, exome sequencing was performed, revealing a de novo pathogenic variant in DNM1L gene.

**Discussion:** The phenotypic spectrum of DNM1L mutation-related encephalopathy includes the presence of epileptic syndromes, as well as cognitive impairment, muscle hypotonia, dystonia and spasticity. Myoclonus and super refractory status epilepticus were reported in other studies and may represent a diagnostic clue.

**Final comments:** Although all described cases have some clinical peculiarities, there is a clinical pattern of great utility in diagnostic suspicion. Patients with mutation in DNM1L gene, may present in the form of a child or adolescent with variable clinical spectrum, ranging from a mild neuropsychomotor delay, often associated with myoclonus, that suddenly develops a refractory epileptic status, frequently having a fever or infection trigger. Iconic cases like these may be of great value, so that diagnosis can be made faster, and the appropriate treatment can be introduced as early as possible.

#### Code: PE223

##### **Myoclonic-chorea in PURA syndrome**

Gustavo L. Franklin<sup>1</sup>, Eli Paula Bacheladenski<sup>2</sup>, Danielle C. B. Rodrigues<sup>2</sup>, Ana C.S. Crippa<sup>2</sup>

<sup>1</sup>Pontifícia Universidade Católica do Paraná, Curitiba PR, Brazil

<sup>2</sup>Universidade Federal do Paraná, Curitiba PR, Brazil

**Case presentation:** A 5-year-old female with a history of neurodevelopmental delay, hypersomnolence, seizures, and feeding disturbance, presented a complex movement disorder. Clinically, there was abnormal facial features, hypotonia, and the patient presented a mixed hyperkinetic movement disorder, consisting of chorea, dystonia, myoclonus, and hand stereotypies. The presence of generalized myoclonus, interposed with those hyperkinetic movements, resembled a "stop-motion" animation (Video 1), similar to the animation technique, in which objects are photographed frames by frame. Brain MRI showed mild frontal cortical atrophy (Fig. 1). Genetic investigation was performed, and CGH-array was performed, finding a pathogenic variant in PURA gene, compatible with PURA Syndrome<sup>1</sup>.

**Discussion:** PURA gene encodes a single-exon transcript that results in a 322 amino acids protein, namely Pur- $\alpha$ , a protein with regulatory functions in gene transcription, DNA replication, RNA transport and mRNA translation. PURA is essential for normal brain development, synapse formation and proliferation of neurons, astrocytes and oligodendrocytes in the central nervous system. PURA-NDDs have recently been identified and still may be underestimated. PURA Syndrome is characterized by neonatal hypotonia, significant neurodevelopmental delay with absence of speech, epileptic seizures, abnormal non-epileptic movements, and lack of independent ambulation in most of the patients. Also, is present in variable frequency: feeding difficulties, ophthalmological disorders, hypersomnolence, hypothermia and central apnea, urogenital malformations, skeletal abnormalities, and congenital heart defects. Since the initial description, 97 different pathogenic variants have been reported, but no

clear genotype-phenotype correlations have emerged so far. The presence of myoclonic-chorea syndrome may be a clue to the final diagnosis.

**Final comments:** Complex hyperkinetic movement disorders in infants with global developmental delay may be an important clue to diagnose Pura Syndrome, being of clinical relevance, since affected patients may be misdiagnosed with dyskinetic cerebral palsy.

#### Code: PE224

##### **Neurodevelopmental disorder with involuntary movements associated with mutation in the GNAO1 gene**

Ana Cristina Nascimento Dias Carneiro<sup>1</sup>, Fernando Nascimento Dias Carneiro<sup>2</sup>, Renan Guimarães Santana<sup>1</sup>, Karina Soares Loutfi<sup>1</sup>, Bruna Ribeiro Torres<sup>1</sup>, Ana Carolina Cardoso Diniz<sup>1</sup>, Laura Maria Silva Thiersch<sup>1</sup>, Thais de Almeida Fonseca Oliveira<sup>1</sup>, Nathalia Jamille Moreira Nascimento David<sup>1</sup>

<sup>1</sup>Fundação Hospitalar do Estado de Minas Gerais, Hospital Infantil João Paulo II, Belo Horizonte MG, Brazil

<sup>2</sup>Universidade de Itaúna, Itaúna MG, Brazil

**Case presentation:** JCMO, 17 years old, male, second child of non-consanguineous parents. No prenatal and delivery complications. At six months, neurodevelopmental departure delay was observed, he was diagnosed with non-progressive chronic encephalopathy and started treatment with physical therapy and speech therapy. He showed improvement, was able to walk and speak at 2 years and 9 months. At age 9, episodes of movement disorders began abruptly. Anti-NMDA autoimmune encephalitis, Sydenham's chorea and ADEM were then suspected. But after workup with CSF, brain MRI and normal laboratory tests, these hypotheses were ruled out. In 2022, he performed Panel Movement and the result was a neurodevelopmental disorder with involuntary movements due to mutation of the GNAO1 gene. He was recently admitted to our service due to dyskinetic status and used various medications. After more than a month of hospitalization, he was discharged, with improvement in chorea and dystonia. He is on Artane, Diazepam, Gabapentin, Clonidine, Clozapine and Topiramate. He has also used Chlorpromazine, Levodopa, Midazolam, Clobazam, Ketamine and Morphine.

**Discussion:** Through a literature review, it appears that the movement disorder associated with the mutation of the GNAO1 gene shows little response to drug treatment. Currently, tetrabenazine is the drug with the greatest benefit, however, it is not available in Brazil and therefore has not been used. Another treatment option described is the use of DBS, but it has not yet been possible to refer the patient to surgery. Improvement was also reported with Topiramate and it was decided to start this treatment. After the introduction of this medication, we were able to reduce the venous drugs up to suspension and keep control of dyskinesia. However, the patient is very sleepy and does not tolerate attempts to reduce oral medications.

**Final comments:** There is no specific treatment for the neurodevelopmental disorder with involuntary movements associated with a mutation in the GNAO1 gene. And controlling the symptoms, especially chorea, is a big challenge.

Code: PE225

**Neurodevelopmental disorder with involuntary movements associated with the wars2 Gene in infant: a case report**Sayonara Sousa Milhomens Marquez<sup>1</sup>, Vanessa Cristina Guedes Silveira<sup>1</sup>, Juliana Carvalho Esper Mundim<sup>1</sup>, Letícia Valadares de Oliveira<sup>1</sup><sup>1</sup>Universidade Federal do Tocantins, Palmas TO, Brazil

**Case presentation:** A 15-month-old girl evolved with fever and tremors associated with ataxy after vaccination of hepatitis A, DTP, OPV y tetra viral. She was born via cesarean, uneventfully. Parents are consanguineous. Her mother had Specific Hypertensive Pregnancy Disease (SHPD) during pregnancy. No history of previous hospitalizations, regular medications, and allergies. Neuropsychomotor development (NPMD): she sat at 6 months, babbles and waves, and didn't walk but stood with support by 12 months. The cranial magnetic resonance imaging (MRI), electroencephalogram (EEG), and cerebral spinal fluid were normal. Diagnostic hypothesis: acute cerebellitis. An intravenous combination of ceftriaxone and acyclovir was given for 10 days, evolving with an improvement in tremors. It was prescribed clonazepam for ambulatorial use. After 3 months, the fever began again, getting worse the tremors and ataxia. Physical exam: without trunk support; decreased muscle strength in lower and upper limbs (LL. and UP.), with hypertonia, reflexes, and distal clonus in LL.; tongue and chin tremors. Genetic analysis, Next Generation Sequencing (NGS), by Movement Program, identified compound homozygous mutations in the WARS2 gene, being the paternally inherited missense variant: c.754C>T, (p.Arg252Cys) with uncertain significance.

**Discussion:** Protein translation is critical for all forms of life, and aminoacyl transfer RNA (tRNA) synthetases (ARSs) play an important role in this process. ARSs ensure the incorporation of correct amino acids in the growing polypeptide chain during protein synthesis. Each protein-genic amino acid is coupled to its corresponding tRNA by a specific ARS. Mitochondrial ARSs are encoded by separate nuclear genes and an increasing proportion of ARS genes has been associated with human disease. WARS2 is a mitochondria-specific AR named tryptophanyl-RNA synthetase 2 and its deficiency can cause heterogeneous clinical presentations (e.g., muscle weakness, peripheral neuropathy, movement disorder, epilepsy), but developmental cognitive delay and complex movement disorders are prevalent mark, and the absence of epileptic seizures can increase patient survival. NGS techniques became widely available and, are a powerful tool to unravel the heterogenic genetic background of MD.

**Final comments:** In children with otherwise unexplained progressive hyperkinetic movement disorders, WARS2-related mitochondrial disease should be included in the list of differential diagnoses.

Code: PE226

**Neurological disorder related to ATP1A3: importance of diagnosis**Ana Luíza Almeida Carneiro<sup>1</sup>, Bruna Torres Homem Fonseca<sup>1</sup>, Aline Fonseca Lima<sup>1</sup>, Alessandra Augusta Barroso Penna e Costa<sup>1</sup>, Fernanda Veiga Góes<sup>1</sup>, Marcela Rodrigues Freitas<sup>1</sup>, Talys Jason Pinheiro<sup>1</sup>, Tania Regina Dias Saad Salles<sup>1</sup>, Ludimila Marins de Almeida Moura<sup>1</sup><sup>1</sup>Instituto Fernandes Figueira, Rio de Janeiro RJ, Brazil

**Case presentation:** JRCS, female, started, at 15 years old, dysphagia initially for solids, progressing to liquids, hand dystonia and anarthria after isolated fever. At the time she

was admitted to another pediatric center for diagnostic investigation, with normal brain MRI, EEG and ENMG. History of mother with undiagnosed psychiatric disorder and progressive gait dysfunction. At age 16 she was hospitalized for malnutrition associated with worsening abnormal movements. Neurological examination evidenced: preserved cognition, motor aphasia, hypomimia, dysphagia, sialorrhea, absence of vomiting reflex; reduced tongue motricity with preserved sensitivity, no myofasciculations; generalized hypotrophy, left worsening upper limb rigidity, strength grade 4+, normal deep reflexes and indifferent plantar cutaneous reflex, asymmetric hand and foot dystonic posture (worse left), bradykinesia, distal muscle atrophy, no ataxia or dysmetria; preserved sensitivity. On admission the previous tests were repeated, in addition to echocardiogram, abdominal and pelvic ultrasound, chest X-ray, cervical spine MRI, and nasopharyngolaryngoscopy, all normal. The dystonia gene panel identified a mutation in the ATP1A3 gene.

**Discussion:** The ATP1A3 gene encodes the  $\alpha$ -3 catalytic subunit of the transmembrane Na<sup>+</sup>/K<sup>+</sup> (+)-ATPase ion pump and is expressed exclusively in CNS neurons. ATP1A3-related neurological disorders of autosomal dominant inheritance have 4 described phenotypes: Rapid Onset Dystonia-Parkinsonism; Alternating Hemiplegia of Childhood; Cerebellar Ataxia, Areflexia, pes cavus, Optic Atrophy and Sensory Hearing Loss (CAPOS); and Developmental Encephalopathy and Epilepsy. The patient had the Rapid Onset Dystonia-Parkinsonism phenotype (or dystonia 12) characterized by asymmetric dystonia of acute or subacute onset associated with features of parkinsonism that evolve in hours to days stabilizing within a month. Usually, the symptoms are triggered by fever, stress, trauma, physical exercise, alcohol intake, and others. The age of onset ranges from 9 months to 55 years. The symptoms do not improve with Levodopa.

**Final comments:** The genetic study has enabled case outcome and appropriate treatment, as well as providing the family with genetic counseling through maternal investigation. Molecular genetic research has become a fundamental tool for elucidating cases previously without a definitive diagnosis.

Code: PE227

**Opsoclonus-mioclonus-ataxia syndrome as first clinical presentation of MECP2 mutation: a case report**Laila Prazeres Schulz Moreira<sup>1</sup>, Isabela Bartholomeu Ferreira da Costa<sup>1</sup>, Bruna Ramos Velani<sup>1</sup>, Maria Avanise Yumi Minami<sup>1</sup>, Carla Andrea Cardoso Tanuri Caldas<sup>1</sup>, Maiave Micaelle Figueiredo de Matos<sup>1</sup>, Rafaela Pichini de Oliveira<sup>1</sup>, Vitor Tumas<sup>1</sup>, Ana Paula Andrade Hamad<sup>1</sup><sup>1</sup>Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Hospital das Clínicas, Ribeirão Preto SP, Brazil

**Case presentation:** A one year seven months old female that was hospitalized in our tertiary reference service with a history of fever, tremor, trunk and gait instability, vomit and irritability for 20 days. At day four in our hospital, she evolved with myoclonia and eye movements that got worst by day seven, pointing for the diagnosis of opsoclonus-myoclonus-ataxia syndrome (OMAS). Patient was born prematurely at 32 weeks, and had motor and speech delay. At corrected age of one year and five months, she could walk with support and had limited monosyllabic vocabulary. She did not have any history of hand shaking, other stereotypes or seizures. Her head circumference was normal. After she presented neurodevelopmental regression with important gait and trunk instability until gait loss. The patient was extensively investigated with tumoral, serology, inflammatory and autoimmune markers, electroencephalogram, metabolic screening and neuroimaging. All tests without suggestive abnormalities

of a specific underlying pathology. We've had collected the genetic test - panel, evidencing a pathogenic MECP2 heterozygous mutation.

**Discussion:** OMAS is a rare neurologic disorder that presents with a combination of characteristic eye movements and myoclonus in addition to ataxia, irritability and sleep disturbance. Typically affects children and often arises as a paraneoplastic phenomenon in children who present with neuroblastoma and related tumors. In addition to the movement disorders often seen in OMAS, developmental stagnation, regression, and alterations in sleep and mood can occur. MECP2 mutation and Rett syndrome are a common genetic disorder, typically affecting females with clinical and neurophatological findings, indicating early developmental arrest. There is no previous database relating OMAS and MECP2 mutation. Movement disorders are frequently related to MECP2 mutation, such as stereotypies, gait abnormalities, broad-based or ataxic gait, spasticity, dystonia, tremor, myoclonus, bruxism, ataxia, choreoathetoid movements and rigidity, but none OMAS relation was previously reported.

**Final comments:** Movement disorders are common in patients with MECP2 mutations. They typically have motor stereotypies, developmental arrest, microcephaly and epilepsy. OMAS often arises as a paraneoplastic disease. Since our patient did not have any evidence of underlying tumors, stereotypies, microcephaly or seizures, the case report gait us to a new atypical Rett Syndrome presentation or to a overlap of both pathologies.

Code: PE228

#### **Paroxysmal Kinesigenic Dyskinesia: when to Diagnose?**

Hanid Fontes Gomes<sup>1</sup>, Naiane Cristina Ferreira Mendes<sup>1</sup>, Renata Beatriz Boechat Quadros<sup>1</sup>, Marlos Melo Martins<sup>2</sup>

<sup>1</sup>Hospital Municipal Jesus, Rio de Janeiro RJ, Brazil

<sup>2</sup>Universidade Federal do Rio de Janeiro, Instituto de Puericultura e Pediatria Martagão Gesteira, Rio de Janeiro RJ, Brazil

**Case presentation:** We report a case of a previously healthy 14-years-old teenager who at age of 11, initiated involuntary movements that affected both arms and legs with an initial frequency of twice a day. Despite being involuntary, the teenager was able to control the movements. After three months, they intensified their frequency, occurring countless times a day, throughout the body, becoming uncontrollable. She reported that she was able to sense when they would occur and have never lost consciousness during these movements. The episodes were triggered by everyday activities like getting out of bed or a chair after a period of physical rest, leading to previous erroneous diagnoses of psychological and psychiatric conditions. There was no information regarding the usage of previous medications or previous diseases. There was no learning commitment or cognitive dysfunction. After some evaluations, she was referred to a Pediatrics Neurology service where Paroxysmal Kinesigenic Dyskinesia was diagnosed, when the introduction of Carbamazepine was indicated, with total control of involuntary movements.

**Discussion:** Paroxysmal Kinesigenic Dyskinesia is a rare disease, with a prevalence of 1/150,000 cases, characterized by abnormal involuntary movements that are precipitated by a sudden movement or startle, without altered consciousness, and repeated several times a day. Evaluating the frequency of types of movements, the most common observed is dystonia (57%), followed by chorea in 6% of patients and ballismus in 1%. Most cases are idiopathic, but certain patients have a family history, which is typically inherited by an autosomal dominant pattern. The first-line treatment is Carbamazepine, but alternative treatments include Lamotrigine, Levetiracetam, Oxcarbazepine, Valproate, Topiramate, and benzodiazepines.

Diagnosis is based primarily on history and clinical observation, confirmed by normal images, Electroencephalogram and laboratory test results. Paroxysmal Non-Kinesigenic Dyskinesia and Epilepsy are the main differential diagnosis to be considered.

**Final comments:** The case refers to Paroxysmal Kinesigenic Dyskinesia, concerning a female teenager with several involuntary movements per day, triggered by movement and routine actions, with no cognitive or learning impairment. None of the events occurred during sleep nor caused altered consciousness. The age of onset was typical, and all complementary investigation was normal. The introduction of Carbamazepine offered a complete resolution of events.

## **Transtornos neuropsiquiátricos e distúrbios de aprendizagem**

Code: PE231

#### **The application of neuromodulation protocols in a child with attention deficit hyperactivity disorder: a case report**

Eduardo Cristhian Oliveira de Souza Mota<sup>1</sup>, Douglas Machado da Costa<sup>1</sup>, Kauê Magalhães Castro dos Santos<sup>1</sup>, Renato Lobato da Costa Nunes<sup>1</sup>, Gabriel Vitor Oliveira de Souza Mota<sup>1</sup>, Alyssa Maria Rigon Bueno<sup>1</sup>, Ana Paula Palheta Faria<sup>1</sup>, Jonas Gabriel Araripe Dantas<sup>2</sup>, Lucas Sousa de Souza<sup>1</sup>

<sup>1</sup>Universidade Federal do Amapá, Macapá AP, Brazil

<sup>2</sup>Centro Universitário Aparício Carvalho, FIMCA, Porto Velho RO, Brazil

**Case presentation:** The Report is based on the application of Neuro Psychophysical Optimization (ONPF) protocols provided by the Radioelectric Asymmetric Conveyer (REAC) in a male child (12 years old) diagnosed by medical and psychological opinion with Attention Deficit Hyperactivity Disorder (ADHD). In this sense, the protocols applied consist of neuromodulation methods in which the machine creates an electrical gradient between the patient and the application probe, triggering ionic flows that influence the restoration of cellular polarity and the optimization of brain areas - especially the prefrontal cortex - and the action of neurotransmitters such as those of dopaminergic and noradrenergic life. Thus, to evaluate the effectiveness of the protocols in relation to the symptomatology and quality of life of the patient, the SNAP-IV test was applied before and after the application of the protocol, evaluating divergences between the periods.

**Discussion:** The application of REAC technology was through 12-session neuromodulation protocols. To evaluate ADHD, the SNAP-IV tests, recognized by the Brazilian Association of Inattention and Hyperactivity Deficit, was used. In this context, this test evaluates the symptomatology of the disorder through 18 questions concerning the patient's daily life and divides the answers into "NOT EVEN A LITTLE," "JUST A LITTLE," "QUITE" and "TOO MUCH" - being classified as pathological the inattention of children who have more than 9 answers "QUITE" or "TOO MUCH." In the pre-cycle period, before the application of the protocols, the patient had 1 answer "NOT EVEN A LITTLE," 4 "JUST A LITTLE," 8 "QUITE" and 5 "TOO MUCH." Subsequently, after the application of the protocols, the tests were performed again, resulting in 1 answer "NOT EVEN A LITTLE," 10 "JUST A LITTLE," 5 "QUITE" and 2 "TOO MUCH." Consequently, these results highlight improvement in the patient's perception of the disorder through the test, demonstrating the therapeutic potential of REAC technology with regard to ADHD.

**Final comments:** Therefore, REAC technology is outlined as an extremely relevant apparatus in the case of Attention Deficit and Hyperactivity, enhancing the non-pathological

functioning of the areas affected by the disorder. Owing to it, there is an improvement in the SNAP-IV test scores, associated with an improvement in the patient's quality of life and symptomatology.

**Code: PE238**

**Diagnostic process of patient with PANDAS syndrome: case report**

Martina Estacia Da Cas<sup>1</sup>, Gabriel Soccol Fassina<sup>1</sup>, Saulo Bueno de Azeredo<sup>1</sup>, Eduarda Vogel Wollmeister<sup>1</sup>, Lucas Lizot Pozzobon<sup>1</sup>, Maria Fernanda Guadagnin<sup>1</sup>, Valéria Tessaro Grandi<sup>1</sup>, Nicolle Surkamp<sup>1</sup>, Thiele do Prado Geller<sup>1</sup>  
<sup>1</sup>Universidade de Passo Fundo, Passo Fundo RS, Brazil

*Case presentation:* Male, 10 years old, referred to psychiatric care due to aggressiveness, stereotyped movements, progressively started 6 months ago, related to an outbreak of COVID-19 in the family - the patient did not show symptoms. At the consultation, the mother reported that the patient performed "twitching," opisthotonic, oculogyric crises, and vocal intonations, in addition to obsessive movements to relieve thoughts that something bad was going to happen. No loss of consciousness during episodes. According to the patient, the crises were preceded by a feeling of restlessness, after which he felt relieved. He had auditory (command voices) and visual (animals) hallucinations, as well as a compulsion for symmetry, organization, and hygiene. Obstetric and pediatric history, he showed twin pregnancy, with preeclampsia, tobacco and alcohol use, without other complications. During management, initially with the hypothesis of obsessive-compulsive disorder, sertraline was started, which led to an improvement in symptoms, except for tics, which worsened. The medication dose was increased and risperidone was added. A new regimen provided an improvement in OCD, but the crises became frequent, with worsening of the command voices - suicide attempts - and lack of sphincter control. Imipramine was added to the regimen. Laboratory tests, neurological evaluation, cranial CT, and EEG were requested. All exams were within the normal range, except ASLO, which was slightly increased. In the neurological evaluation, the hypothesis of pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus (PANDAS) emerged. The patient is still under follow-up using imipramine, sertraline, and risperidone for symptomatic control.

*Discussion:* The hypothesis of pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus (PANDAS) is a disease characterized by tics, obsessive compulsive disorder and motor hyperactivity with abrupt and episodic choreiform movements that affects children between 3 and 12 years of age, and may be related to Group A Streptococcus infections. In view of the manifestations of the syndrome, the above case fits the diagnostic criteria and its course of improvement and abrupt relapses as well.

*Final comments:* Although it is a recently proposed and still little investigated pathology, PANDAS represents a possible model for the relationship of environmental factors in neuropsychiatric disorders.

**Code: PE242**

**Music as a tool in the development of children with autism spectrum disorders (ASD): case reports**

Patricia Loures Rossinol Mendes<sup>1</sup>, Vanessa Loures Rossinol<sup>2</sup>  
<sup>1</sup>Educaminas, Coronel Fabriciano MG, Brazil  
<sup>2</sup>IPEMED, Belo Horizonte MG, Brazil

*Case presentation:* Child musicalization has gradually gained importance as a music therapy tool in the approach of children with autism spectrum disorders (ASD). This is a descriptive study, in which we used musicalization techniques in the school environment in early childhood education classes (kindergarten 2 and 3) and elementary school (1st and 2nd grades) that had at least one child in the group with an ASD. Approaches were made through appropriate interventions guided by the specific characteristics of each ASD child observed in this study. Six children with ASD were followed for months by means of varied techniques of children's musicalization in a collective setting, with the other children of the same age group who did not have ASD.

*Discussion:* The constant observation of these children allowed the analysis that music, in all its forms and possibilities, facilitated learning and neuropsychomotor development, as well as promoted greater social interaction among these children.

*Final comments:* It is believed that, due to its unique characteristic of brain stimulation, music stimulates neuroplasticity in the brain as a whole, breaking the barriers found in these children, providing an opportunity for better use of the music therapy classes/sessions, stimulating social interaction, speech, empathy, among others. However, it is worth pointing out the necessity and importance of conducting new research, since there are few studies on this subject.

**Code: PE245**

**Reduced fidgety movements in child prenatally exposed to SARS-CoV-2: a case report**

Isabelle Diniz Melo<sup>1</sup>, Renata Castro Kehdi<sup>1</sup>, Leticia Regia Lima Cavalcante<sup>1</sup>, Deniele Bezerra Lós<sup>1</sup>, Marylane da Silva Viana<sup>1</sup>, Danielle Macêdo Gaspar<sup>1</sup>  
<sup>1</sup>Universidade Federal do Ceará, Fortaleza CE, Brazil

*Case presentation:* A male baby born by Cesarean section at 37 weeks (APGAR 9/9), weighing 4280 g, stature of 53 cm and cephalic perimeter of 38 cm. The 29 years-old mother (G5P4A1), previously hypertensive, had an active COVID-19 infection during childbirth. She had no other comorbidities. At four months, he presented with motor skills developmental delay, showcasing hypertonia of the lower limbs and axial hypotonia. Subsequently, he was submitted to various evaluations, such as the Hammersmith neurological evaluation, in which he achieved a score of 59 and as Alberta's Infant Motor Scale (scoring 12), attaining a percentile of 10. Finally, he underwent the General Movement Assessment (GMA), in which he presented abnormal fidgety movements, lack of foot-to-foot contact, and hand-to-hand contact, both expected at this age.

*Discussion:* The case under consideration refers to a child, prenatally exposed to the SARS-CoV-2 virus, who presented with motor skills dysfunction. Although many viral maternal infections are well associated with neurodevelopmental disorders, the effects of prenatal exposure to the COVID-19 virus on child development are still not well established. With this in mind, it is important to consider this type of infection's inflammatory potential, which can trigger maternal immune activation, mainly when associated with the inflammatory profile of the first and third semesters, and generate

immunological responses strong enough to impair fetal development. In addition, the General Movement Assessment is a tool that evaluates possible early changes in neurodevelopment and it is already being used to describe abnormal fidgety movements of babies whose mothers had COVID-19 during their pregnancy. Based on the GMA results from the presented case, the child could be at risk for future neurological disorders.

*Final comments:* The consequences of prenatal exposure to the COVID-19 virus are not entirely known. Because of this, neurodevelopmental abnormalities observed in children submitted to these inflammatory conditions should be reported and investigated for further clarification.

#### Code: PE246

##### **Psychiatric manifestations in posterior reversible encephalopathy syndrome**

Ana Cleide Silva Souza<sup>1</sup>, Raphael Condack Melo de Assis Dias<sup>1</sup>, Ricardo Torres Negraes<sup>1</sup>, Robinson Cardoso Machado Yaluzan<sup>1</sup>  
<sup>1</sup>Hospital Infantil Cosme e Damião, Porto Velho RO, Brazil

*Case presentation:* L.S.O., female, 15 years old, hospitalized for peaks of fever, anemia, positive direct coombs, hypocomplementemia and proteinuria >0.5 g/24h. Pulse therapy with methylprednisolone was prescribed for the hypothesis of systemic lupus erythematosus (SLE). Evolved with severe headache and convulsive crises presenting cortical, subcortical, posterior and bilateral hypodensity on cranial tomography. Phenobarbital 150mg/d was started, lamotrigine 25mg/d and due to the persistence of the seizures, phenytoin 300mg/day, valproic acid 1500mg/day and hydroxychloroquine 400mg/d were associated. She had positive antiphospholipid antibodies and, due to severe lupus activity, a high Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 31 was verified. She was again treated with methylprednisolone and cyclosporine with maintenance of prednisone 60 mg and AAS 100 mg/d. Cerebral resonance angiography without alterations. During follow-up, the patient had SLEDAI 39 and was started on 20mg/d of citalopram and 4mg/d of clonazepam and did not experience new convulsive events and psychogenic crises.

*Discussion:* Posterior reversible encephalopathy syndrome (PRES) is diagnosed clinically and radiologically and is characterized by reversible subcortical vasogenic cerebral edema, with characteristic neuroimaging features<sup>1</sup>. PRES has been attributed to many etiologies, including SLE and drug toxicity<sup>2</sup>. It occurs in <1% of these patients, with a higher incidence in young people, with a SLEDAI Index  $\geq 6$  and associated comorbidities<sup>3</sup>. Clinical manifestations include seizures, encephalopathy, "confusion" and "altered mental function"<sup>1</sup>. A proposed mechanism of PRES in SLE patients is T cell activation resulting in the production of inflammatory cytokines, which may contribute to brain endothelial dysfunction. Cytotoxic drugs such as cyclosporine, often used to treat SLE and other inflammatory diseases, can also induce PRES<sup>4</sup>. Psychiatric symptoms occurred before, during, or after the onset of PRES, which is consistent with evidence of psychiatric morbidities in neurological disorders. Despite the term reversible, residual infarctions and subsequent leukomalacia are recognized sequelae of PRES<sup>1</sup>, supporting the likelihood of long-term psychiatric symptoms<sup>5</sup>.

*Final comments:* The diagnosis of PRES requires high clinical and imaging suspicion, and it is necessary to consider it as a rare differential diagnosis for acute changes in mental status.

#### Code: PE250

##### **The management of innovative technologies of radioelectric neuromodulation in a child patient with autism spectrum disorder (ASD)**

Eduardo Cristhian Oliveira de Souza Mota<sup>1</sup>, Alyssa Maria Rigon Bueno<sup>1</sup>, Gabriel Vitor Oliveira de Souza Mota<sup>1</sup>, Kaue Magalhães Castro Santos<sup>1</sup>, Renato Lobato da Costa Nunes<sup>1</sup>, Jonas Gabriel Araripe Dantas<sup>2</sup>, Douglas Machado Costa<sup>1</sup>, Giuliana Almeida da Silvas Santos<sup>1</sup>, Ana Paula Palheta Faria<sup>1</sup>

<sup>1</sup>Universidade Federal do Amapá, Macapá AP, Brazil

<sup>2</sup>Centro Universitário Aparício Carvalho, Porto Velho RO, Brazil

*Case presentation:* Case report performed based on observation of a male child patient (3 years and 10 months old) diagnosed with Autistic Spectrum Disorder (ASD) by medical and psychological opinion, submitted to Neuromodulation therapies provided by the Radioelectric Asymmetric Conveyor (REAC). The referred patient had limitations regarding cognition, neurodevelopment, social-affective skills and communication (non-existent in a vocalized way), common traits to ASD, which directly affect the patient and their family's life quality and mental state. In the same way, the REAC therapy works by creating an electric gradient between the machine and the patient, unleashing an ion flow that recomposes the bioelectrical fields and the cell polarity. Moreover, the therapy influences two other fronts: (1) stimulation of areas of the cortex, especially the prefrontal; (2) Optimization of the action of neurotransmitters on nerve synapses.

*Discussion:* After the application of 3 cycles of 18 sessions, the patient analyzed showed physiocognitive and behavioral improvements: (1) In the body field, the child with ASD highlighted better psychomotor control, coordinating more effectively and concretely balance and spatial orientation. Furthermore, the patient constituted the ability to practice physical activities such as jumping and running in an orderly way. (2) In the cognitive prism, the follow-up of the patient denotes a significant improvement in the communicative capacity, in which, although there is no composition of sentences, there is structuring of responsive faculty and formation of musicality skills. In addition, activities with greater mental requirements, such as puzzles and color identification, are best answered by the patient. (3) Concerning to the behavioral area, there was greater emotional control, with a reduction in the frequency of crises of dysregulation - going from daily to weekly -, greater independence, improvement of the condition of social coexistence and improvement in the structuring of affective relationships, especially with family members.

*Final comments:* Therefore, the evolution of the patient is inferred in an atypical way to the disorder, highlighting positive points for child development in the cognitive, social, communicative and affective areas. Therefore, the possibility of Neuromodulation through the Asymmetric Radio Converter is qualified as a therapeutic proposal in the follow-up of children with Autism Spectrum Disorder.