

**ID do trabalho:** 8

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: UNVEILING SPINOCEREBELLAR ATAXIA 25: FIRST CASE REPORT OF A BRAZILIAN FAMILY**

**Autores:** TENORIO , Renata Barreto<sup>1</sup>; SOARES DE LIRA, José Sávio<sup>2</sup>; CORDELLINI, Marcela Ferreira<sup>1</sup>; DONIS, Karina Carvalho<sup>3</sup>;

**Instituição dos Autores:** (1) Instituto de Neurologia de Curitiba - Curitiba - PR - Brasil; (2) Universidade Federal da Paraíba - João Pessoa - PB - Brasil; (3) Universidade Feredal da Paraíba - João Pessoa - PB - Brasil;

### **Resumo do trabalho:**

Case presentation: we describe a Brazilian family with spinocerebellar ataxia type 25 (SCA25), marked by phenotypic variability and incomplete penetrance. The proband, a 1-year-8-month-old female, presented with progressive ataxia, delayed speech development, and muscle weakness. Neurological examination revealed a broad-based gait, dysmetria, reduced ocular saccades, and absent deep tendon reflexes. Brain MRI showed diffuse cerebellar atrophy, and her Scale for the Assessment and Rating of Ataxia (SARA) score was 15/40 at 4 years of age. Genetic testing identified a novel heterozygous frameshift mutation in the PNPT1 gene (c.2068del; p.Arg690Glufs\*5), classified as likely pathogenic. The father, initially reported as asymptomatic, exhibited mild polyneuropathy and a SARA score of 2/40 at the age of 36. This mutation, located in the critical S1 RNA-binding domain of PNPT1, is associated with mitochondrial RNA processing and disease pathogenesis. Discussion: SCA25 is an autosomal dominant disorder characterized by cerebellar ataxia, peripheral neuropathy, and variable expressivity. This case marks the first documented family in Brazil and South America, expanding the geographic scope of the disorder. The novel PNPT1 variant identified in this family reinforces the role of the S1 domain in disease mechanisms. Phenotypic variability observed within the family aligns with prior reports, where symptoms ranged from severe early-onset ataxia to mild polyneuropathy in adulthood. The incomplete penetrance and age-dependent expressivity highlight the complexity of genotype-phenotype correlations in PNPT1-associated disorders. Computational analyses predict significant impacts on splicing and protein function. Final comments: this case emphasizes the importance of considering SCA25 in the differential diagnosis of progressive ataxias, especially in the presence of cerebellar atrophy and sensory neuropathy. The findings expand the clinical and genetic understanding of SCA25, providing further evidence of the critical role of PNPT1 in mitochondrial RNA homeostasis. Future studies should aim to elucidate the molecular mechanisms underlying SCA25 and identify potential genetic or environmental modifiers influencing its expression. Early diagnosis is essential for improving patient management and genetic counseling

**Palavras-Chave do trabalho:** mitochondrial RNA processing; neurogenetic disorders; PNPT1 gene; spinocerebellar ataxia;

**ID do trabalho:** 10

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: CHARACTERIZATION OF AN ACUTE HEPATIC PORPHYRIA COHORT IN A TERTIARY CENTER IN BRAZIL**

**Autores:** ABDO PAIVA, Michelle<sup>1</sup>; ANDRÉ MACEDO SERAM DA SILVA, André<sup>1</sup>; DE HOLANDA MENDONÇA, Rodrigo<sup>1</sup>; ARAUJO MARTINS MORENO, Cristiane<sup>1</sup>; ZANOTELI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas FMUSP - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Introduction: Acute hepatic porphyrias (AHP) are rare metabolic disorders caused by enzyme deficiencies in the heme synthesis, leading to neurotoxic metabolite accumulation. The most common type of AHP is acute intermittent porphyria (AIP), followed by variegate porphyria (VP) and hereditary coproporphyria (HCP). Diagnosis is primarily made through biochemical testing since penetrance is low. Epidemiological data in Brazil are scarce due to limited diagnostic resources. Methods: We reviewed medical records and complementary exams of AHP patients seen from 2020 to 2024, using Stein et al. (2023) criteria for classification Results: We identified 35 patients from 21 families (median age 41, range: 16–70), with 24 females. Median age at first symptom was 25 years. Racial distribution was equal: 17 white and 18 brown/black. Acute phase biochemical exams (urine ALA, PBG or total porphyrins) were available for 13 patients. Genetic analysis revealed: thirteen AIP patients from nine families with HMBS variants, including c.973C>T, c.518G>A, exon 1 deletion, and c.912+2T>C (VUS); seventeen VP patients from nine families with PPOX variants, with seven families sharing the same c.503G>A variant, one with c.454C>T, and one with exons 5–6 deletion; four HCP patients from three families with CPOX variants, including c.337\_344del, c.758A>G (VUS) and c.1204G>A (VUS). Among 27 patients with acute attacks, all had abdominal pain and 81% developed acute flaccid paralysis. At the time of evaluation, 20 patients were asymptomatic, five had sporadic active porphyria, two had recurrent active porphyria, and eight were latent at-risk. Only three patients received hemin. Discussion: Delayed clinical suspicion, lack of knowledge on

biochemical testing and access to treatment may explain the high prevalence of acute flaccid paralysis in our cohort. Genetic profile suggests VP may be more common in Brazil than previously reported, possibly linked to historical colonization. Expanding genetic studies and improving diagnostic protocols are critical for better care of AHP in Brazil.

**Palavras-Chave do trabalho:** ; acute intermittent porphyria; acute porphyrias; porphyria; variegate porphyria;

**ID do trabalho:** 14

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: A RARE CAUSE OF CHOREA IN CHILDREN CAUSED BY A MUTATION IN ATP8A2**

**Autores:** MONTES GARCIA BARBOSA, Renata<sup>1</sup>; PEREIRA DA SILVA JÚNIOR, Sergio Roberto<sup>1</sup>; PONTES CRUZ, Patricia<sup>1</sup>; DA CRUZ CALDEIRA, Lunielle<sup>1</sup>; ARAÚJO CASTRO, Matheus Augusto<sup>1</sup>; FREUA, Fernando<sup>1</sup>; GUIMARÃES MARCARINI, Bruno<sup>1</sup>; KOK, Fernando<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Case presentation: A 5-years-old girl was referred to our service because of psychomotor delay, abnormal movements and visual impairment, besides of the hypotonia observed when she was 1 month of life. She did not acquire developmental milestones and was unable to sit or produce meaningful speech. When she was 12 years, she manifested epileptic events refractory. The patient had no history of hearing loss. On neurological examination, she had no expressive or receptive language; bilateral ptosis, bilateral optic disc pallor was of note and visual contact was absent. She displayed hypotonia and muscular atrophy involving neck, trunk, and four limbs. Continuous hyperkinetic movements, characterized as chorea, at times choreodystonic, affected her neck, upper, and lower limbs. Screening for inborn errors of metabolism performed were negative. Brain magnetic resonance imaging did not show significant abnormalities. A whole exome sequencing (WES) was performed, disclosing a homozygous frameshift variant, ENST00000381655: chr13:25.577.115; C > CT; p.Arg588Serfs\*5, on the ATP8A2 gene. Discussion: The ATP8A2 (ATPase phospholipid transporting 8A2) gene, located in chromosome 13q12.13, belongs to a family of phospholipid transporting ATPases, which are involved in the transport of aminophospholipids. (1) Biallelic mutations in ATP8A2 cause cerebellar ataxia, impaired intellectual development, and disequilibrium syndrome the classic presentation of CAMRQ4 besides occasionally quadrupedal gait. However, the spectrum of phenotypes caused by ATP8A2 is more variable due to the broad expression pattern of this gene in the brain and eyes. (3) The ATP8A2 phenotype expansion includes dystonia, below average head circumference, mild optic atrophy, developmental delay, and teeth abnormalities, also, was described more recently bilateral ptosis and seizures. This phenotype recently expanded is compatible with the patient described. José Fidel Baizabal Carvallo et al. described that probably less than 50 % of patients have ophthalmoplegia, ptosis and seizures. Neuroimaging may include delayed myelination, atrophy of cortical ribbon, corpus callosum and optic nerves. In this case, patients only have optic atrophy. (2,3) Final comments: Chorea in childhood is caused by an extensive number of etiologies, being ATP8A2 mutations a rare cause, but important to remember especially if with other symptoms described above. The identification of these other symptoms is important in distinguishing patients with ATP8A2 mutations from the many other genetic causes of chorea. Optic atrophy and, less commonly, ophthalmoplegia and ptosis can also be seen which may be helpful in establishing this diagnosis.

**Palavras-Chave do trabalho:** chorea; hyperkinetic movement; neurogenetic disorders;

**ID do trabalho:** 16

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: VPS13D-RELATED MOVEMENT DISORDERS IN TWO BRAZILIAN SISTERS: DESCRIPTION OF NEW VARIANT AND REVIEW OF PHENOTYPIC SPECTRUM**

**Autores:** MENDONÇA, Renata Silva<sup>1</sup>; ALMEIDA, Ana Luiza Viegas<sup>1</sup>; AZZONI, Andreia Braga Mota<sup>1</sup>; OLIVEIRA, Ana Beatriz Arruda Carvalho<sup>1</sup>; DE GUSMAO, Claudio Melo<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas FMUSP - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Case presentation: We report a case of VPS13D-related disorder in two Brazilian sisters. The first sibling, an 8-year-old, exhibited normal neurological development during her first year of life. Between the ages of one and two, she began to exhibit slowly progressive gait impairment, speech difficulties, and involuntary dyskinetic movements of her head and limbs, characterized as generalized chorea. By age two, she experienced her first epileptic seizure, described as focal motor onset with impaired awareness. The second sister, aged 4, had normal neuropsychomotor development until around age two. After this period, she developed a similar but milder progressive gait impairment and involuntary movements compared to her older sister. Her cognitive development remains normal. At age three, she had her first epileptic seizure, also described as focal motor onset. On examination, they presented with language impairment (dysarthria), global mild hypotonia with preserved strength, and normal deep tendon reflexes, with no Babinski sign observed in either sister. They also exhibited continuous hyperkinetic choreiform movements in the limbs and trunk and orofacial dyskinesia. Brain MRI revealed symmetric bilateral hyperintensities in the basal ganglia (putamen and caudate) on T2/FLAIR-weighted sequences. Whole-exome sequencing identified a known likely pathogenic variant in the VPS13D gene, c.2504G>A; (p.Trp835)\*, along with a novel variant, c.9107T>C; (p.Val3036Ala). Sanger analysis confirmed an autosomal recessive inheritance pattern. Discussion: Mutations in VPS13D represent a relatively new and rare cause of neurological disorders. So far, 40 cases have been reported in the literature, presenting a broad clinical phenotype that includes spastic ataxia, spastic paraplegia, and movement disorders. Although clinical presentations are highly variable, two main phenotypes have been suggested: an early-onset phenotype that may include developmental delay, hyperkinetic movements (such as chorea, dystonia, and/or ataxia), epilepsy, and Leigh-like syndrome; and a late onset characterized by pure spastic paraplegia or spastic ataxia with tremor/dystonia. This report enhances our understanding of the differences in presentation based on the age of onset. To further clarify the phenotype associated with VPS13D, we summarize a review of the literature on the cases reported so far. Final Comments: This report provides the first Brazilian description of VPS13D-related movement disorders and introduces a new variant in the gene. These findings enhance our understanding of the heterogeneity of clinical presentations and phenotypes.

**Palavras-Chave do trabalho:** ; chorea; early-onset hyperkinetic movements; VPS13d; VPS13D-related disorders;

**ID do trabalho:** 17

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: GENERALIZED CORTICAL HYPEROSTOSIS (VAN BUCHEM DISEASE): A RARE CASE IN BRAZIL**

**Autores:** DE LUCENA, Larissa Neves<sup>1</sup>; LOURO, Rafaela Julian<sup>1</sup>; MENDES FILHO, Antonio Avelino<sup>1</sup>; MESIAS, André Vinicio Cruz<sup>1</sup>; NEPOMUCENO, Camila Rodrigues<sup>1</sup>; MORENO, Cristiane de Araújo Martins<sup>1</sup>; DE FREITAS, Julian Letícia<sup>1</sup>; ROCHA, Maria Sheila Guimarães<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Santa Marcelina - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Case Presentation: A 21-year-old female patient, daughter of consanguineous parents, born in Tucano, Bahia, Brazil, has exhibited unusual facial features since childhood. During adolescence, she developed headaches, progressive facial paralysis, and hearing loss. Upon examination, she presented with an elongated face with mandibular hypertrophy, without evidence of syndactyly. Complementary diagnostic tests revealed cranial hyperostosis, moderate hearing loss on audiometry, and optic atrophy identified through retinal mapping. Genetic testing confirmed the presence of a pathogenic variant (c.372G>A) in the SOST gene. Discussion: Van Buchem disease (OMIM #239100) is a rare autosomal recessive bone dysplasia caused by a mutation in a regulatory region of the SOST gene, which encodes sclerostin, a protein essential for bone formation by inhibiting osteoblast activity. The mutation results in reduced levels of this protein, leading to progressive bone density increase, causing facial deformities and cranial nerve compression at their foramina, mainly affecting the optic (2nd), trigeminal (5th), facial (7th), and vestibulocochlear (8th) nerves. Clinical complications include optic atrophy, trigeminal neuralgia, facial paralysis, and hearing loss. Sclerosteosis is a phenotypically similar condition but differs from Van Buchem disease by the presence of syndactyly and gigantism, as well as being a more severe form of the disease due to the complete absence of sclerostin, leading to more severe and rapidly progressing complications. Final Comments: This study reports a case with a typical phenotype of Van Buchem disease, confirmed through genetic analysis identifying a pathogenic biallelic mutation on chromosome 17, resulting in Trp124X, a mutation previously described in the SOST gene. Interestingly, all previously reported cases with this mutation in Brazil are from Bahia. Therefore, further studies on this gene and its implications are necessary.

**Palavras-Chave do trabalho:** hyperostosis; SOST; Van Buchem;

**ID do trabalho:** 20

**Área Técnica do trabalho:** Demências e doenças cerebrovasculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: EFFECT OF CANNABIDIOL IN AN ALZHEIMER'S DISEASE MODEL BASED ON STREPTOZOTOCIN INJECTION: AN EXPRESSION ANALYSIS OF CANDIDATE GENES**

**Autores:** MELLO-HORTEGA, João Vitor<sup>1</sup>; TURECK, Luciane Viater<sup>1</sup>; DE OLIVEIRA, Carolina Sales<sup>2</sup>; FERNANDES, Stephanie Moura Araújo<sup>1</sup>; VITAL, Maria Aparecida Barbato Frazão<sup>1</sup>; DE SOUZA, Ricardo Lehtonen Rodrigues<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Paraná - Curitiba - PR - Brasil; (2) Universidade Federal do Paraná - Curitiba - PR - Brasil;

### **Resumo do trabalho:**

Background: Alzheimer's disease (AD) primarily affects cognitive and memory processing, with its pathology linked to proteinopathies and various brain metabolic dysfunctions. Significant efforts are being made to develop new diagnostic methods and treatments for AD. Regarding therapeutic research, studies with cannabidiol (CBD) have highlighted its potential as an alternative treatment due to its anti-inflammatory, antioxidative, and neuroprotective effects. For studying AD, the model based on the intracerebroventricular injection of streptozotocin (STZ) has been widely used, but few studies have assessed the effects of CBD in this model. Additionally, the potential of CBD to modulate gene expression in this model remains underexplored. Objective: This study aims to address this gap by proposing a behavioral and gene expression analysis in STZ-induced rats to observe the effects of CBD in treating patients with late-stage AD diagnoses. Methods: For this analysis, 39 male Wistar rats were subjected to an intracerebroventricular injection of streptozotocin (3 mg/kg), followed by daily intraperitoneal injections of a CBD-rich extract (10 mg/kg) for 10 consecutive days, starting 7 days after surgery to ensure brain stress caused by STZ. The animals underwent behavioral tests, and cortex and hippocampus samples were collected to evaluate the expression of the Camk1d, Cst3, Slc25a5, Gsk3β, Manf, and Vim genes. Results: The analysis showed that CBD treatment did not affect cognitive performance or gene expression levels in healthy rats. However, in animals with STZ-induced dementia, this therapeutic approach worsened performance in tests assessing short-term spatial memory. Furthermore, there was a decrease in Manf gene expression in the prefrontal cortex, an increase in Gsk3β expression in the hippocampus, and Vim gene expression in the prefrontal cortex. Discussion: Based on these analyses, cannabidiol did not impact memory processing or gene expression patterns in healthy animals, demonstrating its safety for non-demented rats. However, in AD model animals, the observed cognitive decline could be linked to gene expression changes, including reduced Manf expression—a neuroprotective protein—and the overexpression of Vim and Gsk3β, genes associated with AD pathology. Comparative analyses with studies evaluating CBD treatment in the same model suggest that CBD offers greater neuroprotective effects when administered shortly after STZ induction. Conclusion: CBD does not offer significant therapeutic benefits in advanced stages of STZ-induced brain damage. Therefore, further investigation into the early administration of CBD is recommended to maximize the therapeutic potential of this compound.

**Palavras-Chave do trabalho:** animal model; cannabinoids; Dementia;

**ID do trabalho:** 22

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: Case Report of a Patient with Familial Amyloid Polyneuropathy Following a Domino Liver Transplant.**

**Autores:** FRANCO, Hamilton Cirne<sup>1</sup>; XAVIER, Karla<sup>2</sup>; SAYAGO, Mariana<sup>2</sup>; SARMET, Max<sup>3</sup>; MALDANER, Vinicius<sup>4</sup>;

**Instituição dos Autores:** (1) Hospital de apoio de Brasília - Brasília - DF - Brasil; (2) Hospital de apoio de Brasília - Brasília - DF - Brasil; (3) Hospital de Apoio de Brasília - Brasília - DF - Brasil; (4) Universidade de Brasília - UNB - Brasília - DF - Brasil;

### **Resumo do trabalho:**

Background: Familial amyloid polyneuropathy (FAP) is an autosomal dominant condition characterized by a sensory-motor neuropathy, often associated with dysautonomia (1). The use of "diseased livers" in domino transplantation was practiced under the assumption that the recipients would not live long enough to develop disease (2). Studies indicate that approximately one-sixth of patients who receive livers from FAP-affected donors may eventually develop the disease (3). Objective: To describe the case of a patient who developed familial amyloid polyneuropathy following a domino liver transplant. Case Report: This is a 75-year-old male patient who underwent a liver transplant in 2010 due to cirrhosis secondary to hepatitis C, receiving a liver from a donor affected by familial amyloid polyneuropathy. In 2021, he began experiencing paresthesia and neuropathic pain in the lower limbs, initially presenting with a short boot distribution. After approximately three months, symptoms began to appear in the upper limbs, in a "glove" distribution, more pronounced on the left side. Shortly thereafter, the patient experienced progressive muscle weakness and cramps predominantly in the thigh area. There was also progressive atrophy of the left upper limb interosseous muscles. The patient had frequent diarrhea and ongoing progressive weight loss. His hypothyroidism was

well-controlled, and there were no signs of diabetes, renal disease, hypovitaminosis, or other significant abnormalities in clinical tests. Due to clinical suspicion of leprosy, an ulnar nerve biopsy was performed in January 2024, which revealed amyloid deposition of TTR Val30Met. The electroneuromyography revealed a sensory-motor polyneuropathy, axonal, symmetric, and more pronounced in the lower limbs. Patisiran was prescribed, but initiation of therapy has not yet been scheduled. Conclusion: Although rare, familial amyloid polyneuropathy in patients who have undergone domino liver transplantation should always be actively screened in order to provide therapeutic options aimed at reducing morbidity and mortality. References: Ball HA, Stevens J, Gillmore JD. Peripheral neuropathy secondary to a 'domino' liver transplant: a case report. J Med Case Rep. 2023 Jun 29;17(1):291. Bourque PR, Shafi S, Jansen GH, McCurdy A, Warman Chardon J. Amyloid Neuropathy Following Domino Liver Transplantation: Response to Diflunisal. JAMA Neurol. 2016;73(4):477-478. Junqueira B, Mestre C. Iatrogenic Amyloid Polyneuropathy Following Domino Liver Transplantation: A Case Report. Cureus. 2024.

**Palavras-Chave do trabalho:** Familiar Amyloid Polyneuropathy; Liver Transplantation; Val30met;

**ID do trabalho:** 27

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: ETIOLOGICAL DIAGNOSIS OF INTELLECTUAL DISABILITY AT BRAZILIAN PUBLIC HEALTHCARE SYSTEM: THE ROLE OF THE FRAGILE X SYNDROME INVESTIGATION USING AMPLIDEX METHOD**

**Autores:** TEIXEIRA, Karina de Oliveira<sup>1</sup>; MESCKA, Caroline Paula<sup>2</sup>; GOMES, Quelen Gonçalves<sup>2</sup>; ARTIGALÂS, Osvaldo<sup>2</sup>; FELIX, Temis Maria<sup>2</sup>; LEISTNER, Sandra<sup>2</sup>; KOWALSKI, Thayne Woycinc<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital de Clínicas de Porto Alegre, Serviço de Genética Médica; Universidade Federal do Rio Grande do Sul, Departamento de Genética, Programa de Pós-Graduação em Genética e Biologia Molecular - Porto Alegre - RS - Brasil; (2) Hospital de Clínicas de Porto Alegre, Serviço de Genética Médica - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Fragile X Syndrome (FXS) is one of the most common causes of inherited intellectual disability (ID) and occurs in individuals with CGG repeat expansion in the 5'UTR region of the FMR1 gene (Xq27.3), primarily affecting males. The molecular diagnosis of the FXS is challenging because the full mutation comprises more than 200 CGG repeats, becoming hard to identify by the conventional PCR techniques. Since 2009, the repeat primed (TP) FMR1 PCR (AmplideX) has allowed the full mutation detection. In 2020, the AmplideX has been implemented in the Laboratório de Genética Molecular of the Serviço de Genética Médica (LGM/SGM) of the Hospital de Clínicas de Porto Alegre (HCPA). Objective: To show the main results of the ID investigation caused by FXS in the LGM/SGM in a five-year period. Methods: It was revised the molecular records of the diagnosed FXS in 2020-2024, that included PCR electrophoresis screening followed by AmplideX for the individuals who had positive or inconclusive screening. For the ones who had negative AmplideX results, the records of the Chromosomal Microarray Analysis (CMA) were also evaluated. Results: Between 2020-2024, 459 individuals with ID and suspected of FXS were screened, of which 5.66% got positive results and were forwarded to AmplideX, which confirmed the full mutation in eight patients (1.74%). Another three patients (0.65%) were diagnosed with premutation (55-200 CGG repeats) and one patient (0.22%) showed the intermediate allele (45-54 CGG repeats). Five of the eight patients with full mutation had mosaicism (1.1%). Considering those 451 patients who had negative screening results, 143 were forwarded to CMA. Of these, CMA results were available for 85 patients, and of these eleven were diagnosed with chromosomal microdeletion/duplication syndromes and another thirteen patients got variants of uncertain significance (VUS). Conclusion: AmplideX has provided the diagnosis of FXS in eight patients (1.74%) and the CMA ratified chromosomal syndromes in another eleven patients (1.53%). Furthermore, will be included clinical data of the patients to analyse the expressivity of the FXS variants, specifically in the mosaicism cases.

**Palavras-Chave do trabalho:** Chromosomal Syndrome; Fragile X Syndrome; Intellectual Disability; Molecular genetics;

**ID do trabalho:** 30

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: ATYPICAL PRESENTATION OF HEREDITARY NEUROPATHY WITH SUSCEPTIBILITY TO PRESSURE PALSY (HNPP) WITH CERVICAL SPONDYLOTIC MYELOPATHY: CASE REPORT OF DIFFICULT DIAGNOSIS.**

**Autores:** ALMEIDA, Danilo Caillaux de<sup>1</sup>; NASCIMENTO, Felipe Tomé do<sup>1</sup>; RIOS, Marianela Mendoza<sup>1</sup>; ARAÚJO, Thiago Gonçalves de<sup>1</sup>; OLIVEIRA, Ana Karine Netto Leite de<sup>1</sup>; FREITAS, Felipe Carneiro de<sup>1</sup>; AMARAL, Carlos Eduardo Pinto do<sup>1</sup>; PIMENTEL, Maria Lucia Vellutini<sup>2</sup>;

**Instituição dos Autores:** (1) Pontifícia Universidade Católica do Rio de Janeiro (PUC-Rio) e Santa Casa da Misericórdia do Rio de Janeiro - Rio de Janeiro - RJ - Brasil; (2) Pontifícia Universidade Católica do Rio de Janeiro (PUC-Rio) e Santa Casa da Misericórdia do Rio de Janeiro - Rio de Janeiro - RJ - Brasil;

#### Resumo do trabalho:

Case presentation: JS, 63 years old, male, from São Gonçalo-RJ. Referred for investigation of the hypothesis of chronic inflammatory demyelinating polyneuropathy. He is the second child of non-consanguineous parents; Mother, one brother, two sisters and two nephews with reported motor and sensory complaints. Complaints of paresthesia for about 30 years, of progressive nature, starting in the right upper limb and, soon after, in the left lower limb. It evolved with atrophy, reduced strength, cervical pain and difficulty in walking. On examination: Spastic gait with a clawing component and tetraparesis of distal predominance with also proximal involvement in the upper limbs. Global hyperreflexia, except for areflexia in Achilles. Bilateral Hoffmann. Cutaneous-plantar reflex: indifferent. No clonus. Amyotrophy of interosseous muscles, thenar and hypotenar region of both hands, in addition to deltoid on the right. Bilateral boot anesthesia and apalesthesia up to the iliac crests. Loss of sense of segmental position in the lower limbs. Laboratory investigation was unremarkable, and electroneuromyography (EMG) showed severe axonal sensory-motor polyneuropathy. Magnetic resonance imaging of the cervical spine revealed disc-osteophyte protrusions from C2-C3 to C6-C7, reducing the amplitude of the spinal canal, which was greater at C4-C5, where a focus of high signal was observed in the spinal cord, suggestive of compressive myelopathy. The neuropathy panel identified a heterozygous variant in the PMP22 gene, consisting of a deletion of approximately 1.4 Mb. The patient was referred for neurosurgery and family counseling. Discussion: HNPP (OMIM# 162500) is an autosomal dominant hereditary motor and sensory neuropathy with a broad spectrum of phenotypes. It is caused by a deletion in the PMP22 gene at 17p11.2. The prevalence is estimated at 7-16/100,000 individuals, but possibly higher due to underdiagnosis. It usually presents as focal, recurrent, episodic, and painless neuropathy preceded by compression of the affected nerve. Symptoms tend to resolve within days or weeks, but chronic deficits may be seen. Chronic sensorimotor polyneuropathy is one of the uncommon but reported manifestations. On examination, muscle weakness and atrophy, sensory signs, reduced tendon reflexes, and pes cavus may be found. Electromyographic study reveals prolonged distal motor latencies, reduced motor conduction velocity, and sensory action potential amplitude. JS presents a family history consistent with autosomal dominant inheritance. His EMG reveals sensorimotor polyneuropathy with features described in HNPP. Neurologic examination, including pyramidal signs, drew attention to the study of the cervical spine, which demonstrated compressive myelopathy. Final considerations: The diagnosis of HNPP can be challenging due to clinical variability. Myelopathy made the investigation difficult, as JS presented with first and second motor neuron signs. JS was diagnosed late.

**Palavras-Chave do trabalho:** ; HNPP; Nerve compression; PMP22 gene;

**ID do trabalho:** 31

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: NERVE ULTRASOUND DETECTS NERVE ATROPHY IN PATIENTS WITH ATAXIA-TELANGIECTASIA: A PILOT STUDY.

**Autores:** CAMELO-FILHO, ANTONIO EDVAN<sup>1</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; ROSA, Rodrigo F<sup>1</sup>; SOARES, Tito BS<sup>2</sup>; PESSOA, ANDRÉ<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>; BRAGA-NETO, PEDRO<sup>1</sup>;

**Instituição dos Autores:** (1) UFC - Fortaleza - CE - Brasil; (2) UECE - Fortaleza - CE - Brasil;

#### Resumo do trabalho:

Background: Ataxia-telangiectasia (A-T) is a rare, autosomal recessive disorder caused by mutations in the ATM gene, which is critical for DNA repair and cellular homeostasis. Hallmark features of A-T include early-onset cerebellar degeneration, peripheral neuropathy, and telangiectasia. While previous studies have characterized the electrophysiological and clinical aspects of A-T, the ultrasonographic morphology of peripheral nerves remains unexplored. This study investigates the role of nerve ultrasound in identifying nerve atrophy in patients with A-T and explores its potential as a diagnostic tool. Objective: To evaluate peripheral nerve morphology using ultrasound in individuals with A-T and determine if nerve atrophy aligns with sensory neuronopathy and axonal neuropathy findings. Methods: Three female patients with genetically confirmed A-T (one with the classic form and two with the variant form) were recruited. Comprehensive clinical assessments included the Scale for the Assessment and Rating of Ataxia (SARA), electrophysiological evaluations (nerve conduction studies [NCS] and electromyography [EMG]), and peripheral nerve ultrasound. Cross-sectional areas (CSAs) of median, ulnar, sural, and tibial nerves were measured using a high-resolution linear probe. Descriptive statistics and qualitative comparisons were used due to the small sample size. Normative data from previous studies served as reference values. Results: All three patients exhibited significant reductions in peripheral nerve CSAs compared to normative data, with a more pronounced atrophy in upper limb nerves. Tibial nerve CSAs were relatively preserved, aligning with the hypothesis that sensory neuronopathy disproportionately affects upper limb nerves due to their higher neural-to-non-neural tissue ratio. Electrophysiological studies revealed sensorimotor axonal polyneuropathy with sensory predominance, non-length-dependent sensory neuronopathy in two patients, and motor denervation consistent with distal motor

axonal neuropathy. No sensory symptoms were reported, but physical examinations revealed distal muscle atrophy, reduced pallesthesia, and absent deep tendon reflexes. Conclusion: This pilot study suggests that peripheral nerve atrophy detected by ultrasound may serve as a marker for sensory neuronopathy in A-T. The findings highlight a potential role for nerve ultrasound in distinguishing inherited sensory neuronopathies from axonal neuropathies and support its inclusion in the diagnostic workup of A-T. Future large-scale studies are needed to validate these findings, investigate correlations between nerve CSA and disease severity, and explore the underlying mechanisms driving nerve atrophy in A-T.

**Palavras-Chave do trabalho:** ATAXIA; NERVE ULTRASOUND; SENSORY NEURONOPATHY;

**ID do trabalho:** 32

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Pôster

## Título do Trabalho: REMARKABLE IMPROVEMENT OF AGRN-ASSOCIATED CONGENITAL MYASTHENIA WEAKNESS AFTER SALBUTAMOL USE

**Autores:** CAMELO-FILHO, Antonio Edvan<sup>1</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; MIYAJIMA, Oliver Reiks<sup>2</sup>; ROSA, Rodrigo Fagundes<sup>1</sup>; SOARES, Tito B S<sup>2</sup>; PESSOA, ANDRE<sup>3</sup>; BRAGA-NETO, Pedro<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>;

**Instituição dos Autores:** (1) UNIVERSIDADE FEDERAL DO CEARÁ - Fortaleza - CE - Brasil; (2) UNIVERSIDADE ESTADUAL DO CEARÁ - Fortaleza - CE - Brasil; (3) UNIVERSIDADE FEDERAL DO CEARÁ - FORTALEZA - CE - Brasil;

### Resumo do trabalho:

Case presentation: Two siblings, a 20-year-old man and a 23-year-old woman, born to consanguineous parents, presented with progressive proximal and distal muscle weakness since early childhood. Clinical assessments revealed global muscle hypotrophy, reduced proximal (grade III) and distal (grade IV) strength, tendon contractures, and hyporeflexia. Electroneuromyography showed an incremental response at high-frequency stimulation consistent with a presynaptic neuromuscular junction disorder. Exome sequencing identified a homozygous p.Val1727Phe pathogenic variant in the AGRN gene. The siblings initially received pyridostigmine without benefit but demonstrated marked improvement after starting salbutamol, a  $\beta_2$ -adrenergic agonist. Discussion: Congenital myasthenic syndromes (CMS) are rare inherited disorders caused by mutations in genes that affect neuromuscular junction transmission. Mutations in the AGRN gene, encoding agrin, a critical protein for acetylcholine receptor clustering, result in post-synaptic CMS. While AGRN-associated CMS is rare, early identification is essential for implementing targeted treatment strategies. Objective: To describe the clinical, genetic, and therapeutic response in two siblings with AGRN-associated CMS, highlighting the spectrum of clinical presentation and the efficacy of salbutamol treatment. Both siblings exhibited significant functional gains following salbutamol treatment. After one month, muscle strength improved, allowing the siblings to rise from a seated position and take steps. Sustained improvement was observed with ongoing salbutamol therapy, with no adverse effects reported. Final comments: These findings underscore the potential of  $\beta_2$ -adrenergic agonists as an effective first-line treatment for AGRN-related CMS. AGRN-associated CMS presents with a spectrum of clinical features, often without classical oculomotor signs such as ptosis or ophthalmoparesis. This case highlights the importance of considering CMS in the differential diagnosis of early-onset progressive muscle weakness and underscores the therapeutic implications of identifying pathogenic AGRN variants. Salbutamol therapy demonstrated significant clinical benefits, reinforcing its role as an effective treatment option. Early genetic diagnosis and appropriate therapeutic intervention can lead to meaningful functional improvements in AGRN-related CMS.

**Palavras-Chave do trabalho:** AGRN; CONGENITAL MYASTHENIC SYNDROME; SALBUTAMOL;

**ID do trabalho:** 35

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: THE DIAGNOSTIC PUZZLE OF SEGAWA'S SYNDROME: A SEMIOLOGICAL INSIGHT INTO CGH1 GENE DELETION

**Autores:** FERRARA NETO, João Ignacio<sup>1</sup>; DE ROSSO, Ana Lucia Zuma<sup>2</sup>; VILAÇA, Celmir<sup>2</sup>; PEREIRA SANTOS, Roberto<sup>2</sup>;

**Instituição dos Autores:** (1) Faculdade de Medicina da Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ - Brasil; (2) Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ - Brasil;

**Resumo do trabalho:**

Case Presentation A 41-year-old lawyer from Rio de Janeiro presented with a progressive right-sided foot deformity that began at age 11. She described it as a “foot problem” that caused tripping and gait disturbances. Despite consulting multiple specialists, no definitive diagnosis was made. Her developmental history included delayed walking at 18 months. Neurological examination revealed cavus deformity, calluses, and signs of microfractures in the left foot. The patient exhibited difficulty tiptoeing, with adduction and internal rotation suggestive of spasticity. Reflexes were brisk, and a questionable Babinski sign was noted, while sensory and cranial nerve examinations were unremarkable. Previous electromyography (EMG) studies were mostly normal, with one suggesting dystonia or spasticity. Initial suspicion of spastic diplegic cerebral palsy was reconsidered after poor response to baclofen. A levodopa trial led to dramatic improvement. Genetic testing confirmed a GCH1 mutation, diagnosing dopa-responsive dystonia (DRD). The patient achieved significant functional recovery and resumed advanced activities after minor treatment adjustments. Discussion Segawa's syndrome, or DRD, is a rare movement disorder caused by mutations in the GCH1 gene, leading to dopamine synthesis deficiency. It typically manifests in childhood with lower-limb dystonia, diurnal fluctuation, and sleep benefit. A hallmark feature is its excellent response to low-dose levodopa. Despite its distinctive clinical presentation, DRD is often underdiagnosed due to conditions that either mimic its symptoms or camouflage themselves as DRD-like syndromes. Dopa-responsive dystonia (DRD) poses diagnostic challenges due to the presence of mimics, which share similar symptoms, and chameleons, which atypically resemble DRD, as discussed below. Mimics 1. Juvenile Parkinson's Disease (JPD): Initially responsive to levodopa but progressive and neurodegenerative. 2. Tyrosine Hydroxylase Deficiency: Features dystonia, hypotonia, and developmental delay, with variable levodopa response. 3. Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency: Impairs dopamine synthesis, presenting with oculogyric crises and poor levodopa response. Chameleons 1. DYT1 Dystonia: An autosomal dominant disorder, typically unresponsive to levodopa, but occasionally showing mild responsiveness. 2. GLUT1 Deficiency: A glucose transporter defect that may present with dystonia partially responsive to levodopa. 3. Spinocerebellar Ataxias (SCA): Certain subtypes, such as SCA3, can mimic DRD in early stages. Final Comments Dopa-responsive dystonia poses diagnostic challenges due to its overlap with mimics and chameleons. A structured diagnostic approach—including clinical evaluation, levodopa trials, and genetic testing—is essential for early recognition and effective treatment. Timely diagnosis and management transform outcomes for this treatable condition, ensuring a significantly improved quality of life.

**Palavras-Chave do trabalho:** Dopa-Responsive Dystonia (DRD); GCH1 Mutation; Levodopa; Mimics and Chameleons; Segawa's Syndrome;

**ID do trabalho:** 36

**Área Técnica do trabalho:** Genética populacional

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: AUTOSOMAL RECESSIVE ATAXIAS IN NORTHEAST BRAZIL: A REGIONAL MULTICENTER CASE SERIES**

**Autores:** CAMELO-FILHO, Antonio Edvan<sup>1</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; ROSA, Rodrigo Fagundes<sup>1</sup>; GOMES, Gustavo Rodrigues Ferreira<sup>2</sup>; MATOS, Paula Camila Alves de Assis Pereira<sup>3</sup>; RANGEL, Deborah Moreira Rangel<sup>3</sup>; LOPES, Ellen Mourão Soares<sup>4</sup>; MARIANO, Tamiris Carneiro<sup>4</sup>; PAIVA, Anderson Rodrigues Brandão<sup>5</sup>; KOK, Fernando<sup>6</sup>; PESSOA, André<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>; BRAGA-NETO, Pedro<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Universidade Estadual do Ceará - Fortaleza - CE - Brasil; (3) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (4) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil; (5) Universidade de São Paulo - São Paulo - SP - Brasil; (6) Universidade de São Paulo - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Background: Hereditary cerebellar ataxias (HCAs) represent a diverse group of neurodegenerative disorders characterized by inherited progressive cerebellar dysfunction. While significant advances have been made in understanding autosomal dominant cerebellar ataxias (ADCAs), autosomal recessive cerebellar ataxias (ARCAs) remain less extensively characterized due to their genetic heterogeneity and lower individual prevalence. This study aims to provide a detailed clinical and genetic characterization of 59 patients with ARCAs in Ceará, Brazil, a region known for its high consanguinity rates. Objective: To analyze the clinical, genetic, and demographic profiles of patients with genetically confirmed ARCAs, identify prevalent subtypes, and highlight the importance of early diagnosis and management in a low-resource setting. Methods: This retrospective study reviewed the medical records of 59 patients with genetically confirmed ARCAs identified between September and November 2024 at three tertiary centers in Ceará. Patients with biallelic variants in ARCA-associated genes were included, while those with ADCAs or unconfirmed genetic diagnoses were excluded. Clinical data, genetic findings, and demographic information were analyzed. The study adhered to ethical guidelines, with approval from the Universidade Federal do Ceará Ethics Committee. Results: From 110 suspected hereditary ataxia cases, 59 patients with ARCAs were identified. The mean age was 28.24 years (range: 4–59), with 62.7% adults (≥18 years). The most common diagnoses were Friedreich's ataxia (FRDA, 20.3%), ataxia-telangiectasia (A-T, 15.3%), and Niemann-Pick type C (NPC, 15.3%), collectively comprising over 50% of cases. Metabolic disorders, including cerebrotendinous xanthomatosis (CTX, 10.2%), were significant contributors to the ARCA spectrum. Rare conditions such as spastic paraplegia 7 (SPG7, 5.1%), neuronal ceroid lipofuscinosis (CLN2/CLN6, 11.9%), and ataxia with vitamin E deficiency (AVED, 1.7%) were also identified. Adult-onset ARCAs were predominantly represented by FRDA and NPC, while pediatric cases mainly included A-T and metabolic disorders. Notably, long-term survivors of A-T and FRDA with milder phenotypes were

identified, suggesting disease variability. Genetic testing facilitated the diagnosis of rare and treatable ataxias such as CTX and AVED, highlighting the importance of early intervention. Conclusion: This study underscores the predominance of FRDA and A-T in the ARCA spectrum in Ceará, Brazil, while emphasizing the diversity of metabolic and rare genetic causes. The high prevalence of ARCAs in this cohort reflects the region's high consanguinity rate and highlights the need for genetic testing to guide diagnosis and management effectively. Continued research and the integration of genetic testing into clinical practice are essential to optimize care for patients with ARCAs.

**Palavras-Chave do trabalho:** ATAXIA; Friedreich's ataxia; RECESSIVE ATAXIAS;

**ID do trabalho:** 37

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: THROMBOTIC MICROANGIOPATHY FOLLOWING GENE THERAPY FOR 5Q-SPINAL MUSCULAR ATROPHY**

**Autores:** CAMELO, Clara Gontijo<sup>1</sup>; MENDONÇA, Rodrigo Holanda<sup>1</sup>; MORENO, Cristiane Araújo Martins<sup>1</sup>; FERREIRA, Juliana Caires de Oliveira Achilli<sup>1</sup>; ORTEGA, Adriana Banzatto<sup>2</sup>; VAN DER LINDEN, Vanessa<sup>3</sup>; CAMPOS, Rejane Souza Macedo<sup>4</sup>; VAN DER LINDEN, Hélio<sup>5</sup>; CUNHA, Natalia Spinola Costa<sup>6</sup>; GIANNETTI, Juliana Gurge<sup>7</sup>; CHAVES, Janaína Monteiro<sup>8</sup>; ZIEGLER, Andreas<sup>9</sup>; ZANOTELI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil; (2) Hospital Pequeno Príncipe - Curitiba - PR - Brasil; (3) Hospital Maria Lucinda - Recife - PE - Brasil; (4) Hospital Israelita Albert Einstein - São Paulo - SP - Brasil; (5) Hospital de Goiânia - Goiânia - GO - Brasil; (6) Universidade de Brasília - Brasília - DF - Brasil; (7) Universidade Federal de Minas Gerais - Belo Horizonte - MG - Brasil; (8) Universidade de Brasília - Brasília - DF - Brasil; (9) Heidelberg University - Germany;

### **Resumo do trabalho:**

Onasemnogene abeparvovec (OA) is the first gene replacement therapy (GT) approved for 5q spinal muscular atrophy (SMA). While effective, it can cause severe side effects, including thrombotic microangiopathy (TMA). The pathophysiology, risk factors, genetic predisposition and management of TMA related to gene therapy remain unclear. This study aimed to evaluate TMA frequency among Brazilian patients treated with OA and characterize their clinical, laboratory and genetic profiles. This retrospective, multicenter study analyzed 294 Brazilian patients with 5q SMA treated with OA between October 2020 and September 2024, of whom seven (2.4%) developed TMA. The average age at OA administration was 20.4 months, and the average weight was 11.5 kg. Three patients had documented infections before OA administration. TMA symptoms appeared within 6–10 days post-infusion. All patients showed hemolytic anemia, thrombocytopenia, and at least one organ dysfunction. Treatment included plasmapheresis in two cases and increased corticosteroid doses in four cases. One patient died from TMA complications. Whole exome sequencing in five patients identified no pathogenic variants linked to TMA. TMA is a rare but severe complication of OA therapy for SMA. So far, no genetic predisposition related to pathogenic variants in genes associated with primary TMA has been identified. However, an infection occurring within 30 days before therapy appears to be a risk factor for this side effect. Prompt recognition and management, often with corticosteroids, are crucial for improving outcomes.

**Palavras-Chave do trabalho:** Gene therapy; genetic predisposition; SMA; thrombotic microangiopathy;

**ID do trabalho:** 38

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: REAL-WORLD EVALUATION OF EXPANSIONHUNTER FOR DETECTING STR EXPANSIONS IN WHOLE-EXOME SEQUENCING DATA: INSIGHTS FROM A CLINICAL DIAGNOSTIC SETTING**

**Autores:** CASTRO, Matheus Augusto Araújo<sup>1</sup>; SILVA, Carolina Rauffus Vilela<sup>1</sup>; KITAJIMA, João Paulo Fumio Whitaker<sup>1</sup>; MONTEIRO, Fabiola Paoli Mendes<sup>1</sup>; SCHLESINGER, David<sup>1</sup>; KOK, Fernando<sup>1</sup>;

**Instituição dos Autores:** (1) Mendelics Análise Genômica - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Background: ExpansionHunter is a bioinformatics tool designed to detect and analyze repeat expansions in short tandem repeats (STRs) using short-read sequencing data. It identifies reads that span, flank, or are fully contained within each repeat in BAM/CRAM files and maps them to the reference genome to estimate the size of the repeat expansion at each locus. STR

expansions are implicated in a variety of neurogenetic disorders. ExpansionHunter has demonstrated considerable sensitivity and specificity in detecting STR expansions from PCR-free whole-genome sequencing data. However, its application to whole-exome sequencing (WES) remains underexplored, even though numerous disease-associated STR loci are located within coding regions. Objective: Here, we present a real-world evaluation of ExpansionHunter's performance for analyzing WES data over a one-year period in a commercial diagnostic center. Methods: ExpansionHunter was applied to 4,658 WES samples. All participants provided informed consent for the use of their genetic data in research. Samples with detected STR expansions, based on reference values from the STRipy database, were included in the analysis. Visual inspection of all alignments was performed using REViewer, a specialized tool for examining read alignments in tandem repeat regions. Reports from physicians who ordered the WES were reviewed to correlate the identified STR genotypes with the clinical information provided. Results: Nineteen samples were identified with expanded alleles: 1 in ATN1, 1 in ATXN2, 2 in ATXN7, 1 in GLS, 13 in DMPK, and 1 in FMR1. Five samples (ATN1, FMR1, and 3 in DMPK) were excluded after visual inspection using REViewer due to likely false-positive results. Clinical data were analyzed for the remaining 14 samples. Of these, 8 (ATXN2, ATXN7, and 5 in DMPK) showed strong concordance between the identified genotype and clinical symptoms, with the ATXN2 expansion later confirmed by PCR. One case (GLS) also exhibited strong correlation, although the expansion was in a heterozygous state with no second variant identified. In the remaining 5 cases, limited or absent clinical data prevented adequate assessment of genotype-phenotype correlation. Conclusions: This study highlights the utility of ExpansionHunter for detecting STR expansions in WES data, emphasizing its potential in clinical diagnostic workflows. Of the 19 identified cases, 14 were supported after visual inspection, with 9 showing strong genotype-phenotype correlation, including cases linked to ATXN2, ATXN7, DMPK, and GLS. This represents an improved accuracy of approximately 0,2% in an unselected pool of WES samples. However, the exclusion of five likely false-positive results underscores the importance of integrating visual validation tools such as REViewer to ensure diagnostic accuracy. This real-world evaluation supports the integration of STR expansion analysis into routine diagnostic pipelines for inherited disorders.

**Palavras-Chave do trabalho:** Exome sequencing; ExpansionHunter; Short tandem repeats;

**ID do trabalho:** 39

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: PROMISING THERAPEUTIC RESULTS IN A CASE OF WILLIAMS-BEUREN SYNDROME ASSOCIATED WITH AUTISM SPECTRUM DISORDER: CASE REPORT**

**Autores:** GOMES, Regiane Maria Ribeiro<sup>1</sup>; PIRES, Jackson Frederico<sup>2</sup>; GRATTÃO, Caroline Cajuela<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Estácio de Sá - Petrópolis - RJ - Brasil; (2) Universidade Nove de Julho - Bauru - SP - Brasil;

### **Resumo do trabalho:**

A female child, born at term, through normal birth, aged 37 weeks and 3 days, with low birth weight and Apgar scores of 3/8. At 30 weeks of gestation, it was found that the baby was small for gestational age. At 6 months, during a routine pediatric consultation, she was referred to a geneticist due to syndromic characteristics and developmental delays. The karyotype was normal and the fluorescence in situ hybridization (FISH) technique demonstrated a microdeletion on chromosome 7, consistent with Williams-Beuren Syndrome (WBS). At 9 months, he underwent a physiotherapeutic evaluation and found delay in motor development, with difficulty in extending the upper limbs for support, hypotonia and inability to sit without support or crawl. She started physiotherapy twice a week, showing significant progress, sitting at 10 months and crawling at 13 months. She started walking at 20 months and was diagnosed with hypothyroidism at the same age. At the age of 3, she was diagnosed with Autism Spectrum Disorder (ASD) and at the age of 5 years and 7 months she presented mitral valve prolapse. Discussion: WBS is a rare multisystem genetic disorder caused by a heterozygous microdeletion on chromosome 7 at position q11.23. Individuals with WBS exhibit a typical phenotype, characterized by a small and hypoplastic nose, thick and large lips, prominent cheeks, and large ears. Supravalvular aortic stenosis is common, among other heart conditions. They often experience delays in neuropsychomotor development, with significant functional impairment. Joint limitations, proprioceptive disturbances, and balance issues negatively impact motor learning and control. WBS does not show any sex or ethnic prevalence, with an incidence of 1:13,000 to 1:25,000 live births. The gold standard for diagnosing WBS is the detection of the deletion using the FISH technique. Generally, children with WBS sit around 14 months and walk from 27 months. Final comments: The importance of early diagnosis and intervention in WBS is emphasized. In this case, physiotherapy was essential in altering the patient's prognosis. The age at which the patient reached developmental milestones, especially considering the concomitance with ASD level 3, was exceptional. Stimulating the development of motor skills and global muscle strengthening were key components of the treatment strategies. All sessions were conducted on the floor, lasting 30 minutes each, in a playful manner, using toys and music, with a focus on motor learning and control.

**Palavras-Chave do trabalho:** Autism spectrum disorder; neurodevelopment; Williams-Beuren Syndrom;

**ID do trabalho:** 43

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **SYMPTOMATIC FEMALE CARRIER OF DUCHENNE MUSCULAR DYSTROFY**

**Autores:** DE OLIVEIRA, Andreia Lira<sup>1</sup>; WESTPHAL FILHO, Fernando Luiz<sup>1</sup>; LOPES, Paulo Roberto Moss<sup>1</sup>; MACHADO FILHO, Walderico Silva<sup>2</sup>; SILVEIRA, Pablo Vinícius Feitosa<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Amazonas - Manaus - AM - Brasil; (2) Universidade Estadual de Campinas - Campinas - SP - Brasil;

### **Resumo do trabalho:**

Case Presentation: A 32-year-old woman, born via uneventful vaginal delivery with normal neuropsychomotor development, reports lower limb weakness since childhood. She has difficulty climbing stairs and experiences episodes of falls. While she can walk normally, she has never been able to run. The symptoms have remained stable over time. She had two male siblings, one of whom died at 15 years of age from cardiac complications related to Duchenne Muscular Dystrophy (DMD). On physical examination, she presented with proximal-dominant tetraparesis, grade 4 strength in shoulder abduction and hip flexion, and evident pseudohypertrophy of the calves. Complementary tests revealed a creatine kinase (CK) level more than 20 times the upper limit of normal and a myopathic pattern on electromyography. Genetic analysis through multiplex ligation-dependent probe amplification (MLPA) and next-generation sequencing (NGS) identified a heterozygous deletion in exons 12–13 of the DMD gene. Cognitive screening showed no abnormalities, with scores of 29/30 and 28/30 on the MMSE and MoCA, respectively. She recently reported precordial pain and is awaiting further cardiological evaluation. Discussion: The DMD gene encodes dystrophin, a protein essential for maintaining sarcolemma integrity during muscle contraction. Pathogenic mutations in DMD reduce muscle fiber resistance to contraction, increasing susceptibility to damage. The disease follows an X-linked recessive inheritance pattern, typically manifesting in males as either Duchenne or Becker muscular dystrophy. Women with heterozygous DMD mutations are usually asymptomatic carriers. However, muscle damage has been reported in 2.5–19% of female carriers, some of whom develop varying degrees of muscle weakness, resembling limb-girdle muscular dystrophies. Additionally, up to 16.7% of female carriers may develop dilated cardiomyopathy. The symptomatic manifestation in females may be attributed to skewed X-inactivation, where the non-mutated DMD allele is silenced, leading to increased transcription of the pathogenic allele and subsequent production of dysfunctional dystrophin. However, some studies have found no correlation between X-inactivation and symptomatic phenotypes in women. Final comments: Although the pathophysiological mechanisms underlying symptomatic DMD mutations in women are not fully understood, dystrophinopathy should be considered in women presenting with limb-girdle weakness, calf hypertrophy, and elevated CK levels.

**Palavras-Chave do trabalho:** Becker; DMD; Duchenne; Dystrophin; Female;

**ID do trabalho:** 45

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **CLINICAL CHARACTERISTICS OF HEREDITARY ATAXIAS IN URUGUAY**

**Autores:** SOMMARUGA, Nicolás<sup>1</sup>; LABAURE, Nicolás<sup>1</sup>; ZAMORA, Andrea<sup>1</sup>; GIMÉNEZ, Santiago<sup>1</sup>; PÉREZ, Gonzalo<sup>1</sup>;

**Instituição dos Autores:** (1) Universidad de la República Facultad de Medicina, Hospital de Clínicas, Instituto de Neurología - Uruguay;

### **Resumo do trabalho:**

Background: Hereditary ataxias are a heterogeneous group of diseases, with great geographic variability, and a global prevalence of 5,48/100.000. To date epidemiological descriptions of hereditary ataxias in Uruguay are lacking. Objective: Describe demographic, genetic and clinical findings of hereditary ataxias in Uruguay. Methods: Descriptive, observational, cross-sectional study of genetically confirmed hereditary ataxia patients. 56 patients evaluated at the Hospital de Clínicas in Uruguay between March 2019- April 2024. Demographic, clinical, imaging and genetic data were obtained. Inclusion criteria: >18 y.o, born in Uruguay, suspicion of hereditary ataxia, accessibility to follow up, agreement to participate. Patients included underwent a genetic SCA panel (SCA 1, 2, 3, 6, 7). If negative, an expanded SCA panel was used (SCA12,17, 23b). If recessive inheritance was suspected, Friedreich ataxia (FA) was tested. If negative, further genetic testing was individually analyzed. Statistical analyses were performed using STATA 16.1 Results: From 56 referred patients, 24 were excluded failing to meet inclusion criteria. Of 32 patients included, 25% came from cities with a terrestrial border with Brazil. Mean age was 50,7 years, with a mean age of onset of 42 y.o (+/- 11.9). 77,1% had positive family history, but only 43% had a notion of heritability. Among the group of suspected autosomal dominant (AD) inheritance, 21 patients reached a molecular genetic diagnosis: 16 SCA 3, 3

SCA 2, 1 SCA 1, 1 SCA 17. Patients with suspected autosomal recessive (AR) inheritance were tested for FA, with two confirmed diagnoses. The remaining case, assessed with an oriented sequencing panel, was diagnosed with Ataxia with oculomotor apraxia type 2. Regarding SCA 3, median number of CAG repeats in ATXN3 gene was 69 (IQ 65-76), with an inversely proportional relationship between this number and age of onset. Gait ataxia (87.5%) was the most common initial symptom. Appendicular ataxia, cerebellar dysarthria and oculomotor signs prevalence was close to 90%. 37,5% presented slow saccades, nystagmus 75%, ocular dysmetria 62,5% and ophthalmoparesis 56%. Bulging eyes were infrequent (18%). Half patients presented pyramidal signs. 25% associated other movement disorders, mainly dystonic features (19%). Conclusion: SCA 3 is the most common AD hereditary ataxia in Uruguay. Most clinical findings were in line with previous reports from southern Brazil. Taking into account geographical proximity and the high prevalence of SCA3 found in northern Uruguay, a link between both subpopulations is possible, and could be further studied. The association of slow saccades with various oculomotor disturbances in a given patient may be a clinical clue for SCA3 diagnosis over SCA2. The small number of AR ataxias may be related to selection bias. This is the first national study of hereditary ataxias in Uruguay, emphasizing its global and regional importance.

**Palavras-Chave do trabalho:** Epidemiology; Hereditary ataxia; Spinocerebellar ataxias; Uruguay;

**ID do trabalho:** 46

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: NEVER-DESCRIBED HOMOZYGOUS PATHOGENIC VARIANTS IN DNAJC6 AS A CAUSE OF DEVASTATING PARKINSONISM IN TWO ADOLESCENT SIBLINGS

**Autores:** PESSOA, ANDRÉ LUIZ SANTOS<sup>1</sup>; MOURAO, ELLEN<sup>2</sup>; RIBEIRO, PAULO<sup>3</sup>; CAMELO, EDVAN<sup>4</sup>; GUSMAO, CLAUDIO<sup>5</sup>; GUSMÃO, THIAGO G<sup>5</sup>; GARCIA, RENATA<sup>5</sup>; KOK, FERNANDO<sup>6</sup>;

**Instituição dos Autores:** (1) UNIVERSIDADE FEDERAL DO CEARÁ-UFC E HOSPITAL INFANTIL ALBERT SABIN - FORTALEZA - CE - Brasil; (2) HOSPITAL INFANTIL ALBERT SABIN - FORTALEZA - CE - Brasil; (3) UNIVERSIDADE FEDERAL DO CEARÁ-UFC - FORTALEZA - CE - Brasil; (4) HOSPITAL UNIVERSITÁRIO WÁLTER CANTÍDIO E HOSPITAL INFANTIL ALBERT SABIN - FORTALEZA - CE - Brasil; (5) HCFMUSP - SÃO PAULO - SP - Brasil; (6) HCFMUSP/ USP - SÃO PAULO - SP - Brasil;

### Resumo do trabalho:

**CASE PRESENTATIONS:** Case 1: A 14-year-old male patient, the first child of a consanguineous couple. At the age of 13, he began to present with extremity tremors that worsened with characteristics of high amplitude and frequency bilaterally, with a cogwheel sign, bradykinesia and postural instability with gait dependent on others, in addition to oromandibular dystonia with dysphagia. Associated the patient presented with significant dysarthria and cognitive impairment. Brain MRI was normal. Complete exome sequencing showed pathogenic nonsense variants in homozygosity p.Cys325\* in DNAJC6. The response to Levodopa was mild, and during dose increase, she presented a sustained condition of ocular supraversion, worsening of tremors and dysphagia. (videos available) Case 2: A 13-year-old female patient. The second daughter of a consanguineous couple. At 12 years of age, she began to present focal epileptic seizures, with the onset of tremors of the extremities that evolved with worsening with characteristics of high amplitude and frequency bilaterally, with cogwheel sign, bradykinesia and postural instability with gait dependent on others, in addition to oromandibular dystonia with dysphagia and cognitive slowing. Brain MRI was normal. (videos available). **DISCUSSION:** Parkinsonism due to DNAJC6 or PARK19 is a complex neurological disorder of early onset whose main features are typical parkinsonian symptoms, including bradykinesia, resting tremor, rigidity and postural instability. Most cases have an early onset with onset before 21 years of age and mainly in the first decade. Associated with are usually delay or regression of neuropsychomotor development, intellectual disability, epilepsy, other movement disorders (e.g. dystonia, spasticity, myoclonus) and psychiatric symptoms that usually precede the motor picture. The disease is rapidly progressive with loss of ambulation by around 10 years of age. We describe two brothers aged 14 and 11 years, with homozygous nonsense pathogenic variants p.Cys325\* in DNAJC6 not described in the medical literature, and absent in population banks of 140 thousand individuals. The combination of the molecular mechanism, with early interruption of protein translation, characteristics of the region where they are found, and the clinical correlation with this gene point to their pathogenicity. Approximately 20 cases have been reported in the medical literature to date. Both presented developmental regression with parkinsonism, dystonia, cognitive regression, dysphagia and intense sialorrhea. The clinical progression was severe and accelerated, causing significant functional deficits, and the response to Levodopa was mild. The older brother had an adverse response to increased dose with ophthalmoparesis characterized by ocular supraversion maintained upwards, opisthotonus position and increased blood pressure.

**Palavras-Chave do trabalho:** DNAJC6; NOVEL VARIANTS; PARK19; PARKINSONISM;

**ID do trabalho:** 47**Área Técnica do trabalho:** Pesquisa translacional, modelos celulares e animais**Tipo do trabalho** Trabalhos Originais**Forma de apresentação:** Pôster

## Título do Trabalho: **MIR-7 REGULATORY PATHWAY IN MPP+--INJURED SH-SY5Y DOPAMINERGIC CELLS**

**Autores:** FERRARI, Sabrina Simplicio de Araújo Romero<sup>1</sup>; SILVA, Leticia Dias dos Santos<sup>1</sup>; DUARTE, Carlos Daniel Moreira<sup>1</sup>; SCHLEMMER, Franciele<sup>1</sup>; TITZE-DE-ALMEIDA, Simoneide Souza<sup>1</sup>; TITZE-DE-ALMEIDA, Ricardo<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de Brasília, Research Center for Major Themes at University of Brasília (UnB) – Parkinson's Disease Unit. Campus Darcy Ribeiro, Central Institute of Sciences, ASS-128. - Brasília - DF - Brasil;

### Resumo do trabalho:

Background: MicroRNAs (miRNAs) are small RNA molecules that serve as post-transcriptional regulators of gene expression by modulating the levels of messenger RNAs (mRNAs) by binding to complementary sequences, thereby inducing gene silencing. Dysregulated miRNAs have been extensively investigated for their diagnostic and prognostic significance in several pathologies. MicroRNA-7 (miR-7) has been associated with pathophysiological processes in Parkinson's Disease (PD), including modulation of alpha-synuclein, dopaminergic neuronal apoptosis, and neuroinflammatory responses. A study focusing on the post-transcriptional regulation of miR-7 levels during dopaminergic injury will enhance our understanding of the underlying mechanisms of PD and identify potential targets for neuroprotection. Objective: We aimed to investigate whether dopaminergic cell injury is associated with changes in non-coding RNAs within the regulatory pathway of miR-7. This study assessed the expression patterns of microRNAs miR-7 and miR-671, the long noncoding RNA Cyrano (OIP5-AS), and the circRNAs CDR1as in MPP+--injured SH-SY5Y cells. Methods: Cells were cultured in DMEM supplemented with fetal bovine serum, Glutamax, and an antibiotic/antimycotic solution. They were exposed to 1-Methyl-4-phenylpyridinium (MPP+) for 24 hours, a neurotoxin that inhibits mitochondrial complex I, causing ATP depletion and cell death. Cell viability was assessed using the MTT assay. RNA molecules were isolated using the RNeasy Plus Mini kit and the mirVana™ kit. The levels of miR-7, miR-671, CDR1as, and Cyrano were quantified via RT-qPCR. Quantification of miR-7 and miR-671 was performed using TaqMan™ kits, while CDR1as and Cyrano were quantified with random primers and SYBR Green methodology. Data normalization was conducted using endogenous and spike-in control genes, and relative expression was determined using the  $\Delta\Delta C_t$  method. Results: SH-SY5Y cells exposed to 1 mM MPP+ for 24 hours exhibited a 2.04-fold increase in CDR1as expression compared to controls ( $P=0.0083$ ). Cyrano showed a slight increase of 1.114, but this change was not statistically significant ( $P=0.3573$ ). miR-671 decreased by 0.251 at 1 mM, while the expression of miR-7 significantly decreased by 0.563-fold (1 mM,  $P=0.024$ ) and 0.420-fold (2 mM,  $P=0.0077$ ). Conclusion: We conclude that cell injury induced by MPP+ significantly alters the expression of key non-coding RNAs within the miR-7 regulatory pathway. The observed 2.04-fold increase in CDR1as expression, along with the significant reduction in miR-7 levels, suggests a potential response to the neurotoxic stress. Future studies should explore the relationship between CDR1as and miR-7 and their roles in dopaminergic cell death.

**Palavras-Chave do trabalho:** CDR1as; Cyrano; miR-671; miR-7; Parkinson's Disease (PD);

**ID do trabalho:** 48**Área Técnica do trabalho:** Doenças Neuromusculares**Tipo do trabalho** Made in Brazil**Forma de apresentação:** Pôster

## Título do Trabalho: **POMPE DISEASE MISDIAGNOSED AS POLYMYOSITIS**

**Autores:** CAMELO-FILHO, Antonio Edvan<sup>1</sup>; MARTINS, Manoel Ricardo Alves<sup>2</sup>; LIMA, Pedro Lucas G S B<sup>2</sup>; DE SOUZA, Jorge Luiz de Brito<sup>3</sup>; MAURICIO, Rebeca Bessa<sup>3</sup>; Nóbrega, Paulo Ribeiro<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará, Fortaleza, Ceará, Brasil - Fortaleza - CE - Brasil; (2) Universidade Federal do Ceará, Fortaleza, Ceará, Brazil - Fortaleza - CE - Brasil; (3) Universidade Estadual do Ceara, Fortaleza, Ceará, Brazil - Fortaleza - CE - Brasil;

### Resumo do trabalho:

Background: Pompe disease, a rare genetic disorder caused by mutations in the GAA gene, leads to the accumulation of glycogen in muscle tissues, resulting in progressive muscle weakness. This case report focuses on a patient presenting with muscle weakness and low back pain, with a clinical suspicion of Pompe disease based on muscle ultrasound findings. Objective: The objective of this study was to confirm the diagnosis of Pompe disease in the patient through genetic and enzymatic testing and to document the specific muscle involvement patterns observed via ultrasound. Methods: A detailed clinical examination was conducted, revealing a predominantly proximal pattern of weakness (Medical Research Council grade 3 in the lower limbs and grade 4 in the upper limbs), significant abdominal wall weakness, and a myopathic gait. Muscle ultrasound was performed to assess the involvement of various muscles, including the tongue, abdominal wall muscles (rectus abdominis, external oblique, internal oblique, and transversus abdominis), and vastus intermedius. Next-generation sequencing (NGS) was used to identify pathogenic variants in the GAA gene, and enzymatic testing measured acid alpha-glucosidase

activity in a dried blood sample. Results: Muscle ultrasound revealed hyperechoic patterns indicative of myopathic compromise in the tongue (Heckmatt Scale grade 4), rectus abdominis (Heckmatt Scale grade 4), external oblique, internal oblique, and transversus abdominis muscles (Heckmatt Scale grade 4), and vastus intermedius (Heckmatt Scale grade 2), with preserved rectus femoris (Heckmatt Scale grade 1). Genetic testing identified two GAA pathogenic variants (c.-32-13T>G—intronic and exon 18 deletion) in compound heterozygosis. Enzymatic testing confirmed Pompe disease with acid alpha-glucosidase activity significantly below normal limits (0.64  $\mu\text{mol/L/hour}$ ; normal range  $4.57 \pm 1.37 \mu\text{mol/L/hour}$ ). ECG and echocardiogram results were normal, and there were no clinical signs of respiratory involvement. Conclusion: The study confirmed the diagnosis of Pompe disease in the patient through genetic and enzymatic testing. The distinct pattern of muscle involvement observed via ultrasound was consistent with Pompe disease, underscoring the importance of comprehensive diagnostic approaches in identifying neuromuscular disorders. This case highlights the utility of muscle ultrasound in conjunction with genetic and enzymatic testing for accurate diagnosis and management of Pompe disease.

**Palavras-Chave do trabalho:** Muscle ultrasound; Neuromuscular; Pompe disease;

**ID do trabalho:** 49

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## Título do Trabalho: ASEPTIC MENINGITIS IN FABRY DISEASE DUE TO A NOVEL GLA VARIANT: AN EXPANDED PHENOTYPE?

**Autores:** Nóbrega, Paulo Ribeiro<sup>1</sup>; FERREIRA, Alliane Milliane<sup>2</sup>; DE MEDEIROS, Alisson Dantas<sup>3</sup>; KOK, Fernando<sup>4</sup>; RANGEL, Deborah Moreira<sup>1</sup>; PESSOA, André Luiz Santos<sup>1</sup>; DE PAIVA, Anderson Brandão Rodrigues<sup>1</sup>; DUARTE, Beatrice Araújo<sup>5</sup>; MORAIS, João Lucas Araújo<sup>5</sup>; MARQUES, Luciana Paim<sup>1</sup>; LIMA, Fabrício Oliveira<sup>6</sup>; BRAGA-NETO, Pedro<sup>1</sup>; MAIA, Fernanda Martins<sup>6</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Hospital Geral do Ceará - Fortaleza - CE - Brasil; (3) Universidade Unichistus - Fortaleza - CE - Brasil; (4) Universidade de São Paulo - São Paulo - SP - Brasil; (5) Universidade Unichristus - Fortaleza - CE - Brasil; (6) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil;

### Resumo do trabalho:

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by mutations in the GLA gene, leading to deficient activity of the enzyme alpha-galactosidase A. This deficiency results in the accumulation of globotriaosylceramide (Gb3) and its deacylated form, lyso-Gb3, causing a wide range of clinical manifestations, including neuropathic pain, skin lesions, and organ dysfunction. Objective: This study aims to describe the clinical presentation, genetic findings, and treatment outcomes of two siblings diagnosed with FD, highlighting the challenges in managing recurrent aseptic meningitis associated with the disease. Methods: Clinical data were collected from two siblings diagnosed with FD. Genetic testing was performed to identify mutations in the GLA gene. Enzyme replacement therapy (ERT) with alpha-galactosidase was administered, and the patients were monitored for clinical symptoms, biochemical markers, and imaging findings. Additional treatments, including intravenous methylprednisolone (IVMP) and immunosuppressive therapy, were used to manage recurrent aseptic meningitis. Results: Case 1 involved a female patient with a heterozygous c.392 T > G (p.Leu131Arg) GLA mutation, elevated lyso-Gb3 levels, and recurrent aseptic meningitis. Despite ERT, she experienced recurrent meningitis, which was managed with IVMP and immunosuppressive therapy, leading to symptom resolution over four years of follow-up. Case 2 involved her 18-year-old brother, who presented with acroparesthesias, hyperhidrosis, headache, recurrent fever, vomiting, dyspnea, and auricular angiokeratomas. He had the same GLA mutation and elevated lyso-Gb3 levels. His brain MRI was normal, and CSF examination during an acute episode revealed mild pleocytosis. Conclusion: FD can present with diverse and recurrent neurological symptoms, including aseptic meningitis, which poses a significant management challenge. Genetic testing and biochemical markers are crucial for diagnosis. ERT is beneficial, but additional immunosuppressive therapy may be required to manage recurrent inflammatory episodes. Long-term follow-up is essential to monitor treatment efficacy and disease progression.

**Palavras-Chave do trabalho:** aseptic meningitis; enzyme replacement therapy; Fabry disease; GLA mutation;

**ID do trabalho:** 50

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## Título do Trabalho: NEW OBSERVATIONS ON MINIFASCICULAR NEUROPATHY WITH SEX-DEPENDENT GONADAL DYSGENESIS: A CASE SERIES WITH NERVE ULTRASOUND ASSESSMENT

**Autores:** BRITO, Lara Albuquerque<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>2</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>2</sup>; DIAS, Daniel Aguiar<sup>2</sup>; BARRETO, André Rodrigues Façanha<sup>2</sup>; FREITAS, Hermany Capistrano<sup>1</sup>; KOK, Fernando<sup>3</sup>; RODRIGUES, Cleonísio Leite<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil - Fortaleza - CE - Brasil; (2) Universidade Federal do Ceará, Fortaleza, Ceará, Brazil - Fortaleza - CE - Brasil; (3) Universidade de São Paulo, São Paulo, São Paulo, Brazil - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Background: Minifascicular neuropathy (MFN) is a rare form of neuropathy characterized by the presence of mini-fascicular formation in nerve biopsies. It has been associated with various genetic conditions, including gonadal dysgenesis. This study investigates a novel likely pathogenic variant in the DHH gene in patients presenting with MFN and associated clinical features. Objective: The primary aim of this study was to characterize the clinical, neurophysiological, and genetic findings in four patients diagnosed with MFN, including one individual with 46, XY complete gonadal dysgenesis. Methods: This retrospective observational study included four patients from two consanguineous and apparently unrelated Brazilian families. Clinical histories, physical examinations, and additional studies were reviewed. High-resolution nerve ultrasound (HRUS) and nerve conduction studies (NCS) were performed to assess nerve morphology and function. Whole exome sequencing (WES) was conducted to identify genetic variants, focusing on a comprehensive neuropathy panel targeting 120 selected genes. The presence of the SRY gene, a marker for the Y chromosome, was also evaluated. Results: All four patients exhibited a striking phenotype characterized by marked trophic changes in extremities, sensory ataxia, and distal anesthesia due to primary demyelinating sensory-motor polyneuropathy. The novel DHH variant, p.(Leu335Pro), was detected in homozygosity in all patients and was absent from population databases, indicating its likely pathogenic nature. Neurophysiological assessments revealed chronic primary demyelinating sensorimotor polyneuropathy with severe sensory involvement. HRUS demonstrated increased cross-sectional areas of the common peroneal nerve in all patients, with variability in total nerve area observed. Conclusion: This study identifies a novel DHH variant associated with MFN in patients, including one with 46, XY complete gonadal dysgenesis. The findings underscore the importance of genetic evaluation in patients with atypical neuropathies and highlight the need for further research to elucidate the mechanisms underlying MFN and its association with gonadal dysgenesis.

**Palavras-Chave do trabalho:** DHH gene; Gonadal dysgenesis; Minifascicular neuropathy;

**ID do trabalho:** 51

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: NEUROIMAGING EVALUATION OF PATIENTS WITH DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES OF GENETIC ETIOLOGY**

**Autores:** RIBEIRO, Giovana Barros e Silva<sup>1</sup>; REIS, Fabiano<sup>1</sup>; COAN, Ana Carolina<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Estadual de Campinas - Campinas - SP - Brasil;

**Resumo do trabalho:**

BACKGROUND: Developmental and Epileptic Encephalopathy (DEE) of genetic etiology often present with overlapping electroclinical phenotypes despite diverse underlying pathogenic pathways. Besides the variability in phenotypic manifestations associated with mutations in single genes, brain neuroimaging pattern correlations remain limited for most cases. OBJECTIVE: This study aimed to describe the neuroimaging findings in patients with DEE of genetic etiology and correlate these findings with genetic mutations and clinical syndromes. METHODS: Patients with a diagnosis of DEE and identification of pathogenic genetic variants associated with the condition were included. All available Magnetic Resonance Imaging (MRI) scans for each patient were evaluated by one experienced neuroradiologist and one epileptologist. RESULTS: A total of 24 patients were included, 70% of whom were female, with a mean age of 19 months at seizure onset. The most frequently observed mutations occurred in the KCNT1 (potassium sodium-activated channel subfamily T member 1) and SCN1A (sodium voltage-gated channel alpha subunit 1) genes, with autosomal dominant inheritance being the most common mode of transmission. The most frequently identified phenotype was Early-Infantile Developmental and Epileptic Encephalopathy (EIDEE), observed in 20% of patients. Neuroimaging findings included delayed myelination (20%), cerebellar atrophy, hippocampal atrophy, incomplete hippocampal inversion, and cortical hyperintensity on T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) sequences. No imaging abnormalities were observed in 20% of cases. Additionally, a Long-Term Epilepsy-Associated Tumor (LEAT) was identified in a patient with a pathogenic mTOR (mammalian target of rapamycin) variant, while focal cortical dysplasia was observed in a patient with a pathogenic NPRL2 (nitrogen permease regulator-like 2) variant. Infantile Epileptic Spasms Syndrome (IESS) was associated with pathogenic variants in the mTOR and PIGA (phosphatidylinositol glycan anchor biosynthesis class A) genes. CONCLUSION: The neuroimaging findings in DEEs of genetic etiology reveal diverse structural abnormalities, with delayed myelination being the most common. Specific features, such as focal cortical dysplasia in NPRL2 mutations and LEAT in mTOR mutations, underscore the potential of integrating genetic and imaging data to refine phenotype-genotype correlations and improve diagnostic precision.

**Palavras-Chave do trabalho:** Developmental and Epileptic Encephalopathy; epilepsy; Neuroimaging;

**ID do trabalho:** 52

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## **Título do Trabalho: TRANSLATION, CROSS-CULTURAL ADAPTATION, AND VALIDATION TO BRAZILIAN PORTUGUESE OF THE CEREBELLAR COGNITIVE AFFECTIVE/SCHMAHMANN SYNDROME SCALE**

**Autores:** SCOTT, Stephanie Suzanne de Oliveira<sup>1</sup>; PEDROSO, José Luiz<sup>2</sup>; ELIAS, Victor Vitalino<sup>3</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>; SOBREIRA, Emanuelle Silva Tavares<sup>1</sup>; DE ALMEIDA, Marcela Patrícia<sup>2</sup>; GAMA, Maria Thereza Drumond<sup>2</sup>; MASSUYAMA, Breno Kazuo<sup>2</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>2</sup>; MOTA, Norberto Anizio Ferreira<sup>3</sup>; BRAGA-NETO, Pedro<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (3) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil;

### **Resumo do trabalho:**

Background: Cerebellar Cognitive Affective Syndrome (CCAS) is characterized by deficits in executive functions, language processing, spatial orientation, and affect regulation in patients with cerebellar disease. The original CCAS scale, developed in English, requires cultural adaptation for effective use in diverse populations. This study focuses on the translation, cultural adaptation, and validation of the CCAS scale into Brazilian Portuguese, addressing the need for appropriate cognitive assessment tools in Brazil. Objective: The primary objective of this study was to translate and culturally adapt the CCAS scale for Brazilian Portuguese speakers, ensuring its reliability and validity for assessing cognitive and affective symptoms in patients with cerebellar disorders. Methods: The study involved a systematic process of translation and cultural adaptation, followed by a validation phase. A total of 100 participants, including individuals diagnosed with cerebellar disorders and healthy controls, were recruited. The scale evaluates ten domains, comprising nine cognitive and one affective domain. Statistical analyses, including association tests, mean comparisons, and Receiver Operating Characteristic (ROC) curve analysis, were conducted to determine optimal cutoff values for each subitem of the scale. Internal consistency was assessed using Cronbach's alpha. Results: The adapted CCAS scale demonstrated good internal consistency, with a Cronbach's alpha of 0.752. The analysis revealed significant differences in cognitive performance between patients with CCAS and controls across various subitems, with optimal cutoff points established for effective differentiation. The study found that 70% of participants were accurately classified into patients with CCAS and controls, indicating the scale's potential utility in clinical settings. Additionally, the cultural adaptation process highlighted the necessity of modifying certain terms to align with Brazilian vernacular. Conclusion: The Brazilian Portuguese version of the CCAS scale is a reliable and valid tool for screening cognitive and affective symptoms in patients with cerebellar disease. This adaptation enhances the ability to assess and diagnose CCAS in the Brazilian population, ultimately contributing to improved patient care and management. Future research should focus on longitudinal studies to further validate the scale's effectiveness in diverse clinical settings.

**Palavras-Chave do trabalho:** Cerebellar Cognitive Affective Syndrome; Cognitive Assessment; Cultural Adaptation; Validation;

**ID do trabalho:** 53

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## **Título do Trabalho: NUTRITIONAL STATUS AND EATING HABITS OF PATIENTS WITH HEREDITARY ATAXIAS: A CASE-CONTROL STUDY**

**Autores:** CARVALHO, Camila Gonçalves Monteiro<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>; SCOTT, Stephanie Suzanne de Oliveira<sup>1</sup>; RANGEL, Deborah Moreira<sup>2</sup>; SOARES, Danyela Martins Bezerra<sup>3</sup>; MAIA, Carla Soraya Costa<sup>3</sup>; MAIA, Carla Soraya Costa<sup>3</sup>; BRAGA-NETO, Pedro Pedro<sup>4</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (3) Universidade Estadual do Ceará - Fortaleza - CE - Brasil; (4) Universidade Estadual do Ceará - Fortaleza - CE - Brasil;

### **Resumo do trabalho:**

Introduction: Hereditary Ataxias (HAs) comprise a wide spectrum of genetically determined neurodegenerative diseases with progressive ataxia as the main symptom. Few studies have evaluated nutritional profile in HA patients and most of these

focused on specific ataxia subtypes. The objectives of this study were: (1) to investigate whether hereditary ataxias were associated with changes in energy expenditure, body composition and dietary intake; (2) to verify differences in these variables according to ataxia subtype, sex, age, and disease severity. Methods: Thirty-eight hereditary ataxia patients from two neurology centers in Northeastern Brazil and 38 controls were evaluated. Body composition was assessed with bio-impedance analysis and dietary intake was estimated with a validated questionnaire (24-hour dietary recall). Results: Mean body mass index (BMI) was lower in HA compared to controls ( $p=0.032$ ). Hereditary ataxia patients showed lower protein intake, higher frequency of dysphagia and higher incidence of nausea and diarrhea. The difference in average estimated caloric intake did not reach statistical significance ( $2359\text{kcal} \pm 622$  in patients x  $2713\text{kcal} \pm 804$  in controls,  $p=0.08$ ). Disease severity measured by SARA scale was not associated with BMI, nor was ataxia subtype (autosomal dominant x non-autosomal dominant ataxias). Conclusion: Hereditary ataxia patients have lower BMI compared to healthy controls. There was no difference in this cohort between dominant or non-dominant ataxia regarding BMI. Weight loss may be a common finding among hereditary ataxias and may affect quality of life in these patients.

**Palavras-Chave do trabalho:** Body composition; Diet; Feeding behavior; Hereditary ataxia; Nutritional assessment;

**ID do trabalho:** 54

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: UNRAVELING HUNTINGTON'S DISEASE IN A NORTHEASTERN STATE OF BRAZIL

**Autores:** DANTAS, Fátima de Menezes<sup>1</sup>; RIOS, Igor da Silva<sup>2</sup>; MARACAJÁ, Norton Lincoln Diniz<sup>2</sup>; DANTAS, Pedro Ricarte Cândido<sup>2</sup>; FREIRE, Felipe Olobardi<sup>2</sup>; SOUZA JÚNIOR, Itajá Dantas de<sup>2</sup>; SILVA, Maria Weryca de Souza Belo<sup>3</sup>; SILVA, Rodrigo Alencar e<sup>3</sup>; GODEIRO JÚNIOR, Clécio de Oliveira<sup>3</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Norte - Scholarship holder of the Programa de Iniciação Científica da Empresa Brasileira de Serviços Hospitalares (PIC/Ebserh/HUOL/CNPq) - Natal - RN - Brasil; (2) Universidade Federal do Rio Grande do Norte - Natal - RN - Brasil; (3) Hospital Universitário Onofre Lopes, Universidade Federal do Rio Grande do Norte - Natal - RN - Brasil;

### Resumo do trabalho:

Background: Huntington's disease (HD) is an autosomal dominant disorder caused by an expansion of the CAG trinucleotide in the HTT gene (4p16.3). This alteration results in the production of an abnormal protein, which accumulates in the brain and leads to motor, cognitive, and psychiatric symptoms. Previous studies have identified some regions in Brazil where, due to specific characteristics such as consanguineous marriages and population isolation, there is an increased prevalence of this disease (clusters). However, the prevalence of HD remains unknown in most parts of the country. Objective: To determine the prevalence of HD in different municipalities of Rio Grande do Norte (RN) and identify potential disease clusters in the state. Methods: A retrospective study was conducted, analyzing medical records of patients followed at a movement disorders outpatient clinic from 2009 to 2024. After statistical analysis, qualitative demographic data were described as frequencies and percentages. Quantitative data were described as medians and interquartile ranges. The prevalence for each municipality was calculated based on data from the 2022 IBGE Census. The study was approved by the local Ethics Committee. Results: A total of 35 patients with HD confirmed by genetic testing participated in the study, including 21 men (60%) and 14 women (40%). The median age of the participants was 48 years (IQR 39.00-61.50). Participants originated from 12 municipalities in RN. In 6 of these municipalities (Pedra Preta, Lajes do Cabugi, Vera Cruz, Pendências, Guamaré, and João Câmara), the prevalence of the disease was higher than the global and Latin American prevalence estimates reported in previous studies, which were 4.88 and 1.85 per 100,000 people, respectively. The median prevalence among these municipalities was 8.73 (IQR 6.94-9.93) per 100,000. In Pedra Preta, the prevalence was 122.9 per 100,000, surpassing the estimated prevalence for cluster regions in Latin America from a prior study, which was 54 per 100,000. Conclusion: Although these are partial results from an ongoing study, the data suggested the existence of an HD cluster in the municipality of Pedra Preta. This cluster shares characteristics with two other clusters identified in Brazil, one in Ervalia-MG (71.87 cases per 100,000) and another in Feira Grande-AL (100 cases per 100,000), both concentrated in small towns, with multiple generations of the same family born and residing in the same location throughout their lives. Furthermore, the data revealed other municipalities in RN with elevated HD prevalence, 5 of which are geographically close, with 2 (Pedra Preta and Lajes do Cabugi) even sharing borders. Continued research may reveal genetic and/or environmental factors that could explain this finding. Finally, we expect that studies like this will contribute to optimizing the diagnosis and treatment of a condition that remains poorly understood even among Brazilian healthcare professionals.

**Palavras-Chave do trabalho:** chorea; Gene Cluster; Genetics; Huntington's Disease; Prevalence;

**ID do trabalho:** 56

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **EPIGENETICS IN FSHD: COULD METHYLATION STATUS UNLOCK ANSWERS FOR DIAGNOSIS, SUBTYPING, AND PROGNOSTICATION?**

**Autores:** DI PACE, Filipe Tupinambá<sup>1</sup>; FERNANDES, Tatiana Ribeiro<sup>1</sup>; LANÇA, Ana Paula dos Anjos<sup>1</sup>; ARTILHEIRO, Mariana Cunha<sup>1</sup>; CAMPOS, Eliene Dutra<sup>1</sup>; DOUSSEAU, Gabriella Corrêa<sup>1</sup>; CAMELO, Clara Gontijo<sup>1</sup>; ZANOTELI, Edmar<sup>1</sup>; MORENO, Cristiane Araújo Martins<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

Background: Facioscapulohumeral muscular dystrophy (FSHD) is the third most common inherited myopathy. The abnormal expression of the DUX4 gene, which is normally hypermethylated and silenced, is the main mechanism of disease. It occurs in the presence of a permissive allele through two mechanisms: (1) contraction of D4Z4 repeats on chromosome 4q35 (95% of cases) or (2) a digenic mechanism, involving mutations in regulatory genes (e.g., SMCHD1), both resulting in D4Z4 hypomethylation. FSHD types 1 and 2 diagnostic tests, and their correlation with clinical severity remain challenging. Investigating epigenetic modifications within and beyond the 4q35 region offers a potential field for improved understanding. Here, we present study exploring the correlation between methylation levels, FSHD subtype, and clinical severity. Objective: To evaluate the D4Z4 repeats methylation levels for diagnostic confirmation, FSHD subtyping, and as a prognostic factor for disease severity. Methods: FSHD patients visits occurred between June and December 2024. Methylation assays were performed using the BSS method. Analyses were focused on diagnostic confirmation, subtype differentiation, and correlation of methylation status with clinical severity scales. Results: Eleven patients were included, 6 females (55%), mean age at appointment was 42y (14-75), and at disease onset 27y (4-68). FSHD was confirmed in all patients, 9 (82%) of them were FSHD1. Seventeen permissive alleles were identified among the 11 patients, 4A161 being the most frequent (53%). Two permissive alleles were found in 6 patients (5 females). Methylation levels were reduced in all patients, with a mean BSSA of 8% (+6) and BSSL of 25.7% (+8,6). BSSX levels were within the normal range for all patients, except for FSHD2 patients. Mean global BSSX was 40,1%(+14,4), and in the FSHD2 group was 21,6% (+-0,5). One of these was tested for D4Z4 repeat size and was in the normal range, confirming FSHD2. Methylation levels using BSSA and BSSL for the 4A and 4AL alleles, respectively, relating to clinical severity, current abilities scale, and ambulation status, showed no significant differences between groups. One FSHD2 patient, carrying two permissive 4A alleles, exhibited 0% methylation level in BSSA and 21% in BSSX, the disease started earlier in life, and he had the worst clinical scores. Conclusion: Methylation status using the BSS method proved to be a reliable test for confirming FSHD and subtyping, as reported in the literature. However, our study did not find any correlation between disease severity and methylation status, which aligns with some studies but contradicts others. The presence of two permissive alleles in FSHD2 patients appears to be an independent risk factor for disease severity. Further studies with larger sample sizes are necessary to better define prognostic factors using epigenetic tests.

**Palavras-Chave do trabalho:** epigenetics; Facioscapulohumeral muscular dystrophy; methylation;

**ID do trabalho:** 57

**Área Técnica do trabalho:** Pesquisa translacional, modelos celulares e animais

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **AGING IMPACT ON CANINE EXOSOMES PRODUCTION, SIZE AND MIRNA CONTENT**

**Autores:** MARINA, Clara Luna<sup>1</sup>; GREUEL, Alexandra Mazer<sup>1</sup>; LAS-CASAS, Lucas<sup>2</sup>; LOPES, Evilly<sup>1</sup>; FERRARI, Sabrina Simplicio de Araújo Romero<sup>1</sup>; RODRIGUES, Márcio Lourenço<sup>3</sup>; DOS REIS, Flavia Coelho Garcia<sup>3</sup>; BOCCA, Anamélia Lorenzetti<sup>4</sup>; TITZE-DE-ALMEIDA, Simoneide Souza<sup>1</sup>; RESENDE, Fernando Francisco Borges<sup>1</sup>; DE SANT'ANA, Fabiano José Ferreira<sup>1</sup>; TITZE-DE-ALMEIDA, Ricardo<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de Brasília - Brasília - DF - Brasil; (2) Fundação Osvaldo Cruz - Rio de Janeiro - RJ - Brasil; (3) Fundação Osvaldo Cruz - Curitiba - PR - Brasil; (4) Fundação Osvaldo Cruz - Ribeirão Preto - SP - Brasil;

### Resumo do trabalho:

Background: The increase in life expectancy worldwide has been accompanied by a higher prevalence of aging-related diseases, highlighting the importance of studying the mechanisms involved in the aging process. Understanding these mechanisms can facilitate the development of effective treatments for these conditions. Exosomes are small, lipid bilayer extracellular vesicles produced by cells that play various roles in the body, primarily in intracellular and intercellular communication. Objective: Given the significance of exosomes in transporting molecules, transcription factors, and miRNAs, and their influence on gene expression, we aimed to investigate whether the prevalence, structure, and content of exosomes in

the plasma of dogs change with age. Methods: We collected 5 mL of blood from young dogs (2 to 6 years old) and elderly dogs (over 12 years old) using EDTA-containing tubes. The blood samples were centrifuged at 300g for 5 minutes, and the plasma was collected from the upper liquid phase. The plasma was then centrifuged at 10,000g for 10 minutes to eliminate debris and residual cells. The supernatant was filtered through 0.22 µm filters and ultracentrifuged at 100,000g for 1.5 hours three times to isolate the plasma exosomes. We characterized the exosomes by assessing their protein and sterol content using commercial kits (Thermo Fisher); we measured yield and size through nanoparticle tracking analysis (NTA); and we examined their morphology and size using Transmission Electron Microscopy (TEM). Finally, miRNA was extracted from the exosomes with the miRNeasy Mini Kit (Qiagen), converted to cDNA using the TaqMan Advanced miRNA cDNA synthesis kit (Thermo Fisher), and quantified by Polymerase Chain Reaction (PCR). Results: We found that older dogs produce fewer exosomes, with lower protein and sterol content compared to young dogs. Additionally, the exosomes from older dogs exhibited greater size heterogeneity, with larger exosomes identified in this group. We also observed reduced miRNA content in the exosomes of older dogs, particularly for miR-19b and miR-29c, which have previously been shown to be downregulated in exosomes from patients with neurodegenerative disorders, especially Parkinson's disease. Conclusion: Our data support previous findings in humans that indicate reduced exosome production in older individuals. This reduction may negatively impact intercellular communication and, consequently, disrupt the normal physiology of organisms, linking it to the aging process. These results underscore the importance of studying the role of exosomes and their cargo in aging and neurodegenerative disorders.

**Palavras-Chave do trabalho:** Aging; Canine; Exosomes; Extracellular-vesicles;

**ID do trabalho:** 58

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: THE DIAGNOSTIC PUZZLE OF LIMB-GIRDLE WEAKNESS: MUSCLE MRI AS A KEY TOOL FOR PHENOTYPIC CHARACTERIZATION

**Autores:** DI PACE, Filipe Tupinambá<sup>1</sup>; MENDONÇA, Rodrigo De Holanda<sup>1</sup>; DA SILVA, Andre Macedo Serafim<sup>1</sup>; CAMELO, Clara Gontijo<sup>1</sup>; MORENO, Cristiane Araújo Martins<sup>1</sup>; ZANOTELLI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

Case Presentation: A 44-year-old man started exercise-induced lower limb cramps, exercise intolerance, and proximal weakness at the age of 14. Symptoms remained stable over time, with only mild progression of proximal weakness and no significant functional impairment. Rhabdomyolysis, myoglobinuria, or fluctuating weakness, was denied. No remarkable family history or consanguinity was reported. On examination, remarkable findings were: axial and symmetrical limb-girdle weakness and bilateral scapular winging, while distal strength and walking unsupported ability were maintained. Creatine kinase (CK) levels were persistently elevated, peaking at 3,000 U/L. A limb-girdle muscular dystrophy (LGMD) was hypothesized, and whole-exome sequencing identified two pathogenic variants in the SGCA gene: c.739G>A (p.Val247Met) and c.86dup (p.His29Glnfs\*15). However, it was unclear whether they were in cis or trans configuration, and genetic segregation analysis wasn't available. Given the atypical clinical presentation, a muscle biopsy was performed, revealing mild myopathic changes and normal expression of alpha, beta, and gamma subunits in immunohistochemistry. Lower limbs muscle MRI revealed: relative sparing of the gluteus maximus compared to the gluteus medius and minimus, with severe fat replacement in most pelvic muscles. In the thighs, fat replacement was present in adductor muscles and the vastus lateralis and intermedius, with a proximal-to-distal gradient in vastus muscles. Notably, the gracilis and sartorius were hypertrophic, while the medial portion of the adductor longus was spared. This MRI pattern strongly suggested sarcoglycanopathy, leading to a definitive diagnosis of alpha-sarcoglycanopathy. Discussion: Sarcoglycanopathies are the third most common recessive LGMD in Brazil, typically occurring in the first decade of life with Duchenne-like presentation. They encompass four subtypes (alpha, beta, gamma, and delta), with alpha-sarcoglycanopathy more commonly associated with missense variants. In rare cases, alpha-sarcoglycanopathy can present as mild myopathy with normal immunohistochemistry on muscle biopsy, which is associated with the capacity of the protein to reach the sarcolemma. Muscle MRI patterns can provide a remarkable diagnostic clue in muscle diseases; in our case, it underscored the utility on diagnosis workup. Final Comments: Clinical phenotyping is essential in workup diagnosis for all muscular disorders. However, deeper investigation is often required, even in positive genetic tests. While muscle biopsy is an important diagnostic tool, it may not always suffice. Muscle MRI offers a powerful complementary approach, enabling detailed phenotypic characterization, and might help resolve complex diagnostic dilemmas, and this case highlights the role of advanced phenotyping tools.

**Palavras-Chave do trabalho:** genotype-phenotype; Muscle MRI; Phenotype characterization; Sarcoglycanopathy;

**ID do trabalho:** 59**Área Técnica do trabalho:** Doenças Neuromusculares**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: PATHOGENIC PNPLA2 GENE VARIANT IN NEUTRAL LIPID STORAGE DISEASE WITH MYOPATHY: A RARE REAL CONDITION**

**Autores:** DE LUCENA, Larissa Neves<sup>1</sup>; NEPOMUCENO, Camila Rodrigues<sup>1</sup>; MENDES FILHO, Antonio Avelino<sup>1</sup>; MESIAS, André Vinício Cruz<sup>1</sup>; FEITOSA, Adriano Alves<sup>1</sup>; LOURO, Rafaela Julian<sup>1</sup>; LIMA, Jéssica Semler de Sá<sup>1</sup>; LEATI, Maria Fernanda Hamamoto<sup>1</sup>; DOUSSEAU, Gabriella Corrêa<sup>1</sup>; ROCHA, Maria Sheila Guimarães<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Santa Marcelina - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Case Presentation: A 45-year-old man, born to consanguineous parents, presented with progressive proximal muscle weakness that began asymmetrically in his right upper limb at age 38 and later progressed to all four limbs. Physical examination revealed asymmetrical proximal weakness, more pronounced in the right shoulder girdle with moderate severity, and mild involvement in the pelvic girdle. Laboratory tests showed significantly elevated creatine kinase (CK) levels (3033 mg/dL). Thigh magnetic resonance imaging (MRI) demonstrated fat infiltration predominantly in the proximal muscles, primarily affecting the posterior compartments while sparing the lateral compartment. Electrophysiological studies indicated an asymmetrical and proximal myopathic pattern. Muscle biopsy revealed intracellular vacuolization, cytoplasmic masses, and subsarcolemmal fat accumulation. Genetic sequencing confirmed a pathogenic intronic variant, homozygous, (c.421-1G>A) in the PNPLA2 gene. Discussion: Neutral lipid storage disease with myopathy (NLSMD - OMIM #610717) is a rare autosomal recessive disorder caused by PNPLA2 gene mutations, which impair adipose triglyceride lipase function. This enzyme is essential for intracellular triglyceride breakdown, and its partial or complete deficiency results in systemic triacylglycerol (TAG) accumulation in various tissues, including skeletal and cardiac muscles, the liver, and peripheral blood. Proximal muscle weakness is the most common initial symptom, typically presenting asymmetrically in the shoulder girdle during the late 20s or early 30s. As the disease progresses, the pelvic girdle and distal muscles become involved, eventually leading to a symmetrical distribution. Notably, ocular and facial muscles, swallowing function, and respiratory capacity remain unaffected. Systemic manifestations may include cardiomyopathy, hepatomegaly, diabetes, chronic pancreatitis, hypertriglyceridemia, and hepatic steatosis. Elevated CK levels are a common finding. A key diagnostic hallmark of NLSMD is the presence of TAG-containing vacuoles in leukocytes, observable in peripheral blood smears. Muscle histology characteristically reveals vacuolar myopathy with lipid accumulation, often with a subsarcolemmal distribution in PNPLA2 deficiency. MRI findings frequently show predominant involvement of the posterior thigh compartment. The disease progresses slowly and lacks episodic fluctuations. Conclusion: Early diagnosis through recognition of clinical, biochemical, and imaging findings is crucial for timely intervention and screening, including cardiac evaluations and endocrine disorders. Ongoing research is exploring potential therapeutic strategies, such as fenofibrate, carnitine and medium-chain triglyceride diet. Given the rarity of the disease, international collaboration is essential to enhance genetic research and deepen our understanding of genotype-phenotype correlations in NLSMD.

**Palavras-Chave do trabalho:** Adipose triglyceride lipase (ATGL); Neutral lipid storage disease with myopathy (NLSMD); PNPLA2 gene;

**ID do trabalho:** 61**Área Técnica do trabalho:** Neurodesenvolvimento**Tipo do trabalho** Casos Clínicos Desafiadores**Forma de apresentação:** Pôster

## **Título do Trabalho: BIOCHEMICAL OR GENETIC SCREENING FOR MSUD? A REAL-WORLD EXPERIENCE.**

**Autores:** SOBRINHO, Livia Maria Ferreira<sup>1</sup>; FERREIRA, Alexandre Magno da Costa<sup>1</sup>; VALVERDE, Bruna Rodrigues<sup>1</sup>; VALÁCIO, Camilla Cosenza<sup>1</sup>; SOBRINHO, Gabriel Ferreira<sup>2</sup>; REFOSCO, Lilian Farret<sup>3</sup>; SCHWARTZ, Ida Vanessa Doederlein<sup>4</sup>;

**Instituição dos Autores:** (1) Universidade Federal de Minas Gerais - Belo Horizonte - MG - Brasil; (2) Universidade Federal de Juiz de Fora - Juiz de Fora - MG - Brasil; (3) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (4) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Maple Syrup Urine Disease (MSUD) is a disorder caused by reduced activity of the branched-chain  $\alpha$ -ketoacid dehydrogenase complex. Objective: To present two complex clinical cases of MSUD, highlighting the critical role of integrating biochemical and genomic analysis for early diagnosis. Methods: This study presents two MSUD cases, highlighting the role of integrated biochemical and genomic analysis for early diagnosis. Results: Patient 1: A 1.6-year-old male, son of healthy, non-consanguineous parents. Newborn screening on day 4 showed a slight increase in leucine, isoleucine, and valine. A 15-day sample was normal, deeming the first result a false positive. Molecular screening, performed at 25 days at the parents' request, revealed the pathogenic variants c.659C>T and c.454G>A in the BCKDHA gene. Aloisoleucine levels confirmed the MSUD

diagnosis. The asymptomatic patient was exclusively breastfed with follow-up by a multidisciplinary team. Management included monthly serum amino acid monitoring and a BCAA-free formula during high-risk catabolic episodes. Exclusive breastfeeding continued for six months without metabolic decompensation. At six months, the patient experienced metabolic decompensation (leucine 800  $\mu\text{mol/L}$ , RR: 47–155) due to COVID-19 infection. Prompt dietary protein restriction prevented clinical repercussions or sequelae. At 1.6 years, the patient had metabolic decompensation (leucine 1400  $\mu\text{mol/L}$ ) during gastroenteritis with ataxia and lethargy. Prompt protein restriction and parenteral support prevented sequelae. Breastfeeding was stopped, and a metabolic formula was introduced. The patient shows normal growth and neurodevelopment. Patient 2: A 4-month-old male, son of healthy, non-consanguineous parents. He was discharged on day 2 but readmitted to the ICU on day 3 with lethargy and seizures. Newborn screening on day 3 was normal; however, amino acid quantification only included phenylalanine levels. The infant's condition deteriorated with refractory seizures and severe encephalopathy. Exome at 15 days showed no clinically relevant variants. At three months, a geneticist raised the possibility of MSUD. Amino acid analysis confirmed the diagnosis - leucine level of 1966.7  $\mu\text{mol/L}$  (RR: 47–155). Reanalysis of the exome identified two BCKDHB gene variants (c.212T>C and c.952-48A>G) both classified as Variants of Uncertain Significance (VUS). Protein restriction and specialized care were initiated, controlling seizures and improving lethargy. Conclusion: These MSUD cases, representing intermittent and classic forms, highlight the importance of integrating clinical, biochemical, and genomic data for diagnosis. Paradoxical findings between molecular and biochemical screening highlight the primacy of clinical evaluation as the cornerstone of diagnosis. Efficient clinical and lab data integration, combined with skilled professionals, is vital for early, precise diagnoses and better outcomes.

**Palavras-Chave do trabalho:** Inborn Errors of Metabolism; Maple Syrup Urine Disease; Neurodevelopmental Disorders; Newborn Screening Genomic Medicine;

**ID do trabalho:** 62

**Área Técnica do trabalho:** Pesquisa translacional, modelos celulares e animais

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: THE ROLE OF PARP1 ENZYME AND MIR-7 IN DOPAMINERGIC CELL INJURY INDUCED BY MPP+**

**Autores:** DOS SANTOS SILVA, Letícia Dias<sup>1</sup>; DE ARAUJO ROMERO FERRARI, Sabrina Simpício<sup>1</sup>; MOREIRA DUARTE, Carlos Daniel<sup>1</sup>; TOLENTINO VALADARES, Rahul Martin<sup>2</sup>; DE OLIVEIRA, Deborah Almeida<sup>1</sup>; SCHLEMMER, Franciele<sup>3</sup>; TITZE-DE-ALMEIDA, Simoneide Souza<sup>1</sup>; TITZE-DE-ALMEIDA, Ricardo<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de Brasília - Brasília - DF - Brasil; (2) Universidade Católica de Brasília - Brasília - DF - Brasil; (3) Universidade de Brasília - Brasília - BA - Brasil;

### **Resumo do trabalho:**

Background: The enzyme poly(ADP-ribose) polymerase 1 (PARP1) is implicated in the death of dopaminergic neurons in Parkinson's disease (PD) through the parthanatos pathway, leading to the formation of PAR polymers that interact with misfolded alpha-synuclein and promote the formation of Lewy bodies. The microRNA 7 (miR-7) exerts a neuroprotective effect in PD by reducing the accumulation of synuclein, oxidative stress, and apoptosis, as well as post-transcriptionally silencing the expression of the PARP1 enzyme. PARP1 inhibitors have proven effective in decreasing the formation of PAR polymers and reducing motor deficits in experimental models of parkinsonism. Objective: This study aimed to assess the involvement of the PARP1 enzyme and miR-7 in the injury of SH-SY5Y dopaminergic cells induced by MPP+. Methods: Cells were cultured in supplemented DMEM and exposed to MPP+ for 24 hours. Cell viability was assessed using the MTT assay. The relative expression of miR-7 was determined by RT-qPCR, while PARP1 protein expression was assessed by Western Blotting (WB). RNA was purified using commercial kits, and TaqMan™ kits were used for miRNA RT-qPCR. Data were analyzed using the  $\Delta\Delta\text{Ct}$  method, normalizing with endogenous genes and spike-in controls. To evaluate the neuroprotective effect, cells were transfected with synthetic miR-7 oligonucleotides (miR-7 mimics) or exposed to the PARP1 inhibitor Olaparib at concentrations 2.5nM, 5nM, and 10nM, and cell viability was measured using the CCK8 assay. Results: Exposure to MPP+ resulted in a significant decrease in cell viability, with reductions of 87%, 81%, 59%, 34%, and 15% at concentrations of 0.5 mM, 1 mM, 2 mM, and 4 mM, respectively ( $P<0.05$ ). Regarding miR-7 expression, cells exposed to 1 mM and 2 mM MPP+ showed reductions of 0.563 and 0.420, respectively. Additionally, PARP1 protein expression increased by 92.25% at 1 mM and 141.16% at 2 mM. Replacement of miR-7 with miR-7 mimics resulted in a slight recovery of 11.13% in cell viability. Treatment with olaparib resulted in a recovery of cell viability by 13.49% and 15.54% at concentrations of 2.5  $\mu\text{M}$  and 5  $\mu\text{M}$ , respectively ( $P<0.05$ ). Conclusion: In conclusion, dopaminergic injury resulted in decreased miR-7 expression, suggesting its role in the cellular response to neurotoxic stress. The accompanying increase in PARP1 protein expression suggests an adaptive response to potential cellular damage. Additionally, the neuroprotective effect of the PARP1 inhibitor Olaparib highlights PARP1's involvement in MPP+-induced cell injury. Collectively, these findings underscore the critical roles of miR-7 and PARP1 in dopaminergic cell injury.

**Palavras-Chave do trabalho:** microRNA; miR-7; Neurodegeneration; Parkinson's disease; PARP1;

**ID do trabalho:** 65

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: FIRST BRAZILIAN CASE OF NEDBAF: EXPANDING THE GENOTYPIC AND PHENOTYPIC SPECTRUM WITH NOVEL GASTROINTESTINAL MANIFESTATIONS**

**Autores:** VALVERDE, Bruna Rodrigues<sup>1</sup>; FERREIRA, Alexandre Magno da Costa<sup>1</sup>; DA SILVA, Ryan Vitor<sup>1</sup>; SOBRINHO, Livia Maria Ferreira Maria Ferreira<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal de Minas Gerais - Belo Horizonte - MG - Brasil;

### **Resumo do trabalho:**

Case Presentation: A 4-year-old girl, daughter of healthy, non-consanguineous parents with no significant family history of genetic diseases, was born at term with normal anthropometric measures and discharged at two days of life. Her development revealed global neuropsychomotor delay: head control at 6 months, sitting at 12 months, walking with support at 2 years and 6 months, and no independent walking or verbal language to date. She has marked deficits in weight and height. Clinical examination showed muscle hypotrophy, short stature, a broad and low nasal bridge, anteverted nares, retrognathia, malar hypoplasia, and global hypotonia. Brain magnetic resonance imaging revealed corpus callosum thinning. Metabolic screening and karyotype (46, XX) were normal. At 1 year and 10 months, whole-exome sequencing identified a heterozygous RAC3 gene variant (c.202C>G; p.(Arg68Gly)), linked to Neurodevelopmental Disorder with Structural Brain Anomalies and Dysmorphic Facies (NEDBAF). From the age of 2 years, the patient developed refractory gastroesophageal reflux disease and severe gastroparesis, leading to malnutrition, dehydration, and recurrent hospitalizations. Oral feeding intolerance persisted despite pyloroplasty, gastrostomy, and endoscopic jejunostomy, which provided minimal benefit. At 3 years and 6 months, she was diagnosed with intestinal failure and managed with enteral nutrition via infusion pump, with adjustments to volume and rate. Despite relative clinical stabilization, the gastric dysfunction and the patient's caloric demands continue to pose a high risk of recurrent malnutrition. Discussion: The RAC3 gene encodes the Ras-related C3 botulinum toxin substrate 3, a GTPase essential for neuronal differentiation and migration. Pathogenic variants in this gene cause NEDBAF, an ultra-rare autosomal dominant disorder marked by moderate to severe psychomotor delay, corpus callosum dysplasia, cortical malformations, hypotonia, dyspraxia, musculoskeletal anomalies, and feeding difficulties. Seizures occur in about half of reported cases. Dysmorphic features include a broad forehead with frontal bossing, high anterior hairline, prominent eyes with upward-slanting palpebral fissures, arched eyebrows, long eyelashes, midface hypoplasia, a wide nasal bridge, and anteverted nares. To date, approximately 15 cases have been documented. The clinical features of this patient overlap with those in the literature, except for severe gastrointestinal involvement, including intestinal failure, which has not been previously reported. The identified RAC3 missense variant (c.202C>G; p.Arg68Gly) is novel and absent from the medical literature. Final Comments: This study reports the first Brazilian patient described in the literature with NEDBAF. It expands the genotypic and phenotypic spectrum of the disease by identifying a novel missense variant and describing new and severe gastrointestinal clinical manifestations associated with this rare condition.

**Palavras-Chave do trabalho:** Gastroparesis; NEDBAF; Neuro-RACopathies; RAC3;

**ID do trabalho:** 67

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: AN UNUSUAL CASE OF AUTISM AND MICROCEPHALY RELATED TO A PATHOGENIC VARIANT OF THE TELO2 GENE.**

**Autores:** LEBRE GAULES, Clarissa<sup>1</sup>; CAMPISTA FERNANDES, Amanda<sup>1</sup>; CREPALDI SOUZA E SILVA, Maria Luiza<sup>1</sup>; COUTO DE CARVALHO, Paula<sup>1</sup>; TAVARES CUTRIM EVERTON, Thayná<sup>1</sup>; DELMIGLIO BENEDUZI, Victoria<sup>1</sup>; DE FREITAS LEITÃO, Mônica<sup>2</sup>; DA SILVA FRANCO, José Francisco<sup>2</sup>;

**Instituição dos Autores:** (1) Pontifícia Universidade Católica de Campinas - Campinas - SP - Brasil; (2) Hospital da Pontifícia Universidade Católica de Campinas - Campinas - SP - Brasil;

### **Resumo do trabalho:**

Case presentation: The patient is a 12-year-old female whose first appointment was due to a severe case of autism spectrum disorder (ASD) associated with dysmorphic features and a significant delay in developmental milestones. She is nonverbal and exhibits behavioral and attention issues, requiring substantial support for daily activities. The patient's family history showed no consanguinity between the parents and no noteworthy events during her perinatal or neonatal period. In her past medical history, she was diagnosed with ASD at the age of four and was undergoing treatment for asthma, atopic rhinitis, and dermatitis for several years. Physical examination revealed a cephalic perimeter at -2 Z-score, confirming microcephaly, along with an intermittent right eye misalignment (exotropia). Additionally, the patient showed a severe impairment in both gross and fine

motor coordination, as well as gait disturbances. A brain MRI, requested for further evaluation, found no abnormalities. Previous exams had revealed spondylolisthesis and scoliosis, and laboratory tests demonstrated a low white blood cells count, due to a reduced number of neutrophils. Follow-up testing, conducted over six weeks, suggests the occurrence of moderate cyclical neutropenia. An exome sequencing test identified two likely pathogenic variants in the *TELO2* gene, found in a compound heterozygous: c.1100G>T (p. Cys367Phe) and c.2296G>A (p. Val766Met). The patient is currently on use of paliperidone, clonidine and cannabidiol. Despite ongoing treatment, she remains nonverbal and unable to perform daily tasks independently. These findings are compatible with You-Hoover-Fong syndrome (OMIM #616954). Discussion: The You-Hoover-Fong syndrome (YHFS) is inherited in an autosomal recessive manner caused by a pathogenic variant of the *TELO2* gene which plays a key role in DNA repair and stability. To our knowledge only 31 cases of YHFS have been reported and the individuals affected usually present global developmental delay, intellectual disabilities, microcephaly, abnormal balance, and movement disorder. Our patient exhibits all the previous clinical features. Other manifestations of YHFS like ocular involvement, sleep disorders, hearing loss, congenital heart disease, seizures, and alterations in muscle tone have been reported. However, our patient's presentation is limited to strabismus, autistic features, and scoliosis, illustrating the syndrome's phenotype variability. While a wide range of neurological symptoms prevails in YHFS, its pathogenesis remains unclear. The immunological involvement of this case such as neutropenia, asthma and allergic rhinitis have been reported in patients with YHFS, these findings being associated with the role of the protein product of the *TELO2* gene and immune signaling. Final comments: This case report aims to shed light on this newly reported syndrome that should be considered a differential diagnosis for patients with autism and microcephaly.

**Palavras-Chave do trabalho:** Autism; Microcephaly; *TELO2* Gene; You-Hoover-Fong Syndrome;

**ID do trabalho:** 68

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: A CHALLENGING CASE OF NYSTAGMUS AND ATAXIA OUTBREAKS

**Autores:** PESSOA, ANDRÉ LUIZ SANTOS<sup>1</sup>; OLIVEIRA, KECIA TAVARES<sup>2</sup>; PESSOA, JOÃO GABRIEL FIGUEIREDO<sup>3</sup>; DE VASCONCELOS, VANESSA DANTAS RIBEIROS<sup>2</sup>; LEITE, PEDRO ARAÚJO<sup>4</sup>; CASTRO, MATHEUS<sup>5</sup>;

**Instituição dos Autores:** (1) UNIVERSIDADE FEDERAL DO CEARÁ-UFC E HOSPITAL INFANTIL ALBERT SABIN - FORTALEZA - CE - Brasil; (2) HOSPITAL INFANTIL ALBERT SABIN - FORTALEZA - CE - Brasil; (3) UTFPR - PONTA GROSSA - PR - Brasil; (4) UNIVERSIDADE FEDERAL DO CEARÁ-UFC - FORTALEZA - CE - Brasil; (5) HCFMUSP - SÃO PAULO - SP - Brasil;

### Resumo do trabalho:

**CASE PRESENTATION:** A 1-year-and-7-month-old male patient, born to a non-consanguineous couple, with delayed speech development and normal motor development. At 1 year and 3 months of age, he began to present episodes of multidirectional nystagmus without accentuation patterns associated with accentuated eyelid opening, irritability and ataxia. The episodes lasted between 10 minutes and 2 hours. The patient was taken to the emergency room and treated with midazolam with good response. He underwent a brain MRI, which was normal, and several video-electroencephalograms that showed adequate brain electrical activity with rare fronto-central epileptiform discharges. However, in the first exams, the patient did not present ictal alterations. Between the episodes, the patient did not present neurological alterations. The episodes were refractory to the use of antiepileptic drugs such as Oxcarbazepine and Levetiracetam, with a decrease in their frequency after the start of Clobazam. Whole exome sequencing showed the p.Gly379Ala variant in heterozygosity in *FRMD5*. Variants in this gene are associated with the phenotype OMIM #620094 NEURODEVELOPMENTAL DISORDER WITH EYE MOVEMENT ABNORMALITIES AND ATAXIA; NEDEMA. After the exam results, the patient underwent a new video-electroencephalogram exam, in which he had episodes of nystagmus and ataxia without epileptiform correlation in the tracing. **DISCUSSION:** Neurodevelopmental disorder with eye movement abnormalities and ataxia (NEDEMA) is characterized by global developmental delay apparent from infancy. Affected individuals show delayed walking with an unsteady gait, variably impaired intellectual development, learning disabilities, and speech difficulties. Abnormal eye movements, which are often noted in early childhood, include opsoclonus, nystagmus, and strabismus. Some patients have seizures, which may be refractory. **FINAL COMMENTS:** This is a very challenging diagnosis since it would be difficult to establish without the NGS exam and/or prior knowledge of the existence of this entity. (VIDEOS AVAILABLE)

**Palavras-Chave do trabalho:** epilepsy; EPISODIC ATAXIAS; *FRMD5*; NEDEMA; RECURRENT NYSTAGMUS;

**ID do trabalho:** 69

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: DELAY IN DEVELOPMENT, IMPAIRED GROWTH, DYSMORPHIC FACIES, AND AXONAL NEUROPATHY (DIGFAN) ASSOCIATED WITH A PATHOGENIC VARIANT IN MORC2: EVOLVING PHENOTYPE**

**Autores:** FREITAS, Monique Oliveira<sup>1</sup>; DIAS, Débora Nogueira Coelho<sup>1</sup>; ESTEVAM, Maria Paula Miscoli<sup>1</sup>; FERNANDES, Eduarda Silva Kingma<sup>1</sup>; LARANJA, Leonardo Hansen<sup>2</sup>; PRUDENTE, Milton Livia Maria Ferreira<sup>1</sup>; SOBRINHO, Livia Maria Ferreira<sup>3</sup>;

**Instituição dos Autores:** (1) Neoclínica Oncologia e Genética - Juiz de Fora - MG - Brasil; (2) Neoclínica Oncologia e genética - Juiz de Fora - MG - Brasil; (3) Universidade Federal de Minas Gerais - Belo Horizonte - MG - Brasil;

### **Resumo do trabalho:**

Case presentation: A six-year-old male patient, the only child of a young, non-consanguineous and healthy couple, was presented. Family history was unremarkable. There were no significant clinical complications during pregnancy. He was born via cesarean section at term (41 weeks) with a weight of 3460g, length of 47cm, head circumference of 36cm, and Apgar scores of 9 and 10. Both mother and child were discharged on the second day postpartum. The patient showed global neuropsychomotor developmental delay. At seven months, microcephaly was observed. Brain MRI was normal. At the evaluation at 1 year and 3 months, the following findings were noted: microcephaly, trigonocephaly, elongated and narrow face, deep-set eyes, high nasal bridge, pectus excavatum, generalized decreased muscle mass, muscle weakness in all four limbs, and reduced deep tendon reflexes. Suspecting a genetic alteration, exome sequencing via NGS was performed at age three, identifying a heterozygous de novo pathogenic variant in the MORC2 gene - c.79G>A; p.(Glu27Lys). The patient exhibited static, non-progressive developmental delay and muscular hypotrophy. He is enrolled in a regular school with support from a teaching assistant and has moderate intellectual disability. His gait is preserved, but he shows significant language delay. Discussion: : Heterozygous pathogenic variants in the MORC2 gene have been associated with global neuropsychomotor developmental delay, dysmorphisms, short stature, intellectual disability, hypotonia, hyporeflexia, and microcephaly since 2016, MORC2 encodes an ATPase involved in chromatin remodeling, DNA repair, and transcriptional regulation. Pathogenic variants in this gene have been associated with a typical phenotype of neurodevelopmental delay and craniofacial dysmorphisms. The clinical and evolutionary description of this case overlaps with the other 20 cases previously reported; Final Comments: Presenting and discussing rare cases among peers is crucial for disseminating knowledge, achieving better disease understanding, and expanding the evolving phenotypic spectrum. Special attention should be given to the developmental trajectory of the condition.

**Palavras-Chave do trabalho:** Developmental disabilities; MORC2 gene; Neomuscular dysplasia; Neuropathy;

**ID do trabalho:** 70

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: CYTOGENETIC AND MOLECULAR CHARACTERIZATION OF RING CHROMOSOME 14 IN THREE PATIENTS WITH EPILEPSY**

**Autores:** DE CARVALHO LEITÃO PIMENTEL, Érico<sup>1</sup>; CRESTI NAVARRO, Rafael<sup>1</sup>; ROLDÃO CORREIA-COSTA, Gabriela<sup>1</sup>; LÚCIA VIGUETTI CAMPOS, Nilma<sup>1</sup>; LONGO ANGELONI, Luise<sup>1</sup>; COAN, Ana Carolina<sup>2</sup>; LUSTOSA MENDES, Elaine<sup>3</sup>; MESCKA, Caroline Paula<sup>4</sup>; FÉLIX, Têmis Maria<sup>5</sup>; GIL-DA-SILVA-LOPES, Vera Lúcia<sup>1</sup>; PAIVA VIEIRA, Társis<sup>1</sup>;

**Instituição dos Autores:** (1) Department of Medical Genetics and Genomic Medicine, School of Medical Sciences, University of Campinas (UNICAMP) - Campinas - SP - Brasil; (2) Department of Neurology, School of Medical Sciences, University of Campinas (UNICAMP) - Campinas - SP - Brasil; (3) Serviço de Genética do Hospital de Clínicas da UFPR - Curitiba - PR - Brasil; (4) Medical Genetics Service, Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (5) Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Ring chromosome 14 - r(14) - is a rare cytogenetic disorder characterized mainly by pharmacoresistant epilepsy and retinal degeneration. Other common features are developmental delay, facial dysmorphisms, short stature, hypotonia, scoliosis and microcephaly. Epileptic seizures in r(14) patients are polymorphic at onset and mainly originate from the mid-temporal and frontal lobes, and are usually severe. It is unlikely to be attributable solely to 14q32 deletions and could also be due to the mitotic instability of the ring, which results in chromosomal mosaicism, mainly with chromosome 14 monosomy. Objective: To describe clinical and cytogenomic findings of three patients with ring chromosome 14 presenting with epilepsy. Methods: G-banded karyotyping was performed with a count of 200 metaphase cells, and chromosomal microarray analysis (CMA) was performed using the CytoScan™ HD array from Affymetrix®. Results: All patients presented with global developmental delay, dysmorphisms and severe epilepsy with early onset. Patient 1, a 6-year-old girl, had seizures characterized by blinking, upward eye deviation, and occasional repetitive hyperextension of the right upper limb, sometimes occurring in clusters with preserved awareness between episodes, followed by postictal drowsiness. Interictal

electroencephalogram (EEG) presented frequent intermittent focal slowing and epileptiform discharges in the temporal regions, with a right side predominance. She has already been treated with valproate, cannabidiol, nitrazepam and levetiracetam, which did not prevent recurrence of seizures. She also had scoliosis, hypotonia, a congenital cyst in the left medial temporal lobe, and atrial septal defect. Karyotype analysis showed a  $r(14) - 46,XX,r(14)(p11.2q32.2)$  - with secondary alterations in 9.5% of cells, mainly chromosome 14 monosomy (8.5%). CMA revealed a deletion of 6 Mb at 14q32. Patient 2, a 5-year-old boy, had seizures characterized by hypertonia and eye deviation. Interictal EEG presented multifocal epileptiform discharges predominantly in the left hemisphere and continuous polymorphic delta activity. He also had occasional aggressive behavior, hypotonia, hypospadias and Tetralogy of Fallot. Karyotype analysis showed chromosomal mosaicism with  $r(14)$  (74%) and isochromosome 14q (19.5%) -  $46,XY,r(14)(p11q32)[148]/46,XY,i(14)(q10)[39]$  - and monosomy 14 in 5.5% of cells. CMA revealed a mosaic trisomy of 14, without other genomic imbalances in chromosome 14. Patient 3, a 10-year-old boy, currently treated with carbamazepine, also had congenital heart disease. Karyotype analysis showed a  $r(14) - 46,XY,r(14)(p11q32)$  - with monosomy 14 in 14.5% of cells. CMA revealed a duplication of 15 Mb and a benign deletion of 320 kb at 14q32. Conclusion: These results support that mitotic instability of  $r(14)$ , with secondary aneuploid cells, can be associated with epileptogenesis. Financial support: FAPESP (#2024/02492-2; #2022/16766-1).

**Palavras-Chave do trabalho:** epilepsy; Mitotic Instability; Ring Chromosome 14;

**ID do trabalho:** 74

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: A RETROSPECTIVE ANALYSIS OF CYTOGENETIC AND CYTOGENOMIC TESTING IN NEURODEVELOPMENTAL DISORDERS: DATA FROM A TERTIARY HOSPITAL IN SOUTHERN BRAZIL

**Autores:** CAMPIOL, Juliana Vargas<sup>1</sup>; SILVA, Bruna Herrmann Janssen<sup>1</sup>; KELLER, Hellen Nicole<sup>1</sup>; PINHO, Maria Clara Freitas<sup>1</sup>; ARTIGALAS, Osvaldo<sup>1</sup>; FELIX, Temis Maria<sup>1</sup>; KOWALSKI, Thayne Woycinck<sup>1</sup>; MESCKA, Caroline Paula<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

Background: Neurodevelopmental disorders are characterized by deficits in the development of cognition, language, behavior, and/or motor skills, which impact personal, social, academic, and/or occupational development. Karyotyping and Chromosomal Microarray Analysis (CMA) stand out among the genetic tests used for diagnosing neurodevelopmental disorders. Objective: To conduct a retrospective analysis, comparing the result profiles obtained through karyotyping and CMA testing in patients with clinical markers suggestive of relevant neurodevelopmental disorders, treated at the Medical Genetics Service of Hospital de Clínicas de Porto Alegre (HCPA). Methods: A retrospective analysis of karyotyping and CMA data was conducted on patients with neurodevelopmental disorders, followed by a comparative analysis of the test results performed between 2018 and 2023 (CAAE n° 70803823.0.0000.5327). Results: During the analyzed period, 2,178 karyotypes were performed, of which 683 (31.36%) were associated with the studied neurodevelopmental disorders, and 1,495 (68.64%) with other clinical conditions. Regarding CMA, 638 tests were performed, 388 (60.81%) targeting neurodevelopmental disorders and 250 (39.18%) for different diseases or conditions. Among 98 patients with clinical markers suggestive of neurodevelopmental disorders who underwent both tests, karyotyping did not detect chromosomal abnormalities in 85 patients (86.7%), detected normal variants in 7 patients (7.1%), and identified cytogenetic alterations potentially linked to neurodevelopmental disorders in 6 patients (6.1%). In the CMA testing, 72 patients (73.5%) had normal results, 7 patients (7.1%) showed variants of uncertain significance (VUS), and 19 patients (19.4%) exhibited copy number variations (CNVs) classified as pathogenic or likely pathogenic. Conclusion: Although approximately one-third (31.36%) of karyotyping requests during the period were focused on neurodevelopmental disorders, only 6.1% of patients tested by both techniques showed abnormal karyotype results. In contrast, the CMA technique identified approximately three times more alterations related to neurodevelopmental disorders compared to karyotyping. Despite the cost and technological challenges of implementing CMA in Brazil, the significant increase in diagnoses provided by this test could substantially improve the prognosis and treatment of patients with neurodevelopmental disorders. Furthermore, an analysis of the clinical data of patients with neurodevelopmental disorders of interest will be conducted, aiming to identify the main pathogenic and probably pathogenic CNVs that may be associated with the individuals' clinical presentation.

**Palavras-Chave do trabalho:** Chromosomal Microarray Analysis; Cytogenetics; Cytogenomics; Karyotyping; Neurodevelopmental Disorders;

**ID do trabalho:** 75

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Casos Clínicos Desafiadores

Forma de apresentação: Pôster

## Título do Trabalho: **Metachromatic Leukodystrophy: A Key Differential in Neuropsychomotor Development Delay – Case Report**

**Autores:** DOS SANTOS, Vanessa Gil humberto<sup>1</sup>; LEÃO, Amanda Melo Leite<sup>2</sup>; SANTOS, William De souza<sup>3</sup>; SILVA, Caroline Grijó e<sup>4</sup>; SILVA, Caroline Grijó e<sup>4</sup>; FRAZÃO, frederico del luca<sup>5</sup>; BERNARDES, Filipe Luiz Oliveira<sup>4</sup>; BERNARDES, Filipe Luiz Oliveira<sup>4</sup>;

**Instituição dos Autores:** (1) inspiralli educação medica - Rio de janeiro - RJ - Brasil; (2) Unigranrio - Duque de caxias - RJ - Brasil; (3) fiocruz - Rio de Janeiro - RJ - Brasil; (4) unigranrio - Rio de Janeiro - RJ - Brasil; (5) PUC - Rio de Janeiro - RJ - Brasil;

### Resumo do trabalho:

**Introduction** Metachromatic leukodystrophy (MLD) is a rare autosomal recessive leukodystrophy caused by ARSA gene mutations, leading to arylsulfatase A deficiency and toxic accumulation of sulfatides. This results in progressive demyelination of the central (CNS) and peripheral nervous systems (PNS), causing motor and cognitive decline. The estimated prevalence ranges from 1:40,000 to 1:160,000 live births. **Objective** To describe the clinical, neuroimaging, and laboratory findings of a patient with MLD, emphasizing diagnostic challenges and the importance of early recognition. **Methods** A retrospective analysis of the patient's clinical and laboratory data was conducted, along with a literature review using PubMed and indexed sources. **Case Presentation** A 26-month-old male, previously healthy, was referred for neuropsychomotor development delay (DNPM). The mother reported axial hypertonia, absence of crawling or independent walking. Initially, language development was normal, with babbling at 6 months and functional speech at 12 months. However, at 18 months, regression with frequent falls, dysarthria, and aphasia was observed. At 14 months, an orthopedic evaluation ruled out musculoskeletal disorders. Neurological examination revealed truncal instability, lower limb spasticity, hyperreflexia, bilateral clonus, and ataxic gait with right-sided claudication. Brain MRI showed confluent white matter hyperintensities on T2/FLAIR, consistent with hypomyelination. The enzymatic panel revealed: Arylsulfatase A activity in leukocytes: 1st test = 11 nmol/h/mg; 2nd test = 2 nmol/h/mg (VR: 320–1200) → Confirmatory for MLD. Galactose 6-sulfatase and Beta-galactosidase → Normal levels. The patient was diagnosed with MLD and started on baclofen for spasticity, along with multidisciplinary rehabilitation (physiotherapy, speech therapy, occupational therapy). **Discussion** MLD should be considered a differential diagnosis for neuropsychomotor delay and regression, especially when common causes are excluded. MRI and enzymatic analysis are critical for diagnosis. Currently, no curative treatment exists. However, hematopoietic stem cell transplantation (HSCT) may delay progression in pre-symptomatic or mildly symptomatic patients. Recently, the FDA approved Lenmeldy, a gene therapy modifying hematopoietic stem cells, offering a new therapeutic approach for MLD. **Conclusion** MLD is a progressive neurodegenerative disorder, where early identification enables optimized management and genetic counseling. Neuropsychomotor regression and milestone loss are critical warning signs. With gene therapy and HSCT advancements, early diagnosis is crucial for potential disease-modifying interventions.

**Palavras-Chave do trabalho:** Metachromatic Leukodystrophy; neurogenetic disorders; Neuropsychomotor Delay;

ID do trabalho: 77

Área Técnica do trabalho: Outros

Tipo do trabalho: Trabalhos Originais

Forma de apresentação: Pôster

## Título do Trabalho: **CYTOSKELETON-RELATED DEFECTS IN INBORN ERRORS OF METABOLISM: INSIGHTS FROM A BRAZILIAN COHORT**

**Autores:** OLIVATI, CAROLINE<sup>1</sup>; SPOLADOR, Gustavo Marquezani<sup>2</sup>; BUENO, Clarissa<sup>3</sup>; PIAZZON, Flavia<sup>3</sup>; BARATELA, Wagner<sup>2</sup>;

**Instituição dos Autores:** (1) GENESIS GENOMICS - São Paulo - SP - Brasil; (2) Genesis Genomics - São Paulo - SP - Brasil; (3) Neurometabolic Unit, USP-SP - São Paulo - SP - Brasil;

### Resumo do trabalho:

**Background:** From a biochemistry point of view, any monogenic disease can be classified as an inborn error of metabolism. Recent studies on categorization of inborn errors of metabolism (IEM) aim to expand the scope of these conditions, incorporating those with no biochemical markers. Ferreira et al. (2018) and Saudubray et al. (2019) introduced the category of cellular trafficking defects in the new nosology of IEM. Cellular trafficking is a highly specialized machinery that facilitates the exchange of signals and metabolites between cellular compartments. It can be divided into subcategories, such as membrane trafficking, membrane contact sites, autophagy, and cytoskeleton-related processes. The cytoskeleton plays a crucial role in intracellular trafficking, organelle positioning, and shaping. **Objective:** This study aims to understand the epidemiology of diseases related to cytoskeletal defects at a single molecular laboratory in Brazil. **Methods:** We actively investigated 47 cytoskeleton-related genes in inborn errors of metabolism affecting the nervous system in 11,911 whole-exome sequencing (WES) samples analyzed in a private laboratory in Brazil from January 1, 2022, to December 31, 2024. **Results:** We identified 32 positive samples (0.27%) associated with 16 different genes, detailed as follows: ACTB (5), FLNA (5), ZFYVE26 (4), DYSF (3), TBCD (2), SPTBN2 (2), BICD2 (1), CDC42 (1), DNM2 (1), ALS2 (1), INPP5E (1), KIF11 (1), KIF5A (1), TUBA1A (2), TUBB2A

(1), and TUBB3 (1). Conclusion: In recent years, new categories of IEM have highlighted the need to integrate molecular biology with classical metabolism. Although they still represent a small percentage of molecular test results, the discovery of new genes associated with cellular trafficking is growing, enabling the inclusion of new subcategories—not limited to intracellular vesicular trafficking but also involving the cytoskeleton. Furthermore, this categorization will be valuable for developing new therapeutic strategies—a challenge that is just beginning.

**Palavras-Chave do trabalho:** Cellular trafficking; Cytoskeleton; Inborn Errors of Metabolism;

**ID do trabalho:** 82

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: LIMB-GIRDLE MUSCULAR DYSTROPHY: CLINICAL AND GENETIC FINDINGS FROM A SINGLE CENTRE**

**Autores:** OLIVEIRA, Louise Makarem<sup>1</sup>; TOMASELLI, Pedro Jose<sup>2</sup>; FREZATTI, Rodrigo Siqueira Soares<sup>2</sup>; PASTORIO, Indianara Keila<sup>2</sup>; WILSON, Lindsay<sup>3</sup>; VANDROVCOVA, Jana<sup>3</sup>; HOULDEN, Henry<sup>3</sup>; REILLY, Mary M<sup>3</sup>; HANNA, Michael G<sup>3</sup>; JUNIOR, Wilson Marques<sup>2</sup>; SOBREIRA, Claudia Ferreira da Rosa<sup>2</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo - Ribeirão Preto - SP - Brasil; (2) Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo - Ribeirão Preto - SP - Brasil; (3) UCL Queen Square Institute of Neurology - England;

### **Resumo do trabalho:**

Background: Limb-girdle muscular dystrophies (LGMD) comprise a vast group of genetically determined disorders presenting predominantly with proximal muscle weakness. Cardiac and respiratory impairment may also occur. The overall prevalence of LGMD ranges from 1 in 14,500 to 1 in 123,000 individuals, with subtypes having varying prevalence rates. In Brazil, calpainopathy and dysferlinopathy have been reported as the most common causes of LGMD in general, while sarcoglycanopathies are more frequently associated with childhood-onset cases. Objective: To describe the genetic profile of a Brazilian cohort of patients with LGMD followed in a single referral centre. Methods: Patients with LGMD were included. Thirty-one families were previously reported in a multicentric Brazilian study. Clinical, laboratory and genetic results were collected using a standardized proforma. Patients were tested using next-generation sequencing (NGS) technology, through targeted gene panels or whole exome (WES). Individuals at risk were tested using Sanger sequencing, and co-segregation analyses were also performed on relatives of patients carrying variants of uncertain significance. Variants were classified according to the American College of Medical Genetics and Genomics Guidelines. Results: A total of 107 patients from 87 families with LGMD were included. 58 were male (54.2%). Consanguinity was reported in 21 families (24%). Before genetic testing, the inheritance pattern was autosomal recessive in 33 families (37.9%), sporadic in 45 families (51.7%), inheritance was not defined in 5 families (5.7%), and autosomal dominant in 4 families (4.6%). Median age at onset was 18 years (range: 2-60) for recessive LGMD (LGMDR) and 22 years (range: 8-49) for dominant LGMD (LGMDD). The median creatine kinase (CK) level was higher in the LGMDR group (14x the upper limit of reference range) compared to the LGMDD group (6x the upper limit of reference range). Among the LGMDD families, only one had a definitive genetic diagnosis (LGMDD3 HNRNPDL-related). Among the LGMDR with a defined genetic diagnosis, the following genes were involved: DYSF in 20 families, CAPN3 in 16, SGCA in 8, ANO5 in 3, SGCB in 2, TCAP in 2, FKR in 2, FKT in 1, TTN in 1, and GMP in 1. A definitive diagnosis was accomplished in 57 families. In 15 additional families, there is a possible gene involved. Conclusion: LGMD is the fourth most common form of dystrophy globally, with potential cardiac and respiratory implications. Our study provides insights into the epidemiology of LGMD within a specialized referral centre. By utilizing NGS and target analysis, we identified genetic variants, further refining their classification. In addition to its prognostic significance, variant identification and classification are crucial for effective genetic counseling. Ultimately, these advances offer hope for the future, as gene therapy continues to rapidly evolve, underscoring the importance of an accurate diagnosis.

**Palavras-Chave do trabalho:** gene panel; genetic diagnosis; Limb-girdle muscular dystrophy; muscular dystrophy; whole exome sequencing;

**ID do trabalho:** 83

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: HEALTH EDUCATION ON ATAXIAS AND MUSCULAR DYSTROPHIES: AN EXPERIENCE REPORT USING EDUCATIONAL AND INFORMATIVE MATERIALS**

**Autores:** VIEIRA, Luan Coelho<sup>1</sup>; LIRA, José Sávio Soares de<sup>1</sup>; GUEDES, Yolanda Rios da Costa<sup>1</sup>; PIMENTEL, Anna Luisa de Melo Lula Lins e<sup>1</sup>; GUEDES, Gabrielly Fernandes de Araújo<sup>1</sup>; MAGALHÃES, Maria Clara Gomes Lacerda Quintans e<sup>1</sup>; PEGORARI, Vinícius Perez<sup>1</sup>; RODRIGUES, Rodrigo Ramalho<sup>1</sup>; MENEZES, Julia Rackel Ferreira de<sup>1</sup>; MAIA, Rayana Elias<sup>1</sup>; DONIS, Karina Carvalho<sup>1</sup>;

**Instituição dos Autores:** (1) UFPB - João Pessoa - PB - Brasil;

#### Resumo do trabalho:

**Background:** When discussing neurogenetic diseases, it is important to remember that their impact affects not only the patient's life but also their entire family and social environment, as the progression of these diseases often necessitates specific care and can lead to increasing dependence. Therefore, early diagnosis of these conditions is essential, both to initiate treatment that may slow down or halt disease progression and to prepare family members to cope with potential challenges. For this, it is crucial for the population to recognize when to investigate and how to act when faced with them. In this context, an educational and engaging initiative was proposed to raise awareness about what genetic ataxias and muscular dystrophies are and how to address them. **Objective:** to report on the educational initiative developed by students, highlighting the impact of the information about these diseases. **Methods:** This is an experience report based on a health education action carried out by medical students (Sep, 2024), in commemoration of the Muscular Dystrophy Awareness Day (09/17) and the International Ataxia Day (09/25), at the Federal University of Paraíba (UFPB) and at the Lauro Wanderley University Hospital (HULW), under the guidance of the League and Extension of Medical Genetics at UFPB. **Results:** The educational activity was carried out over two days and reached around 300 people, including patients, caregivers, and healthcare professionals. On the first day, which took place at HULW, there was a constant flow of patients, enabling productive conversations, with an emphasis on the participation of family members who accompanied the patients to consultations in various outpatient clinics. On the second day, at the UFPB campus, the initiative expanded its reach to students and staff, raising awareness among a broad spectrum of the population. In total, approximately 200 comic books were distributed, capturing the interest of children and their guardians, who praised the playful and accessible approach to complex medical concepts. Around 300 informational leaflets were also distributed, detailing symptoms, warning signs, and the importance of early diagnosis of genetic ataxias and muscular dystrophies. During interactions, it became clear that over 90% of participants were unaware of these conditions. The most common questions were about the early signs of the diseases, which medical specialty to seek, and the availability of treatments within the Unified Health System (SUS). In this context, the initiative generated a positive impact, with participants reporting a sense of confidence in seeking medical help if they or their family members experienced suspicious symptoms. **Conclusion:** The results obtained show that the initiative was successful in raising awareness about genetic ataxias and muscular dystrophies. It was able to fill gaps in knowledge, encourage early diagnoses, and empower the target audience to identify warning signs.

**Palavras-Chave do trabalho:** Hereditary ataxia; muscular dystrophy; neurogenetic disorders; Neuromuscular Disease;

**ID do trabalho:** 84

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **FIRST FAMILY WITH TUBULAR AGGREGATE MYOPATHY ASSOCIATED WITH MUTATION IN THE STIM1 GENE IN THE STATE OF RIO GRANDE DO NORTE**

**Autores:** PEIXOTO, Kaliny Oliveira<sup>1</sup>; YANAGIURA, Mario Teruo<sup>1</sup>; JUNIOR, Mario Emilio Teixeira Dourado<sup>1</sup>; CORREIA, Carolina da Cunha<sup>2</sup>; FONTANA, Pedro Nogueira<sup>2</sup>; SILVA, Lígia Rufino da<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Norte - Natal - RN - Brasil; (2) Hospital Universitário Oswaldo Cruz - Recife - PE - Brasil;

#### Resumo do trabalho:

**BACKGROUND:** Tubular aggregate myopathy is a rare hereditary muscle disease with a phenotypic spectrum, ranging from progressive muscle weakness of childhood onset and elevated creatine phosphokinase levels to adult-onset myalgia without muscle weakness and normal CK levels. The muscle biopsies show the presence of tubular aggregates originating from the sarcoplasmic reticulum due to altered calcium homeostasis. **OBJECTIVE:** to highlight the importance of genetic analysis related to tubular aggregate myopathy. **METHODS:** We describe a family affected by tubular aggregate myopathy associated with mutation in the STIM1 (Stromal Interaction Molecule 1) gene, which encodes an important calcium sensor of the sarcoplasmic reticulum. **RESULTS:** A 33-year-old woman with a history of falls since 10 years old and exercise intolerance, associated with muscle weakness, predominantly proximal in the upper and lower limbs, with slowly progressive worsening. She also presents with myalgia, dyspnea on exertion and hearing loss. Her parents were not consanguineous. On examination, she presents with myopathic gait, tetraparesis, predominantly proximal and in the lower limbs, asymmetric atrophy of the calves, worse on the right, and mild contracture in the ankles and knees. The creatine phosphokinase was elevated (2073 IU/L). Electroneuromyography showed a myopathic pattern. Resonance magnetic of the legs demonstrated symmetric atrophy of the bellies of the soleus and lateral gastrocnemius. Muscle biopsy of the left biceps revealed myopathy with tubular aggregates. Her mother began to present with muscle weakness at 40 years old, with slowly progressive course, myalgia, dyspnea on exertion and hearing loss. On examination, the patient presented with lordotic gait, axial and appendicular weakness, predominantly proximal and in the lower limbs, worse on the right, atrophy of the calves and contractures in the elbows and ankles. Creatine

phosphokinase was 1251 IU/L and electroneuromyography showed a myopathic pattern. Both were diagnosed with myopathy due to tubular aggregates. The genetic study of them revealed a pathogenic variant, in heterozygosity, in the STIM1 gene. The variant chr11:4,023,928 A>C promotes the substitution of the amino acid histidine in codon 109 by proline (p.His109Pro). CONCLUSION: The present series corresponds to the first cases described in Rio Grande do Norte, emphasizing the importance of detecting the gene at an early stage, among the differential diagnoses of rare myopathies. Therefore, the STIM1 gene should be considered for patients with tubular aggregates myopathies involving muscle weakness and/or myalgia in varying degrees.

**Palavras-Chave do trabalho:** Myopathy; STIM1 gene; Tubular Aggregates;

**ID do trabalho:** 86

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: CASE REPORT OF A PATIENT WITH SEVERE METHYLMALONIC ORGANIC ACIDEMIA : A TREATMENT WITH IMPROVEMENT NEUROLOGIC SYMPTOMS**

**Autores:** DOS ANJOS REGADAS, Maria Clara<sup>1</sup>; VIANA, Mariana Landim<sup>1</sup>; DE SOUZA MARTINS , Fernanda Pereira<sup>2</sup>; FERNANDES CARVALHO, Ellaine Dóris<sup>3</sup>; FERNANDES CARVALHO DE ANDRADE , Maria Denise<sup>4</sup>;

**Instituição dos Autores:** (1) Centro Universitário Christus - Unichristus - Fortaleza - CE - Brasil; (2) Universidade Estadual do Ceará, Hospital Geral Dr Cesar Cals - Fortaleza - CE - Brasil; (3) Centro Universitário Christus - Unichristus , Hospital Geral Dr Cesar Cals - Fortaleza - CE - Brasil; (4) Centro Universitário Christus - Unichristus, Universidade Estadual do Ceará, Hospital Geral Dr Cesar Cals E Comissão Técnica de Anomalias Congênitas - Ministério da Saúde - Fortaleza - CE - Brasil;

### **Resumo do trabalho:**

Background: Methylmalonic acidemia (MA) is an inherited disease from the urea cycle characterized by neurometabolic and gastrointestinal manifestations resulting in a decreased function of the mitochondrial enzyme methylmalonyl-CoA mutase and the accumulation of methylmalonic acid. Through a biochemical defect related to propionate metabolism, in the stage of conversion of methylmalonic acid to succinic acid, the disease manifests itself through autosomal recessive heredity originating from an inborn error of metabolism from the group of acute intoxications. Patients with this etiology may exhibit lethargy, coma, intellectual developmental delay, recurrent vomiting, hepatomegaly, respiratory failure and muscular hypotonia. Objective: The purpose of this paper is to report a severe case of a patient with MA taking carnitine. Methods: This study is focused on the detailed description of neurological, laboratory and therapeutic aspects. Results: The drug along with diet therapy maintains the patient's non-toxic biochemical profile, since an increase in persistent ammonia can lead to permanent neurological sequelae. Conclusion: Therefore, MA requires special attention from a multidisciplinary team and a dietary approach of permanent and continuous maintenance to avoid sequelae and even irreversible damage to the patient's health. Case presentation: Female patient, 1 year old, was referred to a neuropediatrician due to delayed psychomotor development, nonspecific cortical atrophy, a history of seizures and admission to the neonatal ICU with a serious condition. Initially, the medical team requested a biochemical profile and found changes in the levels of ammonia (80 micromol/l), acylcarnitine (C3= 5,58micromol/l and C3/C2= 0,38) and methylmalonic acid (3.821,0 mmol/l) and 2-methylcitric acid (not quantified) in the urine, which with clinical findings and complementary tests was compatible with the diagnosis. The gold standard treatment consists of the use of carnitine orally, which works by synthesizing NAG to activate carbamoyl phosphate synthetase I, in addition to diet therapy with balanced formulas with restrictions on the amino acid Isoleucine, Valine, Methionine and Threonine has been shown to be an effective therapy for this condition and are essential to guarantee the necessary supply protein for the patient's physiological demands. Discussion: MA is a challenging disease since it doesn't depend only on medication but also on the active participation of the patient and family in following the diets properly. The cases in the literature shows that progress improves when there is a multidisciplinary combination of patient follow-up. Final comments: The patient exhibits an important evolution of the neurological symptoms by the use of the drug associated with diet. For that reason, it is necessary to train health professionals in the proper screening, diagnosis and management of rare conditions in order to improve patient prognosis.

**Palavras-Chave do trabalho:** carnitine; Inborn Errors of Metabolism; methylmalonic organic acidemia; neurodevelopment; neurogenetic disorders;

**ID do trabalho:** 90

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **VERY-LONG-CHAIN ACYL-CoA DEHYDROGENASE DEFICIENCY (VLCAD) IN A PEDIATRIC PATIENT: CASE REPORT**

**Autores:** RIGOLDI, Lisandra Coneglian de Farias<sup>1</sup>; SANTOS, Mara Lucia Schmidt Ferreira<sup>1</sup>; ZENY, Michelle<sup>1</sup>; SAIKI, Bruno Hideo<sup>1</sup>; DO VALLE, Daniel Almeida<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Pequeno Príncipe - Curitiba - PR - Brasil;

### Resumo do trabalho:

Case presentation: The patient, the first child of a non-consanguineous couple, presented at 2 years and 6 months of age to the hospital with signs and symptoms of heart failure, significant neuropsychomotor developmental delay, a history of hypotonia since the first week of life, feeding difficulties, and irritability. An echocardiogram revealed a left ventricular ejection fraction of 13%. Genetic evaluation via whole-exome sequencing identified a pathogenic variant in the ACADVL gene (c.1102\_1103del, p.Gln368Valfs\*26) and a variant of uncertain significance (c.276C>T). Subsequent acylcarnitine analysis showed elevated medium- and long-chain acylcarnitines (C10, C12, C14, C14:1, C14:2). Dietary and pharmacological treatment with triheptanoin (Dojolvi) at a dose of 0.3 g/kg was initiated. After the first week of treatment, the patient became more active. She continues monthly follow-ups at our outpatient clinic, showing recovery of neurodevelopmental milestones and significant improvement in cardiac function, with the ejection fraction currently at 22%. Discussion: Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD) is a rare autosomal recessive metabolic disorder caused by pathogenic variants in the ACADVL gene, which is essential for mitochondrial  $\beta$ -oxidation of long-chain fatty acids. It presents in three main phenotypes: severe early-onset form, hepatic or hypoketotic hypoglycemic form, and episodic late-onset myopathic form. Symptoms include cardiomyopathy, hypoketotic hypoglycemia, hepatomegaly, rhabdomyolysis, and exercise intolerance. This report describes a severe case of a pediatric patient with VLCAD deficiency treated with triheptanoin, a unique and unprecedented case in Brazil, highlighting clinical evolution and positive outcomes. The patient presented with clinical features consistent with the severe early-onset form of VLCAD deficiency, characterized by cardiomyopathy and developmental delay. Treatment involves dietary modifications and supplementation with medium-chain triglycerides or triheptanoin. One month after initiating triheptanoin, clinical evolution and ejection fraction showed significant improvement. Final comment: VLCAD is a rare genetic disorder that impairs the body's ability to properly metabolize fats. This case highlights the importance of early and accurate diagnosis in cases of cardiomyopathy with symptoms beginning in the neonatal period, along with appropriate therapeutic management. Triheptanoin proved effective in improving the clinical status of a patient with the severe early-onset form, contributing to the reversal of heart failure, improved muscle tone, and recovery of cognitive and motor milestones. No adverse effects were observed with the medication. This report underscores the need for multidisciplinary care and further investigation into targeted therapies.

**Palavras-Chave do trabalho:** ACADVL gene; VLCAD;  $\beta$ -oxidation of fatty acids;

**ID do trabalho:** 91

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **LATE-ONSET LAMA2-RELATED MUSCULAR DYSTROPHY IN NORTHEASTERN BRAZIL: A CASE SERIES**

**Autores:** DANTAS, Fátima de Menezes<sup>1</sup>; GRANGEIRO Sá BARRETO LIMA, Pedro Lucas<sup>2</sup>; GODEIRO JÚNIOR, Clécio de Oliveira<sup>3</sup>; YANAGIURA, Mário Teruo<sup>3</sup>; FIDELIX, Emanuela Coriolano<sup>3</sup>; CAMELO, Clara Gontijo<sup>4</sup>; PESSOA, André Luiz Santos<sup>5</sup>; RANGEL, Deborah Moreira<sup>6</sup>; GOMES, Miguel Inácio Silva<sup>1</sup>; SILVA, Rodrigo Alencar e<sup>3</sup>; AQUINO, Bárbara Cristina Vieira de<sup>3</sup>; CAMELO-FILHO, Antônio Edvan<sup>2</sup>; Nóbrega, Paulo Ribeiro<sup>2</sup>; DOURADO JÚNIOR, Mário Emílio Teixeira<sup>3</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Norte - Natal - RN - Brasil; (2) Hospital Universitário Walter Cantídio, Universidade Federal do Ceará - Fortaleza - CE - Brasil; (3) Hospital Universitário Onofre Lopes, Universidade Federal do Rio Grande do Norte - Natal - RN - Brasil; (4) Departamento de Neurologia, Faculdade de Medicina da Universidade de São Paulo - São Paulo - SP - Brasil; (5) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil; (6) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil;

### Resumo do trabalho:

Background: LAMA2-related muscular dystrophy (LAMA2-MD) is caused by the presence of two pathogenic alleles, either in homozygosity or compound heterozygosity, in the LAMA2 gene. This condition ranges from severe phenotypes with congenital onset to milder manifestations with late onset. Previous studies have associated late-onset LAMA2-MD phenotype with the presence of at least one allele carrying a missense variant. Objective: To describe a series of cases of patients with late-onset LAMA2-MD and to analyze genotype-phenotype correlations. Methods: This is a retrospective study based on medical records of patients followed at neurology services in two states in the Brazilian Northeast (Ceará and Rio Grande do Norte). Results: 12 patients participated in the study, 5 men (41.7%) and 7 women (58.3%), with a mean age of 41.8 years (SD±10.5). The majority of participants (11/12) presented clinical manifestations, with a mean age at symptom onset of 22.5 years (SD±11.6). The most common initial symptoms were muscle weakness (6/11) and epilepsy (2/11). One patient did not present muscle weakness, epilepsy or other symptoms, although his exam results revealed alterations (leukodystrophy and elevated CK). All patients retained the ability to walk until the last date they were evaluated. 9 patients (75%) underwent brain magnetic resonance

imaging, which demonstrated a leukodystrophy pattern, without cortical malformations, in all cases. All participants had elevated CK levels and carried at least one c.2461A>C variant, of which 7 cases were homozygous and 5 were heterozygous. Out of the 5 heterozygous cases, each presented one of the following variants: c.2049\_2050del, c.8556\_8558delAAT, c.7490\_7493dup, c.3976C>T, and deletion of exons 5 to 12. 4 out of the 12 patients (33.3%) were from cities close to the CE-RN border. Conclusion: The analysis corroborated findings from other studies, which associated the presence of missense variants with milder phenotypes of LAMA2-MD, such as late onset of symptoms and preserved ambulation. Interestingly, the presence of at least one c.2461A>C variant in 100% of our patients was higher than the 63% reported in a recent multicenter study that included 27 late-onset LAMA2-MD cases. Based on this finding, we wonder whether the c.2461A>C variant might be more prevalent in the Brazilian Northeast compared to other regions. Furthermore, we believe that the geographic proximity between some municipalities where the same variant associated with late-onset LAMA2-MD cases was identified may suggest the existence of a cluster between the states of CE and RN. Additional studies with a larger number of participants are needed to verify these hypotheses.

**Palavras-Chave do trabalho:** Genetics; Genotype-Phenotype Association; Merosin; muscular dystrophy; Neuromuscular Disease;

**ID do trabalho:** 93

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: IMPACT OF NUSINERSEN INCORPORATION INTO THE PUBLIC HEALTH SYSTEM ON MORTALITY RATES IN BRAZIL.**

**Autores:** FINK, Isabela Alicia<sup>1</sup>; KRUG, Barbara Correa<sup>2</sup>; SCHULER-FACCINI, Lavinia<sup>3</sup>; SCHWARTZ, Ida Vanessa Doederlein<sup>3</sup>;

**Instituição dos Autores:** (1) Universidade Federal de Ciências da Saúde de Porto Alegre - Porto Alegre - RS - Brasil; (2) Secretaria Estadual da Saúde - Porto Alegre - RS - Brasil; (3) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Spinal Muscular Atrophy linked to chromosome 5q (SMA5q) is one of the most frequent genetic neuromuscular diseases. It is caused by variations in the SMN1 gene, leading to motor neuron degeneration and muscle weakness. Nusinersen was the first disease-modifying therapy approved for SMA5q, being approved by ANVISA in 2017, and incorporated into the Brazilian public health system (SUS) in 2019 for SMA types I and II patients. These types are the most severe and have the earliest onset, significantly impacting infant and early childhood mortality. Objective: To analyze the impact of Nusinersen incorporation into the SUS on mortality rates in Brazil. Methods: SMA5q mortality data obtained from the Brazilian Mortality Information System (SIM) and live birth data from the Live Birth Information System (SINASC), between 2015 and 2023, were analysed. Overall mortality rates were calculated per 100,000 population for the 0-4 age group, and infant mortality rates per 1,000 live births. We compared three distinct periods: 2015-2016 (pre-approval, reflecting baseline mortality), 2017-2019 (post-approval, reflecting the period of limited access primarily through judicial means), and 2020-2023 (post-SUS incorporation, reflecting broader access). Results: The mean number of SMA5q individuals in the 0-4 age group who passed away from 2015-2016, 2017-2019, and 2020-2023 were, respectively, 28.5, 32.3 and 29. In the 0-4 age group, the average SMA5q mortality rate was 0.19 per 100,000 population during the pre-approval period (2015-2016), rising to 0.22 during 2017-2019, and decreasing again to 0.20 from 2020 to 2023. The average SMA5q infant mortality rate was 0.0041/1,000 live births (2015-2016), rising marginally to 0.0043 (2017-2019), and decreasing to 0.0036 in the Post-SUS incorporation period. Discussion/Conclusions: Our data suggest that the incorporation of Nusinersen in the SUS is associated with a decrease in the SMA5q Infant mortality (0-1 year), a key indicator for SMA5q type I, the most severe form. Continued monitoring and further analyses, including data stratified by SMA type and investigation of potential contributing factors, are essential to fully evaluate the long-term impact of Nusinersen on SMA5q mortality in Brazil.

**Palavras-Chave do trabalho:** Brazil; Mortality; Nusinersen; Spinal Muscular Atrophy;

**ID do trabalho:** 94

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: MCM3AP VARIANT: LOWER MOTOR NEURON DISEASE WITH DISTINCT PHENOTYPE AND UNIQUE MRI AND ELECTROMYOGRAPHY FINDINGS**

**Autores:** LEMOS, Ana Flávia Andrade<sup>1</sup>; FREZATTI, Rodrigo Rodrigo Siqueira Soares<sup>1</sup>; DE OLIVEIRA, Amanda Vitória Freire<sup>1</sup>; PEREIRA, Mariana Ribeiro<sup>1</sup>; HEMERLY, Matheus Compart<sup>1</sup>; FAVARO, Mateus Gustavo<sup>1</sup>; VIEIRA, Lucas Gondim Briand<sup>1</sup>; TOMASELLI, Pedro José<sup>1</sup>; JUNIOR, Wilson Marques<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo, Ribeirão Preto - Ribeirão Preto - SP - Brasil;

#### Resumo do trabalho:

**Abstract** The MCM3AP gene encodes the germinal center-associated nuclear protein (GANP), a critical mediator in mRNA nuclear export. Mutations in MCM3AP are associated with a spectrum of clinical phenotypes, primarily peripheral neuropathy and intellectual disability of varying severity. Phenotypic variability is influenced by the mutation's location within the gene, emphasizing the importance of genotype-phenotype correlations. These insights are vital for improving diagnostic precision and identifying potential therapeutic targets in MCM3AP-related disorders. **Case Presentation** We describe a 53-year-old female, daughter of non-consanguineous parents, with falls and learning difficulties since infancy. Weakness progressed throughout the years and at first assessment, at 53 yo, she presented with distal-predominant muscle weakness, and globally absent reflexes. Remarkably, she presented with diffuse fasciculations across multiple body regions. No significant sensory deficits were noted. Her father, already deceased, exhibited right upper limb atrophy, while her mother was asymptomatic. Laboratory findings revealed elevated creatine phosphokinase levels of 1000 U/L. Nerve conduction studies revealed low CMAP amplitudes with normal conduction velocities and normal SNAPS. Needle examination revealed motor neuron involvement across cranial, cervical, thoracic and lumbosacral myotomes with acute and chronic denervation features. Whole body muscle MRI (wbMRI) revealed a symmetric selective fatty infiltration predominantly involving anterior and posterior compartments of the leg and short head of the biceps femoris. A genetic panel identified a heterozygous pathogenic variant in the MCM3AP gene. WES revealed two ACMG class 4 variants: c.2790-2A>G (p.Glu1962Lysfs \*14). **Discussion** Pathogenic variants in MCM3AP are typically associated with CMT2 and rarely with dHMN. This case expands phenotypic presentation including a motor neuronopathy with acute and chronic denervation. Additionally, to the best of our knowledge, wbMRI hasn't been described yet and reveals a selective fatty infiltration pattern which may aid in diagnostic approach. **Conclusions** This case illustrates a novel phenotype linked to MCM3AP gene and a distinctive muscle MRI fatty infiltration pattern.

**Palavras-Chave do trabalho:** Fasciculations; Motor neuron dysfunction; MRI fatty infiltration; neurogenetic disorders;

**ID do trabalho:** 95

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: DIAGNOSTIC HYPOTHESES OF AARSKOG SYNDROME OR DUBOWITZ SYNDROME: ATYPICAL CASE OF CORPUS CALLOSUM AGENESIS WITH SEVERE INTELLECTUAL DISABILITY AND MOTOR DEFICIT

**Autores:** DOS SANTOS, Laura Reche<sup>1</sup>;

**Instituição dos Autores:** (1) Faculdade de Medicina de Jundiaí - São Paulo - SP - Brasil;

#### Resumo do trabalho:

Aarskog syndrome is a rare genetic disease, recessive and linked to the X sex chromosome, therefore it predominantly affects males. It is related to the FGD1 gene and mainly causes malformations of the musculoskeletal system. Dubowitz syndrome is also a rare, autosomal recessive and poorly understood genetic disease. It involves numerous anomalies in different body systems. There is no laboratory test for Dubowitz Syndrome, however it is possible to confirm the Aarskog diagnosis with genetic testing. Both can cause neurodevelopmental problems. These two diseases are poorly documented in the medical literature and the reported cases contain a vast heterogeneity of clinical findings and varying symptom intensities. The purpose of this work is to describe the atypical and severe case of this patient with severe intellectual disability, add material for the study of these diseases, compare the expected clinical findings and those that the patient presents. Furthermore, the author did not find another reported case of agenesis of the corpus callosum in other patients with any of these two syndromes, which makes the dissemination of the case described in this work relevant. The patient, from São Paulo, Brazil, was born in 1986 and died in 2024 at the age of 38. He needed mutual assistance throughout his life. There was no diagnostic confirmation of the reported hypotheses, also considering their socioeconomic condition.

**Palavras-Chave do trabalho:** Aarskog Syndrome; Corpus Callosum Agenesis; Dubowitz Syndrome;

**ID do trabalho:** 96

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Pôster

## Título do Trabalho: **OPHTHALMOPARESIS IN MYOTONIC DYSTROPHY TYPE 1**

**Autores:** LIMA, Pedro Lucas Granjeiro Sá Barreto<sup>1</sup>; CAMELO-FILHO, Antônio Edvan<sup>1</sup>; DE OLIVEIRA-JÚNIOR, Pedro Helder<sup>1</sup>; MAURICIO, Rebeca Bessa<sup>2</sup>; RAMOS, Mariana Michiles Santos<sup>1</sup>; DE SOUZA, Jorge Luiz De Brito<sup>2</sup>; DE CASTRO, Julia Viana<sup>1</sup>; DUTRA-JUNIOR, Avelino Missialdes<sup>1</sup>; BRAGA-NETO, Pedro Pedro<sup>1</sup>; NóbREGA, Paulo Ribeiro<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Universidade Estadual do Ceará - Fortaleza - CE - Brasil;

### Resumo do trabalho:

**Introduction:** Myotonic Dystrophy Type 1 (Steinert Myotonic Dystrophy or DM1) is the most frequent muscular dystrophy in adults. This disorder is a monoallelic autosomal disorder caused by pathogenic expansion of CTG trinucleotides in DMPK. DM1 is associated with weakness, muscular atrophy and myotonia. These clinical manifestations may vary from mild to severe. The disease often causes ocular impairment, mostly in the form of posterior subcapsular cataracts, ptosis and slow saccades. The current literature supports the hypothesis of relative sparing of the extrinsic ocular musculature in DM1. However, most recently ophthalmoparesis in DM1 has been increasingly reported in the literature. **Objective:** This study aims to report a series of patients with DM1 presenting with ocular mobility impairment. **Methods:** This was a retrospective observational study including patients with DM1. Patients were identified through an active search in the medical records of the neurology department of our service. **Results:** Three unrelated patients with previous diagnosis of Myotonic Dystrophy Type 1 (Steinert's Disease or DM1) presented with progressive impairment of ocular mobility associated with ptosis. All patients had medical history marked by progressive muscular weakness, diffuse myalgia, frequent falls, postural instability and posterior cataracts compatible with the diagnosis of DM1. They had the genetic confirmation of the diagnosis by the study of were tested for CTG expansion in DMPK Southern Blot analysis. Upon general inspection, the patients had frontal alopecia, "hatchet" facies and bilateral ptosis. Neurological examination revealed diffuse muscular hypotrophy, diffuse muscular weakness, global hyporeflexia and myotonic phenomenon in both hands. No fasciculations or tremors were noticed in these patients. The three patients presented exotropia and bilateral ophthalmoparesis for the 9 cardinal positions of gaze. The ophthalmoparesis was more markedly observed during ocular abduction, impairing the gaze convergence. This specific pattern of ocular paresis resembled an internuclear ophthalmoplegia (INO), with the absence of nystagmus in the abducted eye during the pursuit test. Interestingly, this pattern of impairment suggests a peripheral-muscular cause. We defined this combination of findings as pseudo-INO, as it is similar to an "incomplete" internuclear ophthalmoplegia. This pattern of ophthalmoparesis is a rare manifestation of DM1 and is reported consistently in 3 patients in literature to the best of our knowledge. Those 3 patients in the literature all had very similar presentations compared to ours. **Conclusion:** We presented a series of three patients with Steinert's Disease presenting with an uncommon pattern of ocular impairment. This series provides insights in disease manifestations and may help to identify future DM1 cases. Further studies are necessary to better comprehend the observed phenomenon and to characterize the ocular findings in DM1.

**Palavras-Chave do trabalho:** Myotonic Dystrophy Type 1; Ophthalmoparesis; Steinert's disease;

**ID do trabalho:** 99

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **CLINICAL AND LABORATORY EVALUATION OF A COHORT OF BRAZILIAN PATIENTS WITH CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLÉGIA AND MULTIPLE MTDNA DELETIONS**

**Autores:** SCARPELLINI, Giuliano Roberto<sup>1</sup>; TOMASELLI, Pedro Jose<sup>1</sup>; ESCARSO, Silvia Helena Andriao<sup>1</sup>; SANTORELLI, Filippo M<sup>2</sup>; SOBREIRA, Claudia Ferreira Rosa<sup>1</sup>;

**Instituição dos Autores:** (1) Ribeirão Preto Medical School, University of São Paulo - Ribeirão Preto - SP - Brasil; (2) Fondazione Stella Maris, Pisa - Italy;

### Resumo do trabalho:

**INTRODUCTION:** Chronic progressive external ophthalmoplegia (CPEO) is one of the most common manifestations of mitochondrial myopathies. CPEO is characterized by extraocular muscle weakness and ptosis, with a broad phenotypic spectrum among affected individuals. Mitochondrial defects in CPEO are typically due to primary mtDNA mutations (single large deletions or point mutations) or mutation in nuclear genes responsible for maintaining the integrity and stability of mtDNA, resulting in multiple mtDNA deletions or mtDNA depletion. **OBJECTIVE:** To describe the clinical presentation, progression, and laboratory findings of a cohort of CPEO patients with multiple mtDNA deletions from a single center. **METHOD:** A retrospective review of the medical records of patients diagnosed with CPEO and multiple mtDNA deletions, followed at the Ribeirão Preto Medical School, University of São Paulo, was performed. **RESULTS:** Eighteen patients from 15 families were included. The cohort consisted of 13 women and 5 men, with a mean age of onset of 34.3 years. Ptosis was the most common initial symptom (12 patients), followed by limb weakness (5) and diplopia (1). A high prevalence of muscular symptoms was observed, including

weakness (16 patients) and fatigue (5). On physical examination, 11 patients exhibited lower limb weakness, of whom 7 additionally had proximal upper limb weakness and 4 had cervical weakness. Dysphagia was present in 7 patients and dyspnea with restrictive respiratory dysfunction in 3. Systemic symptoms were also prevalent, including sensory ataxia (6), hypoacusis (2), and gastrointestinal symptoms (2). The most common comorbidities were systemic arterial hypertension (7), diabetes (5), dyslipidemia (2), migraine (2), epilepsy (2) and hypothyroidism (1). During the follow-up period, 9 patients died, with a mean age at death of 62.3 years. Laboratory findings revealed normal creatine kinase (CK) levels in 10 patients, elevated CK levels less than twice the normal limit in 2 patients, and more than three times the normal limit in 2 patients. Five patients exhibited significant elevation of resting blood lactate, and 2 had considerable increases in post-exercise blood lactate. Molecular analysis revealed multiple mtDNA deletions in all patients through polymerase chain reaction and agarose gel electrophoresis. Next-generation sequencing of nuclear genes disclosed variants in POLG, TWNK, RRM2B and TK2. There was an early age of death, but no specific clinical or laboratory characteristics were distinctly linked to an elevated risk of mortality. **CONCLUSION:** This cohort underscores the multisystem involvement in CPEO and highlights the importance of comprehensive clinical evaluation and establishing objective parameters for patient monitoring and follow-up.

**Palavras-Chave do trabalho:** CPEO; follow-up; mitochondrial; multiple mtDNA deletions; ophthalmoplegia;

**ID do trabalho:** 100

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: A YOUNG BOY WITH INFREQUENT EPISODES OF ATAXIA AFTER HEAD TRAUMA: A CASE OF EPISODIC ATAXIA TYPE 9**

**Autores:** BUENO, Manoella Guerra de Albuquerque<sup>1</sup>; PEREIRA, Mariana Ribeiro<sup>1</sup>; FREZATTI, Rodrigo Siqueira Soares<sup>1</sup>; TOMASELLI, Pedro Jose<sup>2</sup>; WILSON, Lindsay<sup>3</sup>; REILLY, Mary M<sup>3</sup>; HANNA, Michael<sup>3</sup>; SOBREIRA, Claudia Ferreira da Rosa<sup>2</sup>; JUNIOR, Wilson Marques<sup>2</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - FMRP-USP - Ribeirão Preto - SP - Brasil; (2) Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo - FMRP-USP - Ribeirão Preto - SP - Brasil; (3) University College London - United Kingdom;

### **Resumo do trabalho:**

**Case presentation:** An 11-year-old boy, born to healthy, non-consanguineous parents, presented with generalized hypotonia following a mild head injury at 11 months of age. The pregnancy was unremarkable, and delivery was normal at term with a normal birth weight and Apgar scores. He achieved steady motor milestone gains and took his first steps at 10 months of age. At 11 months, he had a fall while playing, resulting in minor head trauma, followed by significant vomiting. After that, he was unable to sustain his head and remained hypotonic for up to 20 days, as reported by his mother. There was no previous history of seizures. After recovering from this episode, he resumed normal neurodevelopment milestones without any regression of motor skills. At the age of six, he experienced a second minor head injury, which was accompanied by vomiting and immediately followed by slurred speech, imbalance, mutism and an inability to move. This episode lasted for 30 days, and he recovered in a craniocaudal pattern. There was no family history of episodic paralysis or ataxia. However, it is noteworthy that he had two cousins (from different parents) with a history of febrile seizures and myoclonic epilepsy. He was never evaluated by a neurologist during these episodes. Neurological examination at the age of 7 years old was normal. Brain MRI and EEG were normal and lab exams showed elevated lactate (both on rest and after exercise - 2 and 4 times above normal superior limit, respectively). WES identified a heterozygous pathogenic variant on SCN2A:c.4901G>A (p.Gly1634Asp) gene. This variant was previously described in one single case with similar clinical presentation and is now recognized as Episodic Ataxia type 9. **Discussion:** As a heterogeneous group of disorders, Episodic Ataxias (EA) are characterized by attacks of ataxia often triggered by stressors, such as vaccination, fever, trauma, emotional stress. EA type 9 was recently linked to variants on the SCN2A gene and its phenotype spectrum is still under elucidation. Despite the majority of previously described cases reporting a co-occurrence of seizures or epileptic neonatal/infantile self-limited seizures, this patient did not have any similar symptoms. Similar to previous descriptions, this patient did not experience developmental delay or cognitive impairment and, as one previously described patient, his episodes were triggered by head trauma. **Final Comments:** It is important to highlight that the first episode occurred early in life and its recurrence is far less frequent than what is reported in other cases. Also, his presentation was firstly described as a weakness-related disorder, but, in young patients which are still developing motor abilities, ataxia could be hard to identify. Therefore, it is relevant to consider all the clinical spectrum of episodic ataxias on the differential diagnosis.

**Palavras-Chave do trabalho:** Channelopathies; EPISODIC ATAXIAS; whole exome sequencing;

**ID do trabalho:** 103

**Área Técnica do trabalho:** Demências e doenças cerebrovasculares

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: **IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS OVERLAPPING WITH FMR1 PREMUTATION: A COPATHOLOGY?**

**Autores:** GAMA, Sofia Monaco<sup>1</sup>; GOMEZ, Fernanda Lustosa Cabral<sup>1</sup>; MORAES, Marianna Pinheiro Moraes de<sup>1</sup>; SILVA, Thiago Yoshinaga Tonholo<sup>1</sup>; PEDROSO, José Luiz<sup>1</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

A 59-year-old woman presented with a 2-year history of progressive gait impairment, dementia, and urinary incontinence. Her past medical history was remarkable for early menopause at age 36. Family history included a mother with unspecified dementia, a maternal aunt with idiopathic normal pressure hydrocephalus (iNPH), twin daughters with intellectual disability, and a grandson with autism spectrum disorder. Examination revealed apraxic gait and a MoCA test score of 15/30. Brain MRI showed marked hydrocephalus and tap test was positive. Whole genome sequencing (WGS) identified a pathogenic heterozygous expansion of 114 CGG trinucleotides in the Fragile X Messenger Ribonucleoprotein 1 (FMR1) gene [NM\_002024.6: c.-129CGG[114]]. She was diagnosed with iNPH, overlapping with FMR1 premutation, and referred for neurosurgery evaluation. The fragile X premutation is an expansion disorder involving 55-200 CGG repeats in the fragile X mental retardation 1 (FMR1) gene on the X chromosome, leading to RNA gain-of-function toxicity. The prevalence is 1 in 150–300 females, and 1 in 400–850 males. In childhood, this condition may present with mood disturbance, attention deficit hyperactivity, and social or autism spectrum disorders. In young females, it may manifest as Fragile X-associated primary ovarian insufficiency (FXPOI), the most common genetic cause of primary ovarian insufficiency. The most severe phenotype is fragile X-associated tremor/ataxia syndrome (FXTAS), which primarily affects aging men and less than 20% of aging women with the premutation. FXTAS manifests as intention tremor, cerebellar ataxia, cognitive impairment and neuropathy. iNPH is a disorder of unknown pathology that manifests as gait apraxia, dementia and/or urinary dysfunction. It is estimated that 1.5-5.4% of individuals with dementia have iNPH, and its symptoms are potentially reversible by cerebrospinal fluid shunting, unlike the neurodegenerative causes. It is estimated that 20% of patients with iNPH have at least one relative who may also have the condition. At least four genes have been associated with familial iNPH: CFAP43, CWH43, SFMBT1, and DNAH14, likely exhibiting autosomal dominant inheritance, as observed in our case. Recently, Rasanen et al. conducted a large-scale genome-wide study that identified novel variants in the SLCO1A2, AMZ1/GNA12, MLLT10, CDCA2, C16orf95, and PLEKHG1 genes. Several other potential genes associated with iNPH have been proposed, but remain inconclusive. Regarding FMR1-related disorders, Ota Y et al. reported a case of a FXTAS patient presenting with iNPH. Our case expands the spectrum of FMR1 premutation presentations by adding overlap with iNPH and reinforces the need for genetic investigation in iNPH, particularly when there is a positive family history.

**Palavras-Chave do trabalho:** Dementia; FMR1 premutation; Normal pressure hydrocephalus;

**ID do trabalho:** 104

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **EARLY HYPERCKEMIA AND LIMB-GIRDLE MUSCULAR DYSTROPHY IN CARRIERS OF ANO5 GENE VARIANTS: A CASE REPORT**

**Autores:** SPINOLA REZK, Eduardo Abrão<sup>1</sup>; DANTAS, Gabriela Rossini<sup>1</sup>; FRIGO, Yasmim Nadime Jose<sup>1</sup>; CARVALHO, Ricardo Silva<sup>1</sup>; NAKAO, Natalia de Castro Fim<sup>1</sup>;

**Instituição dos Autores:** (1) Faculdade de Medicina de Botucatu - UNESP - Botucatu - SP - Brasil;

### Resumo do trabalho:

Case Presentation A 36-year-old male presented in 2010 with elevated CPK (30,000 U/L) detected during routine exams. Initial investigations, including a muscle biopsy, showed no significant changes, and the condition was classified as idiopathic. The patient remained asymptomatic until June 2023, when he developed proximal muscle weakness in the left lower limb, difficulty changing direction while running, mild cramps, and progressive weakness, especially when climbing stairs. Family history revealed elevated CPK in his mother and siblings and Amyotrophic Lateral Sclerosis in his maternal grandfather. Complementary tests showed thigh MRI with muscle atrophy and fatty replacement indicative of inflammatory myopathy; muscle biopsy with endomysial fibrosis and fatty replacement; EMG with motor unit involvement in the lower limbs; and genetic sequencing identifying ANO5 gene variants (c.2012A>G and c.2030-3C>A), classified as pathogenic and likely pathogenic, respectively, along with a variant of uncertain significance in the CAV3 gene. Discussion Limb-girdle muscular dystrophies (LGMDs) are a group of myopathies causing progressive weakness in pelvic and scapular girdles. Limb-Girdle Muscular Dystrophy Type R12 (LGMDR12) results from biallelic mutations in the ANO5 gene, involved in sarcolemmal repair. ANO5 mutations are linked to varied phenotypes, including Miyoshi distal myopathy, asymptomatic hyperCKemia, and pseudometabolic forms, with complex genotype-phenotype relationships requiring family studies for diagnostic clarity. This case

highlights the importance of genetic diagnosis in patients with suggestive family history. Variants in the ANO5 gene align with Miyoshi muscular dystrophy and LGMD Type 2L, both recessively inherited. Parental testing confirmed the c.2012A>G (pathogenic) and c.2030-3C>A (likely pathogenic) variants were inherited from the mother and father, respectively, confirming a recessive mechanism. Segregation analysis emphasizes the role of family evaluation in clarifying pathogenic processes. The persistent elevation of CPK since 2010, despite being asymptomatic, underscores the need to monitor CPK levels as potential early indicators of neuromuscular disease. Clinical findings, such as asymmetric weakness and sustained high CPK, are consistent with limb-girdle myopathy. Final Comments This case demonstrates the utility of genetic testing in diagnosing genetic myopathies. Identifying pathogenic ANO5 variants highlights the impact of molecular diagnosis on clinical management, including genetic counseling and family guidance. Prolonged asymptomatic hyperCKemia reinforces the importance of recognizing laboratory abnormalities as early signs of neuromuscular diseases, enabling timely diagnosis and intervention.

**Palavras-Chave do trabalho:** ANO5; Asymptomatic HyperCKemia; Limb-Girdle Myopathy; muscular dystrophy;

**ID do trabalho:** 105

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **PROFILE OF PATIENTS WITH DOWN SYNDROME**

**Autores:** LIMA, Patrícia Cota<sup>1</sup>; REZENDE, Ana Leticia de Souza<sup>1</sup>; SPIES, Isabel Cristina Schwarzer<sup>1</sup>; KUNZLER, Raquel<sup>1</sup>; KARAM, Simone de Menezes<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande - Rio Grande - RS - Brasil;

### **Resumo do trabalho:**

Background: Down Syndrome (DS) is the most common chromosomal disorder and isolated genetic cause of intellectual disability. Diagnosis is usually soon after birth, since the dysmorphic characteristics comprises a fairly typical phenotype. Despite this, karyotyping is mandatory to identify the genetic mechanism. Objective: To evaluate patients profile at an university Medical Genetics Outpatient Clinic and compare access to therapies for individuals born pre- and post-pandemic. Methods: Case series study, based on clinical records of patients who started follow-up from 2019 to 2024. Results: Of the 46 patients identified 58.69% were male, 82.61% of their mothers were over 30 years old in the year they gave birth. Around 65.21% were diagnosed within the first month of life and only one individual was suspected during prenatal care. Regarding age at first genetics consultation, 43.47% were in the first month of life and 39.13% between 32 days and 1 year. Translocation was found in two karyotypes. Regarding stimulation, only 17.39% of them were undergoing it. Discussion: Maternal age over 30 for most of the sample is in line with what is established in the literature since it is the main risk factor for disjunctional defects. The percentage of children diagnosed in the first month can still be seen as low considering that clinical diagnosis is very precise. Early diagnosis of DS can have a significant impact on prognosis as it enables early stimulation. It is essential that children are stimulated through play and interaction with the environment to develop motor, cognitive and verbal skills. However, DS individuals find it more difficult due to motor limitations and problems with assimilating sounds and people. As a result, in terms of cognitive development, "the prognosis is extremely variable and depends directly on the interaction between the family, the doctor and the therapeutic and pedagogical early intervention programs". Therefore, these children take more time to develop their skills than typical children and need early, continuous and multidisciplinary stimulation. Despite the indispensability of these practices, only 13.51% of children assessed were being stimulated according to the guidelines. There was a drop in the percentage of children receiving adequate stimulation compared to another case series carried out at the same clinic in 2018 when 33% were undergoing this type of activity. It may be associated with the COVID-19 pandemic that occurred between the two studies, since there was a reduction in supply and demand for non-urgent health services, due to changes in schedules, canceled appointments and difficulties in performing tests. Final comments: This study outlines the profile of DS patients in recent years. It highlights the drop in stimulations as indicated by the main institutions and the need to change this scenario. Future studies should be conducted to assess the impact of the results found in the long term.

**Palavras-Chave do trabalho:** Down syndrome; Neurodevelopmental Disorders; Neuropsychomotor development; Profile; Stimulation;

**ID do trabalho:** 109

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM: IS THERE A GENETIC ASSOCIATION BETWEEN THE ACE ENZYME I/D POLYMORPHISM AND AMYOTROPHIC LATERAL SCLEROSIS?**

**Autores:** BENTO, DHIOGO DA CRUZ PEREIRA<sup>1</sup>; CAMPOS, JÚLIA BISPO<sup>2</sup>; PRADO, ANA PAULA OLIVEIRA<sup>1</sup>; REIS, ANGELA ADAMSKI DA SILVA<sup>2</sup>; SANTOS, RODRIGO DA SILVA<sup>2</sup>;

**Instituição dos Autores:** (1) Neurogenetics Research Center (NeuroGene), Institute of Biological Sciences (ICB II), Federal University of Goiás. Goiás Association of Rare Diseases (AGORA). - Goiânia - GO - Brasil; (2) Neurogenetics Research Center (NeuroGene), Institute of Biological Sciences (ICB II), Federal University of Goiás. - Goiânia - GO - Brasil;

#### Resumo do trabalho:

Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects the upper and lower motor neurons. It manifests mainly in the sporadic form, accounting for 90 to 95% of cases, while the familial form corresponds for 5 to 10%. The angiotensin-converting enzyme (ACE), a component of the renin-angiotensin-aldosterone system, plays an essential role in cardiovascular homeostasis and blood pressure regulation, and ACE may also be implicated in pathological processes related to neurodegeneration. However, little is known about the allelic and genotypic frequencies of ACE polymorphism in patients with neurodegenerative diseases, especially ALS. Objective: To investigate the association between the I/D polymorphism of the ACE gene and susceptibility to ALS. Methods: This study used a case-control design in which peripheral blood samples were collected for extraction and purification of genomic DNA. Genotyping of the I/D polymorphism of the ACE gene was carried out by real-time polymerase chain reaction (qRT-PCR). The genotypic and allelic frequencies were compared between the groups using Fisher's exact test, adopting a statistical significance level of  $p < 0.05$ . Results: The sample consisted of 74 individuals in the case group and 119 in the control group, matched for gender and age. The mean age was 57.68 years in the case group and 57.18 years in the control group. The majority of ALS patients were men (55.41%) and the classical clinical form predominated (72.97%). The genotype frequencies between the groups were analyzed using inheritance models. In the codominant model, the genotypes in the case group had frequencies of 64.86% (I/I), 29.73% (I/D) and 5.40% (D/D), while in the control group they were 25.21% (I/I), 52.94% (I/D) and 21.84% (D/D). Discussion: The results of this study indicated a predominance of the I/I genotype in the case group and the I/D genotype in the control group. Although there were differences in genotypes between the groups, no statistically significant association was identified between the I/D polymorphism of the ACE gene and susceptibility to ALS. This lack of a direct association can be explained by various factors, such as the complexity of the interaction between genes and the environment, as well as the study's sample limitations. The I or D allele has previously been associated with Parkinson's disease and Alzheimer's disease, however, there are still no associations with ALS in the literature. Conclusion: This pioneering study did not identify a significant association between the I/D polymorphism of the ACE gene and susceptibility to ALS. However, the findings highlight the importance of future investigations with larger and heterogeneous samples, considering the influence of other genetic and environmental factors. Such studies are essential to elucidate the complex genetic interactions and mechanisms underlying ALS.

**Palavras-Chave do trabalho:** Angiotensin Converting Enzyme; Genetic Polymorphism; Keywords: Amyotrophic Lateral Sclerosis; Motor Neuron Diseases;

**ID do trabalho:** 110

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: PHENOTYPIC EXPANSION OF IN ATAXIA WITH OCULOMOTOR APRAXIA: EVIDENCE OF DEMYELINATING NEUROPATHY

**Autores:** RIBEIRO PEREIRA, Mariana<sup>1</sup>; GUERRA DE ALBUQUERQUE BUENO, Manoella<sup>1</sup>; ANDRADE LEMOS, Ana Flávia<sup>1</sup>; FREIRE DE OLIVEIRA, Amanda Vitória<sup>1</sup>; GONDIM BRIAND, Lucas<sup>1</sup>; FAVARO, Mateus Gustavo<sup>1</sup>; SIQUEIRA SOARES FREZATTI, Rodrigo<sup>1</sup>; JOSÉ TOMASELLI, Pedro<sup>1</sup>; MARQUES JUNIOR, Wilson<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Neurologia, Ribeirão Preto, São Paulo, Brasil. - Ribeirão Preto - SP - Brasil;

#### Resumo do trabalho:

Background: Autosomal recessive cerebellar ataxias (ARCA) are characterized by degeneration of the cerebellum and its tracts, typically manifesting before age 30. Additional features may include peripheral neuropathy, movement disorders, and ocular abnormalities. Oculomotor apraxia defines a distinct subgroup. In this subgroup, skin involvement narrows the differential diagnosis, as seen in ataxia-telangiectasia and ataxia-telangiectasia-like disorders, but not in ataxia with oculomotor apraxia (AOA). Four molecularly distinct AOA types have been identified: AOA1 (APTX gene), AOA2 (SETX gene), AOA3 (PIK3R5 gene), and AOA4 (PNKP gene), collectively accounting for up to 20% of ARCA cases. Objective: To analyze clinical, electrophysiological, imaging, and genetic characteristics of patients with confirmed AOA. Additionally, we report novel findings of demyelinating features in nerve conduction studies (NCS) in four patients, contrasting with the predominantly axonal findings previously reported. Methods: Retrospective data collection from patient records using a standardized proforma. Data included sex, age at onset, neurological phenotype, brain MRI, electrophysiological studies, laboratory, and genetic tests. Results: Ten patients with molecularly confirmed AOA were analyzed. Most were male (80%) and presented with poor balance and frequent falls (60%), though two presented with distal weakness. Family history revealed consanguinity and affected siblings in four cases. Neurological examination showed cerebellar ataxia, oculomotor apraxia, and length-dependent sensory-motor polyneuropathy in all patients. Two patients had pes cavus, and two exhibited hyperkinetic movement disorders

(chorea/dystonia in AOA4; tremor in AOA2). Intellectual decline occurred in 40% of patients. By the time of evaluation, 70% required support to walk, and most transitioned to wheelchairs within seven years of symptom onset. Laboratory findings included elevated alpha-fetoprotein (70%), elevated CPK (40%), hypercholesterolemia (40%), and hypoalbuminemia (10%). MRI showed diffuse cerebellar atrophy in three patients and additional brainstem atrophy in other two. NCS identified sensory-motor peripheral neuropathy with demyelinating features in four patients, while the remaining four patients who underwent NCS had axonal findings. Genetically, six patients had a molecular diagnosis of AOA4, three had AOA2, and one had AOA1. Conclusion: These findings highlight a subgroup of AOA patients with demyelinating features in NCS, expanding the phenotypic spectrum of AOA. While cerebellar ataxia remains the hallmark feature, it may not always be the initial symptom. The variability in nerve pathology underscores the complexity of AOA and emphasizes the need for individualized diagnostic and management strategies.

**Palavras-Chave do trabalho:** ATAXIA WITH OCULOMOTOR APRAXIA; CEREBELLAR ATAXIA; PERIPHERAL NEUROPATHY;

**ID do trabalho:** 111

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: A CASE REPORT ON POIRIER-BIENVENU SYNDROME: A VERY RARE DISEASE WITH NEUROLOGICAL SYMPTOMS**

**Autores:** VIANA, Mariana Landim<sup>1</sup>; DOS ANJOS REGADAS, Maria Clara<sup>1</sup>; DE SOUZA MARTINS, Fernanda Pereira<sup>2</sup>; FERNANDES CARVALHO, Ellaine Dóris<sup>3</sup>; FERNANDES CARVALHO DE ANDRADE, Maria Denise<sup>4</sup>;

**Instituição dos Autores:** (1) Centro Universitário Christus - Unichristus - Fortaleza - CE - Brasil; (2) Universidade Estadual do Ceará; Hospital Geral Dr Cesar Cals - Fortaleza - CE - Brasil; (3) Centro Universitário Christus - Unichristus; Hospital Geral Dr Cesar Cals - Fortaleza - CE - Brasil; (4) Centro Universitário Christus - Unichristus; Universidade Estadual do Ceará; Hospital Geral Dr Cesar Cals; Comissão Técnica de Anomalias Congênicas- Ministério da Saúde - DF - Fortaleza - CE - Brasil;

### **Resumo do trabalho:**

**Background:** The neurodevelopmental syndrome Poirier-Bienvenu (POBINDS) is a neurological disorder characterized by a mutation in the CSNK2B gene, including three missense mutations (c.410G > T/p.(Cys137Phe), c.494A > G/p.(His165Arg), and c.3G > A/p.(Met11Ile)), two splicing variants (c.292-2A > T, c.558-3 T > G) and a "frameshift" mutation (c.499delC/p.(Leu167Serfs\*60)). Patients with this syndrome present, in your vast majority, tonic-clonic seizure and intellectual developmental delay. The severity of this condition is variable, having individuals with refractory epilepsy without speech acquisition, while other patients may have treatment sensitive seizures and show adequate neuropsychomotor development. This report case is essential once, the POBINDS prevalence remains with less than a hundred cases in the world, being our patient, probably, the second in Brazil. **Objectives:** The purpose of this article is to report the case of a patient with Poirier-Bienvenu. **Methods:** The case was selected due to its rarity, with the authorization of the legal guardian, in accordance with ethical requirements. The selection considered criteria such as confirmed diagnosis, complete follow-up and relevance to medical practice. **Results:** The substitution of the amino acid for serine possibly explains why delays and other pathologies related to the nervous system are expressive characteristics of this syndrome. **Conclusion:** Thus, there is a clear need for further studies, since there is little information on the pathology of Poirier-Bienvenu Syndrome, making it difficult to find a typical therapeutic approach for this syndrome, with the only treatment being the use of antiepileptic drugs. **Case presentation:** Male patient, 10 years old, consanguineous parents (legitimate cousins), referred to the Geneticist with history of neuropsychomotor development delay, refractory epilepsy and important disturbances, especially in speech. In addition, he had congenital torticollis, macroglossia and gastrostomy on physical examination. This genetic disorder has a chr6:31669.847T>C variant which causes the amino acid phenylalanine in codon 190 to be replaced by serine (p.Phe190ser). Studies report that the substitution for serine is potentially deleterious and the absence of phenylalanine is extremely harmful, as this amino acid is used to form tyrosine, a substance directly related to the production of several important neurotransmitters. **Discussion:** The genetics team requested a whole exoma. The Exam identified a pathogenic variant in the CSNK2B gene. However, the inheritance reported in the case was not inherited from one of the parents, but occurred by chance, appearing for the first time in the patient. **Final comments:** Diagnosis is extremely valuable because the earlier the diagnosis, the better the conditions for treatment, specifically in the field of genetics, information about the disease is important both for managing the illness and for planning reproductive life.

**Palavras-Chave do trabalho:** Consanguineous Parents; CSNK2B gene; epilepsy; Neurodevelopmental Disorders; Poirier-Bienvenu Syndrome;

**ID do trabalho:** 112

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: DIFFERENTIAL DIAGNOSIS BETWEEN CEREBRAL PALSY AND AADC DEFICIENCY WITH EMPHASIS ON MOLECULAR GENETICS

**Autores:** OLIVEIRA, Lorena Maria Britto Garcia<sup>1</sup>; OLIVEIRA, Laura Britto Garcia<sup>2</sup>; ARCHILA, Willianson Collares Rodrigues<sup>2</sup>; ASSUNÇÃO, Mayra Todeschini<sup>3</sup>;

**Instituição dos Autores:** (1) Pontifícia Universidade Católica de Campinas - Campinas - SP - Brasil; (2) Universidade Brasil - Fernandópolis - SP - Brasil; (3) Pontifícia Universidade Católica de Campinas - Campinas - SP - Brasil;

### Resumo do trabalho:

Background Cerebral palsy (CP) encompasses movement and posture disorders with diverse etiologies, historically linked to neurological damage. However, genetic advances reveal that many cases initially diagnosed as CP may involve genetic syndromes or hereditary metabolic disorders. This case highlights the diagnostic journey of a child initially classified with CP, later identified with Aromatic L-Amino Acid Decarboxylase (AADC) deficiency. Objective To highlight the diagnostic challenge of differentiating CP from AADC deficiency and the role of molecular genetics in clinical management. Methods We reviewed the clinical progression, diagnostics, and genetics of a male child diagnosed with CP at six months. Genetic testing at age seven confirmed AADC deficiency, changing the diagnosis and treatment approach. Results A male born via emergency C-section at 36 weeks for IUGR and placental insufficiency presented with severe hypotonia and feeding issues at birth. Developmental delays and CP were suspected early. Persistent hypotonia, oculogyric crises, and anticonvulsant resistance prompted genetic testing, revealing pathogenic DDC variants (p.Arg347Gln, p.Gln190Pro), confirming AADC deficiency. Biochemical tests showed low dopamine (0.60 nmol/min/ml) and high 3-O-methyldopa (2800 ng/mL). Conclusion This case highlights the value of genetic testing in atypical neurology. Early AADC diagnosis enabled tailored care, improving outcomes, and supports broader diagnostics when CP management deviates. Case Presentation An only child of young, non-consanguineous parents, conceived via IVF, was delivered at 36 weeks due to IUGR and reversed flow. Neonatal hypotonia and feeding issues led to a CP diagnosis at six months. Oculogyric crises and anticonvulsant resistance prompted genetic testing at seven, confirming AADC deficiency and changing management. Discussion This case highlights the challenge of distinguishing CP from genetic disorders like AADC deficiency, which should be considered in cases with persistent hypotonia, oculogyric crises, and treatment resistance. Genetic testing enabled a shift to targeted therapies, underscoring the value of early screening and multidisciplinary approaches in managing complex pediatric neurology. Final Comments Integrating genetic analysis into CP diagnostics is crucial for accurate diagnoses, preventing unnecessary treatments, and enabling targeted therapies. This case highlights the value of personalized medicine and molecular genetics in improving outcomes. Further research and awareness are needed to refine criteria and expand genetic testing access in resource-limited areas.

**Palavras-Chave do trabalho:** AADC; CP; Molecular genetics; Pediatric neurology;

**ID do trabalho:** 113

**Área Técnica do trabalho:** Pesquisa translacional, modelos celulares e animais

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: DIFFERENTIAL GENE-GENE CO-EXPRESSION INDUCED BY VALPROIC ACID EXPOSURE IN HUMAN EMBRYONIC CELLS: A COMPILATION OF TRANSCRIPTOMIC DATASETS

**Autores:** FOLETTO, João Vitor Pacheco<sup>1</sup>; MEDEIROS, Yasmin Chaves Scimczak<sup>1</sup>; VIANNA, Fernanda Sales Luiz<sup>1</sup>; SCHULER-FACCINI, Lavinia<sup>1</sup>; KOWALSKI, Thayne Woycincz<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

Background: some neuro- and psychotropic drugs, such as Valproic Acid (VPA), can exert effects on the developing embryo/fetus, increasing the risk of neural tube defects and neurodevelopmental disorders. Although the VPA mechanisms of teratogenesis are not fully understood, it is known that it is related to the dysregulation of pathways essential for embryonic development. Objective: to evaluate the effects of VPA exposure on the pattern of gene co-expression in human embryonic cells (hEC). Methods: the Gene Expression Omnibus (GEO) database was assessed. Only studies of in vitro VPA exposure, without other drugs, in hEC, were included. Samples were processed according to the standard pipelines for each technology in the Galaxy server and R. co-expression analyses were conducted in R language using two different approaches: a hypothesis-free analysis, where all genes in the genome were evaluated with the CEMiTool package, and a hypothesis-driven analysis, where only genes related to Valproic Acid exposure were evaluated with the diffcoexp package. Differentially co-expressed gene pairs were considered significant if the P-Value  $\leq 0.05$  and the Pearson correlation between gene pairs was  $\geq 0.7$ . Results: Fourteen datasets were selected and processed. The identification of co-expression modules using the hypothesis-free strategy

identified 75 modules across nine datasets. The most frequent gene ontologies associated with co-expression modules were related to embryonic development. No common hub genes were observed across the different modules. In the hypothesis-driven analysis, the co-expression pattern was evaluated in five gene ontology groups: the Significant group (composed of affected pathways), the Non-Significant group (composed of unaffected pathways), the Valproic Acid Classic group (presents ontologies already known to be altered by the drug), the Embryonic Development group (includes pathways important for embryonic development) and the Recent Interest group (presents ontologies possibly affected by exposure to valproic acid). For the Classical Valproic Acid and Embryonic Development groups, respectively, the differentially coexpressed gene pairs COL1A1-ASMTL and DDK1-CDH6 were present in five of the 17 datasets evaluated. For the Recent Interest, Non-Significant, and Significant groups, respectively, the differentially co-expressed gene pairs STAM-SOX2, RPL13A-PITX2, and JHY-CTNBB1 were present in six of the 17 datasets evaluated. Finally, the Mann-Whitney test was performed for each of the groups. No statistically significant differences were observed between them. Conclusion: VPA exposure in hECs has gene co-expression modules associated with embryonic development biological processes. The results presented here must be further investigated to comprehend whether this deregulation can also be detected in the baby. To accomplish that, transcriptome analysis from saliva samples collected from newborns will be performed.

**Palavras-Chave do trabalho:** gene expression; in vitro assays; microarray; neurodevelopment; RNA-seq;

**ID do trabalho:** 116

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: **THERE MAY BE MORE TO DOWNBEAT THAN CHIARI.**

**Autores:** CORAZZA, Luíza Alves<sup>1</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>2</sup>; FRANÇA JUNIOR, Marcondes Cavalcante<sup>3</sup>; MARQUES JÚNIOR, Wilson<sup>4</sup>; PEDROSO, Jose Luiz<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal de São Paulo - SP - SP - Brasil; (2) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (3) Universidade Estadual de Campinas - UNICAMP - Campinas - SP - Brasil; (4) Faculdade de Medicina de Ribeirão Preto - USP - Ribeirão Preto - SP - Brasil;

### Resumo do trabalho:

A fifty-seven-year-old male was referred to our service with a three-year complaint of a speech disorder noted at 50, combined with progressive unbalance, leading him assistance required gait at fifty-four, being currently wheelchair bound, as well as right-side sensorineural hypoacusis, visual blurring and a five-year history of erectile dysfunction, associated with urinary incontinency. He did not inform an episodic onset of symptoms. He was born to non-consanguineous parents and had no relatives with similar complaints or with any neurological disease. He had arterial hypertension as sole comorbidity. At neurological examination, he had normal cognition, slurred speech, with spontaneous downbeat nystagmus, horizontal gaze evoked nystagmus, saccadic pursuit, discreetly impaired oculovestibular reflex, with bilateral hypofunction, bilateral dysmetria and dysdiadochokinesis - slightly worse on the right side – bilateral decrease on vibration sense, with no evidence of postural hypotension at general physical examination. Screening for acquired causes of ataxia – autoimmune (including anti-GAD), paraneoplastic, metabolic, infectious, cerebrospinal fluid test and tilt test were unremarkable. Brain MRI showed discrete cerebellar atrophy, with no evidence of Arnold-Chiari malformations, optical coherence tomography showed increased thickness of inner retinal layers in papillomacular bundle and electroneuromyography showed signs of mild sensorial polyneuropathy. Genetic testing was performed, with negative results regarding SCA 1, 2, 3, 7, 8, 10, 17 and RFC1. Lastly, intronic expansion on FGF14 was performed, revealing a 320 GAA repeat expansion, and, thus, the diagnosis of GAA-FGF14-Related Ataxia/SCA27B was made. GAA-FGF14-Related ataxia is an intronic expansion ataxia characterized by slow progressive ataxia, usually beginning with episodic symptoms, with or without mild dysautonomia and polyneuropathy, with or without other extrapyramidal clinical signs, and downbeat nystagmus seems to be a recurrent feature, and may be a propaedeutical clue to the condition.

**Palavras-Chave do trabalho:** Downbeat Nystagmus; Dysautonomia; FGF14; Hearing Loss; Hereditary ataxia;

**ID do trabalho:** 123

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: **SERUM MYOSTATIN AS A CANDIDATE DISEASE SEVERITY AND PROGRESSION BIOMARKER OF SPINAL MUSCULAR ATROPHY**

**Autores:** AMORIM DE ALBUQUERQUE, Ana Letícia<sup>1</sup>; KERSTING CHADANOWICZ, Júlia<sup>1</sup>; CÂMARA GIUDICELLI, Giovanna<sup>2</sup>; PORTELLA STAUB, Ana Lucia<sup>2</sup>; CARPEGIANI WEBER, Arthur<sup>1</sup>; MICHELIN BECKER, Michele<sup>2</sup>; WOYCINCK KOWALSKI, Thayne<sup>2</sup>; SIEBERT, Marina<sup>2</sup>; MORALES SAUTE, Jonas Alex<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil;

#### Resumo do trabalho:

Background: The identification of biomarkers for spinal muscular atrophy is crucial for predicting disease progression, severity, and response to new disease-modifying therapies. Objective: This study aimed to investigate the role of serum levels of myostatin and follistatin as biomarkers for spinal muscular atrophy, considering muscle atrophy secondary to denervation as the main clinical manifestation of the disease. Methods: The study evaluated the differential gene expression of myostatin and follistatin in a lesional model of gastrocnemius denervation in mice, as well as in a meta-analysis of three datasets in transgenic mice models of spinal muscular atrophy, and in two studies involving humans with spinal muscular atrophy. Subsequently, a case-control study involving 27 spinal muscular atrophy patients and 27 controls was conducted, followed by a 12-month cohort study with 25 spinal muscular atrophy cases. Serum levels of myostatin and follistatin were analysed using enzyme-linked immunosorbent assay at a single centre in southern Brazil. Results: Skeletal muscle gene expression of myostatin decreased and of follistatin increased following lesional muscle denervation in mice, consistent with findings in the spinal muscular atrophy transgenic mice meta-analysis and in the iliopsoas muscle of five patients with spinal muscular atrophy type 1. Median serum myostatin levels were significantly lower in spinal muscular atrophy patients (98 pg/mL; 5–157) compared to controls (412 pg/mL; 299–730) ( $P < 0.001$ ). Lower myostatin levels were associated with greater disease severity based on clinician-rated outcomes ( $\text{Rho} = 0.493\text{--}0.812$ ;  $P < 0.05$ ). After 12 months, there was a further reduction in myostatin levels among spinal muscular atrophy cases ( $P = 0.021$ ). Follistatin levels did not differ between cases and controls, and no significant changes were observed over time. The follistatin:myostatin ratio was significantly increased in spinal muscular atrophy subjects and inversely correlated with motor severity. Conclusion: Serum myostatin levels show promise as a novel biomarker for evaluating the severity and progression of spinal muscular atrophy. The decrease in myostatin levels and the subsequent favourable environment for muscle growth may be attributed to denervation caused by motor neuron dysfunction.

**Palavras-Chave do trabalho:** Biomarkers; Myokines; Myostatin; Spinal Muscular Atrophy;

**ID do trabalho:** 124

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## Título do Trabalho: CLINICOGENETIC CHARACTERIZATION AND RESPONSE TO DISEASE-MODIFYING THERAPIES IN SPINAL MUSCULAR ATROPHY: REAL-WORLD EXPERIENCE FROM A REFERENCE CENTER IN SOUTHERN BRAZIL

**Autores:** AMORIM DE ALBUQUERQUE, Ana Letícia<sup>1</sup>; KERSTING CHADANOWICZ, Júlia<sup>1</sup>; POSSEBON BEVILACQUA, Isabela<sup>1</sup>; PORTELLA STAUB, Ana Lucia<sup>2</sup>; BREA WINCKLER, Pablo<sup>2</sup>; WOYCINCK KOWALSKI, Thayne<sup>2</sup>; CARVALHO DONIS, Karina<sup>2</sup>; MICHELIN BECKER, Michele<sup>2</sup>; MORALES SAUTE, Jonas Alex<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil;

#### Resumo do trabalho:

Background: Spinal Muscular Atrophy linked to chromosome 5q (SMA) is an autosomal recessive neurodegenerative disease characterized by progressive proximal muscle atrophy and weakness. Objective: This study addresses the scarcity of research on novel disease-modifying therapies for SMA in Latin America by reporting a real-world experience in Southern Brazil. Methods: This is a single-center historical cohort that included all patients diagnosed with spinal muscular atrophy at a Regional Reference Service for rare diseases. Results: Eighty-one patients were included, of whom 7 died during follow-up. Of the remaining 74 patients, 5.4 % were classified as pre-symptomatic, 24.3 % with SMA type 1, 28.4 % with type 2, 36.5 % with type 3, and 5.4 % with type 4. The mean follow-up time ranged from 1.8 years for pre-symptomatic cases to 8.7 years for SMA types 2 and 3. Approximately 42 % of these patients received specific disease-modifying therapy, of these, 96.8 % received Nusinersen, with 19.4 % transitioning to gene therapy using Onasemnogene Apeparvovec, and 6.4 % starting Risdiplam. Most patients with SMA type 1 were on disease-modifying treatment, whereas only slightly over a third of patients with type 2 and about 10 % of type 3 were receiving such treatments. Among treated patients, 80 % demonstrated improvement in motor performance during the follow-up, with a lesser therapeutic response being associated with late initiation of treatment and low motor function scores at baseline. Conclusion: This real-world study reinforces the effectiveness of disease-modifying therapies for SMA in Brazil within the context of low- and middle-income countries, which is greater the earlier and the better the patient's functional status.

**Palavras-Chave do trabalho:** Nusinersen; Onasemnogene abeparvovec; Risdiplam; Southern Brazil; Spinal Muscular Atrophy;

**ID do trabalho:** 125**Área Técnica do trabalho:** Doenças Neuromusculares**Tipo do trabalho:** Trabalhos Originais**Forma de apresentação:** Pôster

## **Título do Trabalho: IS LATE DIAGNOSIS OF DUCHENNE MUSCULAR DYSTROPHY STILL A REALITY?**

**Autores:** BECKER, Michele Michelin<sup>1</sup>; GURJEL-GIANNETTI, Juliana<sup>2</sup>; ARAÚJO, Alexandra Prufer de Queiroz Campos<sup>3</sup>; COSTA, Marcela Câmara Machado<sup>4</sup>; FÉLIX, Têmis Maria<sup>1</sup>; LOREA, Cláudia Fernandes<sup>1</sup>; ORTEGA, Adriana Banzatto<sup>5</sup>; ZENY, Michelle Silva<sup>5</sup>; KOWALSKI, Thayne Woycinck<sup>1</sup>; WINCKLER, Pablo Brea<sup>1</sup>; MEDEIROS, Leonardo Simão<sup>1</sup>; PINHATI, Clara Catharina<sup>2</sup>; DE MOURA, Ana Carolina Monteiro Lessa<sup>2</sup>; SAUTE, Jonas Alex Morales<sup>6</sup>; NARDES, Flávia<sup>3</sup>;

**Instituição dos Autores:** (1) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (2) Universidade Federal de Minas Gerais - Belo Horizonte - MG - Brasil; (3) Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ - Brasil; (4) Escola Bahiana de Medicina e Saúde Pública - Salvador - BA - Brasil; (5) Hospital Pequeno Príncipe - Curitiba - PR - Brasil; (6) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Duchenne muscular dystrophy (DMD) is a progressive X-linked recessive neuromuscular disorder caused by pathogenic variants in the DMD gene manifesting in early childhood with progressive muscle weakness. First symptoms of muscle weakness usually appear around age of three, however, other signs of the disease like muscle hypertrophy, poor motor skills and social, language and motor delay can be detected earlier. Significant delays in the diagnostic process for DMD have been reported in many countries, with the diagnosis generally being made around five years. Objective: To identify the age at diagnosis of DMD in five neuromuscular centers in Brazil. Methods: A collaborative historical cohort study was conducted in five neuromuscular centers in Brazil, covering cases diagnosed between January 2019 and March 2024. In addition to data from the centers, data on age at diagnosis were obtained from The Brazilian National Network for Rare Diseases (RARAS). Results: The final analytic cohort included 173 DMD individuals. The mean age at which patients were diagnosed with probable DMD based on clinical suspicion was 5.7 ( $\pm 2.7$ ) years, with diagnostic confirmation by genetic testing/muscle biopsy at 6.9 ( $\pm 4.0$ ) years, with medians of 6.0 and 6.8 years, respectively. The mean age at which parents noticed symptoms was 3.4 ( $\pm 1.9$ ) years with a median of 3.0 years. The most frequently observed initial symptoms by parents included frequent falls (35.5%), gait abnormalities (31.4%), difficulties in stair climbing (17.2%), developmental delay (13.6%), and difficulties in rising from the floor (8.9%). The presence of co-occurring neurocognitive conditions was associated with a delay of 1.12 years ( $p=0.008$ ) in the median age at suspected diagnosis and 1.0 years in the median age at diagnosis confirmation ( $p=0.022$ ). Conclusion: These results suggest that while there have been improvements in the age of diagnosis of DMD in Brazil in recent decades, diagnosis still occurs later than ideal and than what has been achieved in high-income countries.

**Palavras-Chave do trabalho:** delay diagnosis; Duchenne muscular dystrophy; time to diagnosis;

**ID do trabalho:** 127**Área Técnica do trabalho:** Transtornos do movimento**Tipo do trabalho:** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: IAXON-BRAZIL HSP NETWORK: THE FIRST BRAZILIAN TRANSLATIONAL RESEARCH NETWORK DEDICATED TO HEREDITARY SPASTIC PARAPARESIS**

**Autores:** MACIEL, Franciele dos Santos<sup>1</sup>; FREITAS, Frederico Arriaga Criscuoli de<sup>1</sup>; ARCILA, Diana Maria Cubillos<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>2</sup>; FABER, Ingrid<sup>3</sup>; PEDROSO, José Luiz<sup>4</sup>; FREUA, Fernando<sup>5</sup>; JUNIOR, Wilson Marques<sup>6</sup>; JUNIOR, Marcondes Cavalcante França<sup>7</sup>; SAUTE, Jonas Alex Morales<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (3) Universidade de Brasília - Brasília - DF - Brasil; (4) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (5) Universidade de São Paulo - São Paulo - SP - Brasil; (6) Universidade de São Paulo de Ribeirão Preto - Ribeirão Preto - SP - Brasil; (7) Universidade Estadual de Campinas - Campinas - SP - Brasil;

### **Resumo do trabalho:**

Background: Hereditary axonopathies (HA) are a group of genetic disorders that cause degeneration of long axons, resulting in symptoms such as spasticity, muscle weakness, and progressive loss of ambulation. A common form of HA is hereditary spastic paraplegia (HSP), which affects the corticospinal tract and currently lacks clinically validated disease-modifying therapies. Research on HSP faces challenges such as the absence of accessible biomarkers and standardized evaluation protocols. Objective: The IAXON-BRAZIL HSP Network was established in 2024, integrating seven research centers in four different regions of Brazil, with the main objective of developing biomarkers and advancing translational HSP research. A shared

database is used to generate robust and globally competitive information. The Hospital de Clínicas de Porto Alegre coordinates the project, which also includes the State University of Campinas, the Federal University of São Paulo, the University of Brasília, the Federal University of Ceará, the University of São Paulo and the University of São Paulo de Ribeirão Preto. Methods: Activities are managed by the Management Committee, consisting of the principal investigator and the coordinator of each center, using the Redcap platform as the data management system. The network involves senior researchers, undergraduate students, graduate students, and collaborating researchers. All procedures are conducted uniformly to obtain a large volume of patient data through validated and standardized methods. Patients are recruited consecutively from their respective research centers. Technical procedures are repeated annually in the study and include collection of biological samples, neuroimaging, physician and patient reported outcomes, performance outcomes, and digital health technologies for movement assessment and gait analysis. Results: To date, three research centers have received ethical approval to conduct network activities, while others are undergoing evaluation by their respective Ethics Committees. In less than a year of operation, the iAXON-BRAZIL HSP Network monitors 53 cases and three controls. Among these, 91% of patients have undergone blood and urine collection, 14.3% underwent skin biopsy, and 5.4% cerebrospinal fluid collection. Complete data from 78.6% of these patients have been collected, demonstrating good adherence to the proposed procedures. Conclusion: The iAXON-BRAZIL HSP Network represents a milestone in collaborative research on HSP in Brazil. Preliminary results indicate the feasibility of developing accessible and efficient biomarkers to evaluate outcomes in rare diseases affecting gait. Furthermore, the use of digital technologies and neuroimaging has the potential to accelerate the validation of disease-modifying and symptomatic therapies, with applications in other rare neurological conditions.

**Palavras-Chave do trabalho:** Biomarkers and Outcome Evaluation; Hereditary Spastic Paraplegia; Research Network;

**ID do trabalho:** 128

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **CLINICAL AND GENETIC PROFILE OF PATIENTS WITH DUCHENNE AND BECKER MUSCULAR DYSTROPHY IN SOUTHERN MARANHÃO**

**Autores:** SILVA, EDUARDO MARIANO CARVALHO<sup>1</sup>; NETO, Marcelino Santos<sup>1</sup>; DIAS, Ismália Cassandra Costa Maia<sup>1</sup>; FERREIRA, Adriana Gomes Nogueira<sup>1</sup>; COSTA, Ana Cristina Pereira de Jesus<sup>1</sup>; DUTRA, Richard Pereira<sup>1</sup>; COSTA, Perpetua do Socorro Silva<sup>1</sup>;

**Instituição dos Autores:** (1) UFMA - Imperatriz - MA - Brasil;

### **Resumo do trabalho:**

**Background.** Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked genetic disorders characterized by progressive muscle degeneration and weakness. DMD typically manifests in early childhood with rapid disease progression, whereas BMD presents later with a milder phenotype. Despite advancements in diagnosis and management, access to specialized care remains limited in underserved regions, emphasizing the need for localized, clinical, and genetic characterization. **Objective:** To analyze the clinical and genetic characteristics of patients diagnosed with DMD and BMD, focusing on critical variables such as age at diagnosis, corticosteroid use, ambulation status, and genetic mutations. **Methods.** A retrospective, observational study was conducted involving 10 male patients diagnosed with DMD (n=8) and BMD (n=2). Data were collected in 2023 and 2024 on various clinical parameters, including age, residence, clinical diagnosis, genetic testing results, family history, corticosteroid use, ambulation status, and the presence of pseudohypertrophy of the calves. Genetic diagnosis was confirmed using Multiplex Ligation-dependent Probe Amplification (MLPA) and genetic panels to identify exon deletions. The Spearman correlation test was applied to evaluate associations between the age of corticosteroid initiation and ambulation loss, as well as the relationship between deletion size and early ambulation loss. **Results.** The mean age of diagnosis for DMD patients was 9 years, while for BMD patients, it was 7 years. Corticosteroid use was initiated in 70% of DMD cases, with an average starting age of 8 years. All DMD patients experienced ambulation loss at an average age of 9 years, reinforcing the aggressive disease progression. Pseudohypertrophy of the calves was present in 80% of patients, serving as an essential clinical indicator. Among BMD patients, ambulation was preserved, underscoring the slower disease course. Genetic analysis identified deletions primarily in exons 49-52 and 50, with some cases involving exons 53-54. The findings indicated a strong positive correlation ( $r=0.90$ ) between the age of corticosteroid initiation and the age of ambulation loss, suggesting potential therapeutic benefits of earlier intervention. In contrast, a weak negative correlation ( $r=-0.16$ ) was found between deletion size and early ambulation loss, indicating a complex genotype-phenotype. **Conclusion.** This study provides valuable insights into the clinical course and genetic landscape of DMD and BMD patients in Southern Maranhão. The findings underscore the importance of early diagnosis and timely corticosteroid therapy in optimizing disease management and preserving mobility. Future efforts should focus on expanding access to genetic testing and refining treatment protocols to better serve this population.

**Palavras-Chave do trabalho:** Becker; Duchenne; Genetic Testing; Keywords: Muscular Dystrophy;

**ID do trabalho:** 129**Área Técnica do trabalho:** Epilepsia**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: 15Q DUPLICATION SYNDROME PRESENTING AS LENNOX-GASTAUT SYNDROME**

**Autores:** LIMA, Márcio Pinheiro<sup>1</sup>; TOMAZ, Gabriela Rodrigues<sup>1</sup>; GREGÓRIO, Marcela<sup>1</sup>; GUILHOTO, Laura Maria de Figueiredo Ferreira<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal de São Paulo, Escola Paulista de Medicina, Departamento de Neurologia e Neurocirurgia - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Case presentation: Male patient, 13 years old, referred to a pediatric epilepsy service at age 6 years. First seizure occurred at 4 years, characterized by upward eye deviation, blinking, and upper limbs tonic posturing. At 4.5 years cervical atonic seizures were noted (head drops), followed by myoclonic, generalized tonic-clonic seizures, and atypical absences. Clinical history included delayed neuropsychomotor development (sat unsupported at 3 years, walked at 5 years, first monosyllables at 5–6 years). Regression in milestones was observed after seizure onset. Prenatal history included maternal age of 41 years and paternal age of 38 years, non-consanguineous parents, and hydrocephalus detected at 3 months gestation. Birth was by uneventful C-section. Postnatal follow-up for hydrocephalus did not require surgical intervention. At examination, patient had a narrow forehead, low anterior hairline, thick straight eyebrows, broad nasal bridge, protruding ears with anteriorly rotated lobes, and hypoplastic teeth. Neurological exam revealed non ambulant patient with poor contact and hand stereotypies. Brain MRI with mild cortical and pronounced cerebellar atrophy, enlarged lateral ventricles (right > left), and thin corpus callosum. EEG findings were frequent epileptiform paroxysms with polyspike-and-wave complexes (1–3 Hz) predominantly in posterior regions, activated by drowsiness with slow but relatively symmetrical background activity. Patient is currently being treated with phenobarbital 5.5 mg/kg/day, clobazam 1.85 mg/kg/day, lamotrigine 6.48 mg/kg/day, sodium valproate 55 mg/kg/day, and 4:1 ketogenic diet. Despite treatment, the patient experiences ~ 10 tonic seizures daily. Discussion: Based on age of onset, seizure and EEG characteristics, drug-resistance, developmental delay, and intellectual disability, the patient meets Lennox-Gastaut syndrome's criteria. Dysmorphic features prompted testing, revealing a pathogenic CNV (dupChr15:24,780,843-28,262,863 in homozygosity) and a VUS in the LRPPRC gene (c.1156C>A:p.(Pro368Thr) in heterozygosity). A molecular panel confirmed 15q11-q13 microduplication, consistent with 15q duplication syndrome. Dup15q syndrome is associated with neurobehavioral disorders, hypotonia, cognitive deficits, language delay, and seizures. Dysmorphic features may include macrocephaly, down-slanting palpebral fissures, epicanthus, expressionless face, clinodactyly, syndactyly, and short stature. Lennox-Gastaut syndrome and cardiac anomalies are also reported. Clinical variability exists even within families. Final comments: The patient's phenotype aligns with the genetic duplication detected, supporting a diagnosis of 15q duplication syndrome presenting as Lennox-Gastaut syndrome.

**Palavras-Chave do trabalho:** drug-resistant epilepsy; epilepsy; facial dysmorphisms; Lennox-Gastaut syndrome; Neurodevelopmental Disorders;

**ID do trabalho:** 131**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: REDEFINING PARS2-RELATED DISORDERS: LONGEST SURVIVAL CASE HIGHLIGHTS CARDIAC AND NEUROLOGICAL SPECTRUM**

**Autores:** MOURA, Eder Alencar<sup>1</sup>; STEPHAN, Bruno de Oliveira<sup>1</sup>; ANDRADE, Fernanda Almeida<sup>1</sup>; LINNENKAMP, Bianca Domit Werner<sup>1</sup>; PEREIRA, Giovanna Napolitano<sup>1</sup>; PIRES, Lucas Vieira Lacerda<sup>1</sup>; MARQUES, Emanuelle Leonilia<sup>1</sup>; CARVALHO, Mariana Lombardi Peres De<sup>1</sup>; KRIEGER, José Eduardo<sup>1</sup>;

**Instituição dos Autores:** (1) INCOR - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

This case involves a 26-year-old female who presented with cognitive impairment, corpus callosum agenesis and Dilated Cardiomyopathy (DCM) due to compound heterozygous variants in the PARS2 gene. Despite receiving advanced myocardial therapy, she succumbed to sudden death, marking the longest documented survival for this condition. Genetic analysis, including whole-exome sequencing, identified two pathogenic variants in the PARS2 gene: NM\_152268.4:c.283G>A and NM\_152268.4:c.832\_839dup. These variants were confirmed to be in compound heterozygous form after segregation analysis with her parents. The patient's sister, who also has corpus callosum agenesis, now awaits molecular investigation. Discussion PARS2 encodes mitochondrial prolyl-tRNA synthetase, which plays a critical role in protein biosynthesis by charging tRNAs with

their corresponding amino acids. Mutations in this gene typically result in early infantile epileptic encephalopathy, with common symptoms such as microcephaly, seizures, intellectual disability, and structural brain anomalies. Although rare, cardiac involvement like Dilated Cardiomyopathy (DCM) has been observed in patients with PARS2 mutations. The current case underscores the importance of considering genetic testing in patients with cognitive impairment and unusual symptoms, such as DCM, as this may reveal rare underlying diseases. Furthermore, the findings in this patient expand the phenotypic spectrum of PARS2-related diseases, demonstrating that cardiac involvement, specifically DCM, can be a life-changing clinical feature. Final Comments This report highlights the longest survival documented for a patient with PARS2-related disease and offers insights into the potential adult manifestation of symptoms. It underscores the importance of molecular diagnostics in identifying rare etiologies of cognitive impairment, especially when accompanied by unusual findings like cardiomyopathy. The findings also emphasize that DCM is a major contributor to morbidity and mortality, particularly those associated with PARS2 mutations. The case further broadens the clinical and genetic spectrum of PARS2 variants, indicating the need for continued research to refine genotype-phenotype correlations and explore potential targeted therapies for PARS2-associated conditions.

**Palavras-Chave do trabalho:** CARDIOMYOPATHY; MITOCHONDRIOPATHY; PARS2;

**ID do trabalho:** 133

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: ULTRA-HIGH-FIELD BRAIN IMAGING AT 7 TESLA MAGNETIC RESONANCE IN LAMA2-RD PATIENTS**

**Autores:** CAMELO, Clara Gontijo<sup>1</sup>; MARTIN, Maria da Graça Morais<sup>1</sup>; CHAIM, Khallil Taverna<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>; LUCATO, Leandro Tavares<sup>1</sup>; FERRACIOLLI, Suely Fazio<sup>1</sup>; LEITE, Cláudia da Costa<sup>1</sup>; ZANOTELI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Introduction: LAMA2-related muscular dystrophy (LAMA2-RD) is an AR disorder that results in muscle weakness, exhibiting a wide range of phenotypic severity. The disease not only impacts muscle strength but also leads to brain abnormalities. High signal intensity in the white matter can be observed on T2-weighted and FLAIR sequences in brain MRI of all patients. In rarer cases, patients may also exhibit cortical malformations. Those with these abnormalities have a higher risk of developing epilepsy and/or intellectual disability. Most patients with cortical malformations present with polymicrogyria in the occipital lobe. Polymicrogyria can sometimes be a difficult malformation to identify, requiring greater expertise from the radiologist as well as higher-quality imaging. The reason why these malformations are almost exclusively localized to this region is still unknown. Currently, there is a knowledge gap regarding whether other brain regions are also affected in LAMA2-RD, and whether more precise imaging could make a difference in identifying cortical malformations or other CNS abnormalities in patients with LAMA2-RD. To the best of our knowledge, all studies on CNS abnormalities in patients with LAMA2-RD have been based on findings from cranial tomography and brain MRI using 1.5 and 3 Tesla scanners. This study aims to compare the brain imaging findings at 7T MRI with the images obtained with 1.5 T or 3T MRI in patients with LAMA2-RD. Method: LAMA2-RD patients who had previously 1.5T or 3T brain MRI were selected, and were submitted to a 7T brain MRI. We included patients with congenital muscular dystrophy (CMD) and limb-girdle muscular dystrophy form (LGMD). Results: Four patients, aged between 26 and 46 years were included. Two patients exhibited the CMD phenotype, and two had the LGMD phenotype. Three patients had epilepsy, and two had intellectual disability. Three patients had 1.5T and 7T images, and one of them (P1) had 3T and 7T images. The images revealed generalized white matter high signal on T2 weighted images at both field strengths, though the 7T MRI provided a more geographic pattern with more low signal intensity structures permeating the diffuse signal abnormality, which we believe might represent dense axonal bundles and vessels. In patients with the CMD phenotype the justacortical white matter was more extensively compromised, and had a more tumefactive aspect in the superior frontal gyrus. Additionally, due to technical limitations of our 7T MRI, related to B1 inhomogeneity, the occipital cortex was difficult to identify, particularly in patients with pronounced kyphosis. Parallel transmission RF shimming integrated (or not) with machine learning might help solve this problem. Conclusions: Both patients with CMD and LGMD related to the LAMA2 gene exhibit CNS abnormalities. The 7T MRI provides better resolution and a more geographic pattern, but did not identify more cortical malformations than previously identified with 3T.

**Palavras-Chave do trabalho:** 7 Tesla; brain MRI; LAMA2;

**ID do trabalho:** 134

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: GENOTYPE-PHENOTYPE CORRELATIONS IN ADULT PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

**Autores:** CAMELO, Clara Gontijo<sup>1</sup>; BRITO, Joemir Jábson da Conceição<sup>1</sup>; ALBUQUERQUE, Marco Antônio Veloso<sup>1</sup>; LIMA, Karlla Danielle Ferreira<sup>1</sup>; RESENDE, Maria Bernadete Dutra<sup>1</sup>; SANTOS, Bruno Moreira<sup>1</sup>; MORENO, Cristiane Araujo Martins<sup>1</sup>; ZANOTELLI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

**Introduction:** Duchenne muscular dystrophy (DMD) is an X-linked disorder that causes progressive limb-girdle muscle weakness, early loss of ambulation (LOA), dilated cardiomyopathy, and respiratory insufficiency. Over the past three decades, the natural history of DMD has significantly evolved, however, the disease burden and genotype-phenotype correlations in adult DMD patients remain underexplored. **Objective:** Describe clinical outcomes and investigate genotype-phenotype correlations in adult DMD patients managed by a specialized care service. **Methodology:** A retrospective cross-sectional study was conducted. **Inclusion criteria** were: (1) patients who lost ambulation with <13 years; (2) patients who lost ambulation by the age of 16y at the latest (intermediate clinical presentation) but had loss-of-function variants (out-of-frame and nonsense); (3) only patients older than 18 years old; (4) only patients using steroids: prednisolone or Deflazacort; (5) only patients with a confirmed genetic diagnosis. **The analyzed outcomes included:** (1) age at LOA; (2) age at initiation of nocturnal BiPAP; (3) history of pneumonia and the age of occurrence; (4) presence and age of onset of dysphagia; (5) presence or absence of intellectual disability. **Genetic variants** were classified in type and location. **Genotype-phenotype correlations** were evaluated by analyzing the relationship between the type and location of genetic variants, age at loss of ambulation, and presence of intellectual disability. **Results:** 52 patients were included in the study, with a mean age of 22.9 y (R: 18–33 y). The mean age at diagnosis was 6.5 y (R: 1–12 years), and the mean age at corticosteroid initiation was 7y (R: 3–11y). The mean age at LOA was 11.5 y (SD ±2.2 y; R: 7–15 y). 23 patients (44%) required nocturnal non-invasive ventilation, with a median age of initiation of 17.5 y (R: 9–23 y). 16 patients (30.8%) had been hospitalized at least once for pneumonia, with a median age at first hospitalization of 21.5 y (r: 15–27 y). 18 patients (34.6%) experienced dysphagia at a mean age of 21y (R: 9–30 y), necessitating dietary modifications. 13 patients (25%) presented with intellectual disability. **Regarding genetic findings,** 34/52 patients (65%) had deletions, 9/52 (17.3%) had duplications, and 6/52 (11.5%) had point mutations in the DMD gene. Four patients with in-frame exon deletions presented with a DMD phenotype, all with deletions involving the N-terminal region. Patients with duplications had an earlier LOA (m: 11.2 years) than those with nonsense mutations (m: 12.6 years; p=0.003). Patients with variants in the central domain had a higher prevalence of intellectual disability (25/52 – (48%) than those with variants in the LN domain (14/52 (26%) (p<0.0001). **Conclusions:** Adult patients with DMD face a high disease burden. Genetic variations can help predict certain clinical outcomes, highlighting the importance of integrating genetic data for personalized management strategies.

**Palavras-Chave do trabalho:** adult; Duchenne muscular dystrophy; genotype-phenotype;

**ID do trabalho:** 135

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: HOMOZYGOUS PATHOGENIC VARIANTS IN RTKN IN TWO CHILDREN WITH NEUROPATHY

**Autores:** CAMELO, Clara Gontijo<sup>1</sup>; BANIMORTADA, Bashar J. A.<sup>2</sup>; MORENO, Cristiane de Araujo Martins<sup>1</sup>; SAMPAIO, Pedro H A M<sup>1</sup>; MOREIRA, Ana Lucila<sup>1</sup>; KOK, Fernando<sup>1</sup>; FERLA, Matteo P<sup>3</sup>; HU, Ying<sup>4</sup>; BONNEMANN, Casten<sup>4</sup>; ZANOTELLI, Edmar<sup>1</sup>; EL-HATTAB, Ayman W<sup>5</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil; (2) College of Medicine, University of Sharjah - United Arab Emirates; (3) 3. Wellcome Centre for Human Genetics, University of Oxford - United Kingdom; (4) Neuromuscular and Neurogenetic Disorders of Childhood Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, - United States; (5) Department of Clinical Sciences, College of Medicine, University of Sharja - United Arab Emirates;

### Resumo do trabalho:

**Introduction:** Hereditary motor neuropathies (HMN) are a group of disorders caused by dysfunction of the lower motor neurons. Numerous genes have been involved in HMN. RTKN is a gene located on chromosome 2 that encodes the Rhotekin protein. Rhotekin functions as a signaling molecule, interacting with Rho scaffold proteins. Rho protein transcripts are prominently expressed in the brain and peripheral nerves. In humans, the RTKN function remains to be fully understood, and here we describe for the first time the clinical phenotype of two patients from unrelated families in Brazil and Sudan, both of whom carry autosomal recessive loss-of-function variants in the RTKN gene. **Methods:** The study included two unrelated patients from Brazil, and from Sudan, who were matched via GeneMatcher. Ancillary exams, and molecular analysis were accessed in both patients, as well as skin fibroblast culture with western blotting and immunofluorescence and protein complex modeling. **Results:** P1: A 10-year-old Brazilian girl presented with progressive global muscle weakness, more pronounced proximally on the lower limbs and distally on the upper limbs since the age of 5. She was the only child of second-cousin parents with an unremarkable

perinatal history and developmental history. At the age of nine years old, she was able to walk only for short distances and couldn't rise from the ground. P 2: a 14-year-old Sudanese boy presented with progressive motor weakness that began at the age of 8, primarily affecting the proximal muscles of both the upper and lower limbs. CK, liver function tests, brain MRI, ECG, echocardiogram, BERA, audiometry, and eye fundoscopy results were normal in both patients. An EMG revealed reduced motor conduction velocities. Muscular ultrasound revealed a neurogenic pattern alteration. P1 had a homozygous variant, c.136\_139del; p.Asp46Metfs\*5 and P2 a homozygous variant, c.169A>T; p.Lys57. According to GTEx data, the RTKN transcript is primarily expressed in the brain, especially in the spinal cord and nerves. Through immunofluorescence analysis of nerve biopsies from the animal model, we observed that the RTKN protein is robustly expressed in peripheral nerves. In the Western blot performed on skin fibroblasts, no differences were observed in the amount of protein expressed compared to the control. Since both patients carried variants in exon 2 (C-domain), we hypothesized that fibroblasts might express an isoform lacking exon 2. However, tissue-specific exon expression analysis confirmed that exon 2 is included in fibroblasts, but exon 1 is not. In fibroblasts, translation initiates in exon 2, resulting in a protein approximately 6–7 kDa smaller than the full-length version. Comparing western blot results from mouse nerve tissue to human fibroblasts, this size difference aligns with the observed findings. Conclusion: Loss-of-function variants in the RTKN gene, which encodes rhotekin, appear to be associated with an autosomal recessive form of HNM

**Palavras-Chave do trabalho:** Genetics; Neuropathy; RTKN;

**ID do trabalho:** 136

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Pôster

## **Título do Trabalho: A CASE OF NEDMAGA: NEURODEVELOPMENTAL DISORDER WITH MOVEMENT ABNORMALITIES, ABNORMAL GAIT, AND AUTISTIC FEATURES**

**Autores:** CORAZZA, Luíza Alves<sup>1</sup>; DOUSSEAU, Gabriella Corrêa<sup>1</sup>; DE FREITAS, Julian Letícia<sup>1</sup>; TORRES, Iara Amorim<sup>1</sup>; ROCHA, Maria Sheila Guimarães<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Santa Marcelina - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

The Zinc-finger SWIM domain-containing 6 protein (ZSWIM6) is highly expressed in the central nervous system and is important to the nervous system development, striatal morphology, and motor regulation. Mutations in this gene have been related to acromelic frontonasal dysostosis (AFND) with severe intellectual disability, schizophrenia and, recently, an entity termed neurodevelopmental disorder with movement abnormalities, abnormal gait, and autistic features (NEDMAGA-[OMIM: #617865]). We describe an 8-year-old which conforms to the last phenotype. An 8-year-old male presented at the pediatric emergency due to uncoordinated involuntary movements. He had no complications at birth or during pregnancy but was deemed more hypotonic than other newborns. He had developmental delay, sitting only at 1 year old and developing gait at three. He never acquired efficient speech. At two, he had episodes of incoercible vomiting, being diagnosed with gastroesophageal reflux, undergoing fundoplication. At five, presented features consistent with autistic behavior: agitation, hyperactivity, manual stereotyped movements, facial tics, which were associated to a happy demeanor and unmotivated smiling. At seven, he experienced episodes of tonic posturing of the left arm and cephalic deviation, interpreted as epileptic events, despite normal electroencephalography (EEG), for once it gave rise to a tonic-clonic seizure. Physical examination showed marked hypotonia, genu varum, and facial dysmorphisms: fine arched eyebrows, depressed nose bridge, broad columella, downturned corners of the mouth, and fine lips, with mouth left often mildly open. Neurological assessment disclosed poor contact with the examiner, non-verbality, preserved strength and sensibility, brisk reflexes, with a flexor cutaneous-plantar response, and a wide based, hypotonic, and underdeveloped gait pattern, with severe trunk instability, requiring bilateral aid. He had stereotyped manual and leg movements, in a shaking quality. Investigation showed normal screening for innate errors of metabolism, organic acids, glycosylation defects, amino acid chromatography; he also had normal aldolase, CK, ammonia, copper and ceruloplasmin. Brain MRI was unremarkable, as well as electroencephalogram, transthoracic echocardiogram, BERA, audiometry and retinal mapping. Genetic testing displayed normal 46XY karyotype, microarray, and no Fragile X expansion. Whole exome sequencing (WES) was performed, revealing a heterozygous pathogenic variant in the ZSWIM6 gene —NM\_020928.2(ZSWIM6):c.2737C>T (p.Arg913Ter). Therefore, in patients with neurodevelopmental delay, movement disorders, gait impairment and autistic features, ZSWIM6 should figure as probable diagnosis.

**Palavras-Chave do trabalho:** facial dysmorphisms; Neurodevelopmental Disorders; Stereotypies; ZSWIM6;

**ID do trabalho:** 137

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: CHARCOT-MARIE-TOOTH DISEASE IN A FAMILY WITH DGAT2 GENE MUTATION: CLINICAL INSIGHTS FROM FOUR CASES**

**Autores:** DE OLIVEIRA, Andreia Lira<sup>1</sup>; WESTPHAL FILHO, Fernando Luiz<sup>1</sup>; LOPES, Paulo Roberto Moss<sup>1</sup>; ALVES, Luiziane Maria da Silva<sup>1</sup>; SILVEIRA, Pablo Vinícius Feitosa<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Amazonas - Manaus - AM - Brasil;

### **Resumo do trabalho:**

Background: Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy, characterized by distal muscle weakness and sensory loss. It is genetically heterogeneous, with over 70 associated genes, traditionally classified into demyelinating, axonal, and intermediate forms. Recent studies have implicated DGAT2, a gene involved in triglyceride biosynthesis, as a potential contributor to autosomal dominant CMT. Variants in DGAT2 remain classified as variants of uncertain significance (VUS) due to limited evidence. Objective: To investigate the association between CMT disease and a VUS in the DGAT2 gene. Methods: Clinical, electrophysiological, and genetic evaluations were conducted on an Amazonian family with peripheral neuropathy consistent with CMT. Results: Patient 1: A 70-year-old male presented with symptoms of plantar dorsiflexion weakness that began at age 54, accompanied by paresthesia in the feet. The condition progressed slowly, leading to bilateral foot paralysis, distal muscle atrophy in the lower limbs, and difficulty walking, as well as weakness and atrophy in the hands. Electroneuromyography (ENMG) revealed symmetrical axonal sensorimotor neuropathy (ASMN) without evidence of demyelinating activity, consistent with a diagnosis of CMT disease. Genetic sequencing identified a VUS in the DGAT2 gene, present in a heterozygous state. Patient 2: A 46-year-old male, son of Patient 1, began experiencing lower limb weakness at the age of 40, accompanied by muscle cramps, numbness and paresthesia. The condition progressed, resulting in increasing weakness and sensory impairments in the hands. ENMG revealed chronic ASMN, symmetrical, severe in degree, predominantly distal, in both upper and lower limbs, with evidence of chronic denervation, consistent with the context of CMT. Genetic sequencing identified a heterozygous VUS within the DGAT2 gene. Patient 3: A 63-year-old male, son of Patient 1, presented with a four-year history of numbness in the lower limbs. The condition progressed to difficulty walking, calf muscle atrophy, and motor deficits in the lower limbs. Physical examination revealed distal symmetrical paraparesis, distal hypopallesthesia and areflexia in lower limbs. Patient 4: A 38-year-old female, daughter of Patient 1, was clinically asymptomatic during her initial evaluation one year ago. At follow-up, she presented with pes cavus and hammer toes, suggestive of an inherited neuropathy. ENMG revealed a symmetrical ASMN with reduced action potential amplitudes in sensory nerves and mild motor involvement. Genetic testing confirmed a heterozygous DGAT2 mutation. Conclusion: The autosomal dominant phenotype observed in this Amazonian family, combined with the DGAT2 variant currently classified as a VUS, suggests a potential pathogenic role for this mutation in CMT. Further family segregation studies and functional analyses are essential to confirm the pathogenicity of this variant.

**Palavras-Chave do trabalho:** Axonal neuropathy; Charcot-Marie-Tooth disease; DGAT2 variant; PERIPHERAL NEUROPATHY; Variant of uncertain significance;

**ID do trabalho:** 138

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: GENETIC AND CLINICAL PROFILE OF TRANSTHYRETIN AMYLOIDOSIS IN AN AMAZONIAN POPULATION**

**Autores:** DE OLIVEIRA, Andreia Lira<sup>1</sup>; MACHADO FILHO, Walderico Silva<sup>2</sup>; BRITO, Tiago Breno de Farias<sup>1</sup>; GALVÃO, Maria de Lourdes Souza<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Amazonas - Manaus - AM - Brasil; (2) Universidade Estadual de Campinas - Manaus - AM - Brasil;

### **Resumo do trabalho:**

Background: Familial transthyretin (TTR) amyloidosis is an autosomal dominant hereditary systemic condition associated with approximately 130 known pathogenic mutations in the TTR gene. The disease is characterized by amyloid protein deposits in various organs, including the peripheral nerve, where it manifests as carpal tunnel syndrome or sensorimotor polyneuropathy. Polyneuropathy begins with small-fiber sensory and autonomic symptoms and progresses to large-fiber sensory and motor impairment. In the heart, amyloid deposits lead to cardiomyopathy, arrhythmias, and conduction defects. Without treatment, the disease progresses to death within approximately 10 years. However, TTR stabilizers and gene silencers can extend survival. In Brazil, the prevalence of the disease is unknown, though it is estimated to affect over 5,000 individuals. The Val30Met mutation is the most common, followed by the Val122Ile mutation. In the Amazonas region, the prevalence and characterization of the disease in the local population remain unknown. Objective: To characterize the genotypic and phenotypic profile of familial TTR amyloidosis in a sample of the Amazonian population. Methods: A cross-sectional observational study was conducted through the review of medical records of individuals attended at a tertiary center in Manaus until January 2025. These individuals

presented pathogenic variants for amyloidosis in the TTR gene, detected through next-generation sequencing (NGS). Results: A total of 46 individuals with pathogenic variants in the TTR gene were identified, with a mean age of 51.6 years and a slight female predominance (56%). Among them, 23 (50%) were native to Manaus, 20 (43%) were from other municipalities in Amazonas, and 3 (7%) were from other states. The mutations identified were Val30Met (65%), Asp58Ala (21%), Thr80Ala (8.6%), Ile127Val (2.1%), and Val122Ile (2.1%). Twenty-eight individuals (60%) presented symptoms, while 18 (40%) remained asymptomatic. Among the symptomatic individuals, 14 (50%) had late-onset disease, 12 (42%) had early-onset, and 2 (8%) had an unknown onset. The most frequently reported initial symptom was paresthesia (89%). Regarding phenotype, 11 individuals (39%) presented polyneuropathy with cardiopathy, 9 (32%) had isolated polyneuropathy, 2 (7%) had isolated cardiopathy, and 6 (21%) had carpal tunnel syndrome. Of the symptomatic individuals, 20 (71%) started specific treatment for the disease, with 15 using TTR stabilizers (tafamidis) and 5 using gene silencers. Conclusion: A higher prevalence of pathogenic TTR mutations was observed in individuals from Manaus. Among the mutations identified, Val30Met was the most common, with only one case of Val122Ile reported. At the time of the study, 60% of the individuals had shown some clinical manifestation of the disease, with most cases involving both neurological and cardiac symptoms. There was also a slight predominance of late-onset presentations.

**Palavras-Chave do trabalho:** Amyloidosis; Transthyretin; TTR;

**ID do trabalho:** 139

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: CLINICOGENETIC CHARACTERIZATION OF CEREROTENDINOUS XANTHOMATOSIS IN BRAZIL

**Autores:** FUSSIGER, Helena<sup>1</sup>; LIMA, PEDRO LUCAS GRANGEIRO SÁ BARRETO<sup>2</sup>; SOUZA, Paulo V S<sup>3</sup>; FREUA, Fernando<sup>4</sup>; HUSNY, Antonette S E<sup>5</sup>; LEÃO, Emília K E A<sup>6</sup>; BRAGA-NETO, Pedro<sup>7</sup>; KOK, Fernando<sup>4</sup>; LYNCH, David S<sup>8</sup>; SAUTE, Jonas A M<sup>9</sup>; Nóbrega, Paulo R<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (3) Federal University of São Paulo - São Paulo - SP - Brasil; (4) Universidade de São Paulo - São Paulo - SP - Brasil; (5) Universidade Federal do Pará - Belém - PA - Brasil; (6) Universidade Federal da Bahia - Salvador - BA - Brasil; (7) Universidade Federal de Ceará - Fortaleza - CE - Brasil; (8) UCL Institute of Neurology - United Kingdom; (9) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

Background: Cerebrotendinous xanthomatosis (CTX) is a rare, inherited lipid storage disease characterized by the accumulation of cholestanol in various tissues, leading to a range of clinical manifestations, including neurological and systemic symptoms. Understanding the genetic and clinical spectrum of CTX is crucial for improving diagnostic and therapeutic strategies. Objective: This study aims to evaluate the clinical and genetic characteristics of CTX patients in Brazil. Methods: We analyzed data from all patients with clinical and molecular or biochemical diagnosis of CTX who were regularly followed at six genetics reference centers in Brazil between March 2020 and August 2023. These centers are located in different regions of the country: University of São Paulo, Federal University of São Paulo, Federal University of Bahia, Federal University of Ceará, Federal University of Rio Grande do Sul, and Federal University of Pará. DNA was extracted from oral swab samples, and whole exome sequencing (WES) was performed. Variants were annotated and filtered using various databases and in-silico predictors. Statistical analysis was conducted using IBM SPSS Statistics 20. Results: The study included 38 patients from 26 families. Consanguinity was reported in 48% of families, and familial recurrence in 26%. Genetic diagnosis confirmed CTX in 37 out of 38 cases, with elevated plasma cholestanol levels in all measured cases. The average diagnostic delay was 16.46 years from the age of first symptoms. The data obtained will contribute to a better understanding of CTX and aid in the development of regional strategies and policies to improve care for affected patients and their families. Conclusion: This study highlights the significant diagnostic delay in CTX patients in Brazil and underscores the importance of genetic testing and plasma cholestanol measurement in the diagnostic process. The findings emphasize the need for increased awareness and early diagnosis to improve patient outcomes. Further research and regional strategies are necessary to expedite the diagnostic process and enhance care for CTX patients.

**Palavras-Chave do trabalho:** Cerebrotendinous xanthomatosis; genetic diagnosis; Plasma cholestanol levels;

**ID do trabalho:** 140

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **RETHINKING RESPIRATORY EVALUATION IN FSHD: EXPLORING RESPIRATORY DYSFUNCTION BEYOND FORCED VITAL CAPACITY**

**Autores:** DI PACE, Filipe Tupinambá<sup>1</sup>; FERNANDES, Tatiana Ribeiro<sup>1</sup>; LANÇA, Ana Paula dos Anjos<sup>1</sup>; ARTILHEIRO, Mariana Cunha<sup>1</sup>; CAMPOS, Eliene Dutra<sup>1</sup>; DOUSSEAU, Gabriella Corrêa<sup>1</sup>; CAMELO, Clara Gontijo<sup>1</sup>; ZANOTELLI, Edmar<sup>1</sup>; MORENO, Cristiane Araújo<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Background: Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disease, being the third most common inherited myopathy. Respiratory symptoms and recommendations for ventilatory support are not commonly reported, even with up to 50% of patients exhibiting reduced forced vital capacity (FVC). FVC in sitting-supine positions is usually equal, suggesting diaphragm sparing, which could be an explanation for lower ventilatory support indication. Routine respiratory evaluations are recommended; however, isolated FVC measurements to guide respiratory care may be insufficient, potentially delaying ideal support. This study analyzes multiple respiratory and clinical parameters. Objective: To evaluate pulmonary function tests (PFT): sitting and supine FVC, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and peak cough flow (PCF), correlating with ambulation status and clinical severity score (CSS), in patients with FSHD. Methods: Three trained physiotherapists conducted respiratory tests between June and December 2024. The analysis compared PFT results across different parameters and correlated them with ambulation status and CSS. Results: 28 patients were included (50% male), mean age of 47y  $\pm$  17. Twenty-six (92,6%) were FSHD1. The average CSS was 6.6  $\pm$  2.3. Among the cohort, 27.5% were wheelchair-bound, and 13.8% were using intermittent ventilatory support. The mean sitting FVC% was 82.5  $\pm$  21, and supine FVC% was 81.4  $\pm$  20.5. Reduced FVC was observed in 39% of patients. Reduced FVC was observed in 25% of patients with CSS < 5 points, and 45% with CSS > 5, including the two lowest values. Wheelchair-bound patients showed reduced FVC in 75% of cases, including the two lowest values, compared to 25% of ambulant patients. MIP and MEP were assessed in 16 patients. MIP was below normal in 56%, including 5 patients with normal FVC. MEP was reduced in all cases, including 10 with normal FVC. PCF, evaluated in all patients, was reduced in 60%, including 7 with normal FVC. Conclusion: Respiratory involvement in FSHD is multifaceted, with variable muscle impairment. In our cohort, over 50% of patients presented at least one reduced PFT parameter, with a higher prevalence and severity in more advanced disease stages (CSS > 5 and wheelchair-bound). Expiratory function was predominantly affected, as demonstrated by MEP and PCF measures, which are not routinely assessed but represent the capacity for fluid clearance and infection prevention. Reduced MIP in patients with normal FVC highlights inspiratory muscle involvement, probably including the diaphragm. The sitting-supine FVC relationship may not reliably indicate normal diaphragm function, as corroborated by imaging and neurophysiological studies. Further studies are needed to clarify respiratory involvement progression and its outcome implications, targeting the ideal time to offer ventilatory support, including cough assist, even without remarkable FVC involvement.

**Palavras-Chave do trabalho:** Facioscapulohumeral muscular dystrophy; Respiratory care; Ventilatory support;

**ID do trabalho:** 143

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **QUALITY OF LIFE IN PATIENTES WITH HEREDITARY SPASTIC PARAPLEGIA IN 4.5 YEARS OF FOLLOW-UP**

**Autores:** RIBEIRO DE SOUZA, Maria Eduarda<sup>1</sup>; ALVES JACINTO-SCUDEIRO, Lais<sup>1</sup>; CARPEGIANI WEBER, Arthur<sup>1</sup>; CUBILLOS ARCILA, Diana Maria<sup>1</sup>; MORALES SAUTE, Jonas<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Hereditary spastic paraplegias (HSP) are rare neurodegenerative genetic disorders characterized by progressive motor dysfunction, leading to reduced locomotor capacity. The full impact of HSP on patients' quality of life (QoL) remains unknown. Objective: This study aimed to assess the QoL of patients with HSP over 4.5 years of follow-up and examine its relationship with disease severity and performance outcomes. Methods: This longitudinal study, conducted from January 2018 to September 2022, included 19 patients with genetically confirmed HSP at baseline (12-SPG4, 4-SPG5, 1-SPG7, 2-SPG3A, and 1 cerebrotendinous xanthomatosis). Follow-up evaluations were conducted after 1.5 years (17 patients) and 4.5 years (11 patients). QoL was assessed using the 36-Item Short Form Health Survey (SF-36), disease severity through the Spastic Paraplegia Rating Scale (SPRS) and motor-SPRS (mSPRS), and performance outcomes (PerFOs) using the 10-meter walk test, Timed Up and Go (TUG) at self-selected and maximal speeds (VMAX), and the 6-minute walk test (6MWT). Results: Patients with HSP scored lower on the SF-36 compared to the general population across all domains, except Bodily Pain. The largest deficit was in Physical Functioning (t(16) = -8.07, p < 0.001; mean difference: -48.1), with a large effect size (Cohen's d = 2.01), followed by General Health and Vitality (p < 0.001; Cohen's d = 1.35 and 1.27, respectively). Cross-sectional analyses

revealed moderate-to-strong negative correlations between Physical Functioning and SPRS, mSPRS, and PerFOs (Rho: -0.550 to -0.757,  $p < 0.035$ ), and a positive correlation with 6MWT (Rho: 0.590,  $p < 0.026$ ). Over 4.5 years, the Social Functioning ( $p < 0.001$ ) and Role Emotional ( $p = 0.035$ ) domains declined significantly across all HSP subtypes, while Mental Health deteriorated in the SPG4 subgroup ( $p = 0.001$ ). Physical Functioning decline correlated negatively with SPRS and mSPRS progression (Rho: -0.693 and -0.624,  $p < 0.030$ ), and General Health decline correlated with TUG-VMAX progression (Rho: -0.714,  $p = 0.047$ ). Conclusion: HSP significantly impairs QoL, particularly in the physical domain, which correlates with disease severity measured by ClinROs. These findings reinforce the validity of SPRS as a key outcome measure in clinical trials, as it captures meaningful QoL changes. While PerFOs are more sensitive to change than SPRS, their clinical significance remains ambiguous due to a lack of associations with QoL deterioration. Additionally, sociocultural, educational, and economic factors may have a greater impact on overall QoL in HSP than motor dysfunction alone.

**Palavras-Chave do trabalho:** biomarker; disease progression; Hereditary Spastic Paraplegia; somatosensory evoked potential;

**ID do trabalho:** 144

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: DECREASED LEVEL OF CONSCIOUSNESS DUE TO IGM HYPER-IMMUNODEFICIENCY: CASE REPORT**

**Autores:** NASCIMENTO, Livia Polisseni Cotta<sup>1</sup>; OURIQUES, Gustavo<sup>1</sup>; MUNIZ, Victória Feitosa<sup>1</sup>; PINTO, Louise Lapagesse de Camargo<sup>1</sup>; GRILLO, Eugênio<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Infantil Joana de Gusmão - Florianópolis - SC - Brasil;

### **Resumo do trabalho:**

Case presentation: A previously healthy 2-year-old, firstborn to a young non-consanguineous couple, was admitted with a decreased level of consciousness, fever and seizures. Diagnosed with acute disseminated encephalomyelitis (ADEM) secondary to COVID-19, he received pulse therapy and immunoglobulin. The epileptic condition was controlled, but motor and cognitive impairment remained. Six months later seizures recurred associated with vomiting and drowsiness. During hospitalization, he presented urinary tract infection, hepatomegaly, hypoalbuminemia, hyponatremia, and arterial hypertension, requiring tracheostomy. Exams showed recurrent epileptiform paroxysms, a destructive lesion in the right parietal and left frontal lobes and encephalomalacia. The mother reported having two brothers who passed away at a young age. Exome sequencing was performed due to the rapid progression of neurological decline and suggestive familial history. It identified three variants of uncertain significance (VUS), in heterozygosity, in the THRA, RYR2, DEAF1 genes, and a probable pathogenic variant: the Xq26.3 deletion. Discussion: The hemizygous Xq26.3 deletion involves the CD40LG, associated with hyper-IgM syndrome 1 (HIGM1) (OMIM # 308230). VUS in the THRA and RYR2 genes are associated with conditions unrelated to the clinical presentation. DEAF1 has been associated with neurodevelopmental delay with hypotonia (recessive) and Vulto-van Silfout-de Vries syndrome (dominant). However, to date, these variants remain as VUS. Primary immunodeficiency syndromes present a wide variety of neurological manifestations. HIGM1 presents with low serum concentrations of IgG, IgA, and IgE with normal/elevated serum concentrations of IgM. Neurological symptoms are often related to opportunistic infections in around 5 to 15% of affected men. Meningoencephalitis is the most common form, characterized by reduced level of consciousness and seizures. Although echovirus and cytomegalovirus infections are the most frequently reported, cases of less common pathogens have been described. Unfortunately, the etiological agent is not found in over half of the cases. In imaging tests the lesions tend to behave in a similar way to acquired immunodeficiency syndrome, which can help suspect HIGM1. Other late neurological symptoms have been observed, suggesting a possible autoimmune etiology. This is an X-linked condition, meaning females are carriers and males are affected. Once the pathogenic variant is identified, testing for at-risk relatives, prenatal testing for a high-risk pregnancy, and preimplantation genetic testing is advised. Final comments: Therefore, with the Exome it was possible to confirm the diagnosis of HIGM1 with neurological complications, probably due to an infection. It provided to the family answers about the evolution of the child and previously healthy child and allowed the couple to receive family genetic and reproductive counseling.

**Palavras-Chave do trabalho:** Decreased level of consciousness; Exome sequencing; Hyper-IgM immunodeficiency; X-Linked Hyper IgM Syndrome;

**ID do trabalho:** 146

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **CEREBELLAR COGNITIVE AFFECTIVE SYNDROME IN SCA27B.**

**Autores:** MACHADO FILHO, Walderico Silva<sup>1</sup>; SANTOS, Nadson Bruno Serra<sup>1</sup>; OLIVEIRA, Andreia Lira de<sup>2</sup>; LOBO, Camila Caroso<sup>1</sup>; REZENDE, Thiago Junqueira Ribeiro<sup>1</sup>; MARTINEZ, Alberto Rolim Muro<sup>1</sup>; TOMASELLI, Pedro José<sup>3</sup>; PEDROSO, José Luiz<sup>4</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>4</sup>; MARQUES JR, Wilson<sup>3</sup>; FRANCA JR, Marcondes Cavalcante<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital de Clínicas da UNICAMP - Campinas - SP - Brasil; (2) Hospital Universitário Getúlio Vargas - Manaus - AM - Brasil; (3) Hospital das Clínicas da FMRP - USP - Ribeirão Preto - SP - Brasil; (4) Universidade Federal de São paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

**Background:** Spinocerebellar ataxia 27B (GAA-FGF14 ataxia; SCA27B) is a recently described form of autosomal dominant ataxia, caused by an intronic repeat expansions in the FGF14 gene. It is characterized by late-onset ataxia associated with downbeat nystagmus. In Brazil, a prevalence of 9% for SCA27B was identified among patients previously diagnosed with idiopathic late-onset cerebellar ataxia (ILOCA). So far, little is known about the frequency and profile of cerebellar cognitive affective syndrome (CCAS) in the disease. The CCAS is characterized by deficits in executive function, linguistic processing, spatial cognition and affect regulation. The Cerebellar Cognitive Affective Syndrome Scale (CCAS-S) is a bedside cognitive screen specifically designed to capture neuropsychological changes in patients with cerebellar ataxia, but its use in SCA27B patients has not yet been pursued. **Objective:** Describe the prevalence and clinical profile of CCAS in patients with SCA27B. **Methods:** This is an observational, multicentric study, including 15 patients with molecular confirmation of GAA-FGF14 expansions enrolled between February/2024 and August/2024. The Brazilian Portuguese version of the CCAS-S was applied by the same rater. A failure score of  $\geq 3$  cognitive domains indicate definite,  $\geq 2$  indicates probable and  $\geq 1$  possible CCAS. **Results:** The mean age and disease duration were  $68.3 \pm 9.6$  and  $13.06 \pm 7.09$  years, respectively. The mean SARA score was  $10.6 \pm 6.9$ . In our sample, 9 (60%) SCA27B patients had definite CCAS, 4 (26%) had probable CCAS and 2 (14%) had possible CCAS. Mean CCAS-S raw score was  $73.6 \pm 22.6$  and the mean number of failed domains was  $3.8 \pm 2.6$ . The cognitive domains with the worst performance were respectively: executive function (93%), linguistic function (66%) and memory and learning (46%). **Conclusions:** It has been observed that CCAS frequently occurs in SCA27B. To assess this, the CCAS-S is an interesting scale that can be easily applied in clinical settings or at the bedside. In our sample, significant involvement of executive function and linguistic processing was identified; however, there was a low prevalence of spatial cognition and affect regulation. On the other hand, memory and learning were impaired in nearly half of the cases.

**Palavras-Chave do trabalho:** CCAS; Cerebellar Cognitive Affective Syndrome; Cerebellar Cognitive Affective Syndrome Scale; GAA-FGF14; SCA27B;

**ID do trabalho:** 150

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: **UNUSUAL PRESENTATION OF POLG-RELATED DISORDER: THE ROLE OF REVERSE PHENOTYPING**

**Autores:** RIBEIRO PEREIRA, Mariana<sup>1</sup>; GUERRA DE ALBUQUERQUE BUENO, Manoella<sup>2</sup>; ANDRADE LEMOS, Ana Flávia<sup>2</sup>; FREIRE DE OLIVEIRA, Amanda Vitória<sup>2</sup>; GONDIM BRIAND, Lucas<sup>2</sup>; FAVARO, Mateus Gustavo<sup>2</sup>; SIQUEIRA SOARES FREZATTI, Rodrigo<sup>2</sup>; JOSÉ TOMASELLI, Pedro<sup>2</sup>; MARQUES JUNIOR, Wilson<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Neurologia - Ribeirão Preto - SP - Brasil; (2) Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Neurologia, - Ribeirão Preto - SP - Brasil;

### Resumo do trabalho:

**Case presentation:** An 8-year-old boy from healthy non-consanguineous parents and typical neurodevelopmental milestones presented at 4 years old with a progressive loss of manual dexterity, particularly difficulty in grasping and manipulating small objects, and frequent falls. These symptoms were slowly progressive over months. On neurological examination, there was mild symmetrical weakness in the upper and lower limbs, worse in proximal muscles, and mild axial weakness. Power was diminished distally and symmetrically in both upper limbs. There was no cognitive decline, no ataxia, and no ophthalmoplegia. NCS showed a symmetric sensory-motor neuropathy with intermediate conduction velocity slowing (ulnar conduction velocity of 43 m/s). Laboratory tests revealed increased serum lactate, 6,9 mmol/L (NR 05–2 mmol/L), mild elevation of CPK 409 (NR below 195 U/L) and aldolase 9,3 (NR below 7,6 UI), and elevated protein levels in CSF, 417 mg/dL (NR 15–60 mg/dL). The diagnosis of CIDP was considered, and IVIG treatment commenced, however, with no effect. Molecular diagnosis was then pursued, and WES revealed two heterozygous variants in the POLG gene (NM\_002693.3:c.2557C>T; p.Arg853Trp and NM\_002693.3:c.1943C>T; p.Pro648Arg). Segregation analysis confirmed the variants were in trans. Discussion: The first variant is ACMG class 5, absent in homozygosity in large databases, including gnomAD and multiple lines of in silico prediction tools, supporting deleterious effects (Revel score 0.881). The second variant is ACMG class 4, which is highly conserved (phyloP100: 7.823), absent in large databases, including gnomAD and multiple lines of in silico prediction, and supports deleterious effect

(Revel score 0.941). Although some clinical features were consistent with those described with this genotype, there were no ophthalmoplegia or ataxia, typically associated with POLG-related disorders. A muscle biopsy was then pursued and, when stained with SDH-COX, revealed COX-negative fibers, which, along with multiple deletions of mitochondrial DNA, further supported the role of the POLG variants as the cause of the disease. Final comments: Reverse phenotyping and functional analysis were crucial in reaching the final diagnosis since this case highlights a mild phenotype of POLG-related disorder compared to what is established in the literature. A "pure neuropathy" phenotype may be the initial presentation of these patients. More research is also needed to understand the role of hyperproteinorrachia in POLG-related disorders.

**Palavras-Chave do trabalho:** MITOCHONDRIOPATHY; PERIPHERAL NEUROPATHY; POLG-RELATED DISORDER;

**ID do trabalho:** 152

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: SOMATOSENSORY EVOKED POTENTIAL AS DISEASE MONITORING BIOMARKER FOR HEREDITARY SPASTIC PARAPLEGIAS**

**Autores:** RIBEIRO DE SOUZA, Maria Eduarda<sup>1</sup>; SPENGLER, Fernando Augusto<sup>1</sup>; FERRARESI BRIGHENTE, Samanta<sup>1</sup>; RODRIGUES LOUZADA, Ana Luiza<sup>1</sup>; POSSEBON BEVILACQUA, Isabela<sup>1</sup>; CUBILLOS-ARCILA, Diana Maria<sup>1</sup>; MORALES SAUTE, Jonas<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Hereditary Spastic Paraplegias (HSP) are a group of genetic disorders leading to the degeneration of long motor and sensory tracts in a progressive course. Clinician-reported outcomes (ClinROs) are the most commonly used endpoints for monitoring these diseases, but they have low sensitivity to detect progression. Therefore, identifying new monitoring biomarkers with higher sensitivity to change is crucial. Objective: to compare the progression of Somatosensory Evoked Potential (SSEP) latencies over time with ClinROs in HSP. Methods: A longitudinal study was conducted on 22 individuals with a genetic diagnosis (13 SPG4, 3 SPG5, 3 SPG7, 2 SPG10, and 1 cerebrotendinous xanthomatosis), with two evaluations over a 4-year interval of upper limb (UL) and lower limb (LL) SSEPs and the Spastic Paraplegia Rating Scale (SPRS) total score and motor items only (mSPRS). Results: In the follow-up time analysis, progression after 4 years was observed only for SPRS and mSPRS, with an annual progression of 1.12 points and 1.02 points, respectively. No statistically significant progression was observed for SSEPs. Disease progression modeled according to disease duration showed worsening in all outcomes. For each additional year of disease, the SPRS worsened by 0.834 points (95% CI 0.62 to 1.04,  $p < 0.001$ ), mSPRS by 0.758 points (95% CI 0.55 to 0.96,  $p < 0.001$ ), SSEP-UL latency by 0.164 ms (95% CI 0.03 to 0.3,  $p < 0.001$ ), and SSEP-LL latency by 1.343 ms (95% CI 0.74 to 1.93,  $p < 0.001$ ). Results for the SPG4 subgroup were similar to those for the overall HSP group. Conclusion: The neurophysiological progression of sensory long tract dysfunction is even slower than the progression of motor findings measured by COAs in HSP. The low sensitivity to change of SSEPs identified suggests that they should not be used as primary endpoints in future clinical trials for disease-modifying drugs.

**Palavras-Chave do trabalho:** biomarker; disease progression; Hereditary Spastic Paraplegia; somatosensory evoked potential;

**ID do trabalho:** 154

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## **Título do Trabalho: PROGRESSIVE SPASTIC TETRAPLEGIA ASSOCIATED WITH SOD1 HAPLOINSUFFICIENCY: AN ULTRARARE CASE REPORT IN A CONSANGUINEOUS FAMILY**

**Autores:** GIGONZAC, THAIS CIDALIA VIEIRA<sup>1</sup>; LINDEN, Helio Van Der<sup>2</sup>; UCHOA, Elza Maria Gonçalves Santos<sup>3</sup>; GIGONZAC, Marc Alexandre Duarte<sup>1</sup>;

**Instituição dos Autores:** (1) CRER e UEG - Goiânia - GO - Brasil; (2) CRER - Goiânia - GO - Brasil; (3) UFG - Goiânia - GO - Brasil;

### **Resumo do trabalho:**

Case Presentation: This is the second child of a consanguineous couple, first-degree cousins, with no gestational or perinatal complications. At 4 months of age, following a febrile episode, the patient presented with delayed motor and speech

development. He never ambulated, is wheelchair-bound, has difficulty grasping objects, and exhibits axial hypotonia but with spastic hypertonia, globally increased deep tendon reflexes, and muscle hypotrophy. Physical examination also revealed macrocephaly, a prominent forehead, deep-set eyes, spasticity in the lower limbs, flexed wrist posture, exhaustible clonus in hands and feet, hyperreflexia, restricted limb extension, mild facial diparesis, an elongated face, and a slightly open mouth. His older sister presents with a similar condition, previously diagnosed as cerebral palsy secondary to perinatal hypoxia, but with clinical findings suggestive of an underlying genetic disorder. Initial genetic testing with a neuromuscular disease panel identified a heterozygous variant of uncertain significance (VUS) in the *DYNC1H1* gene, however, this finding was inconclusive for the described phenotype. Whole-exome sequencing, including mitochondrial DNA analysis, identified a homozygous variant in the *SOD1* gene (superoxide dismutase 1, OMIM #147450), also classified as a VUS. Discussion: The patient's phenotype was consistent with *SOD1* haploinsufficiency, with an inheritance pattern compatible with the family history. According to the Franklin database, this variant is considered likely pathogenic based on PM2, PM4, and PM1 criteria. Unlike the dominant *SOD1* form, which is associated with Amyotrophic Lateral Sclerosis (ALS), the recessive form leads to severe spastic tetraplegia in childhood, suggesting a newly emerging spectrum of *SOD1* haploinsufficiency. There are scientific reports of similar cases, though few have been formally diagnosed due to the syndrome being recently described. Recently, homozygous variants in *SOD1* have been identified as a cause of progressive spastic tetraplegia with axial hypotonia (OMIM #618598), an ultrarare disorder characterized by severe and progressive motor dysfunction in childhood. Final Comments: This case highlights the importance of differential diagnosis in rare genetic conditions, particularly in consanguineous families. Genetic testing of the affected sibling will be essential to confirm familial recurrence of the phenotype. A thorough neurological assessment combined with comprehensive genetic investigation enables a more precise diagnosis of challenging conditions, which need to be reported to expand awareness and recognition of this disorder in undiagnosed cases. Furthermore, a detailed correlation between identified genetic variants and clinical findings is crucial for accurate diagnosis, genetic counseling, and guidance for the multidisciplinary therapeutic team, ultimately improving the family's quality of life.

**Palavras-Chave do trabalho:** Genetic Complementation Tests; Neuromuscular Disease; Rare Disease;

**ID do trabalho:** 156

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: HOMOZYGOUS MUTATION IN THE PRDX3 GENE AND SPINOCEREBELLAR ATAXIA: A CASE REPORT**

**Autores:** GIGONZAC, MARC ALEXANDRE DUARTE<sup>1</sup>; LINDEN, HELIO VAN DER<sup>2</sup>; GOMES, JULIANA CALLEGARIS<sup>3</sup>; GIGONZAC, THAIS CIDALIA VIEIRA<sup>4</sup>;

**Instituição dos Autores:** (1) CRER - Centro de reabilitação e readaptação Dr. Henrique Santillo, UEG e PUC/GO - Goiânia - GO - Brasil; (2) CRER - Centro de reabilitação e readaptação Dr. Henrique Santillo - Goiânia - GO - Brasil; (3) UNIVERSIDADE ESTADUAL DE GOIÁS - Goiânia - GO - Brasil; (4) CRER - Centro de reabilitação e readaptação Dr. Henrique Santillo e UEG - Goiânia - GO - Brasil;

### **Resumo do trabalho:**

Case presentation: This is a case report from the Neurology Department of the Dr. Henrique Santillo State Center for Rehabilitation and Readaptation (CRER-GO). Data were extracted from the patient's medical record, including clinical history, diagnostic hypotheses, examination results, clinical progression, and outcomes. The patient is a 9-year-old male child, the son of consanguineous parents (first-degree cousins). At the initial consultation, he presented with motor difficulties, including frequent falls, difficulty walking quickly and climbing stairs, a sensation of stiffness and heaviness in his legs with progressive worsening, atypical gait, and movement alterations in the upper limbs. Emotionally, he reported feeling apathetic and sad. Regarding intellectual functions, he complained of difficulties with writing. At the age of five, he experienced a febrile episode that resulted in paralysis, though without further deterioration. Initially, a diagnosis of progressive paraparesis was hypothesized. A brain MRI was performed, revealing mild cerebellar atrophy. At the second consultation, he exhibited dyspraxic gait, bradykinesia with mild dysmetria and dysidiadochokinesia, and hyporeflexia in the lower limbs, though without muscle weakness. By the third consultation, the mother reported signs of rapid deterioration, including visual disturbances, a slightly widened gait base, bradykinesia in the upper limbs, and dysmetria. The patient also sustained a right foot fracture due to imbalance. Whole-exome sequencing identified a homozygous mutation in the *PRDX3* gene (c.604G>A), leading to the diagnosis of Spinocerebellar Ataxia, Autosomal Recessive 32 (SCAR32, OMIM 619862). Discussion: The *PRDX3* gene (10q26.11) encodes a mitochondrial protein (peroxiredoxin) with antioxidant function, acting as a crucial protective enzyme against oxidative stress. Its deficiency results in the accumulation of reactive oxygen species, leading to DNA damage. When oxidative stress occurs in neuronal cells, there is an increased risk of neurodegenerative disorders, such as progressive cerebellar ataxia and other neurological conditions. The identified homozygous missense mutation (c.604G>A) resulted in an aspartate-to-asparagine substitution at codon 202 (p.Asp202Asn), affecting a functional and conserved domain of peroxiredoxin. This alteration led to a loss of function, classifying the variant as deleterious and pathogenic. Consequently, SCAR32 pathogenesis involves mitochondrial dysfunction and increased cellular vulnerability to oxidative stress. Final comments: The limited number of reported SCAR32 cases typically involves offspring of consanguineous parents carrying homozygous *PRDX3* mutations. Given the complex genetic nature of this condition and its significant recurrence risk within affected families, rapid etiological diagnosis and genetic counseling are crucial for family guidance and disease management.

**Palavras-Chave do trabalho:** Genetic Counseling; Mitochondrial Dysfunction; SCAR32;

**ID do trabalho:** 157

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: CASE REPORT: ADULT ONSET VANISHING WHITE MATTER DISEASE**

**Autores:** MENDES FILHO, Antonio Avelino<sup>1</sup>; UCHOA, Daniel Santos<sup>1</sup>; OLIVEIRA, Isabela Caldeira de<sup>1</sup>; NEPOMUCENO, Camila Rodrigues<sup>1</sup>; LUCENA, Larissa Neves de<sup>1</sup>; MESIAS, André Vinicio Cruz<sup>1</sup>; LEATI, Maria Fernanda Hamamoto<sup>1</sup>; LOURO, Rafaela Julian<sup>1</sup>; MORENO, Cristiane de Araújo Martins<sup>1</sup>; FREITAS, Julian Leticia de<sup>1</sup>; ROCHA, Maria Sheila Guimarães<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Santa Marcelina - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

**CASE PRESENTATION:** A 39-year-old female patient, born to consanguineous parents, was admitted for evaluation due to a history of progressively slow and impaired gait, impoverished speech, and cognitive decline over six years. According to her brother, the patient developed visual and auditory hallucinations approximately one year before admission. Additionally, he reported a history of migraine-like chronic headaches. The family history revealed a comparable clinical presentation in the patient's sister, characterized by onset at age 2, rapid progression, and death at 19 years old. Neurological examination showed hyperreflexia in all four limbs, bilateral Babinski sign, and a magnetic gait pattern. Dysmetria was observed in both upper and lower limbs. Cognitive assessment revealed severe cognitive impairment despite 12 years of formal education. Brain MRI showed diffuse and symmetrical abnormalities of the cerebral white matter, characterized by a T2 hyperintensity and a T1 hypointensity along with small cystic areas in the frontal lobes on the FLAIR sequences. Laboratory tests revealed elevated FSH and low estradiol levels. Given the clinical history and characteristic radiological findings, diagnosing Vanishing White Matter (VWM) disease was strongly considered. Whole-exome sequencing identified a pathogenic missense variant in the EIF2B3 gene (c.260C>T, p.Ala87Val). **DISCUSSION:** Vanishing White Matter, also referred to as Ataxia of Childhood with Central Hypomyelination, is an autosomal recessive leukodystrophy that typically presents during childhood and follows a progressive course. Most pathogenic variants in the EIF2B3 gene are missense mutations, with the c.260C>T variant described in the literature as being associated with a probable founder effect in the Quebec population. The clinical phenotype of VWM is characterized by ataxia and spasticity, with primary ovarian failure in women. The phenotypic spectrum varies according to the age of onset. In infantile forms, motor symptoms predominate, whereas in adult-onset cases, cognitive decline and psychiatric manifestations are more prominent. Adult forms may also include epilepsy and migraine as part of the clinical presentation. Brain MRI plays a critical role in diagnosing VWM, typically revealing bilateral and symmetrical involvement of the cerebral white matter. This is characterized by hypointensity on T1-weighted sequences and hyperintensity on T2-weighted sequences. As the disease progresses, cyst changes can appear in the affected white matter. **FINAL COMMENTS:** This report underscores the presentation of VWM with symptom onset in adulthood, highlighting the variability in the age of onset observed even in the same family. Furthermore, it emphasizes the crucial role of magnetic resonance imaging in the diagnostic process, particularly in guiding differentiation among various leukodystrophies.

**Palavras-Chave do trabalho:** EIF2B3; Leukodystrophy; Vanishing white matter disease;

**ID do trabalho:** 158

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## **Título do Trabalho: HEALTHCARE DELAY IN NEUROGENETIC DISORDERS OF ADULT ONSET AND THE ROLE OF PREDICTIVE GENETIC TESTING**

**Autores:** ROCHA, DANIELE LIMA<sup>1</sup>; PINHEIRO, JORDANIA DOS SANTOS<sup>2</sup>; FURTADO, GABRIEL VASATA<sup>2</sup>; KOWALSKI, THAYNE WOYCINCK<sup>3</sup>; DONIS, KARINA CARVALHO<sup>4</sup>; CHAVES, MARTA<sup>2</sup>; CHINI, GREICE TOSCANI<sup>2</sup>; MONTE, THAIS LAMPERT<sup>2</sup>; DE CASTILHOS, RAPHAEL MACHADO<sup>1</sup>; SARAIVA-PEREIRA, MARIA LUIZA<sup>5</sup>; SCHULER-FACCINI, LAVINIA<sup>5</sup>; JARDIM, LAURA BANNACH<sup>1</sup>;

**Instituição dos Autores:** (1) UFRGS/HCPA - PORTO ALEGRE - RS - Brasil; (2) HCPA - PORTO ALEGRE - RS - Brasil; (3) SGM/HCPA - PORTO ALEGRE - RS - Brasil; (4) UFPB - JOAO PESSOA - PB - Brasil; (5) HCPA/UFRGS - PORTO ALEGRE - RS - Brasil;

**Resumo do trabalho:**

**Background:** Healthcare delay (HCDe) is a significant yet underrecognized issue in genetic disorders, particularly in tandem nucleotide repeat expansion diseases (TNRED). Understanding factors that influence HCDe is crucial to improving early diagnosis and intervention. **Objective:** This study aimed to assess HCDe in TNRED and determine whether predictive genetic testing (PGT) and other factors impact the time elapsed between symptom onset and access to healthcare. **Methods:** A retrospective review of electronic records was conducted on symptomatic (SC) and pre-symptomatic (PSC) individuals from TNRED families followed between 1998 and 2023. HCDe was calculated as the time difference between symptom onset and healthcare initiation. Variables analyzed included age, diagnosis, sex, education, year of diagnosis, place of residence, index case status, and prior PGT. **Results:** Among 1,100 subjects, 811 SC and 101 PSC were diagnosed with Huntington disease, Huntington disease-like 2, spinocerebellar ataxia types 2, 3, 6, 7, or 10, and Friedreich ataxia. The median (IQR) HCDe was 5 (6) years, with no significant differences among diseases. Over time, the number of annual PSC diagnoses became similar to SC cases. Higher educational levels and recurrent familial cases were associated with shorter HCDe. However, the strongest factor influencing HCDe was PGT: among 33 PSC who later developed symptoms and sought care, HCDe was reduced to 1 year ( $p < 0.0001$ , MW test). **Conclusion:** HCDe remains significant in TNRED, but improved access to information and PGT significantly reduce delays. As molecular diagnoses increase in PSC, further reductions in HCDe are expected, emphasizing the importance of genetic counseling and early screening strategies. **Key words:** Microsatellite Diseases; CAG Repeat Disorders; Delay in Healthcare; Genetic Counseling; Predictive Genetic Testing.

**Palavras-Chave do trabalho:** CAG Repeat Disorders; Delay in Healthcare; Genetic Counseling; **Key words:** Microsatellite Diseases; Predictive Genetic Testing;

**ID do trabalho:** 160

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: NEXT GENERATION SEQUENCE ANALYSES IN TREATABLE NEUROMUSCULAR DISORDERS- ARE WE REALLY USING THE BEST OF IT?**

**Autores:** BETINI, Beatriz Gioppo<sup>1</sup>; DE ARAUJO MARTINS MORENO, Cristiane<sup>1</sup>; GONTIJO CAMELO, Clara<sup>1</sup>; ZANOTELI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil;

**Resumo do trabalho:**

**Background:** In recent years, there has been great progress in the understanding of genetic neuromuscular disorders, improving the course of pathologies previously considered untreatable. Genetic diagnosis based on next-generation sequencing (NGS) panels contribute to accurate and early diagnosis. **Objectives:** The aim of this study was to evaluate the inclusion of genes associated with potentially treatable neuromuscular disorders in commercially available NGS panels provided by the main International and Brazilian laboratories. **Methods:** Through a literature review, we found 77 genes associated with potentially treatable neuromuscular conditions. We evaluated the presence of the selected genes among commercially available NGS panels directed to neuromuscular disorders, myopathy, neuropathy and neuromuscular junction disorders (NJD) offered by nine laboratories. **Results:** a total of 1966 genes from twenty three comprehensive panels were evaluated. The presence of genes associated with potentially treatable conditions was highly variable among different laboratories and panel subtypes: in neuromuscular panels, inclusion of those genes ranged from 5 to 78%. Inclusion rate in myopathy (6 to 56%); NJD (16-82%) and in neuropathy panels (12-29%) were also heterogeneous. **Conclusion:** NGS gene panels can have a high diagnostic yield and are cost-effective for diagnosis of many neuromuscular disorders, but despite the increasing availability of genetic tests in clinical practice, patients continue to face delays in diagnosis and treatment. This report calls attention to the lack of standardization and regulamentation in genetic testing. We believe that the systematic inclusion of genes related to treatable conditions in panels available on the market can facilitate patients' earlier access to specific therapies. This culminates in earlier institution of disease modifying therapeutics, leading to positive impacts on the quality of life of a greater number of patients.

**Palavras-Chave do trabalho:** genetic diagnosis; Genetic Tests; Next generation sequence analysis(NGS); treatable neuromuscular disorder;

**ID do trabalho:** 161

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: TUBB2A-RELATED TUBULINOPATHY PRESENTING WITH GELASTIC CATAPLEXY IN A 40 YEARS OLD MAN

**Autores:** URBANO, João Cláudio<sup>1</sup>; JÚNIOR, Sérgio Roberto Pereira da Silva<sup>1</sup>; CASTRO, Matheus Augusto Araújo<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>; DE VASCONCELOS, José Tarcísio Medeiros<sup>2</sup>; LUCATO, Leandro Tavares<sup>1</sup>; FREUA, Fernando<sup>1</sup>; KOK, Fernando<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil; (2) Hospital Beneficência Portuguesa de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

**Introduction** Tubulinopathies are rare autosomal dominant disorders caused by pathogenic variants in the genes belonging to the tubulin superfamily (TUBA1A, TUBB, TUBB2A, TUBB2B, TUBB3, and TUBG1). These genes are involved in brain structural formation, and their mutations are associated with a spectrum of cortical malformations, ranging from simplified gyral patterns and dysgyria to severe lissencephaly and pachygyria. TUBB2A encodes a neuronal-specific isotype of beta-tubulin related to the rarest form of tubulinopathy, with nineteen patients reported to date. No cases of gelastic cataplexy have been reported among patients with TUBB2A variants, highlighting the importance of clinical characterization of this finding. **Case report** We report a newly diagnosed case of TUBB2A tubulinopathy with a novel clinical finding of gelastic cataplexy, in addition to the already characteristic findings of global developmental delay, cortical malformations, and epilepsy. We report a 40 year-old man who presented to the clinic with a history of global developmental delay, myoclonic epilepsy, gelastic cataplexy and cortical malformations. We performed whole exome sequencing, which revealed a monoallelic variant in TUBB2A (NM\_001069.3:c.620T>C;p.(Leu207Pro) classified as likely pathogenic. This variant is absent from populational databases, has a high REVEL score, and is located in a domain of the protein highly intolerant to missense variation. **Discussion** We provide a detailed report of a patient diagnosed in late adulthood with tubulinopathy caused by a TUBB2A mutation. We highlight the importance of a novel clinical finding of gelastic cataplexy and vertical supranuclear gaze palsy (VSGP), which has not been reported in TUBB2A related tubulinopathy until now. Other clinical findings in the patient are consistent with the few existing case reports of TUBB2A variants, including global developmental delay, epilepsy, and cortical malformations. The clinical spectrum appears to be broad and heterogeneous in both presentation and severity. Gelastic cataplexy refers to a brief collapse with pallor and loss of awareness triggered by hearty laughter. It is recognized as a characteristic feature of Niemann-Pick disease type C (NPC), but may also occur in other genetic disorders, such as Norrie disease and Coffin-Lowry syndrome. In summary, we expand the spectrum of suspected TUBB2A variants to include cases of undiagnosed gelastic cataplexy and VSGP, and preserved ambulation into adulthood, alongside the already established findings of global developmental delay, cortical malformations, and epilepsy.

**Palavras-Chave do trabalho:** cortical malformations; gelastic cataplexy; tubulinopathy;

**ID do trabalho:** 164

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: THE BRAZILIAN VERSION OF THE PATIENT-REPORTED OUTCOME MEASURE OF ATAXIA (PROM-ATAXIA)

**Autores:** SCOTT, Stephanie<sup>1</sup>; MARTINS, Ana Carolina<sup>2</sup>; FURTADO, Gabriel Vasata<sup>2</sup>; DONIS, Karina Carvalho<sup>3</sup>; PROLLA, Helena Ashton<sup>4</sup>; LACROIX, Laura Prolla<sup>4</sup>; BRANDI, Ana Laura<sup>5</sup>; SANTANA, Karine Caregnato<sup>5</sup>; NETO, Pedro Braga<sup>1</sup>; JARDIM, Laura Bannach<sup>6</sup>;

**Instituição dos Autores:** (1) Centro de Ciências da Saúde, Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Centros de Pesquisa Clínica e Experimental, Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (3) Departamento de Genética, Universidade Federal da Paraíba - João Pessoa - PB - Brasil; (4) Faculdade de Medicina, Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (5) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (6) Departamento de Medicina Interna, Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

**Introduction:** The Patient-Reported Outcome Measure of Ataxia (PROM-Ataxia) was presented in 2021 to better understand the health status and well-being of ataxic subjects. The original scale was developed in English; Italian and Chinese versions were already published. Our aim was to translate and culturally adapt the PROM-Ataxia to the Brazilian usage. **Methods:** we followed the ISPOR TCA Task Force guidelines. The lead author of the original version, Dr. Schmähman, gave us permission to translate the original English version “a”(Ea). From the Brazilian committee assembled to perform the task, two independent groups of native Portuguese speakers drafted their initial Portuguese “a” and “b” (Pa and Pb) versions; Pa and Pb were discussed by the committee, and merged into a preliminary version Pc. Pc version was sent to two bilingual native English speakers to independently retranslate the PROM-ataxia back into English versions Eb and Ec. In a new meeting between the translators and the committee, the semantic issues were aligned in a Pd and its reciprocal Ed versions; the consolidated back-translation Ed was sent to Dr. Schmähman, who answered our questions and approved the Ed – and therefore, Pd. The Pd version (reciprocal of Ed) was then submitted to cognitive debriefing with ataxic patients selected using a purposeful sampling technique ensuring

diversity in diagnosis, age, and education. Results: fourteen ataxic patients with FRDA (4), SCA3/MJD (3), SCA2 (3), SCA7 (1), SCA8 (1), POLG/SANDO (1) and SCA23 (1) participated in debriefing – 8 from Rio Grande do Sul (RS) and 6 from Ceará (CE) states, living in extreme South and North latitudes and with very different accents and cultures. Only three semantic expressions differed between RS and CE, and the most colloquial was adopted in a final Pe version: fatigue/tiredness, new abilities/ new things, and route/ way. Patients found that the questionnaire was complete, without any significant missing content related to the physical, mental, and functional dimensions. Some items were found redundant or semantically ambiguous. Overall, conceptual and normative equivalence was achieved between Ea and Pd. Conclusions: The translation and cultural adaptation of the PROM-Ataxia questionnaire to the Brazilian population is ready to go to psychometric external validation and evaluation of sensitivity to change. The Brazilian version will allow cross-country comparability and more representativity of future collaborative multinational research studies.

**Palavras-Chave do trabalho:** Clinical report outcome; Hereditary ataxias; Patient-reported outcome measure of ataxia;

**ID do trabalho:** 165

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: A CASE OF DESANTO-SHINAWI SYNDROME IN BRAZIL WITH A NOVEL VARIANT

**Autores:** SOUZA, Mayla Cristine de<sup>1</sup>; SILVA ZENY, Michelle<sup>1</sup>; ALMEIDA DO VALLE, Daniel<sup>1</sup>; DE SOUZA, Josiane<sup>1</sup>; MOURA DA MATA MACHADO FERREIRA PINTO, Gustavo<sup>1</sup>; CORREA, Graziely Agatha<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Pequeno Príncipe - Curitiba - PR - Brasil;

### Resumo do trabalho:

Case Presentation: A 2-year-old female patient was referred to Pediatric Neurology for neuropsychomotor developmental delay. She is the daughter of healthy, non-consanguineous parents, with no family history of genetic conditions. Born at 30 weeks via vaginal delivery, Apgar scores were 7 at 5 minutes and 8 at 10 minutes. Due to respiratory distress syndrome, she required mechanical ventilation and stayed in the NICU for one month. A cardiology evaluation revealed patent foramen ovale, pulmonary artery stenosis, and patent ductus arteriosus. At 2 years and 4 months, echocardiography showed mild left ventricular hypertrophy, dilation, and mitral valve thickening. Orthopedic evaluation diagnosed osteopenia and bilateral genu varum. At 24 months, she could not walk or speak, showing psychomotor agitation and insomnia. Dysmorphic features included an infiltrated facial appearance, broad nasal base, thickened lips and skin, and bilateral epicanthic folds. At 29 months, she could say two words and stand with support. Hearing loss was diagnosed. Walking with support started at 39 months. By 45 months, neuropsychomotor delay persisted. Exome sequencing identified a pathogenic mutation consistent with DeSanto-Shinawi syndrome, caused by the novel variant chr10:28,608,330 CCTTA>C (c.1068\_1071delACTT - ENST00000354911). Discussion: This heterozygous frameshift mutation (p.Leu356Phefs\*30) leads to a premature stop codon. The phenotype aligns with existing literature: global developmental delay with severe motor and speech impairments, and dysmorphic features (hypertelorism, flat nasal bridge, epicanthal folds, wide mouth, and bulbous nasal tip) (De Santo et al., 2015). Behavioral issues like hyperactivity, insomnia, and psychomotor agitation were consistent with previous reports (Ho et al., 2022; Pasquali et al., 2023). Cardiac abnormalities are rare in DeSanto-Shinawi syndrome, but congenital heart defects, especially in cases with WAC gene deletions, may explain these findings (Quental et al., 2022). Osteopenia and genu varum have not been previously reported, but prematurity might contribute to both conditions. Final Comments: This case shares features common in DeSanto-Shinawi syndrome but presents cardiac abnormalities (less frequent) and skeletal findings (previously unreported). Additionally, the pathogenic variant identified has not been documented before. Further research is needed to clarify genotype-phenotype correlations and optimize clinical management.

**Palavras-Chave do trabalho:** DeSanto-Shinawi syndrome; global developmental delay; WAC;

**ID do trabalho:** 166

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: KOOLEN-DE VRIES SYNDROME AND GLOBAL DEVELOPMENTAL DELAY INVESTIGATION: A CASE REPORT

**Autores:** CORREA, Grazielly Agatha<sup>1</sup>; DE SOUZA, Mayla Cristine<sup>1</sup>; SILVA ZENY, Michelle<sup>1</sup>; ALMEIDA DO VALLE, Daniel<sup>1</sup>; DE SOUZA, Josiane<sup>1</sup>; KLEIN OTTONI GUEDES, Jennyfer Katheryne<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Pequeno Príncipe - Curitiba - PR - Brasil;

**Resumo do trabalho:**

Case Description: A 4-year-old male, son of consanguineous parents, was evaluated for global developmental delay, short stature, facial dysmorphisms, and feeding difficulties. Born prematurely at 33 weeks via cesarean section due to intrauterine growth restriction, he required neonatal ICU care for 22 days due to hypoglycemia. At 1 year, he underwent orchiopexy, and at 1 year and 6 months, genetic investigation was initiated. Initial findings included sensorineural hearing loss in the left ear, mild bilateral conductive hearing loss, and nonspecific imaging results. At 2 years and 7 months, he developed acute strabismus from abducens nerve palsy, with bilateral papilledema but normal retinal mapping. Full exome sequencing and high-density SNP array at 4 years revealed a 503.9 kb heterozygous deletion on chromosome 17q21.31, including the KANSL1 gene. Phenotypic features included prominent helical crus of the ears, bilateral epicanthus, high nasal root, long nasolabial filter, thin lips, convergent strabismus, and thoracolumbar kyphosis. Discussion: Koolen-de Vries Syndrome (KdVS) is a multisystemic genetic disorder caused by a heterozygous deletion on chromosome 17q21.31 or pathogenic variants in the KANSL1 gene. The syndrome is characterized by developmental delay, intellectual disability (75%), and a range of congenital anomalies, hypotonia, epilepsy, and behavioral traits such as a friendly personality (25%). Additional findings include auditory and visual impairments and feeding difficulties, which were noted in this case. The prevalence of KdVS is approximately 1 in 55,000, though this is likely underestimated due to the exclusion of KANSL1 variants. Early genetic diagnosis allows better management of symptoms and family counseling, reducing distress and facilitating timely interventions such as speech, occupational, and physical therapy. Final Comments: This case highlights the importance of early recognition of genetic syndromes in children with developmental delays. Genetic testing plays a critical role in confirming the diagnosis, guiding therapeutic approaches, and providing families with information on prognosis and recurrence risks. Globally, 200 million children under five are at risk of not achieving their full developmental potential, underscoring the need for prompt identification and intervention for conditions like KdVS.

**Palavras-Chave do trabalho:** global developmental delay; KANSL1; Koolen-de Vries Syndrome;

**ID do trabalho:** 167

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: **UNBIASED BIOINFORMATIC AND CLINICAL ANALYSIS IDENTIFIES GFAP AS A POTENTIAL GLIAL BIOMARKER IN SPINAL MUSCULAR ATROPHY**

**Autores:** WEBER, Arthur Carpeggiani<sup>1</sup>; DE OLIVEIRA, Karina Lucia Soares<sup>2</sup>; MAGALHAES, Juliana<sup>3</sup>; AMORIM DE ALBUQUERQUE, Ana Leticia<sup>4</sup>; KERSTING CHADANOWICZ, Júlia<sup>1</sup>; CÂMARA GIUDICELLI, Giovanna<sup>3</sup>; WOYCINCK KOWALSKI, Thayne<sup>5</sup>; MICHELIN BECKER, Michele<sup>5</sup>; SIEBERT, Marina<sup>5</sup>; CÂMARA MACHADO COSTA, Marcela<sup>3</sup>; MORALES SAUTE, Jonas Alex<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Universidade Federal do Rio Grande do Sul - Recife - PE - Brasil; (3) Escola Bahiana de Medicina e Saúde Pública - Salvador - BA - Brasil; (4) Universidade Federal do Rio Grande do Sul - Maceio - AL - Brasil; (5) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil;

**Resumo do trabalho:**

Background: The identification of biomarkers for spinal muscular atrophy (SMA) is crucial for predicting disease progression, severity, and response to new disease-modifying therapies. Objective: This study aimed to investigate potential biomarkers for SMA severity and monitoring in an unbiased manner. Through this analysis, we identified glial fibrillary acidic protein (GFAP), a marker associated with astrocyte reactivation and recently recognized as relevant in neurodegenerative processes, as one of the main hits. Methods: We conducted a meta-analysis of differential gene expression using 15 studies in transgenic mouse models of SMA in neural tissues. Due to studies heterogeneity a metacount was performed, and genes differentially expressed in at least three studies were selected for further analysis. Candidate gene expression was then assessed in two human datasets. Subsequently, a case-control study was carried out, including 25 SMA patients (11 with type 1 and 14 with types 2 or 3, 10 of whom were receiving disease-modifying therapies) and 24 age- and sex-matched controls. This was followed by a 12-month cohort study of SMA patients, in which serum levels of GFAP and neurofilament light chain (NfL) were analyzed using single molecule array (SIMOA). Results: A total of 134 genes were differentially expressed in the metacount, 122 of which had human orthologs. Among them, 24 showed altered expression in SMA patient datasets, and only five exhibited consistent expression changes across studies. Of these, two were specifically expressed in the central nervous system, including GFAP. Serum GFAP levels were reduced in SMA patients compared to controls ( $p=0.014$ ), with differences across SMA types—higher in type 1 ( $p=0.028$ ) and were higher in patients with two SMN2 copies ( $p=0.03$ ). GFAP levels were higher in treated patients at baseline ( $p=0.01$ ). NfL levels were increased in SMA patients compared to controls ( $p=0.009$ ), varied by SMA type (higher in type 1,  $p=0.001$ ) and functional status (higher in non-sitters,  $p=0.001$ ), and were higher in patients with two SMN2 copies ( $p=0.016$ ). Only NfL changed after 12 months ( $p=0.02$ ) and accurately distinguished cases from controls (ROC=0.682, 95% CI 0.32–0.832,  $p=0.03$ ). GFAP and NfL levels were mutually correlated (Rho=0.375,  $p=0.013$ ). Conclusion: Through an unbiased biomarker search, we identified GFAP as a candidate with reduced expression in neural tissues of SMA mice and patients.

Serum analysis confirmed its decreased levels in SMA, with associations to disease type, SMN2 copy number, and treatment status. This pioneering identification of a glial biomarker highlights the role of astrocyte reactivity in SMA pathophysiology and its association with neurodegeneration, as indicated by correlations with NfL levels.

**Palavras-Chave do trabalho:** Bioinformatics; biomarker; GFAP; NfL; SMA;

**ID do trabalho:** 168

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: AP1G1 GENE MUTATION IN A PATIENT WITH ASD: PHENOTYPIC SPECTRUM CHARACTERIZATION OF USMANI-RIAZUDDIN SYNDROME**

**Autores:** GIGONZAC, THAIS CIDALIA VIEIRA<sup>1</sup>; LINDEN, Hélio Van Der<sup>2</sup>; GIGONZAC, Marc Alexandre Duarte<sup>1</sup>;

**Instituição dos Autores:** (1) CRER e UEG - Goiânia - GO - Brasil; (2) CRER - Goiânia - GO - Brasil;

### **Resumo do trabalho:**

**Case Presentation:** In this report, we present a case of ASD associated with a pathogenic variant in the AP1G1 gene, previously described as causing Usmani-Riazuddin Syndrome, a rare autosomal recessive condition. The patient is an 11-year-old male, diagnosed with nonverbal ASD, exhibiting global developmental delay, reduced social interaction, preserved eye contact, and disinterest in toys. His parents report compulsive eating, inappropriate behaviors in public settings, and episodes of intense restlessness. Cytogenetic analysis and molecular testing for Fragile X syndrome detected no alterations. After a thorough clinical evaluation, including a detailed review of gestational history, prenatal and perinatal data, a whole-exome sequencing (WES) analysis was performed. This analysis identified a biallelic pathogenic variant in AP1G1, confirming its association with Usmani-Riazuddin Syndrome, an autosomal recessive neurodevelopmental disorder. **Discussion:** The identification of genetic alterations in specific genes related to ASD provides a deeper understanding of the biological mechanisms underlying autism and other complex neurodevelopmental conditions. The AP1G1 gene, located on chromosome 16q22, encodes a subunit of the AP-1 adaptor protein complex, which is crucial for intracellular vesicle trafficking. Mutations in this gene disrupt neuronal homeostasis, impacting cellular pathways essential for neural development. A study by Usmani et al. (2021) described three patients from two unrelated consanguineous families with homozygous pathogenic variants in AP1G1. The affected individuals presented with global developmental delay, intellectual disability, hypotonia, spasticity, epilepsy, and psychiatric disorders, including aggression, hyperactivity, compulsive behavior, and autistic features. The current case exhibits a phenotypic overlap between ASD and Usmani-Riazuddin Syndrome, suggesting that this mutation may serve as an etiological factor contributing to the autism phenotype. Given that only a limited number of cases have been reported in the literature, this study expands the clinical spectrum of the syndrome and underscores its relevance in the neurogenetics of autism. **Final Comments:** The identification of pathogenic variants in AP1G1 highlights the importance of genetic evaluation in individuals with ASD, especially in cases with atypical manifestations or associated neurological comorbidities. Current therapeutic approaches for behavioral management in ASD include pharmacological treatment and multidisciplinary interventions. However, future strategies may explore genetic modulation and regulation of cellular pathways affected by AP1G1. This report contributes to expanding knowledge on the intersection between ASD and rare genetic conditions, emphasizing the need to integrate genetic testing into clinical practice to enable more precise diagnoses and personalized therapeutic interventions.

**Palavras-Chave do trabalho:** Molecular Diagnosis; Neurodevelopmental Disorders; Pathogenic Mutations;

**ID do trabalho:** 170

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: CASE SERIES OF 13 HEREDITARY ATAXIA PATIENTS FROM THE CHILOE ISLANDS, CHILE**

**Autores:** FERNÁNDEZ TOLEDO, ELÍAS<sup>1</sup>; CHAPARRO-SOLANO, HENRY MAURICIO<sup>2</sup>; SAFFIE AWAD, PAULA<sup>3</sup>;

**Instituição dos Autores:** (1) UNIVERSITY OF CONCEPCION, HOSPITAL GUILLERMO GRANT BENAVENTE, CONCEPCION - Chile; (2) DEPARTMENT OF MOLECULAR MEDICINE, CLEVELAND CLINIC, CLEVELAND, OH - United States; (3) CLÍNICA SANTA MARÍA, SANTIAGO - Chile;

**Resumo do trabalho:**

**Background:** The Chiloé Islands, located in southern Chile, comprise a geographically and genetically isolated region of roughly 166,000 inhabitants with a high percentage of Indigenous ancestry and consanguinity rates compared to the general Chilean population. Hereditary ataxias (HAs) are rare neurodegenerative disorders with an estimated prevalence of 0.31 to 41 per 100,000 inhabitants (1). Their considerable genetic heterogeneity poses a significant diagnostic challenge. Previous Chilean data reported spinocerebellar ataxia type 3 and Friedreich's ataxia as the most prevalent autosomal dominant (AD) and autosomal recessive (AR) forms, respectively (2). **Objective:** To describe a case series of 13 patients with HAs from the Chiloé Islands. By studying this unique cohort, we aimed to identify the genetic variants implicated in HAs and characterize their phenotypes. **Methods:** We evaluated 13 patients from Chiloé with gait disorders consistent with HAs. A comprehensive neurological and family history was obtained; all individuals underwent the Scale for the Assessment and Rating of Ataxia (SARA) and the Montreal Cognitive Assessment (MoCA). Brain CT/MRI, electromyography (EMG), and laboratory tests were performed in most cases. Common HAs expansions (e.g., SCA1, SCA2, SCA3, SCA6) were screened and whole-exome sequencing (WES) was conducted for all patients. The study was approved by the local Institutional Review Board and informed consent was obtained. **Results:** A total of 13 individuals (8 males, 5 females), aged 16 to 77 years, met the inclusion criteria. The mean age at onset was 45 years (range 12–63), and the average disease duration was 10.7 years. Gait disturbances were observed in all cases. Eight showed an AD pattern, while 5 had AR inheritance. Polyneuropathy was reported in 9 patients and spasticity was noted in 5. Oculomotor abnormalities were present in 6 cases. Common HAs expansions studies were negative and WES reported only one disease-causing variant, it was a spastic ataxia patient with a likely pathogenic variant in SPG7. Neuroimaging revealed varying degrees of cerebellar atrophy and, in some, brainstem involvement. EMG confirmed peripheral neuropathy in most cases. Detailed findings are listed in Table 1. **Conclusion:** This study outlines the clinical and molecular characteristics in patients with HA from an underrepresented and isolated population. Only one disease-causing variant (SPG7) was detected. Common causes of HAs were absent, highlighting the need for comprehensive genetic testing in regions with unique demographic and genetic backgrounds. Emerging technologies, such as Long-read Sequencing (LRS), should be implemented to discover new expansions such as FGF14, ZFH3, RFC1, and others (3), in populations with unique genetic and demographic characteristics.

**Palavras-Chave do trabalho:** Exome sequencing; Hereditary ataxia; underrepresented population;

**ID do trabalho:** 171

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## **Título do Trabalho: IDENTIFICATION OF METABOLIC PATHWAYS AND KEY GENES ASSOCIATED WITH ATYPICAL PARKINSONISM USING A SYSTEMS BIOLOGY APPROACH**

**Autores:** PASQUALOTTO, Amanda<sup>1</sup>; DA SILVA, Vinicius<sup>1</sup>; PELLENZ, Felipe Mateus<sup>1</sup>; SCHUH, Artur Francisco Schumacher<sup>1</sup>; SCHWARTZ, Ida Vanessa Doederlein<sup>1</sup>; SIEBERT, Marina<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil;

**Resumo do trabalho:**

Atypical parkinsonism (AP) is a group of complex neurodegenerative disorders with marked clinical and pathophysiological heterogeneity. The use of systems biology tools may contribute to the characterization of hub-bottleneck genes, and the identification of its biological pathways to broaden the understanding of the bases of these disorders. A systematic search was performed on the DisGeNET database, which integrates data from expert curated repositories, GWAS catalogues, animal models and the scientific literature. The tools STRING 11.0 and Cytoscape 3.8.2 were used for analysis of protein-protein interaction (PPI) network. The PPI network topography analyses were performed using the CytoHubba 0.1 plugin for Cytoscape. The hub and bottleneck genes were inserted into 4 different sets on the InteractiveVenn. Additional functional enrichment analyses were performed to identify Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and gene ontology for a described set of genes. The systematic search in the DisGeNET database identified 485 genes involved with Atypical Parkinsonism. Superimposing these genes, we detected a total of 31 hub-bottleneck genes. Moreover, our functional enrichment analyses demonstrated the involvement of these hub-bottleneck genes in 3 major KEGG pathways. We identified 31 highly interconnected hub-bottleneck genes through a systems biology approach, which may play a key role in the pathogenesis of atypical parkinsonism. The functional enrichment analyses showed that these genes are involved in several biological processes and pathways, such as the glial cell development, glial cell activation and cognition, pathways were related to Alzheimer disease and Parkinson disease. As a hypothesis, we highlight as possible key genes for AP the MAPT (microtubule associated protein tau), APOE (apolipoprotein E), SNCA (synuclein alpha) and APP (amyloid beta precursor protein) genes.

**Palavras-Chave do trabalho:** Atypical parkinsonism; Corticobasal degeneration; Lewy body dementia; Multiple system atrophy; Progressive supranuclear palsy;

**ID do trabalho:** 173

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: THE COMPLEX SPECTRUM OF ATP1A3 RELATED DISORDERS

**Autores:** REBELO PROCACI, Victor<sup>1</sup>; DA HORA, Raphael Pinheiro Camurugy<sup>1</sup>; GOMES, Anna Maria<sup>1</sup>; DE LIMA, Pedro Lucas Grangeiro de Sá Barreto<sup>2</sup>; FERRER, João Victor Cabral Correia<sup>1</sup>; MAIA, Debora Palma<sup>3</sup>; CARDOSO, Francisco Eduardo Costa<sup>3</sup>; LINDEN, Helio van der<sup>4</sup>; KRUEGER, Mariana Braatz<sup>5</sup>; LEÃO, Emília Katiane Embiruçu de Araújo<sup>6</sup>; SILVA, Thiago Yoshinaga Tonholo<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>2</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>1</sup>; PEDROSO, José Luiz<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (2) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (3) Universidade Federal de Minas Gerais - Belo Horizonte - MG - Brasil; (4) Centro de Reabilitação Dr. Henrique Santillo - Goiânia - GO - Brasil; (5) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil; (6) Universidade Federal da Bahia - Salvador - BA - Brasil;

### Resumo do trabalho:

Introduction ATP1A3 related disorders have a complex clinical presentation and can manifest from childhood to adulthood, presenting as differential diagnosis to several diseases with ataxia, hemiparesis, parkinsonism, dystonia, fever, encephalopathy, epileptic seizures, psychosis, among other features. The description of a clinical spectrum in a Brazilian cohort of patients is essential for better disease characterization and development of new therapeutic methods. Objectives To present a case series of patients diagnosed with mutations in the ATP1A3 gene, through the analysis of medical records from the neurology outpatient clinic of the Universidade Federal de São Paulo and multiple Brazilian universities. Methods This is a retrospective case series that analyzed medical records from the neurology outpatient clinic of the Universidade Federal de São Paulo, Universidade Federal do Ceará, Universidade Federal de Minas Gerais and private offices from the authors and included patients with an established diagnosis of ATP1A3 mutation, independent of the phenotype presented. Clinical and genetic data were acquired through medical records analysis. Results We identified 23 cases with a known mutation in ATP1A3, 15 males and eight females. Age of onset varied from less than a year to 17-year-old. We found six phenotypes, five classical and one complex: 10 alternating hemiplegia of childhood (AHC); four cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensorineural hearing loss syndrome (CAPOS); three rapid-onset dystonia parkinsonism (RDP); two developmental and epileptic encephalopathy 99 (DEE99); two fever-induced paroxysmal weakness and encephalopathy (FIPWE); one relapsing encephalopathy with cerebellar ataxia (RECA); one complex phenotype that resembled CAPOS but overlapped with several phenotypes. Seizure was present in seven AHC patients, two CAPOS, two DEE99, one FIPWE. Dystonia was present in all phenotypes. Fever induced symptoms were present in all phenotypes, except RECA. EEG showed abnormalities in six patients (one DEE99, one CAPOS and four AHC). Brain MRI showed abnormalities in six patients (two DEE99, one CAPOS, one AHC, one RDP and one RECA). We found that c.2401G>A (p.Asp801Asn) variant was the most common in our cohort, present in three patients with AHC. Conclusions Our cohort highlights the phenotypic heterogeneity and overlap of classic phenotypes in ATP1A3 related disorders, emphasizing the need to consider a combination of neurological symptoms instead of classifying phenotypes in separate syndromes. More research is needed to clarify the spectrum of this disorder and phenotypical implications from different variants reported.

**Palavras-Chave do trabalho:** ; ATP1A3; Genetics; genotype-phenotype;

**ID do trabalho:** 175

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: NEW VARIANT OF THE NEK1 GENE IDENTIFIED IN A BRAZILIAN PATIENT WITH AMYOTROPHIC LATERAL SCLEROSIS

**Autores:** BENTO, DHIOGO DA CRUZ PEREIRA<sup>1</sup>; ALVES, Marcos Alexandre Carvalho<sup>2</sup>; SANTOS, Kamilla de Faria<sup>3</sup>; PRADO, Ana Paula Oliveira<sup>1</sup>; ROUDÃO, Paula Martins Alves de Castro<sup>4</sup>; REIS, Angela Adamski da Silva<sup>3</sup>; SANTOS, Rodrigo da Silva<sup>3</sup>;

**Instituição dos Autores:** (1) Neurogenetics Research Center (NeuroGene), Institute of Biological Sciences (ICB II), Federal University of Goiás. Goiás Association of Rare Diseases (AGORA) - Goiânia - GO - Brasil; (2) Mater Dei Premium Hospital - Goiânia - GO - Brasil; (3) Neurogenetics Research Center (NeuroGene), Institute of Biological Sciences (ICB II), Federal University of Goiás (UFG) - Goiânia - GO - Brasil; (4) Dr. Henrique Santillo Rehabilitation and Readaptation Center - Goiânia - GO - Brasil;

### Resumo do trabalho:

Case presentation: A male patient was evaluated at the Neuromuscular Diseases Outpatient Clinic of the Dr. Henrique Santillo Rehabilitation and Readaptation Center in Goiânia-GO, Brazil. The first symptoms manifested in February 2020, with pain in the calves, weakness in the hands, muscle atrophy and, later, falls, reduced walking speed, dyspnea and dysphagia. Imaging tests carried out in September 2021 showed microangiopathy and vertebral stenosis at C3-C4, without nerve root involvement. Spirometry indicated a reduction in forced vital capacity and electroneuromyography showed diffuse lower motor neuron

involvement. Functional assessment using the ALS Functional Rating Scale-Revised (ALSFRRS-R) showed a drop in the score from 27 to 17 points in six months, indicating progressive loss of motor functions, and the Medical Research Council (MRC) muscle strength scale revealed weakness in the upper and lower limbs. Eight months after the onset of symptoms, the patient developed respiratory failure, requiring non-invasive mechanical ventilation. Genetic sequencing identified a variant of uncertain significance (VUS) in heterozygosity in the NEK1 gene (c.1560C>T / p. Asn520= / rs1762065873), not described in genetic databases. In silico predictors classified the variant as potentially deleterious, suggesting the need for further studies to elucidate its clinical relevance. Discussion: Studies indicate that heterozygous variants with loss of function in the NEK1 gene are associated with 2-3% of sporadic and familial ALS cases. NEK1, located at 4q33, participates in cell cycle regulation, ciliogenesis, mitochondrial permeability and DNA repair. Its variants can cause mitotic defects, abnormal chromosome segregation and cell apoptosis. Although the exact mechanisms are still uncertain, variants in NEK1 have been identified in different domains of the protein and associated with mutations in genes such as SOD1, TDP-43 and C9orf72. Studies show that heterozygous mutations in NEK1 reduce its expression and increase DNA damage in stem cell-derived neurons. The discovery of this variant represents a breakthrough in understanding the genetics of ALS, offering prospects for the development of diagnostic biomarkers and potential therapeutic strategies. Final comments: This report emphasizes the relevance of genetic research in ALS, with the identification of a novel variant in the NEK1 gene with a potential impact on the pathogenesis of the disease. Although the exact mechanisms of its influence remain undefined, the relationship of this gene with critical cellular processes points to the need for additional studies to elucidate its functional role, which are essential to validate its pathogenicity and explore its clinical implications in the prognosis and management of the disease.

**Palavras-Chave do trabalho:** Amyotrophic Lateral Sclerosis; Gene NEK1; Genetic variants; Precision medicine;

**ID do trabalho:** 178

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: **WHOLE EXOME SEQUENCING UTILITY FOR THE MOLECULAR DIAGNOSIS OF PEO: A LARGE BRAZILIAN COHORT**

**Autores:** MORENO, Cristiane Araujo Martins<sup>1</sup>; FONSECA, Alulin Tácio Quadros Santos Monteiro<sup>1</sup>; CAMELO, Clara Gontijo<sup>1</sup>; FERNANDES, Tatiana Ribeiro<sup>1</sup>; DOUSSEAU, Gabriella Corrêa<sup>1</sup>; DI PACE, Filipe Tupinamba<sup>1</sup>; NOBREGA, Paulo Ribeiro<sup>2</sup>; CAMELO-FILHO, Antonio Edvan<sup>2</sup>; SILVA, Andre Macedo<sup>1</sup>; KITAJIMA, João Paulo<sup>3</sup>; SCHLESINGER, David<sup>3</sup>; ZANOTELLI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil; (2) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (3) Mendelics Genomica - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Background: Chronic progressive external ophthalmoplegia (CPEO) is the most common manifestation of mitochondrial diseases and is characterized by bilateral symmetrical progressive ptosis and reduced ocular motility. CPEO can be isolated or accompanied by other muscular symptoms such as fatigue and weakness (PEO) or accompanied by extramuscular symptoms due to systemic involvement of mitochondrial dysfunction (PEO+). Both mtDNA and nDNA can be affected in mitochondrial diseases. Most common genetic variants that cause PEO are point mutations at mtDNA, large scale deletions at mtDNA or pathogenic variants in nuclear genes interfering at mitochondrial function. The most common method used for the molecular studies in these conditions includes direct mitochondrial DNA sequencing from muscle or urine, however those procedures are available only in few tertiary Centers across the Country. Diagnostic rates from CPEO using whole exome sequencing from oropharyngeal swab are not well defined in the literature and conventional methods for next generation sequencing alignment are not proper for mitochondrial deletions detection. Here we present a detailed molecular analysis of WES from 43 patients presenting confirmed PEO and PEO+ to explore the exome utility as first tier of PEO investigation. Patients and Methods: Patients had a confirmed diagnosis of mitochondrial myopathy and PEO. We reviewed clinical and histologic data from chart. Whole exome sequencing was performed from swab DNA and raw data was reviewed. Large scale deletions were analyzed from CRAM files using eKLISe software. Results: 46 patients were selected through chart review, but 3 patients were excluded due to low mtDNA coverage at WES. Patients were 46 ±22 years old (11 male e 31 female), of those 36 patients presented PEO and seven patients presented PEO+. A conclusive molecular confirmation was obtained for 21 patients in the PEO group: mt large-scale deletion (n=12); POLG(n=6), MYH2(n=1), SLC24A4(n=1), and TMM41(n=1); and for three patients in PEO+ group: MT-TK (n=1), MT-ND1(n=1), and NDUFA2(n=1). Of the PEO group, three additional patients presented multiple DNA deletions suggesting a mitochondrial deletion syndrome and two patients were heterozygous for a pathogenic variant in a candidate recessive gene (POLG2 and TK2). Discussion and Conclusion: PEO is a common manifestation among mitochondrial diseases and the most common presentation of mitochondrial myopathies. Using a specific software, WES was able to analyze both nuclear DNA and mtDNA and found a definite molecular diagnosis in 58% of PEO and 30% of PEO+, and it showed strong candidates in additional 5 PEO patients. Large-scale deletion was detected in twelve patients; however, this was possible only after using a specific pipeline. We believe swab WES should be in the first tier for the diagnosis of mitochondrial myopathies after adjusting the pipeline to detect large mtDNA-deletions.

**Palavras-Chave do trabalho:** Mitochondrial Myopathy; PEO; WES;

**ID do trabalho:** 179

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: BENEFICIAL NUCLEOSIDES REPOSITION AT TK2D: THE FIRST BRAZILIAN COHORT OF TREATED PATIENTS.**

**Autores:** MORENO, Cristiane Araujo Martins<sup>1</sup>; FERNANDES, Tatiana Ribeiro<sup>1</sup>; ARTILHEIRO, Mariana Cunha<sup>1</sup>; TORRES, Gabriel Saboia de Araujo<sup>1</sup>; OKU, Mariana Hiromi Manoel<sup>1</sup>; DI PACE, Filipe Tupinamba<sup>1</sup>; DOUSSEAU, Gabriella Corrêa<sup>1</sup>; PAIVA, Michelle Abdo<sup>1</sup>; SILVA, Andre Macedo<sup>1</sup>; FONSECA<sup>1</sup>, Alulin Tácio Quadros Santos Monteiro<sup>1</sup>; CAMELO, Clara Gontijo<sup>1</sup>; ZANOTELI, Edmar Cristiane<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - Sao Paulo - SP - Brasil;

### **Resumo do trabalho:**

Background: Thymidine kinase 2 (TK2) is the enzyme responsible for the phosphorylation of deoxyribonucleosides deoxythymidine and deoxycytidine to deoxythymidine and deoxycytidine monophosphates, respectively. Both are phosphorylated to generate the deoxynucleosides triphosphates needed for the replication of mtDNA. Biallelic pathogenic variants within the TK2 gene result in TK2 deficiency (TK2d) and lead to DNA maintenance defects and depletion of mitochondrial DNA. This condition presents with a progressive and threatening myopathy with a high lethality specially among cases presenting symptoms in the first year of life. A supplementation therapy using monophosphate nucleosides to bypass the biochemical defect was developed and showed pronounced clinical benefits at open-label trials, enhancing the importance of an early diagnosis and early treatment to change the natural history of the disease. At present, there is a compassionate program that could benefit patients presenting aggressive forms of the disease. Here we present clinical findings and follow up of eight Brazilian patients receiving the nucleosides reposition through compassionate program. Patients and Methods: Eleven patients followed at Medicine School of University of São Paulo (FM/USP) were receiving supplementation therapy with deoxynucleosides (DThd and dCtd) in a compassionate program by the sponsor, offered orally at a dosage of 400mg/kg/day for each compound. Patients are evaluated every 3 months. Motor function was performed using MFM32, MFM20 or ChopIntend according to the age of the patient or maximum motor ability. Timed tests were performed (6MWT, 5XSTS, Gowers, 4 steps climb) as well fatigue and life quality scale selected by patient's age. Results: Patients were 20(+/-16) years old, two presented infantile-onset and nine presented childhood-onset. All of them were severely affected and attended to the requirements for the compassionate program. The protocol was approved by ANVISA in addition to the Clinical Hospital at FM/USP. One was followed for 21 months and presented an increase of points at Chop-Intend, increased weight, decreased time-on ventilation and regained the ability to swallow. One patient had 12 months followed up, one patient had 9 months followed up, three patients were on treatment for 6 months, and the five remaining presented had a follow up of 3 months. All patients presented an increase at MFM-32 total, D1 domain and spirometry. Seven patients were able to perform the 6MWT and all of them presented an increase in the distance walked. Discussion: TK2d is a progressive disease with high mortality rates. However, due to a potential treatment capable of changing the natural history of the disease, the early recognition of this disease is urgent. We demonstrated positive from the first patients receiving the treatment in Brazil.

**Palavras-Chave do trabalho:** Mitochondrial Myopathy; Nucleosides; TK2;

**ID do trabalho:** 180

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: FUNCTIONAL ASSESSMENT OF PATIENTS WITH MITOCHONDRIAL MYOPATHY CAUSED BY TK2 AND POLG**

**Autores:** FERNANDES, Tatiana Ribeiro<sup>1</sup>; LANÇA, Ana Paula dos Anjos<sup>1</sup>; ARTILHEIRO, Mariana Cunha<sup>1</sup>; DI PACE, Filipe Tupinambá<sup>1</sup>; DOUSSEAU, Gabriella Corrêa<sup>1</sup>; CAMELO, Clara Gontijo<sup>1</sup>; ZANOTELI, Edmar<sup>1</sup>; MORENO, Cristiane Araujo Martins<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Background: Mitochondrial myopathy is a multisystemic disease affecting primarily the muscles due to energetic failure resulted from mitochondrial dysfunction. Due to a dual genome regulation, it might be caused by changes in mitochondrial or nuclear DNA. Changes in TK2 and POLG nuclear genes cause mtDNA maintenance defects leading to mitochondrial diseases. The progression of motor deficits compromises patients' functional abilities, impacting their daily life activities. However data regarding natural history of the disease and their functional assessment is still lacking. Objective: To evaluate motor function

scale (MFM) results, respiratory function tests, performance measures and timed tests in a sample of 14 patients with mitochondrial myopathy. Methods: It is a transversal non-interventional study with an initial evaluation data of 14 patients with mitochondrial myopathy (10 TK2 and 4 POLG). The following outcomes were assessed: motor function scale (MFM), forced vital capacity (FVC), peak cough flow (PCF), 6-minute walk test (6MWT), 5-repetition sit-to-stand test (5XSTS), time to ascend and descend 4 steps and time to rise from the floor. Results: In TK2 group, total MFM scores ranged from 43 to 89 out of a maximum of 96 points, suggesting variability in overall motor impairment. In POLG group, it ranged from 84 to 94, with a more homogeneous motor impairment. At each scale domain, TK2 group had predominant impairment in D1 domain (standing and transfer skills), average percentage of  $47 \pm 26$ . In D3 domain (distal motor functions), the average percentage was  $99 \pm 2$ , suggesting minimal impairment in this function group. POLG patients performed better (D1  $87\% \pm 13$  and D3 at  $100\% \pm 0$ ) suggesting less motor function impairment. All patients had FVC below 80% of the predicted value, while 7 had values below 50%, indicating significant respiratory impairment in both groups. One POLG patient had an FVC of 38% and was unable to perform motor function tests. All TK2 patients had PCF below 360L/min, and 7 had values below 260L/min, indicating ineffective coughing, while POLG achieved a mean PCF of  $355 \pm 102$  L/min, indicating that despite a below-predicted FVC, there was better cough effectiveness compared to TK2 patients. Timed tests varied substantially, indicating different levels of functional capacity, but POLG patients performed better and had less fatigability. Conclusions: We revealed significant differences between patients with mitochondrial myopathy caused by TK2 and POLG. TK2 patients showed greater motor impairment, especially in standing and transfer skills, more fatigability and lower MFM scores. Both groups exhibited pronounced respiratory impairment, however, POLG patients demonstrated better cough effectiveness compared to TK2. These findings highlighted that combining clinical scales like MFM, performance measures and timed motor skill tests can provide a comprehensive view of patients' functional capacities, essential for monitoring disease.

**Palavras-Chave do trabalho:** DNA Polymerase Gamma; Mitochondrial Myopathies; Thymidine Kinase;

**ID do trabalho:** 182

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **RELIABILITY OF PERFORMANCE OUTCOMES IN INDIVIDUALS WITH HEREDITARY SPASTIC PARAPLEGIA**

**Autores:** POSSEBON BEVILACQUA, Isabela<sup>1</sup>; CUBILLOS ARCILA, Diana Maria<sup>1</sup>; CARPEGGIANE WEBER, Arthur<sup>2</sup>; VIEIRA MOTTA, Bárbara<sup>2</sup>; FARIA ROSA, Bruna<sup>2</sup>; WESCHENFELDER, Cesar Augusto<sup>2</sup>; RIBEIRO DE SOUZA, Maria Eduarda<sup>2</sup>; HERINGER BERNARDINO, Pablo Jhuan<sup>3</sup>; MORALES SAUTE, Jonas Alex<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul, Programa de Pós Graduação em Ciências Médicas - Porto Alegre - RS - Brasil; (2) Universidade Federal do Rio Grande do Sul, Faculdade de Medicina - Porto Alegre - RS - Brasil; (3) Universidade Federal de Ciências da Saúde de Porto Alegre, Faculdade de Medicina - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Assessing gait performance in Hereditary Spastic Paraplegia (HSP) is challenging due to disease variability, its progressive nature, and daily fluctuations in motor performance. The Timed Up and Go (TUG) and 10-Meter Walk Test (10MWT) are considered the most sensitive clinical outcome assessment for HSP, yet their reliability remains underexplored. Objective: To assess the test-retest reliability of the TUG and 10MWT, determine the optimal number of repetitions for accurate results, and evaluate inter-rater reliability. Methods: Seventeen individuals with HSP (mean disease duration  $15.9 \pm 11.1$  years; SPG types: SPG4 [47.1%], SPG10 [17.6%], UKN [17.6%], SPG7 [11.8%], SPG76 [5.9%]) performed the TUG and 10MWT. Tests were administered by an experienced evaluator and compared with assessments from four less experienced raters in two sessions spaced 7–14 days apart. Each participant performed three trials at a self-selected speed (SSS) and one at maximum speed. Repeatability analysis included previously collected data from 36 participants for the TUG and 43 for the 10MWT. Test-retest reliability was assessed using intraclass correlation coefficients (ICCs), and the minimal detectable change (MDC) was determined using the standard error of measurement. Results: Excellent reliability was observed for the TUG-SSS when comparing the first measure with the mean of three trials and with the best attempts (ICC = 0.995 and 0.986). The difference between the initial assessment and the mean of three trials was 0.52s (95% CI: 0.08–0.96; MDC=1.92), while the difference between the initial assessment and the best attempt was 1.49s (95% CI: 0.91–2.07; MDC=3.17). For the 10MWT-SSS, excellent reliability was also observed when comparing the first measure with the mean of three trials and with the best attempts (ICC = 0.995 and 0.999). The difference between the initial assessment and the mean of three trials was 0.13s (95% CI: -0.07–0.35; MDC=0.81), while the difference between the initial assessment and the best attempt was 0.61s (95% CI: 0.28–0.94; MDC=1.77). In test-retest, ICCs for the TUG ranged from 0.946 to 0.971 and from 0.937 to 0.971 for the 10MWT, considering the first measure, the mean of three measures, and the best time. Inter-rater analysis showed good reliability for the TUG-SSS (ICC = 0.882) and excellent reliability for TUG at maximum speed (ICC = 0.984), 10MWT at SSS (ICC = 0.959) and maximum speeds (ICC = 0.990). Conclusion: The TUG and 10MWT are reliable tools for assessing functional performance in individuals with HSP, demonstrating excellent stability and precision. Since the mean differences between a single test and multiple tests were lower than the MDC, a single administration of the TUG and 10MWT is sufficient for reliable assessment. These findings confirm their validity as essential outcome measures for multicenter clinical trials and support the optimization of testing protocols.

**Palavras-Chave do trabalho:** 10-Meter Walk Test; Gait Performance; Hereditary Spastic Paraplegia; Performance Outcomes; Timed Up and Go;

**ID do trabalho:** 184

**Área Técnica do trabalho:** Genética populacional

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: EPIDEMIOLOGICAL CHARACTERIZATION OF RARE DISEASES IN BRAZIL: A RETROSPECTIVE STUDY OF THE BRAZILIAN RARE DISEASES NETWORK**

**Autores:** DE OLIVEIRA, Bibiana Mello<sup>1</sup>; BERNARDI, Filipe Andrade<sup>2</sup>; BAIOSCHI, João Francisco<sup>2</sup>; ACOSTA, Angelina Xavier<sup>3</sup>; RIBEIRO, Erlane Marques<sup>4</sup>; SAUTE, Jonas Alex Morales<sup>5</sup>; SANTOS, Mara Lucia Schmitz Ferreira<sup>6</sup>; COSTA, Marcela Câmara Machado<sup>7</sup>; DE MENEZES, Marilaine Matos<sup>7</sup>; BOA SORTE, Ney<sup>3</sup>; AMORIM, Tatiana<sup>8</sup>; FERRAZ, Victor Evangelista de Faria<sup>9</sup>; SCHWARTZ, Ida Vanessa Doederlein<sup>10</sup>; ALVES, Domingos<sup>11</sup>; FÉLIX, Têmis Maria<sup>5</sup>; GROUP, Raras Network<sup>1</sup>;

**Instituição dos Autores:** (1) Rede Nacional de Doenças Raras - Porto Alegre - RS - Brasil; (2) Rede Nacional de Doenças Raras - Ribeirão Preto - SP - Brasil; (3) Hupes-UFBA - Hospital Universitário Professor Edgard Santos - Salvador - BA - Brasil; (4) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil; (5) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (6) Hospital Pequeno Príncipe - Curitiba - PR - Brasil; (7) Escola Bahiana de Medicina e Saúde Pública - Salvador - BA - Brasil; (8) APAE Salvador - Salvador - BA - Brasil; (9) Hospital das Clínicas FMUSP - Ribeirão Preto - Ribeirão Preto - RS - Brasil; (10) Hospital de Clínicas de Porto Alegre / UFRGS - Porto Alegre - RS - Brasil; (11) USP Ribeirão Preto - Ribeirão Preto - SP - Brasil;

### **Resumo do trabalho:**

Background: The Brazilian Policy for Comprehensive Care for People with Rare Diseases was implemented in 2014, however national epidemiological data on rare diseases (RDs) remain limited and primarily focused on specific conditions. To address this gap, the Brazilian Rare Diseases Network (RARAS), composed of university hospitals, neonatal screening reference services, and rare disease reference services, was established in 2020. This study aimed to conduct a comprehensive national epidemiological analysis of individuals with RDs in Brazil. Methods: A retrospective survey was performed using data from 12,530 participants assisted in 2018 and 2019 at 34 healthcare facilities affiliated with RARAS. Data demographics, diagnostic pathways, clinical manifestations, and treatment modalities were analyzed. Results: Data showed a median age of 15 years, with 50.5% female participants. Skin color classification indicated that 47.4% were admixed. A confirmed diagnosis was observed in 63.2%, with phenylketonuria (PKU), cystic fibrosis (CF), acromegaly, osteogenesis Imperfecta, and dystrophinopathies as the most common conditions. Global developmental delay, seizures, short stature, intellectual disability, and hypotonia were the most frequent clinical manifestations. The average diagnostic odyssey spanned 5.4 years ( $\pm 7.9$ ). Among the confirmed diagnoses, 52.2% were etiological (biochemical: 42.5%; molecular: 30.9%), while 47.8% were clinical. Prenatal diagnoses accounted for 1.2%. Familial recurrence and consanguinity rates were 21.6% and 6.4%, respectively. Treatment primarily involved drug therapy (55.0%) and rehabilitation (15.6%). The Public Health System funded most diagnoses (84.2%) and treatments (86.7%). Hospitalizations were reported in 44.5% of cases, with a 1.5% mortality rate, primarily due to motor neuron disease and CF. Conclusion: This study represents a pioneer nationwide epidemiological investigation of RDs in Brazil, offering novel insights into the prevalence, diagnostic challenges, and management of these conditions. It highlights a prolonged diagnostic odyssey, with a notable prevalence of PKU and CF, possibly associated with the specialized services network, which included newborn screening services. The findings underscore the importance of advancing healthcare policies and resource allocation to improve outcomes for individuals with RDs.

**Palavras-Chave do trabalho:** Brazil; Diagnostic odyssey; Epidemiology; Public Health; Rare Diseases;

**ID do trabalho:** 187

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: TWO SISTERS, SAME VARIANTS, AND STRIKINGLY DIFFERENT OUTCOMES: EXPANDING THE PHENOTYPIC SPECTRUM OF CAD DEFICIENCY BEYOND URIDINE-RESPONSIVE EPILEPTIC ENCEPHALOPATHY**

**Autores:** GUIMARAES MARCARINI, Bruno<sup>1</sup>; ONEDA SAKAI, Eric<sup>1</sup>; ALENCAR MOURA, Eder<sup>1</sup>; PONTES, Patricia<sup>1</sup>; GARCIA, Renata<sup>1</sup>; PEREIRA DA SILVA, Sergio Roberto<sup>1</sup>; BUENO, Clarissa<sup>1</sup>; KOK, Fernando<sup>1</sup>;

**Instituição dos Autores:** (1) HCFMUSP - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Case presentation: We report two sisters carrying biallelic pathogenic variants in the CAD gene. The older sister presented at 1 year old with early-onset epileptic encephalopathy, progressive neurodevelopmental regression, refractory seizures, and megaloblastic anemia. Despite multiple anti-seizure medications, seizure control remained poor and she experienced multiple episodes of status epilepticus. Following significant neurological deterioration, a molecular diagnosis was established only at age 7 through exome sequencing, which identified two compound heterozygous pathogenic variants c.571C>T;p.(Arg191\*)/c.5429G>A;p.(Arg1810Gln). Uridine supplementation was introduced late (at age 7), after which seizures ceased, and the family reported improvements in swallowing function. By age 14, she required a feeding tube and tracheostomy for respiratory and nutritional support. In contrast, the younger sister exhibited only mild intellectual disability (IQ 65), without seizures up to her last evaluation at age 12. Genetic testing confirmed the same compound heterozygous CAD variants. Her diagnosis was established at age 7, but she is 13 and still not on uridine supplementation due to internal hospital processes and financial constraints. Discussion: CAD deficiency is a rare autosomal recessive metabolic disorder that results from impaired de novo pyrimidine biosynthesis. It is typically characterized by early-onset epilepsy, developmental delay and hematologic abnormalities. While the response to uridine therapy remains incompletely understood, emerging evidence suggests significant clinical benefits. This case highlights a marked intra-familial clinical variability. Final comments: To our knowledge, this is the first reported case of CAD deficiency presenting only with mild intellectual disability, despite the absence of uridine supplementation. These cases expand the known phenotypic spectrum of the disorder beyond the typical presentation of epileptic encephalopathy.

**Palavras-Chave do trabalho:** CAD deficiency; epilepsy; global developmental delay;

**ID do trabalho:** 188

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **FACIOSCAPULOHUMERAL DYSTROPHY: IN SEARCH OF A BRAZILIAN EPIDEMIOLOGICAL PROFILE**

**Autores:** DOUSSEAU, Gabriella Correa<sup>1</sup>; DI PACE, Filipe Tupinambá<sup>2</sup>; CAMELO, Clara Gontijo<sup>2</sup>; FERNANDES, Tatiana Ribeiro<sup>2</sup>; LANÇA, Ana Paula dos Anjos<sup>2</sup>; CAMPOS, Eliene Dutra<sup>2</sup>; MORENO, Cristiane Araújo Martins<sup>2</sup>; ZANOTELI, Edmar<sup>2</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas HC FMUSP - São Paulo - SP - Brasil; (2) Hospital das Clínicas HC HMUSP - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Background: Facioscapulohumeral dystrophy (FSHD) is an autosomal dominant muscular dystrophy caused by abnormal DUX4 gene activation due to changes in the D4Z4 region on chromosome 4. It affects 5–12 per 100,000 people, with symptoms typically appearing in the second or third decade, though onset can occur at any age. The condition affects both genders equally and can range from mild weakness to significant disability. Objectives: It aims to describe the onset, progression, and severity of FSHD symptoms, along with distinguishing clinical factors, socioeconomic impacts, and effects on daily quality of life. Methods: This is an observational study of FSHD in the Brazilian healthcare system from 1 January 2024 to 1 January 2025. Results: A cohort of 38 patients were included, aged 11–78y (median: 46y; IQ: 33.5–55), evenly distributed by sex (50% male, 50% female). Symptom onset occurred between ages 4–57y (median: 21y; IQ: 13–40), with disease duration at baseline ranged from 5–62y (median: 19y; IQ: 10–27). Among participants, 84.2% underwent genetic confirmation —44.7% by methylation assay, 39.5% by D4Z4 contraction analysis and 15.78% are awaiting testing, with diagnoses supported by phenotype and family history. Regarding symptom onset, 60.5% reported the shoulder girdle as the initial site, 13.1% facial, 7.9% axial, and 5.2% pelvic girdle. Interestingly, while only 26.3% reported facial weakness, 86.8% had examiner-detected facial involvement (OR 17.55, 95% CI: 5.60–63.5,  $p < 0.0000001$ ). In terms of mobility, 89.5% retained walking ability, with 18.4% needing assistance, and 7.9% relying on a wheelchair for long distances. Exclusive wheelchair use was reported in 10.5% of patients. Respiratory function, measured by forced vital capacity (FVC), ranged from 27–133% of predicted values (median: 87%; IQ: 64–90), with 18.4% requiring non-invasive ventilatory support. All patients were orally fed, and none needed gastrostomy, although 13.1% had dysphagia, and 18.4% had dysarthria or dysphonia. Spinal deformities were seen in 79% of patients: 44.7% had hyperlordosis, 5.3% kyphoscoliosis, and 28.9% both. Pain was reported by 76.3%, with 23.7% pain-free. Regarding mood disorders, 21% had anxiety, 5.3% depression, and 7.9% had both. Comorbidities included hearing impairment (13.1%), heart disease (13.1%), and retinopathy (2.6%). When asked about self-perceived severity, 13.1% considered their condition mild, 55.2% moderate, and 42.1% severe, with 10.5% unsure. Conclusion: This study highlights the clinical variability and impact of FSHD, providing valuable insights into disease progression and patient experience. The findings are crucial for improving diagnostic accuracy, identifying clinical markers, and developing targeted therapeutic strategies to enhance patient care and outcome.

**Palavras-Chave do trabalho:** ; Brazilian; dystrophy; epidemiological; Facioscapulohumeral;

**ID do trabalho:** 189

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: EFFECT OF A 12-WEEK PROTOCOL OF STRENGTH AND FUNCTIONAL EXERCISES ON TREATMENT OF MOTOR SYMPTOMS IN INDIVIDUALS WITH HEREDITARY SPASTIC PARAPARESIS: ADAPTIVE CROSSOVER RANDOMIZED CLINICAL TRIAL**

**Autores:** MOTTA, Bárbara Vieira<sup>1</sup>; BEVILACQUA, Isabela Possebon<sup>2</sup>; ARCILA, Diana Maria Cubillos<sup>2</sup>; WEBER, Arthur Carpeggiani<sup>1</sup>; WESCHENFELDER, Cesar Augusto<sup>1</sup>; ROSA, Bruna Faria<sup>1</sup>; BERNARDINO, Pablo Jhuan Heringer<sup>3</sup>; MARTINEZ, Flávia Gomes<sup>4</sup>; DE SOUZA, Maria Eduarda Ribeiro<sup>3</sup>; SAUTE, Jonas Alex Morales<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul, Faculdade de Medicina - Porto Alegre - RS - Brasil; (2) Universidade Federal do Rio Grande do Sul, Programa de Pós Graduação em Ciências Médicas - Porto Alegre - RS - Brasil; (3) Universidade Federal de Ciências Médicas de Porto Alegre, Faculdade de Medicina - Porto Alegre - RS - Brasil; (4) Universidade Federal do Rio Grande do Sul, Faculdade de Educação Física - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Hereditary spastic paraplegias (HSP) are a rare neurodegenerative genetic disorder characterized by spastic hypertonia, hyperreflexia, muscle weakness in the lower limbs, and impaired vibratory sensation, resulting in the gradual loss of balance and walking ability. Due to clinical and genetic heterogeneity, as well as functional deficits, defining sensitive biomarkers for use in clinical trials and evaluating the disease course is challenging. Objective: To assess the effect of a 12-week strength and functional exercise protocol on the motor symptoms in individuals with hereditary spastic paraplegia and to analyze the sensitivity to change of the Clinician-Reported Outcome measures, performance outcomes, and Digital Health Technology. Methods: This is an adaptive cross-over randomized clinical trial. Initially, 20 patients diagnosed with HSP will be recruited. The study will be adapted based on an interim data analysis after 24 weeks, which will assess whether the effect is promising, favorable, or unfavorable through statistical analysis. The performance tests will be used to define the adaptation of the study's sample size. Outcomes will be measured through the disease stage, Spastic Paraplegia Rating Scale, Ashworth Scale (Lower Limbs), muscle strength test (Medical Research Council), muscle strength test using handheld dynamometry, Timed Up and Go, 10-meter walk test at maximum and self-selected speeds, kinematic gait evaluation, Clinical Global Impression of Change scale, Fall Efficacy Scale - Brazilian Version, Goal Attainment Scale, and the SF-36 Quality of Life Questionnaire. After randomization, the intervention group will have two online sessions per week, each lasting 60 minutes, for 12 weeks. Participants will be reassessed immediately at the end of the interventions, and group crossover will be conducted. Preliminary Results: To date, 15 participants have been included. The sample consists of 53,3% female participants. The mean age of participants is 47,27 years ( $\pm 15.89$ ), indicating a wide age range. The mean duration of the disease among participants is 17.73 years ( $\pm 10.04$ ). Regarding disease subtypes, 53,3% of participants were diagnosed with SPG4, 13,3% with SPG 7, 13,3% with SPG10 and 20% are unknown type. Concerning the disease stage, 6,7% of participants are in stage 1, 26,7% in stage 2, 33,3% in stage 3 and 33,3% in stage 4. We will have the results of the comparison between treatments only after the conclusion of the study. Conclusion: The findings of this study may contribute to the development of an exercise protocol aimed at treating motor symptoms associated with the disease. Furthermore, the results may assist in identifying the sensitivity to change and clinical meaningfulness of the changes in clinical outcome assessments and digital health technologies. This information is crucial for the design of symptomatic and disease-modifying therapy trials.

**Palavras-Chave do trabalho:** Biomarkers; Clinical Outcomes; Exercise Protocol; Hereditary Spastic Paraplegia; Motor Symptoms;

**ID do trabalho:** 190

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: CMAP SCAN AND WEARABLE BIOSENSORS: NEW POTENTIAL BIOMARKERS TO MONITOR COQ7-RELATED DISTAL MOTOR NEUROPATHY WITH PYRAMIDAL FEATURES**

**Autores:** LIMA, Izadora Vieira Bolzani Lopes<sup>1</sup>; SANTOS, Nadson Bruno Serra<sup>1</sup>; MARTINS, Aldrin Pedroza<sup>1</sup>; DE LIMA, Fabricio Diniz<sup>1</sup>; SILVEIRA, Cynthia<sup>1</sup>; DE REZENDE, Thiago Junqueira Ribeiro<sup>1</sup>; MARTINEZ, Alberto Rolim Muro<sup>1</sup>; JR., Marcondes Cavalcante França<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Estadual de Campinas - UNICAMP - Campinas - SP - Brasil;

**Resumo do trabalho:**

Background To date, there are approximately 11 genes involved in the biosynthesis of coenzyme Q10, collectively called COQ genes. Recently, a new subtype of distal motor neuropathy with pyramidal features caused by biallelic COQ7 variants was identified (1). This new clinical entity is associated with endogenous COQ10 deficiency, and therefore potentially treatable with supplementation of this cofactor. For this reason, clinical tools to monitor disease progression and response to therapy are needed. Motor number estimation (MUNE) using the CMAP Scan-Fit technique and gait analyses using wearable inertial sensors (WIS) emerge as interesting candidates. The first relies upon a method proposed by Prof. Hugh Bostock that uses Bayesian statistics and a detailed stimulus-response curve to compute MUNE (2). The second enables the computation of multiple stance and gait parameters using wearable devices (3). Objectives To evaluate whether MUNE and WIS-derived parameters correlate with clinical severity in patients with COQ7-related disease. Methods Six symptomatic patients with COQ7-related disease underwent CMAP Scan-Fit MUNE in the right abductor digiti minimi (ulnar nerve) using a Neurosoft Litebox electromyographer and gait analyses using the APDM® Movement Monitoring inertial sensor system. The present study was approved by the local ethics committee and all patients were given written informed consent. Of the 6 patients selected, 5 were able to perform gait assessment (the other was no longer able to walk). Regarding the CMAP Scan, one patient did not tolerate repeated supramaximal stimuli and was therefore excluded from the analyses. We then assessed whether these parameters correlated with the Spastic Paraplegia Rating Scale (SPRS) scores, using Spearman correlation coefficients. Results Mean age and disease duration were 40,6 years(y) and 30,1y, respectively. All patients had lower limb spasticity and distal muscle wasting. None of them had ataxia or sensory abnormalities. Regarding MUNE, we observed a positive direct correlation with SPRS scores ( $p = 0.553$ ). WIS-derived parameters also correlated with SPRS scores: Step duration (s) " $p$ " = 0.548; elevation at midswing (cm) " $p$ " = 0.759; gait cycle duration (s) " $p$ " = 0.736; and cadence (steps/min) " $p$ " = -0.771. Conclusion Although exploratory, these data suggest that advanced tools – such as MUNE and WIS-derived gait analysis – add to standard clinical evaluation in COQ7-related disease. Our results should be validated in larger cohorts followed longitudinally.

**Palavras-Chave do trabalho:** CMAP Scan; Coenzyme Q10; COQ7; inertial sensors; wearable devices;

**ID do trabalho:** 192

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: RELATIONSHIP BETWEEN ADMISSIONS FROM CEREBRAL PALSY IN INFANTS IN BRAZILIANS REGIONS FROM 2014 TO 2024: EPIDEMIOLOGICAL ANALYSIS**

**Autores:** BRITTO, Maria Clara Souto de<sup>1</sup>; RIBEIRO, Manuella Pimenta Medeiros Netto<sup>1</sup>;

**Instituição dos Autores:** (1) Medicina Zarns - SSA - BA - Brasil;

**Resumo do trabalho:**

Background: Cerebral palsy (CP) is a heterogeneous group of permanent motor disorders that develop from non-progressive issues in the developing fetal or infant brain. It is characterized by a range of motor impairments, including spasticity, dyskinesia, and ataxia, which result from damage to the brain's motor control centers. CP is multifactorial and complex, with a combination of genetic, prenatal, perinatal, and postnatal factors contributing to its development. Risk factors include premature birth, low birth weight, infections, and hypoxic-ischemic injury. The impact of CP on affected individuals is profound, not only in terms of physical disability but also in social, psychological, and cognitive domains. Objective: This study aims to analyze the epidemiological profile of the relationship between admissions and age from cerebral palsy in Brazil from 2014 to 2024. Methodology: Descriptive, cross-sectional, and observational study using secondary data from the SUS Hospital Information System (SIH/SUS) regarding hospitalizations for epilepsy in Brazil. The period considered was between 2014 and 2024, and the variable used was hospitalizations per age 0-19 comparing Brazilian regions. Results: From 2014 to 2024, a total of 237 children aged 0-19 were hospitalized for cerebral palsy in Brazil. Among the Brazilian regions, the Southeast leads these hospitalizations significantly, with 128 cases (53,9%), followed by the Northeast with 49 (20.6%), South with 24 (10.1%), North with 19 (8.02%), and Central-West with 17 (7.17%). The Southeast region, which is home to nearly half of Brazil's population, has more investments in healthcare programs to diagnose and treat various neurological disorders, including cerebral palsy. Additionally, many patients must seek help outside their region, migrating to the Southeast, due to extreme poverty and lack of assistance. When analyzing age groups, children under 1 year old had the highest number of hospitalizations due to PC in the past decade, with 73 cases (30.8%). This was followed by the 15-19 age group with 51 cases, 1-4 years with 49 cases (21.5%), 10-14 years with 36 cases (15.1%), and 5-9 years with 28 cases (11.8%). This is primarily due to the multifactorial severity of cerebral palsy, which, combined with respiratory, neurological, and feeding comorbidities, can lower the survival rate and life quality without intensive and specialized medical care. Conclusion: The study shows the significant regional differences in the hospitalization rates for cerebral palsy in Brazil, with the Southeast region leading due to greater healthcare infrastructure and investment. The high hospitalization rates, particularly among children under 1 year old, highlight the critical vulnerability of infants with cerebral palsy, whose condition often involves severe complications. These challenges reinforce the need for early diagnosis and specialized interventions to improve quality of life for affected individuals.

**Palavras-Chave do trabalho:** ; Cerebral Palsy; Hospitalizations; Infants;

**ID do trabalho:** 193

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: INVESTIGATION OF FATTY ACID BETA-OXIDATION DEFECTS IN RIO GRANDE DO SUL

**Autores:** RODRIGUES NUNES, Marcela<sup>1</sup>; FASOLO FRANCESCHETTO, Bianca<sup>2</sup>; FARRET REFOSCO, Lilia<sup>2</sup>; FISCHINGER MOURA DE SOUZA, Carolina<sup>3</sup>; DOEDERLEIN SCHWARTZ, Ida Vanessa<sup>2</sup>; GAZZOLA ZEN, Paulo Ricardo<sup>1</sup>; MELLO DE OLIVEIRA, Bibiana<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal de Ciências da Saúde de Porto Alegre/Santa Casa de Porto Alegre - Porto Alegre - RS - Brasil; (2) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (3) Hospital de Clínicas de Porto Alegre/Casa dos Raros - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

**BACKGROUND:** Fatty acid  $\beta$ -oxidation defects (FAODs) constitute a heterogeneous group of disorders in the fatty acid transport chain and mitochondrial  $\beta$ -oxidation. These conditions affect energy homeostasis, primarily in the liver, heart, and skeletal muscles, and often present with multi-system involvement, including potentially life-threatening manifestations. FAODs are inherited as autosomal recessive disorders and have a variable presentation, which may manifest in the neonatal period or at later stages. **OBJECTIVE:** This study aimed to clinically characterize patients diagnosed with FAODs in the state of Rio Grande do Sul, including clinical, biochemical, genetic aspects, and therapeutic management. **METHODS:** A retrospective observational study was conducted, with data collected from medical records submitted by attending physicians through an electronic form. Patients with a confirmed diagnosis of FAODs, residing in or diagnosed in the state of Rio Grande do Sul, were included. The study received ethical approval. **RESULTS:** A total of 16 patients were included, 62.5% of whom were female, with a mean age of 19.2 years (range: 0-51 years). The majority (75%) were white, and 75% were born in Rio Grande do Sul. The most common signs and symptoms included hypoketotic hypoglycemia (81.3%), liver dysfunction (68.8%), seizures (56.3%), and vomiting (56.3%). The most frequent diagnoses were Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD, n=5, 31.3%) and Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD, n=3, 18.8%). The average time to diagnosis was 5.14 years (range: 0 months to 21.4 years). Diagnosis was predominantly made in the context of a metabolic crisis (56.3%). The diagnostic confirmation was mainly based on genetic analysis (87.5%) and acylcarnitine profile by tandem (81.3%). Regarding management, 93.8% of patients received nutritional therapy, with carnitine supplementation (50%), triheptanoin (43.8%), and medium-chain triglycerides (25%) as the most frequent components. Four patients required alternative nutritional support. There were two recorded deaths (12.5%). **CONCLUSION:** The results reinforce the multi-systemic and heterogeneous nature of FAODs, highlighting the prolonged diagnostic odyssey. Clinical management emphasizes the importance of nutritional and multidisciplinary therapy. In the context of rare diseases, FAODs require additional efforts in research, professional training, and the implementation of public policies that enable early diagnoses, especially through the effective implementation of neonatal screening and effective treatments.

**Palavras-Chave do trabalho:** Fatty acid  $\beta$ -oxidation defects (FAODs); Rare Diseases; Rio Grande do Sul;

**ID do trabalho:** 194

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: MYOCLONIC-ATONIC EPILEPSY IN A PEDIATRIC PATIENT: DIAGNOSTIC AND MANAGEMENT CHALLENGES OF DOOSE SYNDROME

**Autores:** RODRIGUES NUNES, Marcela<sup>1</sup>; MELLO DE OLIVEIRA, Bibiana<sup>1</sup>; BAIERLE GUARANÁ, Bruna<sup>1</sup>; SIMEONI AMADO, Tais<sup>1</sup>; LIMA ROCHA, Daniele<sup>1</sup>; LUDOVICO, Leticia<sup>1</sup>; PEDELHES SILVA, Laysla<sup>1</sup>; PICCOLI LUCAS, Karen Daniela<sup>1</sup>; LIMA SCORTEGAGNA, Mariana<sup>1</sup>; BALESTRIN, Raquel Cristina<sup>1</sup>; TONON, Tássia<sup>1</sup>; MARTINS DIOGO, Alessandra<sup>1</sup>; ALVES VIEIRA, Tatiane<sup>1</sup>; POZZEBON DA SILVA, Larissa<sup>1</sup>; MALGAREZI MORAES, Natasha<sup>1</sup>; BARBOSA TRAPP, Franciele<sup>1</sup>; RIEGEL-GIUGLIANI, Mariluce<sup>1</sup>; FISCHINGER MOURA DE SOUZA, Carolina<sup>1</sup>; GIUGLIANI, Roberto<sup>1</sup>;

**Instituição dos Autores:** (1) Casa dos Raros - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

**CASE PRESENTATION** A 5-year-old male presented with neuropsychomotor regression, hypotonia, refractory epilepsy, and behavioral changes. Born at 36 weeks via vaginal delivery complicated by shoulder dystocia, prenatal care was uneventful until three maternal bleeding episodes at 32 weeks. Development was normal until 6 months, followed by regression, loss of head control, and hypotonia. Frequent infections ensued, including three hospitalizations for sepsis. Autoimmune disease was initially

suspected. At 1 year and 2 months, he was referred to a geneticist for worsening hypotonia and seizures. At 2 years, autism spectrum disorder (ASD) was diagnosed by his neurologist. Brain MRI showed a thin corpus callosum with ectatic trigones and occipital horns; follow-up MRI revealed prominent Virchow-Robin spaces with an intact corpus callosum. EEGs showed generalized spike-wave discharges, electrographic seizures, and epileptiform activity exacerbated by photostimulation. A multi-gene panel for epilepsy and ataxia was negative, but a developmental and movement disorder panel identified a heterozygous VUS in SLC6A1 gene (p.His198Arg). Physical examination revealed minor dysmorphic features, pectus excavatum and reduced muscle trophism with preserved strength. Clinical evaluation and data review enabled the reclassification of the genetic variant in SLC6A1 gene, supported by the identification of the same substitution and other de novo substitution affecting the same codon (p.His198Pro) registered in 2023. A 2024 publication provided functional evidence demonstrating the pathogenic mechanism of the p.His198Arg variant. Based on clinical correlation and novel evidence, the variant was reclassified as likely pathogenic, confirming the diagnosis of myoclonic-atonic epilepsy (MAE). Current management includes sodium valproate, clobazam, and a ketogenic diet, which has improved seizure control. **DISCUSSION:** MAE, also known as Doose syndrome, is a rare epileptic syndrome characterized by developmental delay, hypotonia, intellectual disability, and multiple seizure types, including myoclonic-atonic, tonic-clonic, and absence seizures. Neurodevelopmental disorders, such as ASD and ADHD, are common. Gastrointestinal symptoms, including constipation and diarrhea, are frequent. The patient presented a classic clinical course of MAE. The diagnosis was confirmed after a comprehensive review of the genomic finding, highlighting the importance of systematic and longitudinal monitoring of literature and international genomics repositories to enable data reassessment and diagnostic conclusions in such cases. The ketogenic diet proved particularly beneficial, consistent with reports suggesting its early introduction in refractory cases. **FINAL COMMENTS:** This case underscores the importance of a multidisciplinary approach, including genetic testing and dietary interventions, in managing MAE. Early diagnosis and targeted therapy can improve outcomes in this challenging condition.

**Palavras-Chave do trabalho:** Developmental Regression; Doose; Ketogenic Diet; Myoclonic-Atonic Epilepsy; SLC6A1;

**ID do trabalho:** 197

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: THE JOURNEY OF DIAGNOSIS: CHALLENGES IN IDENTIFYING WILLIAMS-BEUREN SYNDROME IN THE INTERIOR OF CEARÁ**

**Autores:** DO NASCIMENTO, Cláudio José Alves<sup>1</sup>; DOURADO, Sindy Maria Menezes<sup>2</sup>;

**Instituição dos Autores:** (1) Clínica Escola de Neurologia Infantil da Ibiapaba - Tianguá - CE - Brasil; (2) Universidade CEUMA - Imperatriz - MA - Brasil;

### **Resumo do trabalho:**

Williams-Beuren Syndrome (WBS) is a rare genetic disorder caused by a deletion on chromosome 7, leading to cognitive difficulties, heart problems, and distinctive facial features. Genetic diagnosis, typically conducted using techniques like FISH or DNA microarray, is the gold standard. However, financial barriers may prevent these tests, leading to clinical diagnoses. **CASE PRESENTATION:** A 12-year-old boy from a rural city in Ceará, with no family history of genetic disorders, was diagnosed with WBS at age 7 after clinical evaluation. His diagnosis was based on delayed motor and speech development, cognitive difficulties, and facial features suggestive of the syndrome. Since early life, the child showed delays in both motor skills and speech. At 1 year and 8 months, he began walking but was delayed in speaking. At school, he struggled with reading, writing, and abstract concepts. At 2 months, the child underwent surgery for a bilateral inguinal hernia with no complications. Physical examination revealed typical WBS facial features, such as a low nasal bridge, wide mouth, and spaced teeth. The child was diagnosed with cardiac issues, these being mitral and tricuspid insufficiency. He also exhibited excessive sociability, often seeking interactions with strangers. Based on clinical signs, WBS was suspected. Although the diagnosis aligned with WBS, genetic confirmation through tests like FISH or DNA microarray was recommended. Due to the family's financial constraints, genetic testing was not performed, leaving the diagnosis clinically-based. The mother reported mobility issues and the need for physical therapy, but treatments were interrupted by financial difficulties, as were psychopedagogical and psychological follow-ups. The child currently receives annual follow-ups with a cardiologist and geneticist and weekly visits to a pediatric dentist. **DISCUSSION:** The clinical diagnosis allowed for the initiation of management but the lack of genetic confirmation complicated planning more specific interventions. While the clinical diagnosis is valuable, it doesn't provide a full understanding of the child's needs. Limited access to genetic testing due to financial barriers is a significant challenge, especially for low-income families. This case highlights the importance of public health policies ensuring access to genetic testing for more accurate diagnoses and interventions. **FINAL COMMENTS:** This case emphasizes the importance of genetic diagnosis for managing rare conditions like Williams-Beuren Syndrome. The lack of access to genetic testing due to financial constraints limits proper management of the syndrome. Public policies that ensure access to genetic testing are crucial to improving early diagnosis and care for children with rare genetic conditions like WBS.

**Palavras-Chave do trabalho:** Challenges; genetic diagnosis; Williams-Beuren Syndrome;

**ID do trabalho:** 203

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **EVALUATION OF RAAVRH74 ANTIBODIES SEROPREVALENCE: INSIGHTS FROM THE LARGER TESTED COHORT OF DUCHENNE PATIENTS IN BRAZIL**

**Autores:** FRANCO DA GRAÇA, Felipe<sup>1</sup>; GONTIJO CAMELO, Clara<sup>2</sup>; BANZZATTO ORTEGA, Adriana<sup>3</sup>; GROSSKLAUSS, Luis Fernando<sup>4</sup>; DE HOLANDA MENDONCA, Rodrigo<sup>2</sup>; ANTONIO VELOSO DE ALBUQUERQUE, Marco<sup>2</sup>; RABELO DE BRITO, Mariana<sup>1</sup>; CAVALCANTE FRANÇA JR, Marcondes<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Estadual de Campinas - Campinas - SP - Brasil; (2) Universidade de São Paulo - São Paulo - SP - Brasil; (3) Hospital Infantil Pequeno Príncipe - Curitiba - PR - Brasil; (4) Universidade Federal de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

With the increasing utilization of viral vector-based gene therapies, knowing the seroprevalence of the virus-specific antibodies is crucial for estimating the pool of eligible patients within a population. Recombinant AAV serotype rh74 (rAAVrh74) is a vector used in Delandistrogene Moxeparvovec (DM), the first gene therapy approved for treating Duchenne muscular dystrophy. Its seroprevalence in the North American population is acknowledged to be low (13,9%). However, these data remain unknown for other demographic groups. In the present study 44 Brazilian patients aged between 3 and 11 years were tested, all with a confirmed diagnosis of Duchenne muscular dystrophy. Each participant had a single blood sample collected, which was analyzed for total binding antibodies against rAAVrh74 using an enzyme-linked immunosorbent assay (ELISA). Antibody levels below 1:400 were classified as not elevated or seronegative. Antibody positivity occurred in 12 out of 44 cases (27.2%), significantly higher than observed in previously described populations. However, when evaluating the patients' locations, we observed that 7 of the positive cases resided in the state of Paraná, where 8 patients were tested, resulting in a positivity rate of 87.5%. When excluding the patients from Paraná from the analysis, we found a positivity rate of 13.8%, similar to that reported in the North American population. Although further studies are needed, we present the largest cohort of Brazilian patients tested for anti-AAVRh74 antibodies to date. Additionally, we report for the first time the potential presence of a serological cluster in the state of Paraná. These findings have important implications for the eligibility of Brazilian patients for AAVrh74-based gene therapies and underscore the importance of regional assessments in evaluating treatment accessibility.

**Palavras-Chave do trabalho:** ; Duchenne muscular dystrophy; Gene therapy; rAAVrh74;

**ID do trabalho:** 204

**Área Técnica do trabalho:** Genética populacional

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **Waardenburg Syndrome: A Rare Genetic Disorder with Variable Phenotypic Expression and Sensorineural Hearing Loss – Case Report**

**Autores:** DOS SANTOS, Vanessa Gil Humberto<sup>1</sup>; SANTOS, William de Souza<sup>2</sup>; LEÃO, Amanda Melo Leite<sup>3</sup>; ALVES, Jorge Luiz<sup>4</sup>; DE FARIAS, Poliana Marcela Silva<sup>5</sup>; DA CUNHA, Lais Felix Teixeira<sup>6</sup>; MOREIRA, Lais Borneo<sup>6</sup>; BERNARDES, Filipe Luiz Oliveira<sup>3</sup>;

**Instituição dos Autores:** (1) inspiralli educação Médica - Rio de Janeiro - RJ - Brasil; (2) Fiocruz - Rio de Janeiro - RJ - Brasil; (3) unigranrio - Rio de Janeiro - RJ - Brasil; (4) unig - Rio de Janeiro - RJ - Brasil; (5) Puc - Rio de Janeiro - RJ - Brasil; (6) puc - Rio de Janeiro - RJ - Brasil;

### Resumo do trabalho:

Introduction Waardenburg syndrome (WS) is a rare autosomal dominant genetic disorder characterized by pigmentary anomalies and sensorineural hearing loss (SNHL). It is caused by mutations in the PAX3, MITF, and SOX10 genes, which regulate neural crest cell differentiation and migration. The syndrome exhibits variable expressivity and incomplete penetrance, leading to heterogeneous phenotypic manifestations. Case Report A family from Duque de Caxias, Brazil, with a strong history of WS, exhibited diverse clinical presentations. The father, diagnosed with WS, transmitted the mutation to five of his nine children. Clinical findings included: 29-year-old son: Congenital deafness, blue eyes, and poliosis (white forelock). Two brothers: Partial hearing loss, blue eyes, poliosis, mild clinodactyly, and neurodevelopmental delay. Two sisters: Bilateral profound deafness, blue eyes, and poliosis. These phenotypic variations highlight the broad clinical spectrum of WS, emphasizing differences in genetic expression even among affected individuals within the same family. Discussion WS is associated with abnormal melanocyte development, affecting pigmentation and inner ear morphogenesis. The clinical diagnosis is based on the

Waardenburg criteria, which include pigmentary abnormalities, SNHL, and craniofacial dysmorphisms. Complementary diagnostic tools include: Audiometry and otoacoustic emissions for assessing hearing impairment. Magnetic resonance imaging (MRI) and computed tomography (CT) to evaluate cochlear and cranial development. Genetic analysis to identify mutations in PAX3, MITF, and SOX10, confirming the diagnosis and guiding genetic counseling. Management requires a multidisciplinary approach, including early auditory intervention, hearing aids, cochlear implants when indicated, and genetic counseling to assess recurrence risk and inform affected individuals. Conclusion This case report underscores the phenotypic heterogeneity of WS and the importance of early diagnosis in optimizing therapeutic strategies. Detailed clinical characterization and genetic screening are crucial for individualized patient management and minimizing disease impact.

**Palavras-Chave do trabalho:** Medical Genetics; Neural Crest Development; Pigmentation Disorder; Sensorineural Hearing Loss; Waardenburg Syndrome;

**ID do trabalho:** 205

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: PHENOTYPING P.ILE480MET: A DIHYDROLIPOAMIDE DEHYDROGENASE DEFICIENCY CASE SERIE**

**Autores:** SAKAI, Eric Oneda<sup>1</sup>; MARCARINI, Bruno Guimarães<sup>1</sup>; MOURA, Eder Alencar<sup>1</sup>; CRUZ, Patrícia Pontes<sup>1</sup>; BARBOSA, Renata Montes Garcia<sup>1</sup>; JUNIOR, Sergio Roberto Pereira da Silva<sup>1</sup>; FREUA, Fernando<sup>1</sup>; BUENO, Clarissa<sup>1</sup>; KOK, Fernando<sup>1</sup>;

**Instituição dos Autores:** (1) HCFMUSP - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Case presentation: We present three patients with the diagnosis of dihydrolipoamide dehydrogenase deficiency (DLDD). Patient 1 is a 41 yo female who started with developmental delay, hypotonia and prostration at 2 yo. She has suffered exacerbations related to stress or strong emotions, and noted some improvement with thiamine in these episodes. She has evolved with spastic tetraparesis particularly in the lower limbs, slurred speech and peripheral neuropathy. Despite her limitations, she is independent in daily life. Patient 2 is a 37 yo male sibling of patient 2, who begins with an insidious presentation of developmental delay. At 6 yo started spastic tetraparesis, ataxia, strabismus, dysphonia, and dysarthria. His symptoms fluctuate, worsen at the end of the day or after repeating a task. We noted some worsening after stopping rehabilitation. Brain nuclear magnetic resonance (NMR) shows hypomyelination of globus pallidus, substantia nigra and lentiform nuclei. Thiamine 200 mg/day and vitamin E have been used. Patient 3 is a 9 yo boy who had an insidious presentation of developmental delay. At 2 yo, began the weakness in the lower limbs, with progressive symptoms and exacerbations. He has severe intellectual disability, dysarthria, spastic tetraparesis, severe dystonia and peripheral neuropathy. Brain NMR shows hypomyelination in globus pallidus, posterior putamen, hypothalamus, substantia nigra, periaqueductal region, and dentate nuclei. His rehabilitation is poor. Thiamine 200mg/day has been used. Discussion: The DLDD is an inborn error of metabolism, autosomal recessive, that has a dysfunction of the E3 subunit of branched-chain alpha-ketoacid dehydrogenase,  $\alpha$ -ketoglutarate dehydrogenase,  $\alpha$ -ketoadipate dehydrogenase, and pyruvate dehydrogenase complexes. The phenotypic spectrum ranges from early-onset neurologic manifestation to adult-onset liver involvement. Our 3 patients presented with early-onset neurologic manifestation starting at 2 years old with delayed development and spastic tetraparesis. Patient 3 has the most rapidly progressive phenotype and the worst symptoms, including moderate to severe intellectual disability and dystonia. Patients 1 and 3 have peripheral neuropathy. No patient demonstrated cardiologic involvement. All patients presented hyperlactatemia, neuroimaging changes, especially in the globus pallidus and substantia nigra. The molecular diagnosis was provided after whole exome sequencing, identifying the variant ENST00000205402:c.1440A>G(p.Ile480Met). Final comments: The DLDD has a neurological phenotype that can vary in symptoms and severity. Our case series shows 3 patients with manifestations of the same variant in two unrelated families. No biochemical profile was specific for DLDD as mentioned in other literature. Thiamine and rehabilitation seem the most benefits. Due to the lack of literature, it is inconclusive what would be the best management, as well as the long-term prognosis.

**Palavras-Chave do trabalho:** Dihydrolipoamide Dehydrogenase Deficiency; DLD; DLDD; E3 Deficiency; Leigh Syndrome;

**ID do trabalho:** 207

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: GENETIC FACTORS ASSOCIATED WITH MOTOR CHANGES IN AUTISTIC CHILDREN ATTENDED BY THE GENETIC COUNSELING PUBLIC SERVICE IN GOIAS, BRAZIL**

**Autores:** GIGONZAC, MARC ALEXANDRE DUARTE<sup>1</sup>; CADO, Jéssica Regina Castor<sup>2</sup>; GIGONZAC, Thais Cidalia Vieira<sup>3</sup>;

**Instituição dos Autores:** (1) CRER - Centro de Reabilitação e Readaptação Dr. Henrique Santillo, SES/GO, UEG e PUC-GO - Goiânia - GO - Brasil; (2) UEG - Goiânia - GO - Brasil; (3) CRER - Centro de Reabilitação e Readaptação Dr. Henrique Santillo, SES/GO e UEG - Goiânia - GO - Brasil;

#### Resumo do trabalho:

**Background:** The understanding of Autism Spectrum Disorder (ASD) has significantly evolved since its first mention in the DSM-I (1952). The current classification (DSM-5) reflects a broad spectrum of symptoms, including deficits in social interaction, communication challenges, and repetitive behaviors. Motor delays, present in over 80% of children with ASD, are often overlooked despite their impact on functionality and quality of life. The multifactorial etiology of ASD, encompassing genetic, environmental, and developmental factors, highlights the need for integrated therapeutic and genetic approaches. **Objective:** This study aims to describe motor alterations in autistic children attended by the Genetic Counseling public service in Goiás, Brazil. **Methods:** This retrospective study analyzed genetic and clinical data from children diagnosed with ASD, aged 0-12 years, who were evaluated at the public Genetic Counseling service (LAGENE) – CRER/SES-GO. Genetic data were cross-referenced with international databases (OMIM, Decipher, HPO) to identify variants associated with motor and cognitive impairments. Interdisciplinary therapeutic strategies, including physiotherapy and occupational therapy, were assessed for their impact on motor development and overall quality of life. **Results:** The study identified significant genetic contributions to ASD, with over 1,000 implicated genes. Key mutations in SHANK1, RYR1, and FGD1 were associated with motor and social developmental delays. Additionally, mutations in EP400, CACNA1D, QARS1, and FGD1 were found to play important roles in motor dysfunction. Among the sample, motor milestones such as walking and head control were achieved later than expected. **Conclusion:** Early genetic screening and therapeutic interventions are critical for optimizing developmental outcomes in children with ASD. Multidisciplinary approaches targeting motor and cognitive development enhance functionality and social inclusion. These findings emphasize the importance of combining genomic insights with tailored rehabilitation strategies, offering a framework for improved ASD management and setting new standards of care.

**Palavras-Chave do trabalho:** Genetic variants; Motor Development; Therapeutic Interventions;

**ID do trabalho:** 208

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: GENOMIC INVESTIGATION OF AUTISM SPECTRUM DISORDER: A CASE REPORT OF A 21Q11.2 MICRODELETION

**Autores:** GIGONZAC, MARC ALEXANDRE DUARTE<sup>1</sup>; MEDEIROS, Fabíola Figueiredo<sup>2</sup>; MENDANHA, João Victor de Paula<sup>3</sup>; GIGONZAC, THAIS CIDALIA VIEIRA<sup>4</sup>;

**Instituição dos Autores:** (1) CRER/SES-GO, UEG e PUC-GO - Goiânia - GO - Brasil; (2) PUC-GO - Goiânia - GO - Brasil; (3) PUC/GO - Goiânia - GO - Brasil; (4) CRER/SES-GO E UEG - Goiânia - GO - Brasil;

#### Resumo do trabalho:

**Case Presentation:** This study reports the genomic investigation of a 9-year-old male patient diagnosed with Autism Spectrum Disorder (ASD) through a public health service. The child, referred for evaluation at the Laboratory of Human Cytogenetics and Molecular Genetics of the Dr. Henrique Santillo State Center for Rehabilitation and Readaptation (CRER-GO), presented neuropsychomotor delays, including delayed trunk control, sitting, and walking, despite physiotherapy sessions. Conventional karyotype analysis and FISH testing for Angelman Syndrome showed normal results, leading to further genomic investigation using Chromosomal Microarray Analysis (CMA). The CMA revealed a de novo microdeletion of 248.87Kb at locus 21q11.2, affecting the POTES and C21orf15 genes, both of which have unknown or poorly understood neurodevelopmental roles. The discovery highlights the necessity of advanced genetic screening techniques for a deeper understanding of the molecular basis of ASD. **Discussion:** The POTES gene was initially described as encoding a protein involved in various tissues such as prostate, ovary, and placenta, but its function in the brain remains unclear. Recent studies suggest that POTES may be involved in apoptotic pathways linked to synaptic dysfunction, a hallmark of ASD. The C21orf15 gene, on the other hand, has no known phenotypic correlations but is juxtaposed to AUTS12, a candidate gene for autism susceptibility. Although the direct impact of POTES and C21orf15 deletions on ASD remains uncertain, this study supports their potential regulatory role in neurodevelopment. CMA has been increasingly recognized as a first-line genetic test for individuals with developmental delays, intellectual disabilities, ASD, and congenital anomalies. Compared to traditional karyotype analysis, which detects chromosomal alterations in only 3% of cases, CMA provides a higher diagnostic yield of 10-15%, allowing for the detection of copy number variations (CNVs) associated with neurodevelopmental disorders. These findings emphasize that large-scale genomic approaches are essential for identifying rare, non-syndromic genetic variants contributing to ASD. **Final Comments:** Despite advances in genetic research, the heterogeneous etiology of ASD continues to pose diagnostic challenges. The identification of a de novo microdeletion in POTES and C21orf15 suggests new genetic loci for further investigation. Future research should integrate next-generation sequencing (NGS) and functional studies to elucidate the neurobiological pathways associated with these genes. Increasing access to genomic screening techniques in public health systems is crucial for early diagnosis, personalized interventions, and improved therapeutic strategies for individuals with ASD.

**Palavras-Chave do trabalho:** ASD; C21ORF15; GENETIC SCREENING; POTES;

**ID do trabalho:** 209

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: A CASE REPORT OF POIRIER-BIENVENU SYNDROME: A VERY RARE DISEASE WITH NEUROLOGICAL SYMPTOMS**

**Autores:** VIANA, Mariana Landim<sup>1</sup>; REGADAS, Maria Clara dos Anjos<sup>1</sup>; DE SOUZA MARTINS, Fernanda Pereira<sup>2</sup>; FERNANDES CARVALHO, Ellaine Dóris<sup>3</sup>; CARVALHO DE ANDRADE, Maria Denise Fernandes<sup>4</sup>;

**Instituição dos Autores:** (1) Unichristus - Fortaleza - CE - Brasil; (2) Hospital Dr. César Cals - Fortaleza - CE - Brasil; (3) Unichristus e Hospital Dr. César Cals - Fortaleza - CE - Brasil; (4) Unichristus, Universidade Estadual do Ceará (UECE) e Hospital Dr. César Cals - Fortaleza - CE - Brasil;

### **Resumo do trabalho:**

**Background:** The neurodevelopmental syndrome Poirier-Bienvenu (POBINDS) is a very rare genetic and neurological disorder characterized by a mutation in the CSNK2B gene, including three missense mutations (c.410G > T/p.(Cys137Phe), c.494A > G/p.(His165Arg), and c.3G > A/p.(Met1Ile)), two splicing variants (c.292-2A > T, c.558-3 T > G) and a "frameshift" mutation (c.499delC/p.(Leu167Serfs\*60)). Patients with this syndrome present, in your majority, tonic-clonic seizure and intellectual developmental delay. The severity of this condition is variable, having individuals with refractory epilepsy without speech acquisition, while others may have treatment sensitive seizures and show adequate neuropsychomotor development. **Objectives:** The purpose of this paper is to report and discuss the case of a patient with Poirier-Bienvenu. **Methods:** The case was selected due to its rarity once, the POBINDS prevalence remains with less than a hundred cases in the world. The selection considered criteria such as confirmed diagnosis, complete follow-up and relevance to medical practice. **Results:** The substitution of the amino acid for serine possibly explains why delays and other pathologies related to the nervous system are expressive characteristics of this syndrome. **Conclusion:** Thus, there is a clear need for further studies, since there is little information on the pathology of Poirier-Bienvenu Syndrome, making it difficult to find a typical therapeutic approach for this syndrome, with the only treatment being the use of antiepileptic drugs. **Case presentation:** Male patient, 10 years old, consanguineous parents, legitimate cousins, referred to the Geneticist with history of neuropsychomotor development delay, refractory epilepsy and important disturbances, especially in speech. In addition, he had congenital torticollis, macroglossia and gastrostomy on physical examination. POBINDS has a chr6:31669.847T>C variant which causes the amino acid phenylalanine in codon 190 to be replaced by serine (p.Phe190ser). Studies report that the substitution for serine is potentially deleterious and the absence of phenylalanine is extremely harmful, as this amino acid is used to form tyrosine, a substance directly related to the production of several important neurotransmitters. **Discussion:** The whole exome identified a pathogenic variant in the CSNK2B gene. However, the inheritance reported in the case was probably not inherited from one of the parents, appearing for the first time in the patient. The other case related, such as our patient, had a history of neuropsychomotor development delay and even on treatment with antiepileptic drugs they still had epilepsy. **Final comments:** Diagnosis is extremely valuable because the earlier the diagnosis, the better the conditions for treatment, specifically in the field of genetics, information about the disease is important both for managing the illness and for planning reproductive life in an extremely rare condition.

**Palavras-Chave do trabalho:** Consanguineous Parents; CSNK2B gene; epileps; Neurodevelopmental Disorders; Poirier-Bienvenu Syndrome;

**ID do trabalho:** 210

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: INTRAVENOUS DELIVERY OF HUMAN IMMATURE DENTAL PULP STEM CELLS DELAYS DISEASE PROGRESSION AND ENHANCES NEURONAL SURVIVAL IN A MURINE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS**

**Autores:** MATOS, Alexandre Hilario Berenguer<sup>1</sup>; COSER, Lilian<sup>2</sup>; PORTELLA, Giuliana<sup>2</sup>; CARTAROZZI, Luciana<sup>2</sup>; ARALDI, Rodrigo<sup>3</sup>; WENCESLAU, Cristiane<sup>4</sup>; OLIVEIRA, Alexandre Leite Rodrigues<sup>2</sup>; KERKIS, Irina<sup>5</sup>; FRANÇA-JR, Marcondes Cavalcante<sup>1</sup>;

**Instituição dos Autores:** (1) Department of Neurology, University of Campinas - Campinas - SP - Brasil; (2) Department of Structural and Functional Biology, University of Campinas - Campinas - SP - Brasil; (3) BioDecision Analytics Limited - São Paulo - SP - Brasil; (4) Cellavita Scientific Research Limited - Valinhos - SP - Brasil; (5) Genetics Laboratory, Butantan Institute - São Paulo - SP - Brasil;

**Resumo do trabalho:**

**Background:** Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by motor neuron degeneration, leading to muscle weakness, atrophy, and paralysis. Excitotoxicity plays a key role in ALS pathophysiology. Human immature dental pulp stem cells (hDPSCs) exhibit anti-inflammatory, anti-apoptotic, and neurotrophic properties, suggesting potential therapeutic benefits. **Objectives:** The aim of this study was to investigate the therapeutic potential of intravenous delivery of hDPSCs in a murine model of ALS (SOD1G93A mice). **Methods:** A case-control study was conducted with three experimental groups at two timepoints (15th week and end-stage) (hDPSC, n=11; vehicle, n=10; non-transgenic, n=10). To track cell distribution, hDPSCs were labeled with Qtracker 655 and detected 24 hours post-transplantation. Treatment was administered at the asymptomatic phase (10th week) via a single intravenous dose ( $1 \times 10^6$  cells/kg). Animals were euthanized (n=5) at the 15th week, and lumbar spinal cords were processed for Nissl staining (neuronal survival), immunofluorescence (astrocytosis, microglial reactions, synaptic coverage). Behavioral assessments, including neurological score, motor performance (rotarod), body weight, and survival probability, were conducted weekly until end-stage. **Results:** Transplanted hDPSCs were detected in the lumbar spinal cord, mainly in Rexed lamina IX, 24 hours post-injection, confirming targeted delivery. Treatment significantly improved neuronal survival (83% vs. 27%,  $p < 0.05$ ) compared to the vehicle group. Moreover, cell therapy attenuated gliosis, reduced astrocytosis and microglial reactivity ( $p < 0.05$ ), and preserved synaptic integrity ( $p < 0.05$ ). Behavioral improvements included delayed motor deficits, later disease onset, reduced weight loss, and prolonged survival (~10 days). **Conclusion:** Overall, our findings demonstrate the therapeutic potential of hDPSCs in a murine model of ALS. Intravenous delivery enhanced neuronal survival, reduced gliosis and preserved synapses. These effects were associated with delayed disease progression, as evidenced by attenuated motor deficits, reduced weight loss, later onset of disease symptoms and extended the survival in treated animals. Thus, our preclinical findings provide evidence that this stem cell lineage may be a promising therapeutic strategy for ALS.

**Palavras-Chave do trabalho:** ALS; Cell Therapy; hDPSC;

**ID do trabalho:** 211

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: LONG-TERM PROGRESSION OF CLINICIAN-REPORTED AND GAIT PERFORMANCE OUTCOMES IN HEREDITARY SPASTIC PARAPLEGIAS

**Autores:** CUBILLOS-ARCILA, Diana Maria<sup>1</sup>; DARIVA MACHADO, Gustavo<sup>1</sup>; FEIJÓ MARTINS, Valeria<sup>1</sup>; BIELEFELDT LEOTTI, Vanessa<sup>1</sup>; SCHÜLE, Rebecca<sup>2</sup>; PEYRÉ-TARTARUGA, Leonardo Alexandre<sup>1</sup>; MORALES SAUTE, Jonas Alex<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Heidelberg University - Germany;

**Resumo do trabalho:**

**Introduction:** Hereditary spastic paraplegias (HSPs) are a heterogeneous group of neurodegenerative diseases in which little is known about the most appropriate clinical outcome assessments (COAs) to capture disease progression. The objective of this study was to prospectively determine disease progression after 4.5 years of follow-up with different clinician-reported (ClinRO) and gait performance outcomes (PerFOs). **Methods:** Twenty-six HSP patients (15 SPG4, 5 SPG7, 4 SPG5, 2 SPG3A) participated in this single-center cohort study in which the ClinRO: Spastic Paraplegia Rating Scale; and the PerFOs: 10-meters walking test and timed-up and go (TUG), at self-selected and maximal walking speeds; Locomotor Rehabilitation Index; and 6-min walking test were performed at baseline and after 1.5 (18 patients) and 4.5 (13 patients) years. **Results:** In the 3-year interval between the second and third assessments, significant progressions were only found in PerFOs, while in the overall 4.5 years of follow-up, both PerFOs and ClinROs presented significant progressions. The progression slopes of COAs modeled according to the disease duration allowed the estimation of the annual progression of the outcomes and sample size estimations for future clinical trials of interventions with different effect sizes. TUG at maximal walking speed was the only COA capable of differentiating subjects with a worse compared to a stable/better impression of change and would require the smallest sample size if chosen as the primary endpoint of a clinical trial. **Discussion:** These findings indicate that both performance and clinician-reported outcomes can capture long-term progression of HSPs, with some PerFOs presenting greater sensitivity to change. The presented data are paramount for planning future disease-modifying and symptomatic therapy trials for this currently untreatable group of diseases.

**Palavras-Chave do trabalho:** clinical outcomes assessment; clinician-reported outcomes; gait analysis; Hereditary Spastic Paraplegias; Performance Outcomes;

**ID do trabalho:** 212**Área Técnica do trabalho:** Doenças Neuromusculares**Tipo do trabalho:** Trabalhos Originais**Forma de apresentação:** Pôster

## **Título do Trabalho: PERIPHERAL NERVE ULTRASOUND FINDINGS IN BRAZILIAN PATIENTS WITH SYMPTOMATIC HEREDITARY TRANSTHYRETIN AMYLOIDOSIS**

**Autores:** CAMELO-FILHO, Antonio Edvan<sup>1</sup>; COVALESKI, Anna Paula Paranhos Miranda<sup>2</sup>; BRITO, Lara Albuquerque<sup>3</sup>; RODRIGUES, Cleonísio Leite<sup>3</sup>; MOREIRA, Ana Lucila<sup>4</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará / Neurologia do Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (2) Hospital das Clínicas Universidade Federal de Pernambuco / RARUS Recife - Recife - PE - Brasil; (3) Neurologia do Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (4) Hospital das Clínicas da Faculdade de Medicina da USP - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Background: Hereditary transthyretin amyloidosis (ATTRv) is a progressive, multisystem disorder caused by pathogenic variants in the TTR gene, resulting in the misfolding of transthyretin proteins and subsequent amyloid deposition in tissues. Peripheral neuropathy is a hallmark feature of TTR amyloidosis, often contributing to significant morbidity. Objective: We studied the role of nerve ultrasound in identifying increased cross-sectional areas (CSA) in patients with ATTRv polyneuropathy in Brazil. Methods: This observational study included patients with genetically confirmed ATTRv followed in two tertiary centers in Brazil. Comprehensive clinical assessments, including electrophysiological evaluations, were performed. Peripheral nerve ultrasound was conducted by two neurosonologists using 12MHz and 15MHz linear probes to measure the CSAs of the median nerve, brachial plexus, and C6 root. Normative data from previous studies were used as reference values. Statistical analyses compared CSA measurements across groups. Results: Thirty-one symptomatic patients were evaluated, 17 males (55%), with a mean age of 56.25 years (range: 34 to 81yo). The most common variants were Ile107Val, observed in 10 patients (32.2%), Val30Met, and Val122Ile, each identified in nine patients (29%). Less frequent mutations included Ala97Ser and Gli67Glu (one patient each, 3%). One case (3%) of compound heterozygosity involving Val30Met and Val122Ile was also detected. Electroneuromyography confirmed polyneuropathy in 26 patients (83%). Neuromuscular ultrasound revealed patterns of nerve enlargement in specific regions. Enlargement of the median nerve was observed at the wrist (mean CSA of 10.2 mm<sup>2</sup>, SD 2.95,  $p < 0.05$ ) and in the arm (mean CSA of 9.8 mm<sup>2</sup>, SD 1.8,  $p < 0.05$ ) but not at the forearm (mean CSA of 6.85 mm<sup>2</sup>, SD 2.04,  $p < 0.05$ ). The supraclavicular plexus also exhibited enlarged values with a mean CSA of 70.82 mm<sup>2</sup> (SD 18.8,  $p < 0.05$ ), and the C6 nerve root showed a mean CSA of 8.55 mm<sup>2</sup> (SD 1.38,  $p < 0.05$ ), also with significant enlargement. These findings highlight the utility of neuromuscular ultrasound as a non-invasive tool in ATTRv, complementing traditional methods and possibly contributing to the detection and management of this condition. Conclusion: This study suggests that increased median nerve CSA in the wrist and arm, supraclavicular plexus, and C6 root are present in ATTRv in Brazil, as suggested in previous studies. More extensive studies are warranted to validate these findings, explore the relationship between nerve CSA and disease progression, and establish nerve ultrasound as a standard tool for monitoring TTR-related neuropathy.

**Palavras-Chave do trabalho:** Familiar Amyloid Polyneuropathy; NERVE ULTRASOUND; TTR;

**ID do trabalho:** 214**Área Técnica do trabalho:** Doenças Neuromusculares**Tipo do trabalho:** Trabalhos Originais**Forma de apresentação:** Pôster

## **Título do Trabalho: BARRIERS TO GENETIC COUNSELING AND TESTING IN WOMEN AT RISK OF BEING DYSTROPHINOPATHY CARRIERS: A QUALITATIVE STUDY IN BRAZIL**

**Autores:** WESCHENFELDER, Cesar Augusto<sup>1</sup>; ROSA, Bruna Faria<sup>2</sup>; HOEFEL, Alice Maria Luderitz<sup>3</sup>; DONIS, Karina Carvalho<sup>4</sup>; SAUTE, Jonas Alex Morales<sup>5</sup>;

**Instituição dos Autores:** (1) Clinical Neurogenetics research group, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. - PORTO ALEGRE - RS - Brasil; (2) Clinical Neurogenetics research group, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. - porto alegre - RS - Brasil; (3) Graduate Program in Medicine: Medical Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - Porto Alegre - RS - Brasil; (4) Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. - Porto Alegre - RS - Brasil; (5) Department of Internal Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - PORTO ALEGRE - RS - Brasil;

### **Resumo do trabalho:**

Background: Although dystrophinopathies predominantly affect males, approximately 30% of female carriers may present symptoms, including muscle weakness and cardiac complications, making genetic counseling a crucial process. A recent survey

conducted in Brazil revealed that slightly more than half of at-risk women underwent genetic testing, while about one-third did not receive genetic counseling or testing offers, highlighting the insufficient adherence to international care guidelines for carriers. Objective: To conduct a qualitative study to understand the barriers related to access to genetic counseling and testing. Methods: This is a qualitative case study in which 19 out of 123 women at risk of being dystrophinopathy carriers, who had participated in the aforementioned survey, were interviewed. These participants were from four regions of Brazil, and the study explored aspects such as genetic counseling, availability and uptake of genetic testing, perception of genetic risk, knowledge about muscle weakness and cardiac involvement, medical follow-up, and empowerment in genetic information. The interviews were transcribed and analyzed using NVIVO software to identify recurring patterns and themes. Results: Findings indicated that the low frequency of genetic counseling was primarily associated with healthcare professionals' lack of awareness regarding this condition. Some participants reported difficulties in obtaining an early diagnosis and accessing specialized services. Limited infrastructure in certain regions of the country and a lack of awareness about the availability of genetic testing were identified as major barriers. Additionally, while some women were aware of their genetic risk and chose to avoid further pregnancies, others were unaware of their carrier status and its implications. Knowledge about the risks of muscle weakness and cardiac involvement also varied; some women acknowledged the need for medical follow-up, whereas others were unaware of this necessity. Conclusion: The findings of this study highlight the need to improve public policies aimed at female carriers of dystrophinopathies in Brazil, particularly in regions with limited access to specialized services. Strengthening medical education on genetic counseling and expanding genetic testing availability for carriers are essential measures to ensure better follow-up for these women and prevent disease-related complications.

**Palavras-Chave do trabalho:** aconselhamento genético; distrofinopatias; DMD; portadoras;

**ID do trabalho:** 215

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: SKELETAL MUSCLE CELLS OF A NOVEL KNOCKOUT CELL MODEL OF LIMB-GIRDLE MUSCULAR DYSTROPHY SUBTYPE 2G/R7 (LGMD2G/R7) EXHIBIT DIFFERENTIATION DEFECTS LINKED TO AN IMBALANCED REDOX STATUS**

**Autores:** DA ROSA-JUNIOR, Neilton Teixeira<sup>1</sup>; PEREIRA, Bruna Leticia da Silva<sup>2</sup>; SALATINO-OLIVEIRA, Angélica<sup>3</sup>; VIEIRA, Camila<sup>3</sup>; LEIPNITZ, Guilhian<sup>4</sup>; CHIELA, Eduardo Cremonese Filippi<sup>5</sup>; SOLARI, José Ignácio Gonzales<sup>6</sup>; LASTA, Nicolas<sup>3</sup>; SAUTE, Jonas Alex Morales<sup>7</sup>; BALDO, Guilherme<sup>6</sup>;

**Instituição dos Autores:** (1) Graduate Program in Medicine: Medical Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - porto alegre - RS - Brasil; (2) Graduate Program in Genetics and Molecular Biology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - PORTO ALEGRE - RS - Brasil; (3) Laboratório Centro de Terapia Gênica, Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (4) Department of Biochemistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - Porto Alegre - RS - Brasil; (5) Department of Physiology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - Porto Alegre - RS - Brasil; (6) Department of Physiology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - Porto Alegre - RS - Brasil; (7) Department of Internal Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: LGMD2G/R7 is a rare neuromuscular disorder associated with pathogenic variants in the TCAP gene, which encodes telethonin, a known sarcomere structural protein that has only recently been linked to the regulation of cell signaling. No cell model currently exists to study the pathological mechanisms underlying the symptoms of LGMD2G/R7. Objective: This study aimed to create a novel knockout cellular model of TCAP gene variants using gene editing in C2C12 cells and to characterize intrinsic cellular changes associated with muscle functional aberrations. Methodology: The CRISPR-Cas9 system was used for gene editing, along with microscopy, enzyme activity assays, flow cytometry, and protein expression analysis. All redox experiments were performed in myoblast cells. Cell death assays and immunoblotting were conducted on day 5 of differentiation, while imaging experiments were carried out on days 1, 3, and 5 during differentiation. Results: Two knockout clones were successfully generated. Microscopy analysis on days 1, 3, and 5 revealed reduced differentiation into myotubes in the knockout clones (CLT4 [T4 Clone] and CLT11 [T11 Clone]) compared to wild-type (WT) cells. MHC expression levels were lower in the knockout clones, supporting the observation of differentiation defects. Redox status experiments showed alterations in antioxidant defenses. The CLT4 clone exhibited increased levels of malondialdehyde, a product of degenerative lipid peroxidation, along with increased activity of superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST), and reduced catalase (CAT) and glucose-6-phosphate dehydrogenase (G6PDH). The CLT4 clone also showed elevated levels of reduced glutathione (GSH). The CLT11 clone exhibited increased activity of SOD, CAT, GST, and glutathione reductase (GR). The activity of G6PDH in the CLT11 clone was similar to that of the WT group, but GSH levels were lower in the CLT11 clone compared to WT. Cell death studies showed that the CLT4 clone exhibited increased apoptosis, while the CLT11 clone did not. Conclusion: Neuromuscular disease models frequently exhibit sustained oxidative stress. Both cell lines generated in this study displayed predominantly increased antioxidant activity, suggesting the presence of oxidative stress, supported by elevated levels of malondialdehyde. As indicated in the literature, increased apoptosis may result from oxidative stress or reduced telethonin expression. Oxidative stress is known to inhibit differentiation, although differentiation defects may

also arise from the lack of telethonin, as observed in the CLT4 and CLT11 clones. Taken together, our data suggest that these cell lines mimic aspects of the disease, and the pathogenesis of LGMD2G/R7 may involve multiple processes, including cell death, differentiation defects, and oxidative stress.

**Palavras-Chave do trabalho:** Differentiation Defects; Gene Editing; Knockout Cell Model; Limb-Girdle Muscular Dystrophy (LGMD2G/R7); Oxidative Stress;

**ID do trabalho:** 216

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **MAPLE SYRUP URINE DISEASE IN AN INFANT WITH PERSISTENT HYPOGLYCEMIA AND EPILEPTIC SEIZURES: A CASE REPORT**

**Autores:** DE LUCENA, Patrícia Trindade<sup>1</sup>; BRAGA, Sarah Maria Pontes<sup>1</sup>; PEREIRA, Victor Hugo Soares<sup>1</sup>; SOBREIRA FILHO, Joselito<sup>1</sup>; SIQUEIRA, Ana Cecília<sup>1</sup>; ALVES, Lucas Victor<sup>1</sup>;

**Instituição dos Autores:** (1) Instituto de Medicina Integral Professor Fernando Figueira - Recife - PE - Brasil;

### Resumo do trabalho:

**CASE PRESENTATION:** Male patient, 5 months old, son of non-consanguineous parents, with no reported perinatal complications. He was born at term (41 weeks), by caesarean section, weighing 3778 grams and with an Apgar score of 08/10. He was discharged from the maternity ward after 48 hours of life. She was breastfed and supplemented with infant formula. On the 5th day of life, he developed hypotonia, difficulty sucking and epileptic seizures and was admitted to the intensive care unit (ICU), where he remained for 39 days, 13 of which were under mechanical ventilation. He was discharged from hospital, taking levetiracetam. After 30 days, he presented decompensation of epileptic seizures, associated with apnea, cyanosis and hypoglycemia, as well as changes in urinary odor, and was admitted to the ICU again. A metabolic investigation was carried out, which showed lactate 8.4 mmol/L, ammonia 152 mmol/L, insulin and a normal urine summary. Brain MRI showed hypersignal on T2 sequences in the periventricular and cerebellar white matter, thalamus, midbrain and pons, with diffusion restriction. Spectroscopy showed a drop in the level of N-acetyl aspartate and an increase in the peaks of creatine and choline, with an abnormal peak of branched-chain amino acids and alpha-acetoacids. Amino acid chromatography was carried out, which showed increased levels of leucine (2390.8 µmol/L), isoleucine (624.6 µmol/L) and valine (378.4 µmol/L). The exome showed a pathogenic variant in homozygosity in the DBT gene, chromosome 1, confirming the diagnosis of Maple Syrup Urine Disease type II (MSUD2). **DISCUSSION:** Maple Syrup Urine Disease (MSUD) is a metabolic disorder of autosomal recessive origin, caused by a reduction in the activity of the  $\alpha$ -branched chain ketoacid dehydrogenase (BCKDC) complex, the second step in the degradation pathway of the branched chain amino acids (BCAA) leucine, isoleucine and valine. The classic form begins in the neonatal period, and its signs and symptoms include: maple syrup odor in the cerumen and urine, lethargy, apnea, opisthotonus, progressing to respiratory failure. The disease can lead to death or cause neurological sequelae such as developmental delay and stereotyped movements. Diagnosis is established by identifying pathogenic biallelic variants in one of the genes encoding BCKDC subunits: BCKDHA, BCKDHB or DBT. Treatment consists of dietary leucine restriction, BCAA-free foods, cautious supplementation with isoleucine and valine and liver transplantation, aimed at replacing the damaged BCKDC with the functional enzyme, which provides patients with an unrestricted diet and protects them from metabolic crises, but does not reverse the pre-existing psychomotor deficiency. **CONCLUSION:** MSUD, in its classic form, is a serious metabolic disorder of the neonate and infant, capable of leading to death or irreversible neurological damage if not diagnosed early, which reinforces the need to include this disease in neonatal screening.

**Palavras-Chave do trabalho:** amino acids; infant; Maple Syrup Urine Disease; metabolic disorder;

**ID do trabalho:** 218

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: **THE IMPACT OF INTERRUPTIONS IN ATXN10 EXPANSIONS ON CLINICAL FINDINGS OF SPINOCEREBELLAR ATAXIA TYPE 10**

**Autores:** HASAN, ALI<sup>1</sup>; FURTADO, GABRIEL VASATA<sup>2</sup>; MIGLORINI, ELAINE CRISTINA<sup>3</sup>; MERGENER, RAFAELLA<sup>2</sup>; MASSUYAMA, BRENO<sup>4</sup>; PEDROSO, JOSÉ LUIZ<sup>4</sup>; TEIVE, HELIO GHIZONI<sup>5</sup>; ASHIZAWA, TETSUO<sup>6</sup>; SARAIVA-PEREIRA,

MARIA LUIZA<sup>7</sup>; JARDIM, LAURA BANNACH<sup>7</sup>;

**Instituição dos Autores:** (1) Programa de Pós-Graduação em Genética e Biologia Molecular, Universidade Federal do Rio Grande do Sul - PORTO ALEGRE - RS - Brasil; (2) Centro de Pesquisa Clínica e Experimental, Hospital de Clínicas de Porto Alegre - PORTO ALEGRE - RS - Brasil; (3) Hospital de Clínicas de Curitiba - CURITIBA - PR - Brasil; (4) Hospital São Paulo, Universidade Federal do Estado de São Paulo - SÃO PAULO - SP - Brasil; (5) Universidade Federal do Paraná - CURITIBA - PR - Brasil; (6) Methodist Hospital and Houston Methodist Research Institute - United States; (7) Universidade Federal do Rio Grande do Sul - PORTO ALEGRE - RS - Brasil;

**Resumo do trabalho:**

Background: Spinocerebellar ataxia type 10 (SCA10), due to an ATTCT repeat expansion in ATXN10, has variable expressivity and the role of interruptions in the repeat (ATTCTint+) is not clear. Objective: We aimed to describe potential relations between ATTCTint+ and age at onset, seizures and neurologic severity in a group of ataxic and non-ataxic carriers from Brazil. Methods: Data on family, origin, age at onset (AO) and seizures, plus DNA were obtained from symptomatic carriers already diagnosed in Porto Alegre, Curitiba and São Paulo, Brazil. Ataxics and their relatives were invited to be evaluated through FARSadl, SARA, NESSCA, ICARS and INAScount; a SARA  $\geq$  or  $\leq$  2.5 classified carriers as ataxic or non-ataxic. Repeat-primed PCR (RP-PCR) defined the expansions as with (ATTCTint+) or without (ATTCTint-) interruptions. Comparisons between groups were performed according to distribution of variables, for a p level of 0.05. Results: among 78 ataxic carriers, earlier AO ( $p=0.039$ ) and higher occurrences of epilepsy ( $p<0.0001$ ) were seen in subjects with ATTCTint+ than in those with ATTCTint-. Thirty-four ataxics, 7 non-ataxics and 10 related controls performed FARSadl, SARA, NESSCA, ICARS and INAScount, that were worse in ataxics than in the other subjects ( $p=0.006$ ), but did not discriminate non-ataxics from controls. The 11 ataxic ATTCTint+ carriers had higher SARA scores than the 23 ATTCTint- carriers per year of disease duration ( $r=0.879$ ,  $\beta=0.45$ ,  $p=0.0001$ ). Similar effects were seen with ICARS. Conclusion: ATTCTint+ carriers had earlier AO, more seizures and worse ataxia scores per disease duration than ATTCTint- ones. Interruptions in the expanded repeat have a real pathogenic role in this disease.

**Palavras-Chave do trabalho:** ATTCT; ATTCT interruptions; ATXN10; non-ataxic carriers; SCA10;

**ID do trabalho:** 220

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: MOVEMENT DISORDERS IN HEREDITARY SPASTIC PARAPLEGIA

**Autores:** GONZALEZ SALAZAR, CARELIS DEL VALLE<sup>1</sup>; DINIZ DE LIMA, FABRICIO<sup>1</sup>; SILVEIRA, CYNTHIA<sup>1</sup>; FRANÇA JR, MARCONDES<sup>1</sup>;

**Instituição dos Autores:** (1) UNIVERSIDADE ESTADUAL DE CAMPINAS - CAMPINAS - SP - Brasil;

**Resumo do trabalho:**

Background: Hereditary spastic paraplegias (HSP) are a genetically heterogeneous group of over 90 disorders primarily characterized by progressive lower limb spasticity and weakness. HSP is classified as uncomplicated when these are the unique neurological manifestations (often accompanied by urinary urgency) and as complicated when additional neurological features, including movement disorders, are present. Objective: To characterize the prevalence and clinical features of HSP-related movement disorders in a large Brazilian cohort. Methods: We analyzed a cohort of 367 patients with HSP under regular follow-up at the Neurogenetics Outpatient Clinic of the University of Campinas (UNICAMP), Brazil. Of these, 246 patients had a genetically confirmed diagnosis of HSP and were included in the study. Results: Movement disorders were identified in 68 out of 246 patients (27.6%). Among patients with HSP-related movement disorders, there was male predominance (57.4%) and mean age at onset was  $20\pm12.7$  years. The most prevalent movement disorders were ataxia ( $n=54$ , 79.4%), parkinsonism ( $n=32$ , 47.1%), and action tremor ( $n=26$ , 38.2%). The most frequent genotypes associated with HSP-related movement disorders were SPG11 ( $n=17$ ), SPG7 ( $n=14$ ), and CAPN1 ( $n=13$ ). Conclusion: Movement disorders were observed in nearly one-quarter of patients with HSP, serving as a valuable clinical marker for diagnosing complicated HSP. Recognizing these features enhances the understanding of genotype-phenotype correlations and supports more precise diagnosis. Furthermore, some of these movement disorders are amenable to treatment and should be actively sought in clinical practice.

**Palavras-Chave do trabalho:** Complicated Hereditary Spastic Paraplegia; Genotype; Movement Disorders;

**ID do trabalho:** 221

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **EXPRESSION OF MIR-19B AND MIR-7 IN SERUM-DERIVED EXOSOMES FROM RBD PATIENTS AS POTENTIAL BIOMARKERS**

**Autores:** FERRARI, Sabrina Simplicio de Araújo Romero<sup>1</sup>; OLIVEIRA, Deborah Almeida de<sup>1</sup>; BALIEIRO, Talita Guimarães<sup>2</sup>; MARINA, Clara Luna<sup>1</sup>; TITZE-DE-ALMEIDA, Simoneide Souza<sup>1</sup>; BRANDÃO, Pedro Renato de Paula<sup>2</sup>; TITZE-DE-ALMEIDA, Ricardo<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de Brasília - Brasília - DF - Brasil; (2) Hospital Israelita Albert Einstein - Brasília - DF - Brasil;

### Resumo do trabalho:

**Background:** MicroRNAs (miRNA) are small RNAs that regulate gene expression. Aberrant miRNAs may serve as potential biomarkers for the diagnosis and prognosis of neurodegenerative diseases. REM Sleep Behavior Disorder (RBD) is characterized by the enactment of dreams during REM sleep. The progression from idiopathic RBD to Parkinson's disease (PD) and Dementia with Lewy Bodies underscores its significance as a clinical indicator in the early stages of these synucleinopathies. Studies have shown that miR-19b levels are altered in patients with RBD, before the onset of motor symptoms, suggesting its potential as an early biomarker for the prodromal phase of these disorders. Additionally, miRNA miR-7 has been implicated in the underlying mechanisms of PD, including the regulation of alpha-synuclein, dopaminergic cell death and neuroinflammation. **Objective:** The aim of this study was to evaluate the expression levels of miR-19b and miR-7 in exosomes isolated from serum samples of patients diagnosed with probable RBD. This research aims to investigate the potential of these specific microRNAs as biomarkers for RBD. **Methods:** The samples were collected from patients participating in the PROBE-PD - Epidemiological Study on Established and Prodromal Parkinson's Disease in Brazil Project (Candangolândia, Distrito Federal). Peripheral venous blood was collected from 4 controls and 4 patients with RBD using serum collection tubes. After 30 minutes, the samples were centrifuged at 2000 x g for 10 min and maintained at 4°C. The serum was stored into 2 mL cryovials at -80°C. For exosomes isolation, the serum was then centrifuged at 10,000g for 10 minutes to eliminate debris and residual cells. The supernatant was filtered through 0.22 µm filters and ultracentrifuged at 100,000 x g for 1.5 hours, repeated three times. Exosomes were characterized by assessing their protein content using commercial kits (Thermo Fisher). For miRNA extraction, the miRNeasy Mini Kit (Qiagen) was utilized, followed by conversion to cDNA using the TaqMan Advanced miRNA cDNA synthesis kit (Thermo Fisher), and quantified by Quantitative Polymerase Chain Reaction (qPCR). Data analysis was performed based on relative expression using the delta-delta Ct method ( $2^{-\Delta\Delta CT}$ ). **Results:** Exosomes from patients with RBD showed a higher protein content compared to the control group. qPCR analyses revealed increased expression levels of miR-19b and miR-7 in the RBD group. The miRNA content was relatively homogeneous across groups, indicating stability for accurate relative gene expression analyses. ROC curve analysis showed statistical significance for the combination of miR-19b and miR-7 ( $P = 0.0209$ ), with an Area Under the Curve (AUC) of 1.0. **Conclusion:** The increased expression of these microRNAs suggests that miR-19b and miR-7 could serve as potential biomarkers for identifying patients with RBD. However, our data require validation in independent cohorts of individuals.

**Palavras-Chave do trabalho:** microRNAs (mRNAs); miR-19b; miR-7; Parkinson's Disease (PD); REM Sleep Behavior Disorder (RBD);

**ID do trabalho:** 222

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: **EXPLORING GENETICS LANDSCAPE OF HEREDITARY SPASTIC PARAPLEGIAS: FINDINGS FROM A LARGE BRAZILIAN COHORT IN A MULTICENTRIC COLLABORATIVE RESEARCH EFFORT**

**Autores:** SILVEIRA, Cynthia<sup>1</sup>; GONZÁLEZ-SALAZAR, CARELIS<sup>1</sup>; DINIZ DE LIMA, Fabrício<sup>2</sup>; TREVISAN PEREIRA, Rosana Aparecida<sup>1</sup>; CARVALHO DONIS, Karina<sup>3</sup>; CUBILLOS-ARCILA, Diana Maria<sup>3</sup>; TOMASELLI, Pedro José<sup>4</sup>; GRAZIANI POVOAS BARSOTTINI, Orlando<sup>5</sup>; DE FREITAS, Júlian Letícia<sup>5</sup>; PAIVA MAGALHÃES ORTEGA, Roberta<sup>6</sup>; ROSEMBERG, Sérgio<sup>6</sup>; FREUA, Fernando<sup>7</sup>; TEIXEIRA CAMARGOS, Sarah<sup>8</sup>; SABINO DE OLIVEIRA, Daniel<sup>9</sup>; MAROCO CRUZEIRO, Marcelo<sup>9</sup>; GHIZONI TEIVE, Helio Afonso<sup>10</sup>; NADIELY VICTOR DA SILVA, Bruna<sup>11</sup>; CARDOSO VALE, Thiago<sup>9</sup>; KOK, FERNANDO<sup>7</sup>; LUIZ PEDROSO, José<sup>5</sup>; MARQUES JUNIOR, Wilson<sup>4</sup>; MORALES SAUTE, Jonas Alex<sup>3</sup>; CAVALCANTE FRANÇA JUNIOR, Marcondes<sup>1</sup>;

**Instituição dos Autores:** (1) UNIVERSIDADE ESTADUAL DE CAMPINAS - CAMPINAS - SP - Brasil; (2) UNIVERSIDADE ESTADUAL DE CAMPINAS - SÃO PAULO - SP - Brasil; (3) UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL - PORTO ALEGRE - RS - Brasil; (4) UNIVERSIDADE DE SÃO PAULO - RIBEIRÃO PRETO - SP - Brasil; (5) UNIVERSIDADE FEDERAL DE SÃO PAULO - SÃO PAULO - SP - Brasil; (6) IRMANDADE DA SANTA CASA DE MISERICÓRDIA DE SÃO PAULO - SÃO PAULO - SP - Brasil; (7) UNIVERSIDADE DE SÃO PAULO - SÃO PAULO - SP - Brasil; (8) UNIVERSIDADE FEDERAL DE

MINAS GERAIS - BELO HORIZONTE - MG - Brasil; (9) UNIVERSIDADE FEDERAL DE JUIZ DE FORA - JUIZ DE FORA - MG - Brasil; (10) UNIVERSIDADE FEDERAL DO PARANÁ - CURITIBA - PR - Brasil; (11) UNIVERSIDADE FEDERAL DA PARAÍBA - JOÃO PESSOA - PB - Brasil;

#### Resumo do trabalho:

**Introduction:** Genetic heterogeneity is a hallmark of hereditary spastic paraplegias (HSPs) with more than 90 associated genes reported so far. Despite that, few studies have attempted to characterize the genetic epidemiology of HSPs, particularly the highly admixed Latin American population which remains poorly characterized. **Objective and Methodology:** This study aims to represent the genetic profile of HSP in a large, multicentric Brazilian cohort (Brazilian HSP Genetics Consortium), recruited through a collaborative effort involving ten research groups across five states (São Paulo, Rio Grande do Sul, Minas Gerais, Paraná, and Paraíba), and to evaluate the diagnostic yield of next-generation sequencing (NGS) for suspected HSP cases. **Results and discussion:** The present cohort is composed of 689 patients (372 men and 317 women) from 507 families. Declared consanguinity was reported in 95/507 families, absent in 299/507 and unknown/unavailable in 113/507. Considering all families, 236 were inconclusive or not genetically tested yet. From those index cases who underwent NGS, 188/507 (37,08%) had non-diagnostic results whereas 319/507 (62,91%) had diagnostic results. The top five most frequent genotypes were: SPG4 [SPAST] 64/507 (12,62%), SPG11 48/507 (9,47%), SPG7 23/507 (4,54%), SPG76 [CAPN1] 19/507 (3,75%) and SPG5A [CYP7B1] together with SPG3A [ALT1] 17/507 (3,35%). Apart from the 'known' HSP genes, we also uncovered newly recognized genes associated with the HSP phenotype: COQ7 gene variants were present in 6 patients from 5 families, RNASEH2B was present in two HSP sisters, SNAPC4 present in two siblings and SPTAN1 (SPG91) one of the last gene reported with HSP appearing in 2 relatives with the described variant p.[Arg19Trp] and also copy number variants in SPAST with a large deletion and duplication. **Conclusion:** This study highlights the importance of multicentric studies to better characterize HSPs, emphasizing the value of the Brazilian population in the epidemiological context, the genetic heterogeneity of HSP, the role of next-generation sequencing for genetic diagnosis, and the need for further genetic analyses for inconclusive cases.

**Palavras-Chave do trabalho:** Brazilian; exome; Hereditary Spastic Paraplegias; neurodegenerative; Next-generation sequencing;

**ID do trabalho:** 223

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: CASE REPORT: NUS1 GENE DELETION CAUSING DEVELOPMENTAL DELAY, MYOCLONUS AND ATAXIA

**Autores:** UENISHI, Lucas Toshio<sup>1</sup>; SPELTRI, Gabriel Casella<sup>1</sup>; PEREIRA, Jackeline Neves<sup>1</sup>; SENEOR, Daniel Delgado<sup>1</sup>; GOMEZ, Fernanda Lustosa Cabral<sup>1</sup>; TOMAZ, Gabriela Rodrigues<sup>1</sup>; FERREIRA JR., Luiz José Malta Gaia<sup>1</sup>; SILVA, Thiago Yoshinaga Tonholo<sup>1</sup>; PEDROSO, José Luiz<sup>1</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal de São Paulo - São Paulo - SP - Brasil;

#### Resumo do trabalho:

**Case Presentation** A 14-year-old female patient from Japan but currently living in Brazil was brought to our clinic due to "tremors and cognitive delay". Her mother noticed that, by the time she was five months of age, the patient started having brief and involuntary movements in her extremities, mainly in action. On physical examination, the phenomenology was compatible with multifocal myoclonus. In addition, she reported that the patient had always had learning difficulties, especially in language development, and a formal neuropsychological test evidenced mild to moderate intellectual disability. Our physical examination also revealed mild ataxia (seen as limb dysmetria and ataxic gait). Antenatal and perinatal history was unremarkable. Her father was of Japanese descent and her mother was Brazilian. Magnetic resonance imaging of the brain was normal. Electroencephalogram showed a slower posterior dominant rhythm, but no epileptic activity. A genetic aetiology was suspected and Whole Exome Sequencing (WES) was performed, demonstrating a  $\approx 1,5$  Mbp deletion in the long arm of chromosome 6, in heterozygosity, encompassing the NUS1 gene, a variant classified as pathogenic. **Discussion** The NUS1 gene, located in 6q22.1, encodes a 293-amino acid protein that forms the Nogo-B receptor, a subunit of the dehydrololichyl diphosphate synthase. This enzyme plays an important role in protein glycosylation<sup>1</sup>. Pathogenic variants of NUS1 were first identified in a family with a congenital disorder of glycosylation but, since then, the spectrum of phenotypes has been expanding<sup>2</sup>. Most subsequent case series reported individuals with heterozygous mutations that presented with global developmental delay, prominent language impairment, generalized epilepsy, movement disorders (mainly a multifocal myoclonus), and mild ataxia. It is noteworthy that most patients did not present with developmental regression (but rather a delay), and the associated ataxia seemed to be either stable or slowly progressive, slightly differing from the progressive myoclonic epilepsies/ataxias<sup>3-5</sup>. In our case, the phenotype of the patient is compatible with the NUS1 gene mutation, as she exhibited all of these features but epilepsy. **Final Comments** NUS1 mutation should be considered in patients with global developmental delay and multifocal myoclonus, associated with epilepsy or ataxia.

**Palavras-Chave do trabalho:** ATAXIA; Developmental delay; Myoclonus; NUS1;

**ID do trabalho:** 224

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **RYR1-ASSOCIATED MYOPATHY: WHEN A RECESSIVE PHENOTYPE PROMPTS MANAGEMENT IN HETEROZYGOUS CARRIERS**

**Autores:** FRANZONI, Fábio de Melo<sup>1</sup>; DA CRUZ, Henrique Cian<sup>1</sup>; DE OLIVEIRA, Amanda Fernanda Martins<sup>1</sup>; FARIA, Matheus Moura<sup>1</sup>; FROES, Lucas<sup>1</sup>; PÉRICO, Arthur Arenas<sup>1</sup>;

**Instituição dos Autores:** (1) Unicesumar - Maringá - PR - Brasil;

### Resumo do trabalho:

Case Presentation: A 47-year-old male patient was referred to a geneticist in 2024 due to progressive muscle weakness, ptosis, external ophthalmoplegia, elevated CPK, kyphoscoliosis, and low bone mass. His congenital ptosis was suspected since birth, because of delayed eye opening. He wore glasses from early childhood due to myopia but denied motor delays. Over time, muscle weakness worsened, alongside increasing ptosis and kyphoscoliosis. His vision deteriorated after 40, and he reported erectile dysfunction. His history included prediabetes, dyslipidemia, myopia, anxiety disorder, and dental fragility. He had no prior surgeries and regularly engaged in strength training. No family history of similar conditions was reported, though his father died in his 40s following anesthesia induction, suspected to be malignant hyperthermia (MH). Various psychiatric disorders were noted in the family. Initial tests, including neuromuscular evaluations, echocardiography, ultrasound, stress testing, and electromyography, were unremarkable, but bone densitometry indicated osteopenia. Whole exome sequencing identified a homozygous pathogenic variant in the RYR1 gene (c.11314C>T; p. (Arg3772Trp)), linked to congenital myopathy 1B (OMIM:255320), an autosomal recessive disorder. The geneticist advised on the management of myopathy and MH susceptibility, recommended genetic screening of first-degree relatives and referred the patient for a sleep study, urology consultation, physiotherapy and supervised exercise. Discussion: MH is triggered by anesthetics but can remain undetected without exposure. Myopathy symptoms, such as cramps, rigidity, and weakness, may indicate MH susceptibility. Heterozygous gain-of-function RYR1 mutations increase MH risk, whereas homozygous recessive mutations cause myopathy. Given the patient's homozygous status, both parents were likely heterozygous carriers. His father's death, initially attributed to anaphylaxis, may have been an undiagnosed MH episode. Although the patient denied parental consanguinity, his family's small-town origin may suggest a common ancestor transmitting the mutation. This highlights the importance of genetic screening in myopathy patients and their families, particularly for RYR1 mutations, because of increased MH risk. In cases of myopathy with elevated CPK, genetic evaluation is crucial to identify dystrophies, metabolic myopathies, and ion channel disorders, ensuring a more complete treatment approach. Final Comments: Patients with idiopathic myopathy and elevated CPK, despite unremarkable biochemical, electromyographic, and imaging findings, should undergo genetic investigation. RYR1 mutations contribute to congenital myopathies that may manifest in childhood or adulthood. Genetic counseling is essential for these patients, as family members carrying RYR1 variants may be at risk for MH, requiring clinical management to mitigate potential complications.

**Palavras-Chave do trabalho:** Congenital Structural Myopathies; Genetic Counseling; Malignant Hyperthermia; Muscular Diseases; Ryanodine Receptor Calcium Release Channel;

**ID do trabalho:** 225

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **CASE REPORT: PRPS1 MUTATION CAUSING MOTOR NEUROPATHY, DEAFNESS, OPTIC ATROPHY AND ATAXIA**

**Autores:** UENISHI, Lucas Toshio<sup>1</sup>; ABREU, Fernanda Ferreira<sup>1</sup>; MACHADO, Lara Santos<sup>1</sup>; MENDES, Larissa Braga<sup>1</sup>; FERREIRA, Leonardo Villaverde Buback<sup>1</sup>; BARRETO, Maria Eduarda Shhessarenko Fraife<sup>1</sup>; SILVA, Thiago Yoshinaga Tonholo<sup>1</sup>; PEDROSO, José Luiz<sup>1</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

Case Presentation A 36-year-old male patient was brought to our clinic due to progressive gait disturbance. He reported slowly progressive weakness since he was 25, initially affecting the right leg but subsequently involving the left one. Lower limbs strength was graded 4 (mMRC scale) with hypoactive reflexes and pes cavus. He could still walk without assistance, and it was evident that he also had a wide-based ataxic gait, disproportionate to his weakness. His past medical history was noticeable for congenital deafness and a well-controlled non-structural focal frontal epilepsy since he was 20. Physical examination also revealed bilateral optic atrophy without visual acuity impairment, a pendular horizontal nystagmus and tongue atrophy with

fasciculations. Neuraxis MRI was normal. Nerve conduction and electromyography study was remarkable for signs of denervation and reinnervation in all segments and conduction block in the right median and ulnar nerves not associated with entrapment. Sensory nerve conduction was normal. A genetic etiology was suspected and whole exome sequencing (WES) was performed in the patient and his parents. WES yielded an hemizygous missense mutation in the PRPS1 gene: 706C>T; (p.Leu236Phe), classified as pathogenic. His parents, who were otherwise healthy, did not present the variant. Discussion The PRPS1 gene, located in Xq22.3, encodes the phosphoribosyl pyrophosphate synthetase 1, an enzyme that plays an important role in nucleotide synthesis. Pathogenic variants of PRPS1 are associated with many conditions 1. PRPS1 superactivity syndrome (MIM 300661) is a condition characterized by hyperuricemia resulting in childhood gout, sometimes associated with neurodevelopmental delay, hypotonia, ataxia and deafness. Nonsyndromic sensorineural deafness (MIM 304500) may also be a presentation. A type of X-linked Charcot-Marie-Tooth disease, CMTX5 (MIM 311070), is attributed to PRPS1 mutations and, besides motor and sensory neuropathy, hearing loss and optic neuropathy are also common features. Finally, the most severe phenotype is Arts syndrome (MIM 301835), a condition characterized by early onset, before the age of two, of deafness, global developmental delay, ataxia, peripheral neuropathy and optic atrophy, with a reported mortality of 80% before the age of six 2-3. Interestingly, our patient did not fit in an exact phenotype, but still, he presented with deafness, optic atrophy, ataxia and a motor neuropathy without sensory involvement. Final Comments PRPS1 mutation can cause a spectrum of diseases and, in some cases, their clinical features can overlap significantly. Early onset of deafness, optic atrophy, hyperuricemia and peripheral neuropathy should raise concern for PRPS1-related diseases.

**Palavras-Chave do trabalho:** Charcot-Marie-Tooth disease; Deafness; Hyperuricemia; Optic Neuropathy; PRPS1;

**ID do trabalho:** 226

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: **BRAIN STRUCTURAL SIGNATURE IN SCA27B: A MULTIMODAL MRI STUDY**

**Autores:** SANTOS, NADSON BRUNO SERRA<sup>1</sup>; LOBO, CAMILA CAROSO<sup>1</sup>; NOVIS, Luiz Eduardo<sup>2</sup>; REZENDE, Thiago Junqueira Ribeiro<sup>1</sup>; MARTINEZ, Alberto Rolim Muro<sup>1</sup>; TOMASELLI, pedro jose<sup>3</sup>; PEDROSO, Jose Luiz<sup>4</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>5</sup>; MARQUES JR, Wilson<sup>6</sup>; FRANÇA JR, Marcondes Cavalcante<sup>1</sup>;

**Instituição dos Autores:** (1) UNICAMP - CAMPINAS - SP - Brasil; (2) UNICAMP - RIO DE JANEIRO - RJ - Brasil; (3) USP RP - Ribeirão Preto - SP - Brasil; (4) UNIFESP - SÃO PAULO - SP - Brasil; (5) UNIFESP - SAO PAULO - SP - Brasil; (6) USP RP - RIBEIRAO PRETO - SP - Brasil;

### **Resumo do trabalho:**

Background: Spinocerebellar ataxia 27B (SCA27B) is a recently described autosomal dominant ataxia caused by intronic GAA expansions at FGF14. It is a late-onset condition characterized by the presence of downbeat nystagmus, peripheral neuropathy, vestibular dysfunction and episodic features. So far, little is known about the pattern of central nervous system involvement in SCA27B and how it correlates with its clinical phenotype. Objective: To characterize in vivo the pattern of cerebral and cerebellar structural abnormalities in SCA27B. Methods: This is a multicentric Brazilian study that included 10 patients (7 men/3 women) with molecular confirmation of SCA27B and 10 age and sex-matched healthy controls. All subjects underwent 3T MRI scans. High resolution T1 scans were then used for morphometric analyses: Cerebral gray matter was assessed using FreeSurfer whereas cerebellar structures were analyzed using CerebNet. Between-group comparisons were assessed using ANCOVA adjusted for age, sex and brain volumes. Results: Mean age and disease duration of patients were 68.4 and 5.1±5.6 years, respectively. Mean SARA score was 11.3±6.5. Resting tremor (57%) and abnormal vestibulo-ocular reflexed (57%) were frequent in this cohort. Morphometric analyses revealed that the SCA27B group had right Cerebellar ( $p = 0,017$   $d = 0,68$ ) and Vermian ( $p = 0,043$   $d = 0,74$ ) volumetric reduction. The volumes of the left cerebellum correlated with disease duration ( $p = 0.04$ ). No cerebral change was found in patients with SCA27B relative to controls ( $p>0.05$ ). Conclusions: Cerebellar damage is present, but mild in SCA27B. This contrasts to other monogenic ataxias, where cerebellar and/or brainstem atrophy are remarkable. In subjects with late-onset ataxias, the presence of clinic-radiological dissociation is a useful clue for SCA27B. Further studies with larger cohorts are needed to validate and expand these findings.

**Palavras-Chave do trabalho:** Cerebellar atrophy; Neuroimaging; SCA27B;

**ID do trabalho:** 227

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **PRELIMINAR RESULTS OF PERFORMANCE OUTCOMES AND GAIT DESCRIPTION OF PATIENTS FROM THE REDE IAXON-BRAZIL HSP**

**Autores:** CUBILLOS-ARCILA, Diana Maria<sup>1</sup>; ARRIAGA CRISCUOLI DE FARIAS<sup>2</sup>, Frederico<sup>1</sup>; HENRIQUES NEHM, Johanna<sup>1</sup>; RIVEIRO DE SOUZA, Maria Eduarda<sup>1</sup>; CARPEGIANI WEBER, Arthur<sup>1</sup>; VIEIRA MOTA, Barbara<sup>1</sup>; HERINGER, Pablo<sup>1</sup>; DE CASTRO, Paula<sup>1</sup>; DOS SANTOS MACIEL, Franciele<sup>1</sup>; RIVEIRO Nóbrega, Paulo<sup>2</sup>; FABER, Ingrid<sup>3</sup>; PEDROSO, José Luiz<sup>4</sup>; FREUA, Fernando<sup>5</sup>; MARQUES JUNIOR, Wilson<sup>6</sup>; CAVALCANTE FRANÇA JUNIOR, Marcondes<sup>7</sup>; MORALES SAUTE, Jonas Alex<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (3) Universidade de Brasília - Brasília - DF - Brasil; (4) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (5) Universidade de São Paulo - São Paulo - SP - Brasil; (6) Universidade de São Paulo de Ribeirão Preto - Ribeirão Preto - SP - Brasil; (7) Universidade Estadual de Campinas - Campinas - SP - Brasil;

### Resumo do trabalho:

**Background:** Hereditary spastic paraplegias (HSP) are a group of neurodegenerative genetic disorders that lead to a progressive reduction in walking ability. The IAXON-BRAZIL HSP multicenter research network has as one of its priorities to identify biomarkers sensitive to change that can be used as outcomes in future clinical trials, as well as to characterize gait according to disease subtypes. **Objective:** The aim of this study was to describe the preliminary results of the performance outcomes and spatio-temporal parameter of gait at baseline evaluations. **Methods:** This cross-sectional study assessed 38 patients with molecular or clinical diagnosis of HSP (9-SPG4, 1-SPG5, 6-SPG7, 7-SPG76, 1-SPG30, 14- no clear diagnosis of the subtype) from June to December 2024. The recently modified Spastic Paraplegia Rating Scale (SPRS), the patient-reported outcome Activities of Daily Living part of the Friedreich Ataxia Rating Scale (FARS-ADL) and its disease staging (FARS-Staging) and the performance outcomes (PerFOs): the timed-up and go (TUG) and 10-meters walking test (10MWT) at self-selected (SSWS) and maximal walking speed (MWS) were applied. Additionally, 18 out of the 38 patients who do not use walking aids were assessed with the 6 inertial measurement unit system (IMU) to describe the spatiotemporal gait parameters and three of the basic TUG skills (turning speed, time to stand up and sit down). **Results:** In the total group of patients, both the TUG and the 10MWT showed a moderate correlation with the FARS-staging and SPRS ( $Rho =$  from 0.698 to 0.790,  $p < 0.001$ ), and a low to moderate correlation with disease duration and FARS-ADL ( $Rho =$  from 0.356 to 0.536,  $p < 0.05$ ). Regarding spatio-temporal parameter of gait with IMU, gait speed and cadence at SSWS showed a strong correlation with SPRS ( $Rho = -0.834$  and  $-0.807$ ,  $p < 0.001$ ), and moderate correlation with FARS-staging and ADL ( $Rho =$  from  $-0.431$  to  $0.798$ ,  $p < 0.001$ ). Gait speed at MWS had a strong correlation with FARS-staging ( $Rho = -0.809$ ,  $p < 0.01$ ) and moderate correlation with SPRS, duration of disease and FARS-ADL ( $Rho =$  from  $-0.515$  to  $-0.796$ ,  $p < 0.01$ ). TUG-Skills at MWS performed better than at SSWS and had a moderate correlation with FARS-ADL and Staging ( $Rho =$  from 0.436 to 0.758,  $p < 0.05$ ). No variable from the TUG-skill or spatiotemporal parameter correlated with disease duration, except cadence at MWS ( $Rho = -0.521$ ,  $p < 0.01$ ). **Conclusion:** The initial results of the network show that the PerFOs and some of the spatiotemporal gait parameters have a significant association with classic clinical outcomes, including patient reported outcomes. Expanding the sample size will allow for the analysis of these parameters in specific subtypes, and longitudinal follow-up will help in understanding the most sensitive parameters, as well as the clinical relevance of such changes for defining the main outcomes to be used in future clinical trials, as well as for monitoring in clinical practice.

**Palavras-Chave do trabalho:** digital health technologies; gait analysis; Rare Disease; Spastic Paraplegias; timed functional tests;

**ID do trabalho:** 228

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **BEYOND PERIODIC PARALYSIS: A CASE SERIES OF ANDERSEN TAWIL SYNDROME**

**Autores:** RANGEL, Deborah Moreira<sup>1</sup>; FERRAZ DE ABREU, Bruno Nunes<sup>2</sup>; BESSA, Paula Emanuele De Lima<sup>1</sup>; BARRETO, Esther Grangeiro<sup>1</sup>; CARNEIRO, Kalina Livia Lopes<sup>1</sup>; MATOS, Paula Camila Alves de Assis Pereira<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (2) Hospital Geral de Fortaleza - Fortaleza - BA - Brasil;

### Resumo do trabalho:

**Background:** Andersen-Tawil is a genetic Neuromuscular disorder marked by the triad: episodic flaccid muscle weakness, cardiac abnormalities such as ventricular arrhythmias and structural anomalies. **Objective:** To describe the clinical manifestations and discuss symptomatic treatment of this rare disease. **Methods:** Data were collected from medical records. Verbal consent was obtained from the patient. **Cases report:** We report three members of a family with similar phenotypical aspects of disease. Patient 1 is a 37-year-old woman with a history of episodic weakness and exercise intolerance. She is the daughter of woman with a previous history of arrhythmias. On the physical exam she presented mild proximal thigh weakness

and fifth digit clinodactyly. Cardiac screening showed no structural abnormalities or arrhythmias. She still reports persistent disability associated to fatigue and anxiety. She is currently being treated with acetazolamide (500 mg/day) and sertraline. She reports mild improvement. Patient 2 is a 17-year-old man, the son of patient 1, has a previous record of episodic weakness, frequent falls, exercise and stress induced weakness. He is also a person living with Autism Spectrum Disorder (ASD) with no developmental delay, hypothyroidism and Keratoconus. He had a normal neurologic examination but had syndactyly of toes 2 and 3 and widely spaced eyes. Cardiac screening also have not revealed evident abnormalities. He still reports stress induced weakness and muscular pain. He is being treated with acetazolamide (750 mg/day) and has started on aerobic exercises with moderate functional improvement. Patient 3 is the younger son of Patient 1, he is an 8-year-old boy with delay in motor milestones and communication difficulties currently under investigation to Autism Spectrum Disorder. He has also been treated for hypothyroidism. He has experienced fever associated with weakness episodes, pain and falls since he was 2 years old. At physical examination he also has fifth digit clinodactyly, but without neurological motor abnormalities at exam and without cardiac abnormalities at this point. He is being treated with acetazolamide (250 mg/day) and neuroleptics for behavioral symptoms. He has good motor symptoms control but still has behavioral difficulties. At genetic investigations all our three patients have heterozygous mutations in gene KCNJ2, c.136C>G (p.ARG46GLY). Conclusion: This case series highlights three patients with a rare disease and unusual manifestations of Autism Spectrum Disorder and hypothyroidism, with partial control of occasional motor symptoms and fatigue with acetazolamide and lifestyle modification. We show signs such as dysmorphism and the possibility of arrhythmia as clinical clues for Andersen-Tawil syndrome in cases of periodic paralysis.

**Palavras-Chave do trabalho:** Acetazolamide; Andersen-Tawil Syndrome; Familial Periodic Paralysis;

**ID do trabalho:** 229

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: Cognitive impairment in Huntington's Disease: the role of screening tools in a brazilian referral center.**

**Autores:** GOMES, Ingrid Lorena da Silva<sup>1</sup>; LAGO MIRANDA, Guilherme<sup>1</sup>; RAMOS GONÇALVES, Taina Fatima<sup>1</sup>; ARB-SABA, Roberta<sup>1</sup>; CESAR DE AZEVEDO, Sonia Maria<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital do Servidor Público Estadual - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Introduction: Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by progressive motor, psychiatric, and cognitive dysfunction. Cognitive impairment starts in the early stages of the disease and progress over time, affecting multiple domains, increasing disability. Objective: To describe the cognitive impairment profile of patients with HD using cognitive screening tools and compare the findings with current literature. Methods: A retrospective chart review was conducted on patients with genetically confirmed HD who were followed at a reference center in São Paulo between January 2024 and January 2025. Data from cognitive screening tests, Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and/or the Semantic Verbal Fluency (FVS), were analyzed. Cognitive performance was categorized into the domains of attention, executive function, language, memory, and visuospatial perception. Patients without cognitive evaluation records were excluded. Results: Seven patients diagnosed with HD were evaluated, five women and two men. All diagnoses were confirmed by genetic testing, with CAG trinucleotide repeat expansions in the HTT gene ranging from 40 to 46. Mean age was 59.8 years and educational backgrounds varied from incomplete elementary education to postgraduate degrees. Symptom onset ranged from 2 to 11 years prior, with a mean disease duration of 7.5 years. All patients underwent at least one cognitive screening test (MMSE or MoCA). Attention and memory deficits were universally present, and executive dysfunction was identified in all patients assessed for this domain. Four of six patients demonstrated visuospatial impairment and language remained relatively preserved, except in two cases, which corresponded to the patients with the longest disease duration. Discussion: According to the literature, the cognitive domains most affected in the early stages of HD include executive function, processing speed, attention, working memory, and deficits in social cognition. It correlates with the initial relative preservation of predominantly cortical functions such as language, semantic memory, and spatial orientation, which do not critically depend on subcortical pathways. The selective dysfunction of the striatum explains why cognitive functions involving subcortical circuits are typically the first to be affected. As neurodegeneration progresses, brain atrophy advances, ultimately leading to global cognitive impairment. Conclusion: Cognitive analysis is essential to evaluate HD patients. Tools such as MMSE and MoCA are accessible, cost-effective, and useful for identifying affected cognitive domains, even in the early stages of the disease. Our findings reinforce the characteristic progression of HD and suggest that cognitive assessment may aid in monitoring disease evolution, guiding therapeutic interventions, particularly in settings with limited access to comprehensive neuropsychological evaluation.

**Palavras-Chave do trabalho:** Cognitive Assessment; cognitive decline; Huntington's Disease;

**ID do trabalho:** 230

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **TAMM41-ASSOCIATED MITOCHONDRIAL MYOPATHY**

**Autores:** MORENO, Cristiana Araújo Martins<sup>1</sup>; GONTIJO, Clara Camelo<sup>1</sup>; FONSECA, Alulin Tácio Quadros Santos Monteiro<sup>1</sup>; SCHLESINGER, David<sup>2</sup>; ZANOTELI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Faculdade de Medicina da Universidade de São Paulo (FMUSP) - São Paulo - SP - Brasil; (2) Mendelics - São Paulo - SP - Brasil;

### Resumo do trabalho:

**Introduction** The TAMM41 gene encodes a mitochondrial protein with cytidine diphosphate-diacylglycerol synthase activity which is an essential early step in the biosynthesis of phosphatidylglycerol and cardiolipin, a mitochondria-specific phospholipid that is important for many mitochondrial processes. TAMM41 biallelic variants were previously described in three unrelated individuals with a mitochondrial myopathy presenting lethargy at birth, hypotonia, developmental delay, generalized weakness and ptosis. Here we report one additional case to reinforce the genetic evidence for this novel gene. **Materials and Methods** Patient and both relatives were clinically examined. Chart was reviewed to collect information about diagnosis and ancillary exams. Muscle biopsy was performed when patient was 5 years old, and the slides were reviewed by the authors. DNA was extracted from swab from patient and both relatives. Whole exome sequencing was performed in 2019 and expanded for a trio in 2024 when the causative variants were identified. **Case Report** A 19-year-old female patient, child of non-consanguineous parents, presented with delayed motor development. Hypotonia and difficulty with head control were noted at 2 months of age. Between 2 and 4 years of age, she experienced frequent falls, difficulty rising up from the floor. At 4 years old, she presented with recurrent respiratory infections with progressive worsening of weakness at each episode, without returning to baseline strength. At 7 years of age, she suffered a cardiac arrest during hospitalization for pneumonia, requiring tracheostomy and gastrostomy. Since then, she was not able to walk and could only stay seated with no support. By the age of 19, she was fully dependent on mechanical ventilation and exclusively fed via a gastrostomy tube. She was cognitively oriented. She presented with myopathic facies, ptosis, and ophthalmoparesis affecting upward gaze and abduction. Muscle weakness was generalized and severe. CK levels were normal; A muscle biopsy showed increase of connective tissue, and the presence of fibers with reduced oxidative succinate dehydrogenase (SDH) and cytochrome c oxidase (COX) activity. Trio research WES confirmed compound heterozygous variants in TAMM41: c.410C>T, (p.Pro137Leu) and c.874G>A, (p.Gly292Ser). **Discussion** Mitochondrial membranes have a high content of cardiolipin which is important for several processes. TAMM41 was recently described as a cause of mitochondrial myopathy. There is only one paper where the three previously reported patients presented an early onset hypotonia, lethargy, and failure to thrive. Patients developed a variable degree of motor delay, progressive external ophthalmoplegia, ptosis and myopathic face. There are only few reports of myopathy presenting with decrease SDH staining at muscle histology.

**Palavras-Chave do trabalho:** MITOCHONDRIOPATHY; Myopathy; Neuromuscular;

**ID do trabalho:** 231

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **PROGRESSION OF MUSCLE ACTIVATION AND CO-CONTRACTION IN PATIENTS WITH HEREDITARY SPASTIC PARAPLEGIA OVER THREE YEARS OF FOLLOW-UP**

**Autores:** CUBILLOS-ARCILA, Diana Maria<sup>1</sup>; IVANISKI-MELLO, André<sup>1</sup>; FEIJÓ MARTINS, Valeria<sup>1</sup>; PEYRÉ-TARTARUGA, Leonardo Alexandre<sup>2</sup>; MORALES SAUTE, Jonas Alex<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil; (2) Univesidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

**Background:** Hereditary Spastic Paraplegia (HSP) refers to a group of degenerative genetic diseases characterized by spasticity, muscle weakness, and gradual loss of the ability to walk. The clinical and genetic variability of these conditions makes it difficult to establish biomarkers for their progression. Surface electromyography provides a set of key variables for understanding spasticity, muscle activity, normal gait, and pathological gait. **Objective:** The aim of this study was to describe the preliminar results of the progression and correlation of muscle activation and co-contraction in patients with HSP over three years of follow-up. **Methods:** This longitudinal study assessed 18 patients with molecular or clinical diagnosis of HSP at baseline (12-SPG4, 4-SPG5, 1-SPG7, 1-SPG3) and 10 patients after 3 years of follow-up (7-SPG4, 2-SPG5, 1-SPG3) from June 2019 to October 2022. The recently modified Spastic Paraplegia Rating Scale (SPRS), The muscle activity of the vastus lateralis, biceps femoris, tibialis anterior, and medial gastrocnemius were assessed through surface electromyography while walking on a 7-

meter platform. The co-contraction index was calculated. Results: After three years of follow-up, the muscle activity of the four muscles did not show a statistically significant difference ( $p > 0.05$ ). The vastus lateralis was the only variable that demonstrated a significant correlation with SPRS in the overall HSP group ( $\text{Rho} = 0.534$ ,  $p < 0.049$ ). No correlation was found between the progression of EMG variables and SPRS progression in the overall HSP group. Conclusion: The initial results suggest that muscle activation of the vastus lateralis could be an interesting variable to explore. However, the sample size was too small for a robust longitudinal analysis of these variables. Surface electromyography is a valuable tool for understanding spasticity and gait in various diseases, and it will be important to continue exploring this assessment to define key outcomes for future clinical trials, as well as for monitoring in clinical practice.

**Palavras-Chave do trabalho:** digital health technologies; gait analysis; Rare Disease; Spasticity; Superficial electromyography;

**ID do trabalho:** 232

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: **CLINICAL AND GENETIC LANDSCAPE IN SPG4 BRAZILIAN COHORT FROM A MULTICENTRIC STUDY**

**Autores:** CHU, Karen Mei<sup>1</sup>; SILVEIRA, Cynthia<sup>1</sup>; GONZÁLEZ-SALAZAR, Carelis<sup>1</sup>; DE LIMA, Fabrício Diniz<sup>1</sup>; DONIS, Karina Carvalho<sup>2</sup>; CUBILLOS-ARCILA, Diana Maria<sup>3</sup>; TOMASELLI, Pedro José<sup>4</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>5</sup>; DE FREITAS, Júlían Letícia<sup>6</sup>; ORTEGA, Roberta Paiva Magalhães<sup>6</sup>; ROSEMBERG, Sérgio<sup>6</sup>; FREUA, Fernando<sup>7</sup>; TEIVE, Helio Afonso Ghizoni<sup>8</sup>; KOK, Fernando<sup>7</sup>; PEDROSO, José Luiz<sup>5</sup>; JUNIOR, Wilson Marques<sup>4</sup>; SAUTE, Jonas Alex Morales<sup>2</sup>; JUNIOR, Marcondes Cavalcante França<sup>1</sup>;

**Instituição dos Autores:** (1) UNICAMP - Campinas - SP - Brasil; (2) UFRGS - Porto Alegre - RS - Brasil; (3) UFRGS - Porto Alegre - SP - Brasil; (4) USP-RP - Ribeirão Preto - SP - Brasil; (5) UNIFESP - São Paulo - SP - Brasil; (6) Santa Casa - São Paulo - SP - Brasil; (7) USP-SP - São Paulo - SP - Brasil; (8) UFPR - Curitiba - PR - Brasil;

### **Resumo do trabalho:**

Background: Hereditary Spastic Paraplegia Type 4 (SPG4) is the most prevalent subtype of hereditary spastic paraplegia (HSP), a heterogeneous group of progressive neurodegenerative disorders. SPG4 is caused by genetic variants in the SPAST gene, which encodes the protein spastin. It is classified as a pure HSP, predominantly characterized by progressive weakness and spasticity in the lower limbs, as well as hyperreflexia and urinary disturbances. The global incidence of SPG4 is estimated at 3 cases per 100,000 people. Within the group of autosomal dominant HSPs, SPG4 accounts for up to 40% of cases. Objective: To describe the phenotypic and genotypic landscape in Brazilian patients with SPG4. Methods: The analysis included 112 patients from 63 families, recruited from seven centers in 3 different Brazilian states. Clinical characteristics reported during clinical consultations were analyzed, along with genetic variants identified through molecular testing. Results: The patient group analyzed consisted of individuals aged less than 1 year to 92 years, as the median age of this cohort is 53 years. The age of onset ranged from less than 1 year to 71 years, with a mean onset age of 30 years. There were 27 and 85 with pediatric and adult onset, respectively. All, but 2 had pure phenotype. The two exceptional cases were presented with polyneuropathy. 37 were in use of cane and 10 were in use of wheelchairs. There were 46 variants identified: 18 missenses (39,13%), 8 frameshift deletion (17,39%), 6 nonsense (13,04%), 5 splice site (10,87%), 2 CNV (4,35%), 2 frameshift duplication (4,35%), 2 intronic (4,35%), 1 in frame deletion (2,17%), 1 in frame duplication (2,17%) and 1 stop codon loss (2,17%). During the analysis of these variants, 19 novel variants were identified. Conclusions: SPG4 has a relatively homogeneous phenotype, but heterogeneous genetic landscape in Brazilian patients.

**Palavras-Chave do trabalho:** Genotype-Phenotype Correlation; SPAST; SPG4;

**ID do trabalho:** 233

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **SPASTIC ATAXIA TYPE 5 AND RETINITIS PIGMENTOSA: EXPANDING THE PHENOTYPE OF AFG3L2 GENE.**

**Autores:** RANGEL, Deborah Moreira<sup>1</sup>; BESSA, Paula Emanuele de Lima<sup>1</sup>; FERRAZ DE ABREU, Bruno Nunes<sup>1</sup>; BARRETO, Esther Grangeiro<sup>1</sup>; MONTEIRO, Dina Andressa Martins<sup>1</sup>; PESSOA, Andre Luiz Santos<sup>2</sup>; CARNEIRO, Kalina Livia Lopes<sup>1</sup>; MATOS, Paula Camila Alves de Assis Pereira<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (2) Universidade Federal do Ceará - Fortaleza - CE - Brasil;

**Resumo do trabalho:**

Case presentation: We report a case of a 21-year-old male, from a consanguineous union, who presented with generalized tonic clonic and myoclonic seizures at nine years old, later evolving with developmental regression, progressive weakness and lactic acidosis. Signs of polyneuropathy, myopathy, facial hypotonia and spastic tetraparesis were present at physical examination. He is currently being treated with phenobarbital 90 mg/day, topiramate 200 mg/day, clonazepam 2,5 mg/day and levetiracetam 200 mg/day, with well-controlled seizures. Retinal imaging has demonstrated retinitis pigmentosa. Electroencephalogram evidenced very frequent interictal epileptiform activity in central regions, in addition to base activity disturbance. Exoma showed homozygous mutation in gene AFG3L2 chr18:12.340.334 T>G p.Tyr616Cys. Discussion: Spastic ataxia type 5 is a rare autosomal recessive neurodegenerative disease, characterized by childhood-onset cerebellar ataxia, spasticity, dystonia and progressive myoclonic epilepsy. The clinical phenotype associated with variations in AFG3L2 was recently expanded to include oculomotor apraxia and extrapyramidal features. The variable clinical manifestations of AFG3L2 mutations have been explored in literature, however with no mention of associated retinitis pigmentosa. Final Comments: This case report provides evidence of a broader spectrum of clinical phenotypes associated with this rare diagnosis. SPAX5 should be considered in childhood-onset cerebellar ataxia, myoclonic epilepsy and spasticity.

**Palavras-Chave do trabalho:** AFG3L2 gene; Progressive myoclonic epilepsy; Spastic ataxia type 5;

**ID do trabalho:** 235

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: MUCKLE-WELLS SYNDROME: A DIAGNOSTIC CHALLENGE IN A CASE SERIES**

**Autores:** FERRAZ DE ABREU, Bruno Nunes<sup>1</sup>; MATOS, Paula Camila Alves de Assis Pereira<sup>1</sup>; BESSA, Paula Emanuele de Lima<sup>1</sup>; BARRETO, Esther Grangeiro<sup>1</sup>; CATUNDA, Amanda Vale<sup>1</sup>; PITOMBEIRA, Milena Sales<sup>1</sup>; RANGEL, Deborah Moreira<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil;

**Resumo do trabalho:**

Background: Muckle-Wells syndrome is a rare autosomal dominant autoinflammatory syndrome marked by episodic fever, rash and arthralgia associated with late-onset deafness and renal amyloidosis. Its neurologic manifestations may include hearing loss and chronic meningitis. Objective: To report unusual neurologic manifestations of this rare disease. Methods: We collected data from medical records about clinical manifestations and treatment. Results: Herein we report two cases from the same family. Case 1 is a 27-year-old male with a medical history of recurrent episodes of fever, oral ulcers and conjunctivitis since the first month of life and development delay. He had developed generalized seizures that were not always associated with the symptoms aforementioned. His electroencephalogram (EEG) was compatible with generalized epileptic activity. Until now, he has no evidence of hearing loss or nephropathy. Current treatment consists in antiseizure drugs and monoclonal antibody Interleukin-1 (Canakinumab) with good clinical response. Case 2 is a 48-year-old female, the mother of the patient reported above, who has had recurrent episodes of arthralgia, conjunctivitis and fever since her second decade of life. During those episodes, she also experienced focal seizures and started antiseizure drugs since then, with good control over the last twenty years. Conventional EEG has not witnessed epileptiform activities. Past medical history included migraine and fibromyalgia. She is currently on treatment with canakinumab and has experienced moderate improvement in fever episodes, but still reports pain episodes. Both our patients have genetic confirmation of heterozygous mutation in the NLRP3 gene. Conclusion: We report two cases of a family with NLRP3 gene mutations and clinical features compatible with Muckle-Wells syndrome presenting epilepsy as an unusual manifestation and disease stability with canakinumab use.

**Palavras-Chave do trabalho:** Hereditary Autoinflammatory Diseases; Muckle-Wells Syndrome; NLRP3 gene;

**ID do trabalho:** 236

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: CHUNG-JANSEN SYNDROME: PRESENTATION OF AN ATYPICAL PHENOTYPE OF A RARE AND RECENTLY DESCRIBED AUTOSOMAL DOMINANT NEUROPSYCHIATRIC CONDITION.**

**Autores:** DA SILVA, Danilo Jorge<sup>1</sup>; COSTA, Victor de Oliveira<sup>1</sup>; DE ASSIS, Thamyrez Quezia<sup>1</sup>; CRUZEIRO, Marcelo Maroco<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Universitário da Universidade Federal de Juiz de Fora - Juiz de Fora - MG - Brasil;

**Resumo do trabalho:**

Case presentation: A 33-year-old man with a history of slight difficulty walking since childhood, without delays in neuropsychomotor development. He sought neurological care due to a sudden worsening of gait at age 28, described as difficulty in moving the lower limbs with painful thighs, and was investigated in a hospital setting under suspicion of acute myopathy, likely of viral infectious nature, receiving supportive treatment. ENMG showed findings compatible with chronic myopathy with proximal predominance without irritative findings. MRI demonstrated mild atrophy and symmetrical fat replacement of the musculature in the posterior and medial compartments of the thighs, without edema. No elevation of creatine kinase or aldolase was observed, and the patient returned to baseline gait within a few weeks, maintaining mild gait ataxia. His previous medical history had psychiatric disorders (major depression in association with generalized anxiety disorder and panic disorder), metabolic syndrome, hypothyroidism and bronchial asthma. Since he continued to exhibit an insidious worsening of gait over the years, use of wheelchair, and painful cervical dystonia he was submitted to extensive clinical and complementary investigation (including muscle biopsy), but only the molecular study shows additional results. Exome sequencing revealed a autosomal dominant variant in the PHIP gene, located on chromosome 6q14 -NM\_017934.7:c.455C>G:p.(Ser152\*), classified as probably pathogenic and compatible with Chung-Jansen syndrome (CHUJANS). Discussion: CHUJANS was described in 2018 as a rare genetic condition of autosomal dominant nature that affects about 400 people worldwide, commonly resulting from de novo mutations. It is typically characterized by developmental delays, intellectual disability, and behavioral problems, which are the most frequent manifestations observed, varying between 91% and 100% of cases depending on the (rare) cohort considered. Behavioral/psychiatric changes, obesity/overweight, dysmorphisms, and visual abnormalities follow in frequency. Hypotonia and gait/postural instability occur in up to 35% of individuals. This case reports an atypical presentation of very rare neurological syndrome, where intellectual deficit and developmental delay are uncommonly not observed, but psychiatric-related changes and gait abnormalities are prominent, along with the typical finding of metabolic syndrome. There are no cohorts consistently reporting myopathy in association with CHUJANS Final comment: This work describes an atypical phenotype of a rare condition that was only recently described in the literature, with its first cohort published in 2018 and no large case series published yet. It is a syndrome still poorly understood by the medical literature, and it is hoped that the case report can contribute to amplify the identification of individuals with the condition and that we can develop a better treatment in the future beyond symptomatic control.

**Palavras-Chave do trabalho:** Chung-Jansen; Myopathy; Rare Disease;

**ID do trabalho:** 239

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: CLINICAL SPECTRUM AND DISEASE PROGRESSION AMONG C9ORF72 BRAZILIAN CARRIERS**

**Autores:** VIEIRA, LUCAS GONDIM BRIAND<sup>1</sup>; PEREIRA, MARIANA RIBEIRO<sup>1</sup>; LEMOS, ANA FLÁVIA ANDRADE<sup>1</sup>; FAVARO, MATEUS GUSTAVO<sup>1</sup>; OLIVEIRA, AMANDA VITÓRIA DE FREIRE<sup>1</sup>; ALVES, GUSTAVO MAXIMIANO<sup>1</sup>; FREZATTI, RODRIGO SIQUEIRA SOARES<sup>1</sup>; DOS SANTOS, DIOGO FERNANDES<sup>2</sup>; TUMAS, VITOR<sup>1</sup>; TOMASELLI, PEDRO JOSÉ<sup>1</sup>; MARQUES JR, WILSON<sup>1</sup>;

**Instituição dos Autores:** (1) DEPARTAMENTO DE NEUROCIÊNCIAS E CIÊNCIAS DO COMPORTAMENTO, FACULDADE DE MEDICINA DE RIBEIRÃO PRETO, UNIVERSIDADE DE SÃO PAULO - RIBEIRÃO PRETO - SP - Brasil; (2) UNIVERSIDADE FEDERAL DE UBERLÂNDIA - UBERLÂNDIA - MG - Brasil;

**Resumo do trabalho:**

Background: Expansion of the hexanucleotide G4C2 of the C9orf72 gene is a recognized cause of a disease with a phenotypic spectrum which encompasses amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and ALS-FTD complex disorder. Importance of genetic diagnosis includes genetic counseling and life planning. Objective: To analyse the clinical pattern and its progression in a series of individuals with pathogenic C9orf72 expansions. Methods: Clinical, neurophysiological, radiological and genetic data of individuals with confirmed C9orf72 hexanucleotide G4C2 expansion were gathered from their records. Affected individuals were recruited from the neuromuscular, neurogenetic and cognitive outpatients clinic in our University Hospital. Additionally, genetic testing was offered to at-risk relatives who were 18 or older and provided their informed consent. Results: Forty individuals were confirmed with C9orf72 hexanucleotide G4C2 expansion, but twenty-nine individuals met the criteria for this study and were included. The mean time of follow-up was 2.04 years. Predictive testing identified six individuals that remain asymptomatic, with mean age at last assessment of 39,16 years. The mean age for disease onset was 58.08 years. The most common presenting symptom was asymmetric lower limb weakness (8/23 of symptomatic patients). Among symptomatic patients 16 presented with exclusively upper and lower motor neuron involvement (MND), and only three patients presented with dementia. On the last visit, all the MND patients exhibited upper and lower motor neuron signs, meeting the Gold Coast diagnostic criteria for ALS. Of note, only one patient exhibited exclusively lower motor neuron disease at the first assessment. The mean time of disease follow up for patients presenting with MND was 1.31 years. Seven patients deceased with a mean disease duration of 2.85 years (eight months to four years). Nine individuals had no family

history. Twenty-two individuals underwent electrodiagnostic study. Twelve individuals underwent magnetic resonance imaging (MRI). In 8 of them bilateral corticospinal tract hyperintensity was found, including two asymptomatic individuals. None of the individuals had motor band sign. Conclusion C9orf72 gene expansion associated disorder is an important cause of genetic ALS/FTD. Patients with sporadic ALS may carry the C9orf72 expansion. MND due to C9orf72 expansion appears to have a faster progression to death compared to classical ALS. Genetic testing is important for patients and families for life planning and genetic and reproductive counseling.

**Palavras-Chave do trabalho:** Amyotrophic Lateral Sclerosis; C9orf72; Frontotemporal Dementia; Motor Neuron Diseases; Predictive Genetic Testing;

**ID do trabalho:** 240

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: ATYPICAL NESCAV SYNDROME DUE TO A KIF1A VARIANT: INSIGHTS INTO GENETIC AND CLINICAL HETEROGENEITY.**

**Autores:** ANDRADE, Luccas Almeida<sup>1</sup>; GAMA, Sofia Mônaco<sup>1</sup>; PROCACI, Victor Rebelo<sup>1</sup>; SILVA, Thiago Yoshinaga Tonholo<sup>1</sup>; PEDROSO, José Luiz<sup>1</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>1</sup>;

**Instituição dos Autores:** (1) Department of Neurology; Universidade Federal de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

An 11-year-old girl presented with delayed psychomotor development since infancy, alongside severe behavioral and psychiatric abnormalities and autism spectrum disorder (ASD). The patient was born healthy following an uncomplicated, full-term pregnancy to non-consanguineous parents, but her aunt and grandaunt had a neurological impairment diagnosed as cerebral palsy. Neurological examination revealed impaired visual acuity (20/60 bilaterally), temporal optic atrophy, vertical nystagmus, spasticity, and mild cerebellar ataxia. Metabolic screening was unremarkable, and brain MRI showed cerebellar atrophy. Whole exome sequencing identified a heterozygous pathogenic KIF1A variant [c.760C>T; (p.Arg254Trp)], confirming the diagnosis of NESCAV syndrome. The Kinesin Family Member 1A (KIF1A) gene encodes a motor protein crucial for anterograde axonal transport. Pathogenic variants cause KIF1A-associated neurological disorder (KAND), a group of rare progressive neurodegenerative conditions. These variants may be inherited recessively or dominantly, with the most severe phenotypes often linked to de novo variants. KAND presents with neurodevelopmental delay, hereditary spastic paraplegia (types 30A/B), autonomic and sensory neuropathy, intellectual disability, autism, optic nerve atrophy, seizures, or NESCAV syndrome. The latter is a childhood-onset neurodegenerative disorder characterized by progressive spasticity, gait impairment, developmental delay, intellectual disability, neuropsychiatric symptoms, and cortical visual impairment. Other features include axonal peripheral neuropathy, ataxia, dystonia, dysautonomia, and optic atrophy. Some cases exhibit developmental regression, mainly affecting motor function. Imaging may reveal cerebellar atrophy and corpus callosum thinning. It represents a major differential diagnosis for hereditary spastic paraplegia type 11 (SPG11), as it also manifests with progressive spastic paraparesis, corpus callosum abnormalities, and other overlapping clinical and imaging findings. This case highlights a rare KAND phenotype due to a heterozygous pathogenic KIF1A variant, manifesting as NESCAV syndrome with prominent ASD-like symptoms and a family history suggestive of an autosomal dominant inheritance pattern - an uncommon presentation, as such severe phenotypes typically arise from de novo variants.

**Palavras-Chave do trabalho:** autism spectrum disorder; Hereditary Spastic Paraplegia; KIF1A-associated neurological disorder; NESCAV syndrome; optic nerve atrophy;

**ID do trabalho:** 243

**Área Técnica do trabalho:** Demências e doenças cerebrovasculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: EVALUATING GENETIC TESTING AND COUNSELING FOR DOMINANTLY INHERITED ALZHEIMER'S DISEASE IN CHILE: CHALLENGES AND INSIGHTS**

**Autores:** JIMENEZ, DANIEL ANDRES<sup>1</sup>; HERNANDEZ, AURORITA<sup>2</sup>; LAVADOS, MANUEL<sup>1</sup>; LLIBRE GUERRA, JORGE JESUS<sup>3</sup>; ZIEGEMEIER, ELLEN MARIE<sup>3</sup>;

**Instituição dos Autores:** (1) Universidad de Chile - Chile; (2) Psicología clínica - Chile; (3) Washington University in St. Louis - United States;

**Resumo do trabalho:**

Background: Alzheimer's disease (AD) is the most common cause of dementia worldwide and one of the major health challenges of our time. Inherited or familial forms of AD (FAD) represent a small proportion of cases, typically presenting symptoms at a younger age and often accompanied by a strong family history of early-onset dementia. Although age is the strongest risk factor for developing the disease, approximately 10% of cases manifest symptoms before the age of 65, the arbitrary cut-off for defining early-onset AD. This group includes most dominantly inherited forms of AD caused by mutations in three genes: amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2). Chile has implemented a National Plan for Dementia, but it does not include tailored diagnostic or therapeutic interventions for DIAD (dominantly inherited Alzheimer's disease) populations. In this context, there is a need to enhance medical genetic services and family counseling in Chile to garner additional support from stakeholders and policymakers. Objective: The primary aim of this study is to describe our experience in assessing patients and families referred to our center for genetic testing to confirm a potential DIAD diagnosis. We also discuss the main barriers to identifying new DIAD families across Chile and evaluate the feasibility and acceptability of the genetic counseling and testing process for DIAD families in the country. Methods: Between June 2023 and December 2024, we received 15 referrals at our center in Santiago, Chile. All patients were referred by cognitive neurologists who suspected an autosomal dominant form of AD. Demographic, clinical, and family history data were recorded to calculate a modified Goldman Score. Index patients highly suspicious for DIAD underwent dementia panel testing through our alliance with the Dominantly Inherited Alzheimer Network (DIAN), including the genes ABCA7, ADAM10, AKAP9, APP, CHMP2B, FUS, GRN, MAPT, PLG2, PLD3, PRNP, PSEN1, PSEN2, SORL1, TARDBP, TREM2, VCP, and APOE. Results: Only two patients had a modified Goldman Score highly suggestive of DIAD. No pathogenic DIAD mutations were identified. One tested patient was homozygous for the Apolipoprotein e4 (APOE4) risk variant (c.388T>C; p.Cys130Arg), while the other patient was heterozygous for the same variant. Conclusion: Most patients and families did not meet the criteria for probable DIAD. Patients and families expressed interest in genetic testing based on a family history of AD, but in most cases, the age at onset was after 65. We identified two APOE4 carriers presenting with early-onset AD, consistent with literature suggesting that APOE4 influences the age of onset in sporadic forms of AD. Increased awareness of genetic forms of AD and the importance of detailed family histories in patients with symptom onset before age 65 is essential.

**Palavras-Chave do trabalho:** Dominantly inherited Alzheimer's disease; Genetic Counseling; Genetic Testing;

**ID do trabalho:** 244

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: ACUTE FLACCID PARALYSIS REVEALING ACUTE INTERMITTENT PORPHYRIA ASSOCIATED WITH ATYPICAL PLEXUS THICKENING MIMICKING GUILLAIN BARRE SYNDROME CAUSED BY A HETEROZYGOUS HMBS MUTATION - A CASE REPORT**

**Autores:** BRAGA MUNARETO, Matheus Luís<sup>1</sup>; ALVES DA SILVA, Matheus<sup>1</sup>; ARAÚJO FERNANDES, Alex<sup>1</sup>; MIRANDA DE MENDONÇA, Amanda<sup>1</sup>; FARIA DONADON, Ana Luísa<sup>1</sup>; BRAGANÇA RODRIGUES MATIAS, Rafael<sup>1</sup>; MESQUITA DE SOUZA, Eduardo<sup>1</sup>; FERREIRA LIMA, Karlla Danielle<sup>1</sup>; MONTEIRO DE SIQUEIRA CAMPOS, Christiane<sup>1</sup>; MACHADO BAETA, Alex<sup>1</sup>;

**Instituição dos Autores:** (1) BP - A Beneficência Portuguesa de São Paulo - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Case presentation A 42 years old female patient underwent plastic surgery in the breast and abdominal wall. Three days postoperatively, she was readmitted due to severe hyponatremia and abdominal pain, associated with an intestinal pseudo obstruction (Ogilvie syndrome). Two weeks after the initial symptoms, she started with an ascendent acute flaccid paralysis. Her medical and familial history were unremarkable. There were no psychiatric symptoms. Her neurological examination showed prominent motor symptoms with bilateral facial palsy, decrement in muscle tonus and strength, global areflexia and mild sensory loss, most prominent on vibratory sensation. Besides the initial suspicion of acute intermittent porphyria (AIP), a CSF analysis was normal and her nerve MRI showed diffuse thickening and enhancement of both brachial and lumbosacral plexus, atypical for AIP. However, her delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) were positive in urine analysis, and a prompt treatment with hemin was made for 14 days, leading to a symptoms stabilization. She was later discharged for rehabilitation. A NGS analysis showed a heterozygous c.652-2del in the HMBS gene. Discussion The acute porphyrias are rare genetic disorders which impairs heme metabolism. There is a wide range of clinical symptoms, like psychiatric, motor symptoms, abdominal pain, and others. Laboratorial findings include hyponatremia and abnormal ALA and PBG results. There are few case reports of abnormalities in plexus MRI in patients with AIP, like in our case, and we suggest that, like in acute inflammatory neuropathies, the plexus MRI may be a useful tool to help diagnosing these patients. Final comments The recognition of acute porphyrias is necessary, because it is a treatable genetic disorder, and treatment delay may lead to poor outcomes. We suggest that the use of plexus MRI may help in the diagnosis of AIP in the right clinical settings, but more studies are necessary to determine the accuracy of this test modality.

**Palavras-Chave do trabalho:** acute intermittent porphyria; case report; nerve MRI;

**ID do trabalho:** 245**Área Técnica do trabalho:** Outros**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: CASE REPORTS: GLUTARIC ACIDURIA TYPE 1 WITH MITOCHONDRIAL PHENOTYPE**

**Autores:** CALDEIRA, Lunielle Da Cruz<sup>1</sup>; BARBOSA, Renata Montes Garcia<sup>1</sup>; CASTRO, Matheus Augusto Araujo<sup>2</sup>; CRUZ, Patrícia Pontes<sup>1</sup>; JUNIOR, Sergio Roberto Pereira da Silva<sup>1</sup>; MOTA, Jorio Almino De Alencar Arrais<sup>1</sup>; SANTOS, Vanessa Catarine Silva Abreu Ribeiro Dos<sup>1</sup>; BUENO, Clarissa<sup>1</sup>; KOK, Fernando<sup>1</sup>; FREUA, Fernando<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - SAO PAULO - SP - Brasil; (2) Universidade de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Case Presentation: A 26-year-old female patient experienced metabolic decompensation at 10 months of age, leading to significant cognitive and motor impairment, including generalized dystonia with a prominent oromandibular component. She also presents with focal impaired awareness epilepsy and is entirely dependent on others for activities of daily living (ADLs). The diagnosis of glutaric aciduria type 1 (GA1) was established despite a normal amino acid chromatography. Molecular analysis identified two pathogenic heterozygous variants: c.1144G>A (p.Ala382Thr) and c.680G>C (p.Arg227Pro). Discussion: Initially, the clinical presentation suggested a mitochondrial disorder phenotype, as the biochemical profile was normal, making organic acidemias a less likely diagnosis. However, one of the identified variants, c.680G>C (p.Arg227Pro), has been reported to retain 10% to 85% of glutaryl-CoA dehydrogenase enzymatic activity, which may explain the preserved urinary excretion of glutaric acid observed in previous organic acid analysis. The exome sequencing ultimately confirmed GA1, an autosomal recessive inborn error of metabolism caused by biallelic pathogenic variants in the GCDH gene. This deficiency leads to the accumulation of glutaric acid and 3-hydroxyglutaric acid, resulting in neurotoxicity. Clinically, patients are typically asymptomatic at birth, but macrocephaly may develop within the first months of life. Metabolic decompensation usually occurs between 6 and 18 months, often triggered by infections or catabolic stress, leading to acute encephalopathy, developmental regression, and movement crises. Most patients develop progressive dystonia, often severe, along with motor and cognitive impairment. In "low excretors," the clinical course may be more insidious, without acute encephalopathic crises but with ongoing neurological deterioration. Final Comments: Early diagnosis is crucial, as encephalopathic crises and their severe clinical consequences can be prevented through appropriate metabolic management, including a low-lysine diet, carnitine supplementation, and emergency preventive measures. The patient's prognosis depends heavily on early diagnosis and adherence to treatment. Newborn screening using tandem mass spectrometry is critical for the early detection of GA1 and is already being implemented in São Paulo and Brasília. However, it is important to highlight that "low excretors" may exhibit a normal biochemical profile, making molecular confirmation essential for a definitive diagnosis.

**Palavras-Chave do trabalho:** glutaric aciduria type 1; low excretors; mitochondrial phenotype; Newborn screening;

**ID do trabalho:** 246**Área Técnica do trabalho:** Neurodesenvolvimento**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: CASE REPORT - ALAZAMI SYNDROME: A RARE CAUSE OF NEURODEVELOPMENTAL DISORDER**

**Autores:** EXPÓSITO NUNES, Anna Carolina<sup>1</sup>; ARAUJO, Carolina de Souza<sup>2</sup>;

**Instituição dos Autores:** (1) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (2) Universidade Federal de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Background: Alazami syndrome is a genetic disorder with an autosomal recessive inheritance, caused by pathogenic loss-of-function variants in the LARP7 gene. It is characterized by global developmental delay, intellectual disability, autism spectrum disorder, growth retardation, dysmorphic features, and occasionally other congenital systemic abnormalities. The LARP7 protein is a chaperone necessary for RNA stability and function. Objective: To present the case of a 22-year-old female patient with developmental delay, intellectual disability, and dysmorphic features caused by pathogenic variants in the LARP7 gene. Methods: Clinical data were obtained from the medical record. Genomic analysis was performed using peripheral blood lymphocytes with whole-exome sequencing (WES) via Next-Generation Sequencing (NGS). Variant interpretation followed the guidelines of the American College of Medical Genetics (ACMG). Case presentation: The proband is the only daughter of a non-consanguineous couple, with no gestational or perinatal complications. She was born at term by vaginal delivery and was small for her gestational age. There was no family history of genetic diseases. At birth, facial dysmorphisms and congenital clubfoot

were observed. The patient developed global developmental delay, intellectual disability, ophthalmologic abnormalities, constipation, and recurrent urinary tract infections. Between the ages of 2 and 4, she experienced epileptic seizures. Among the observed dysmorphic features were a triangular face, deep-set eyes, broad forehead, ocular hypertelorism, bulbous nose, narrow palate, retrognathia, and thoracolumbar scoliosis. Anthropometric data showed low weight, short stature, and head circumference between the 10th and 25th percentiles. Karyotype and SNP-array tests were normal for a female patient. Whole-exome sequencing identified a pathogenic homozygous variant in the LARP7 gene: c.679C>T; p.Arg227\* NM\_016648.4. Discussion: To date, just over 50 cases of Alazami syndrome have been reported worldwide. The patient's phenotype is consistent with other previously reported cases, particularly global developmental delay, growth restriction, and short stature. The most commonly reported dysmorphic features include a broad nose, malar hypoplasia, wide mouth, and abnormal teeth positioning. Of these, only the bulbous nose was observed in our case. Microcephaly is a commonly described finding in most patients but was not present in our case. All previously reported variants have been frameshift mutations, resulting in loss of function, which was also demonstrated in our study. The variant identified in this patient has not been described in other studies. Conclusion: We present a case of global developmental delay associated with dysmorphic features caused by a pathogenic homozygous variant in the LARP7 gene. We emphasize the importance of whole-exome sequencing in investigating neurodevelopmental disorders.

**Palavras-Chave do trabalho:** ; Alazami syndrome; Intellectual Disability; LARP7;

**ID do trabalho:** 247

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **SLOWLY PROGRESSIVE ALS-SOD1 DISEASE: REPORT OF ONE PATIENT**

**Autores:** DE LUCENA, Larissa Neves<sup>1</sup>; NEPOMUCENO, Camila Rodrigues<sup>1</sup>; MESIAS, André Vinicio Cruz<sup>1</sup>; LEATI, Maria Fernanda Hamamoto<sup>1</sup>; LOURO, Rafaela Julian<sup>1</sup>; MENDES FILHO, Antonio Avelino<sup>1</sup>; DE FREITAS, Julian Leticia<sup>1</sup>; MORENO, Cristiane de Araújo Martins<sup>1</sup>; ROCHA, Maria Sheila Guimarães<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Santa Marcelina - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Case presentation: A 58-year-old female patient with onset of symptoms at age 51, characterized by involuntary contractions predominantly in the lower limbs, gradually progressing to the upper limbs, associated with intermittent cramps. There were no dysphagia, dyspnea, dysphonia, or mood changes. Neurological examination revealed grade IV muscle strength, the presence of the split hand sign, and hyperreflexia. Electroneuromyography demonstrated signs of chronic denervation and reinnervation in the bulbar, cervical, thoracic, and lumbosacral segments, with findings compatible with active denervation (fibrillations, sharp waves, and complex fasciculations) in the cervical, thoracic, and lumbosacral segments. Sensory conduction remained intact, suggesting diffuse lower motor neuron involvement. The genetic panel for ALS showed a previously reported pathogenic heterozygous variant (p.Val120Leu; c.358G>C) in SOD1. Discussion: SOD1 mutations account for approximately 2% of cases of sporadic ALS (sALS). Rapidly progressive mutations account for about 50% of cases of SOD1-ALS, causing accelerated motor decline and shorter survival. In contrast, slowly progressive mutations lead to gradual deterioration, often associated with survival greater than 10 years. The p.Val120Leu (c.358G>C) variant in the SOD1 gene is a rare mutation, previously described in several cases, including in the Brazilian and Spanish populations, all presenting slowly progressive disease and predominant involvement of the lower limbs. Here, we report an additional case presenting with cramps, mild atrophy, and mild weakness with 7 years of disease duration and a stable slope of ALSFRS. Bulbar and respiratory function are also stable, in contrast to the rapid decline classically associated with mutations in this gene. Tofersen has been approved for SOD1-positive ALS. However, the study may be biased because the slow progression of some SOD1 mutations may mask or exaggerate their effects, making it difficult to differentiate between response to treatment and the natural progression of the disease. Conclusion: This case highlights the complexity of SOD1-related motor neuron disease and the importance of individualized patient assessments. In light of a potentially treatable condition, clinical description and natural history of the disease are fundamental in order to understand the prognosis, define treatment response outcomes, and increase diagnostic awareness regarding this condition.

**Palavras-Chave do trabalho:** ALS-SOD1; Motor Neuron Diseases; Slowly progressive;

**ID do trabalho:** 248

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: X-LINKED INTELLECTUAL DISABILITY ASSOCIATED WITH GENE RAB39B HOMOZIGOSIS: A CASE REPORT

**Autores:** ROQUE, Julia Breda<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Municipal Dr Mario Gatti - 3830 - SP - Brasil;

### Resumo do trabalho:

X-Linked Intellectual Disability (XLID) is a highly heterogeneous condition caused by mutations in X chromosome genes. Both, deletions and duplications on the X chromosome, make important contributions to disease phenotypes (Wang et al., 2023). At least 215 XLMR conditions and mutations have been characterized in 83 different genes. (Giannandrea et al., 2010). So far, mutations in more than 140 X chromosome genes, including RAB39B, have been associated with XLID (Wang et al., 2023). According to Mignogna et al. (2001), Wang et al. (2023) and Lesage et al. (2015), loss-of-function mutations in the RAB39B gene have been associated with XLID, Parkinson's disease, autism spectrum disorders (ASDs), epileptic seizure and macrocephaly. This case report refers to T.G.A., 25 years old, male, with Autism Spectrum Disorder level II and X-linked intellectual disability with neuropsychomotor development delay, aggressive and impulsive behaviors. He was submitted to genomic sequencing which showed a homozygous deletion involving the RAB39B gene, which is associated with Waisman Syndrome. This syndrome, in addition to intellectual disability, is associated with Parkinsonism. A 2nd degree family member kinship (nephew) of index case also submitted to sequencing, with the same finding. Under follow-up at the neurology genetics and movement disorder service at Clinics Hospital in Campinas, and at APAE, a specialized rehabilitation service. Patient takes valproic acid and risperidone as medicines to control aggression and impulsivity. Tremors in upper limbs persists. RAB39B is a neuronal RAB GTPase that encodes a small GTP enzyme protein that participates in vesicular membrane trafficking in eukaryotic cells (Wang et al., 2023; Mignogna et al., 2001). GTPase RAB39B drives GluA2/GluA3  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) maturation and trafficking, determining AMPAR subunit composition at glutamatergic postsynaptic neuronal terminals. Absence of RAB39B leads to increased surface expression of GluA2-lacking Ca<sup>2+</sup>-permeable AMPARs, which results in an immature spine state caused by unsuccessful neuronal dendritic spine refinement associated with cognitive deficits, explaining how the increased dosage of RAB39B loss-of-function mutations lead to cognitive impairment and the pathogenesis of XLID (Mignogna et al., 2001; Giannandrea et al., 2010). According to Wilson et al. (2014), genetic studies have demonstrated that loss of RAB39B causes pathologically defined PD, and their results link the loss of a single gene involved in neuronal organization and synaptic function to the early manifestation of both ID and neurodegeneration and suggest that the loss of RAB39B dysregulates a-synuclein.

**Palavras-Chave do trabalho:** Autism Disorder; Parkinson Disease; Rab39B; X-Linked Intellectual Disability;

**ID do trabalho:** 249

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: POLG-RELATED SANDO PRESENTS WITH HYPERTROPHIC OLIVARY DEGENERATION: A CASE REPORT.

**Autores:** FERNANDES, Eduarda Rosa<sup>1</sup>; NAGATA, Glauco Kody<sup>1</sup>; DEVENS, Leticia Bassani<sup>1</sup>; HAUBRICH, Carolina Heck<sup>1</sup>; VERZA, Caroline Schiochet<sup>1</sup>; KRUM, Vitória<sup>1</sup>; FUSSIGER, Helena<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital São Lucas da PUCRS - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

Case presentation: A 38-year-old woman was referred to neurogenetics for further investigation of her progressive cerebellar ataxia symptoms. These began at age 32 with dizziness and imbalance, initially associated with severe headaches. Over time, her symptoms progressively worsened, including gait difficulties requiring support and mild dysarthria. She also reported occasional headaches, muscle cramps, urinary urgency with incontinence episodes, and lower-limb paresthesia. However, she denied dysphagia, diplopia, or cognitive complaints. On examination, she exhibited moderate dysarthria, vertical and horizontal ophthalmoparesis in both eyes, a low-amplitude, high-frequency hand tremor, mild dysmetria, dysidiadochokinesia in the upper limbs, gait ataxia, and diffuse hyporeflexia. Her family history indicated a possible hereditary neurodegenerative disorder. Her parents are consanguineous (first cousins). Her medical history included hypothyroidism and dyslipidemia, managed with Simvastatin 20 mg, Levothyroxine 50 mcg, and Amitriptyline 25 mg daily. Cranial MRI showed diffuse cerebellar atrophy, involving the middle cerebellar peduncles. Changes in the bulbar olives suggested hypertrophic olivary degeneration (HOD), potentially linked to neurodegenerative processes in infratentorial brain regions. An electrodiagnostic study identified significant peripheral neuropathy with axonal sensory involvement, especially in the lower limbs, consistent with severe chronic axonal neuropathy. Given the progressive cerebellar ataxia, evidence of atrophy, HOD, and a family history of hereditary neurodegenerative disease, a panel of ataxia-related genetic tests was performed. This identified a homozygous pathogenic variant (c.2243G>C; p.Trp748Ser) in the POLG gene. Discussion: Hypertrophic olivary degeneration (HOD) is caused by lesions in the Guillain-Mollaret Triangle, comprising the dentato-rubro-olivary pathways. This triangle includes the contralateral dentate nucleus, the ipsilateral red nucleus, and the ipsilateral inferior olivary nucleus. Unlike other forms of neuronal degeneration, HOD is characterized by hypertrophy rather than atrophy. Common HOD etiologies include vascular lesions, toxicity, trauma,

surgery, vascular malformations, and tumors. Clinically, HOD presents with palatal myoclonus, ocular myoclonus, nystagmus, Holmes tremor, and cerebellar and brainstem dysfunction symptoms such as dizziness, diplopia, and blurred vision. POLG-related disorders are increasingly recognized as a potential etiology. The clinical spectrum ranges from milder phenotypes like Progressive External Ophthalmoplegia to severe forms like Spinocerebellar Ataxia with Epilepsy. In this case, the patient's features align with SANDO syndrome. Final Comments: POLG mutations have a broad spectrum of clinical presentations. In practice, the co-occurrence of ophthalmoparesis and ataxia with HOD should raise suspicion of a mitochondrial disorder.

**Palavras-Chave do trabalho:** ATAXIA; Olivary Degeneration; ophthalmoplegia;

**ID do trabalho:** 250

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: NARROWING OF TRIGEMINAL AND VESTIBULOCOCHLEAR NERVES WITH DIFFUSE TAPERING OF THE CERVICAL AND DORSAL SPINAL CORD AS CLUES TO DIAGNOSIS OF A RFC1 RELATED DISORDER IN A ELDERLY PATIENT - A CASE REPORT**

**Autores:** BRAGA MUNARETO, Matheus Luís<sup>1</sup>; ALVES DA SILVA, Matheus<sup>1</sup>; ARAÚJO FERNANDES, Alex<sup>1</sup>; MIRANDA DE MENDONÇA, Amanda<sup>1</sup>; FARIA DONADON, Ana Luísa<sup>1</sup>; BRAGANÇA RODRIGUES MATIAS, Rafael<sup>1</sup>; MESQUITA DE SOUZA, Eduardo<sup>1</sup>; GUIMARÃES DE QUEIROZ, André Luiz<sup>1</sup>; ROCHA MARUSSI, Victor Hugo<sup>1</sup>; MACHADO BAETA, Alex<sup>1</sup>;

**Instituição dos Autores:** (1) BP - A Beneficência Portuguesa de São Paulo - São Paulo - SP - Brasil;

### **Resumo do trabalho:**

Case presentation A 71 years old female patient presented to neurological evaluation with a four year history of lower limb paresthesias associated with episodic vertigo. In the last six months, she presented with unsteady gait, clearly worsening with the eyes closed. She also developed episodic urinary retention. For some years, she also had a chronic cough with no associated pulmonary disease. She had no familial history of neurological disorder. She had systemic arterial hypertension and hypothyroidism. The neurological examination showed globally hypoactive deep tendon reflexes, pseudoathetosis of upper limb when the eyes were closed, a positive Romberg test and hypoesthesia with a distal-to-proximal gradient in the limbs, worse in the lower limbs. Her electroneuromyography showed marked axonal sensory polyneuropathy, affecting all four limbs, with distal predominance. The screening for more common etiologies for sensory neuronopathies, like Sjögren disease and vitamin deficiencies, was unremarkable. Her brain MRI showed signs of diffuse volume loss in the brain, with some predominance in the cerebellar hemispheres and thinning of the trigeminal nerves and the left vestibulocochlear nerve. Her spine MRI showed diffuse tapering of the cervical and notably dorsal spinal cord, with hypersignal alteration in T2/FLAIR in the posterior cord, mainly at the C1-C2 to C7 level. These findings, associated with the clinical complaints, lead to a suspicion of a RFC1 related disorder, confirmed later with genetic testing. Discussion The diagnosis of ataxia is difficult and may be delayed in many cases. There are a lot of causes of late onset cerebellar ataxias and, recently, the discovery of RFC1 related disorders changed the understanding of this group of diseases. Besides the classic CANVAS (cerebellar ataxia, neuropathy and vestibular areflexia), there are other clinical clues to these disorders, like chronic cough, for example. Some radiological findings, like thinning of cranial nerves and spinal cord tapering, may be additional hints to the diagnosis. Final comments We present a case of ataxia investigation in the elderly, with clinical and radiological clues to a RFC1 spectrum disorder. This case showed the importance of recognizing the classical clinical and radiological findings, highlighting the value of a good medical history associated with a critical interpretation of complementary findings.

**Palavras-Chave do trabalho:** CANVAS; case report; RFC1 related disorder;

**ID do trabalho:** 251

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: REFRACTORY EPILEPTIC SEIZURES IN A NEONATE WITH PYRIDOXINE-DEPENDENT EPILEPSY**

**Autores:** BRAGA, Sarah Maria Pontes<sup>1</sup>; BRAGA, Sarah Maria Pontes<sup>1</sup>; DE LUCENA, Patrícia Trindade<sup>1</sup>; DE LUCENA, Patrícia Trindade<sup>1</sup>; PEREIRA, Victor Hugo Soares<sup>1</sup>; PEREIRA, Victor Hugo Soares<sup>1</sup>; ALVES, Lucas Victor<sup>1</sup>; ALVES, Lucas Victor<sup>1</sup>; FILHO, Joselito Sobreira<sup>1</sup>; FILHO, Joselito Sobreira<sup>1</sup>; SIQUEIRA, Ana Cecília<sup>1</sup>; SIQUEIRA, Ana Cecília<sup>1</sup>;

**Instituição dos Autores:** (1) IMIP - Recife - PE - Brasil;

**Resumo do trabalho:**

**CASE PRESENTATION:** A 2-month-old female patient, the second child of non-consanguineous parents, presented her first bilateral tonic-clonic seizure at 30 minutes of age. Her condition was stabilized and she was discharged from the hospital after two days. On the 4th day of life, she returned to the hospital presenting a status epilepticus and was admitted to the intensive care unit (ICU). She was prescribed with phenobarbital and levetiracetam, with good seizure control until two months of age, when she developed febrile peaks and worsening of the paroxysmal events after vaccination. Again in status epilepticus, she was readmitted to the ICU and underwent orotracheal intubation, sedation and optimization of therapy with anti-crisis drugs. As the patient continued to have seizures despite adequate doses of phenobarbital, levetiracetam, phenytoin, midazolam and ketamine, a ketogenic diet and a therapeutic trial with pyridoxine replacement were started, with the epileptic episodes ceasing in less than 24 hours. Magnetic resonance imaging showed the only alteration to be the presence of a megacisterna magna. An interictal electroencephalogram during sleep revealed multifocal epileptic activity and disorganization of baseline activity. Exome showed two heterozygous pathogenic variants in the ALDH7A1 gene, confirming the diagnosis of pyridoxine-dependent early onset epilepsy 4 (EPEO4). After the diagnosis, pyridoxine therapy was maintained and weaning off the other anti-crisis drugs and the ketogenic diet was carried out without complications. **DISCUSSION:** Pyridoxine-dependent epilepsy (PDE) is a rare metabolic disorder of genetic etiology caused by biallelic pathogenic variants in the ALDH7A1 gene, which results in a deficiency of the enzyme  $\alpha$ -aminoacidate-semialdehyde dehydrogenase (antiquitin), leading to the accumulation of toxic metabolites and a secondary deficiency of pyridoxal-5'-phosphate (PLP), the active form of pyridoxine (vitamin B6). This condition typically manifests with neonatal seizures that are refractory to conventional anti-crisis drugs. Treatment with pyridoxine is effective in stopping seizures in patients with PDE and the response can be immediate or delayed. Therefore, therapeutic testing in neonates with refractory epileptic seizures should be instituted and maintained until the result of the genetic test. **CONCLUSION:** PDE is a metabolic disorder that is severe in neonates and can lead to neurodevelopmental delays, refractory epileptic seizures and death. It is an epilepsy of genetic etiology with good response to monotherapy treatment and, for this reason, its early diagnosis and treatment are crucial for a favorable outcome.

**Palavras-Chave do trabalho:** drug-resistant epilepsy; epilepsy; Inborn Errors of Metabolism;

**ID do trabalho:** 252

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: A RARE MUTATION ASSOCIATED WITH DUCHENNE DYSTROPHY IN TWINS: A CASE REPORT.**

**Autores:** KARPEJANY, Natália Rebeca Alves de Araújo<sup>1</sup>; KARPEJANY, Natália Rebeca Alves de Araújo<sup>1</sup>; KARPEJANY, Natália Rebeca Alves de Araújo<sup>1</sup>; DE FREITAS, Melissa Fernandes Vilela<sup>2</sup>; DE FREITAS, Melissa Fernandes Vilela<sup>2</sup>; DE FREITAS, Melissa Fernandes Vilela<sup>2</sup>; NAKAMURA, Gabriela Yumi<sup>2</sup>; NAKAMURA, Gabriela Yumi<sup>2</sup>; NAKAMURA, Gabriela Yumi<sup>2</sup>; ROMANO, Danielle Cortellazzi Colonna<sup>2</sup>; ROMANO, Danielle Cortellazzi Colonna<sup>2</sup>; ROMANO, Danielle Cortellazzi Colonna<sup>2</sup>; DA SILVA, Sabrina Borges<sup>2</sup>; DA SILVA, Sabrina Borges<sup>2</sup>; DA SILVA, Sabrina Borges<sup>2</sup>; MOURA, Ademir Aragão<sup>1</sup>; MOURA, Ademir Aragão<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Universitário da Universidade Federal do Piauí - Teresina - PI - Brasil; (2) Universidade Nove de Julho, São Paulo - SP - São Paulo - SP - Brasil;

**Resumo do trabalho:**

**Case presentation:** Two 28-year-old male identical twins, with delayed motor development (walking at 3 years), started experiencing recurrent falls at age 6 due to proximal muscle weakness in the lower limbs. The condition progressively worsened, leading to loss of ambulation by age 9, requiring the use of wheelchairs. Investigation for myopathy was initiated, and muscle biopsy in one of the brothers revealed a dystrophic pattern with "moth-eaten" fibers, but no dystrophin levels were reported. At 18 years, genetic testing confirmed Duchenne Muscular Dystrophy, identifying a deletion of four bases in exon 34 of the DMD gene (c.4686\_4689delAAAG p.R1562Sfs\*8). MLPA testing showed no deletions or duplications, so full sequencing was performed. At 20 years, both brothers developed respiratory involvement (requiring BiPAP) and cardiac dysfunction, managed with medications. CPK levels were elevated (>2000 U/L) during the investigation. There is no family history of myopathies, and their younger brother (17 years old) remains asymptomatic. The mother did not undergo genetic testing. Currently, the patients are using wheelchairs, with reduced strength in all four limbs, but more pronounced in the lower limbs. They present severe restrictive ventilatory dysfunction, with recurrent respiratory infections despite supportive treatment and use of corticosteroids. **Discussion:** Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by mutations in the DMD gene, leading to the absence or dysfunction of dystrophin, a critical protein for muscle integrity. Despite its rarity, DMD is the most prevalent form of muscular dystrophy in childhood, predominantly affecting males, as demonstrated in the current case. The disease is characterized by progressive muscle weakness and functional decline, with onset typically in early childhood. Although the clinical history and biopsy findings were highly suggestive of the disease, the genetic diagnosis was delayed in this case. Furthermore, it was not confirmed through MLPA, a first-line confirmatory test that detects the most common pathogenic variants in DMD. In DMD the most commonly affected exons are 51 and 53; however, in this case, the finding was a four-base deletion in exon 34. Early treatment of DMD with corticosteroids can delay disease progression. In this case, the twins received a late diagnosis (at 18), but recent studies have demonstrated long-term benefits, even if treatment is

initiated later.<sup>1,2</sup> A maternal genetic testing and genetic counseling is recommended for the family, particularly considering the asymptomatic younger brother. Final comments: This case highlights the diagnostic challenges of Duchenne Muscular Dystrophy (DMD), particularly when standard tests like MLPA fail to detect mutations. It emphasizes the need for comprehensive genetic testing, including full gene sequencing, in uncertain cases.

**Palavras-Chave do trabalho:** Duchenne muscular dystrophy; Genetic Tests; neurogenetic disorders;

**ID do trabalho:** 253

**Área Técnica do trabalho:** Outros

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Pôster

## **Título do Trabalho: SLEEP DISORDERS IN CEREBROTENDINOUS XANTHOMATOSIS: A CASE SERIES**

**Autores:** BARBOSA, Liandra Rayanne Sousa<sup>1</sup>; CAMELO-FILHO, Antônio Edvan<sup>1</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; MOURA, Alissa Elen Formiga<sup>2</sup>; PESSOA, Andre Luiz Santos<sup>3</sup>; BRAGA-NETO, Pedro<sup>1</sup>; SOBREIRA-NETO, Manoel Alves<sup>1</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (3) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil;

### **Resumo do trabalho:**

Background: Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disorder caused by mutations in the CYP27A1 gene, leading to the accumulation of cholestanol and cholesterol in various tissues. This study aims to explore the neurophysiological, clinical, and sleep characteristics of CTX patients. Objective: The objective of this study was to evaluate sleep disturbances and related clinical features in patients with CTX, using both subjective and objective measures. Methods: Four patients with genetically confirmed CTX were monitored at Hospital Universitário Walter Cantídio (HUWC—UFC). Clinical evaluations included general physical and neurological examinations, cognitive assessments using the Mini-Mental State Examination (MMSE), and ataxia grading with the Brazilian-validated Scale for Assessment and Rating of Ataxia. Sleep evaluations involved the Epworth Sleepiness Scale, International Restless Legs Syndrome Study Group Rating Scale, Morningness-Eveningness Questionnaire, and Pittsburgh Sleep Quality Index. Objective sleep data were collected using polysomnography (PSG) and wrist actigraphy. Results: All patients reported sleep disturbances, with two using psychotropic drugs. Subjective evaluations indicated daytime sleepiness, snoring, and maintenance insomnia. Objective findings from PSG revealed reduced sleep latency, decreased REM sleep, and increased N2 and N1 sleep stages. One patient exhibited moderate obstructive sleep apnea (OSA) and high periodic limb movements index. Actigraphy data from one patient showed stable sleep onset and offset times, with a mean total sleep time of 8 hours and 10 minutes, but indicated fragmented sleep with multiple awakenings. Conclusion: Patients with CTX experience significant sleep disturbances, including reduced REM sleep and potential OSA. These findings highlight the need for comprehensive sleep evaluations in CTX patients to better manage their sleep-related symptoms.

**Palavras-Chave do trabalho:** Cerebrotendinous xanthomatosis; polysomnography; sleep disturbances;

**ID do trabalho:** 254

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: PERIPHERAL AXONAL NEUROPATHY AS A PHENOTYPE OF MITOCHONDRIAL TRIFUNCTIONAL PROTEIN TYPE 2 DEFICIENCY IN AN ADOLESCENT: A CASE REPORT**

**Autores:** PEREIRA, Victor Hugo Soares<sup>1</sup>; DE LUCENA, Patrícia Trindade<sup>1</sup>; BRAGA, Sarah Maria Pontes<sup>1</sup>; DE MEDEIROS, Fabíola Lys<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Universitário Oswaldo Cruz - Recife - PE - Brasil;

### **Resumo do trabalho:**

Patient with a history of walking difficulties noticed by the parents since the beginning of this developmental milestone, first evaluated at the age of 3 years when the child was still couldn't run. No previous history of neuropsychomotor developmental delay. When he started school, he also noticed weakness in his lower limbs, characterized by difficulty and fatigue in activities such as writing and playing with a ball. The discomfort did not vary throughout the day, but there were days when the discomfort was more subtle, while others were more intense. No significant time course of the weakness was observed. No other

neurological complaints. She was not taking any medications. Neurological examination showed global hypotonia with distal predominant atrophy, cavus feet, widening of the anterior part of the feet with hammer toes, tendon retraction in the Achilles tendon bilaterally. There was a loss of distal strength in the lower limbs and the presence of a staggering gait. There were also pyramidal signs in the lower limbs such as plantar skin extension and mild spasticity. Electroneuromyography showed non-length dependent axonal motor polyneuropathy. MRI of the neuroaxis showed slight venous contrast enhancement of the roots of the cauda equina. No changes in cerebrospinal fluid analysis. Complete sequencing of the exome and mitochondrial DNA was requested with the finding of a variant of uncertain significance in homozygosity in the HADHB/PDHA1 genes associated with mitochondrial trifunctional protein 2 deficiency (NM\_000183.3: c.397A>G:p.(Thr 133Ala)). The patient remains under the care of the Neuromuscular Diseases Outpatient Clinic, still without multiprofessional therapies and with nutritional supplementation. Mitochondrial trifunctional protein type 2 deficiency is a rare genetic disorder associated with altered metabolism of long-chain fatty acids. The genes associated with this deficiency are HADHA and HADHB, which encode subunits of the enzyme complex. Variations in these genes can lead to changes in the conformation of the protein and to its instability with significant functional impairment. It is an autosomal recessive disorder. Clinically, there are phenotypes associated with the severity of the deficiency. The neonatal onset phenotype is fatal, the childhood onset phenotype is associated with metabolic and hepatic alterations, while the adolescent onset phenotype evolves into a neuromyopathic state with recurrent myalgia, peripheral neuropathy, and rhabdomyolysis. Diagnosis is made by measuring high levels of long-chain acylcarnitines or by genetic sequencing. Treatment is based on nutritional measures, such as limiting the intake of long-chain fatty acids, and avoiding the development of metabolic crises, such as avoiding prolonged fasting and infectious processes.

**Palavras-Chave do trabalho:** mitochondrial diseases; neurogenetics; Neuromuscular Diseases;

**ID do trabalho:** 257

**Área Técnica do trabalho:** Demências e doenças cerebrovasculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: FURTHER CHARACTERIZATION OF NIT1-ASSOCIATED CEREBRAL SMALL VESSEL DISEASE: CLINICAL, GENETIC, AND RADIOLOGICAL FINDINGS**

**Autores:** LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; NEPOMUCENO, Camila Rodrigues<sup>2</sup>; FREITAS, Julian Letícia<sup>2</sup>; CAMELO-FILHO, Antônio Edvan<sup>1</sup>; PESSOA, André Luiz Santos<sup>3</sup>; PAIVA, Anderson Rodrigues Brandão<sup>4</sup>; ELSHAFIE, Reem<sup>5</sup>; MORENO, Cristiane De Araújo Martins<sup>4</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Hospital Santa Marcelina - São Paulo - SP - Brasil; (3) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil; (4) Universidade de São Paulo - São Paulo - SP - Brasil; (5) Kuwait Medical Genetic Center - Kuwait;

### **Resumo do trabalho:**

**Background:** The Nitrilase 1 (NIT1) protein is a member of the nitrilase protein family. The precise function of NIT1 in human physiology and disease is not yet fully understood. The gene encodes a highly conserved enzyme whose amidase function is required to catalyze the recycling of deaminated glutathione (dGSH), a side product of several metabolic reactions, into 2-ketoglutarate and cysteinylglycine leading to glutathione. Two independent research groups have recently associated biallelic loss-of-function variants in NIT1 to cerebral small vessel disease in six unrelated families. **Objective:** To further describe the phenotypic and genetic spectrum of NIT1-related small vessel disease. **Methods:** Patients were identified through an active search for NIT1 pathogenic variants in the databank of a Clinical genomics laboratory and by using GeneMatcher. Attending physicians were contacted to check for clinical and radiological findings. Informed consent was obtained following the Declaration of Helsinki, and the local ethical committee approved the study. Whole exome sequencing (WES) was performed on DNA extracted from oral swab samples. Clinical histories, physical examinations, and MRI findings were reviewed. **Results:** The study included three unrelated patients - two from Brazil and one from Kuwait. Patients had a mean age of 39 years at the last follow-up. All patients had biallelic NIT1 pathogenic variants. Age of disease onset varied from early childhood – in one patient – to the third decade of life – in the other two. All patients had cognitive dysfunction as the initial manifestation, mostly represented by executive impairment, attention deficit, and mood disorders. The cognitive manifestations occurred isolatedly in one patient (Patient 1). The remaining two patients had dysarthria associated with myoclonus (Patient 2) or hemiparesis (Patient 3). All patients had similar Brain MRI abnormalities, with dilated perivascular spaces, white matter hyperintensities, lacunes, and microbleeds. **Conclusion:** We reported three new cases of NIT1-small vessel disease, a novel leukoencephalopathy with very typical imaging findings. All patients presented clinical features compatible with previous reports. The abnormalities in MRI seem to be a distinct feature of the condition and may allow for a high level of diagnostic suspicion.

**Palavras-Chave do trabalho:** Intracerebral hemorrhage; NIT1; Nitrilase 1; Small vessel disease;

**ID do trabalho:** 258**Área Técnica do trabalho:** Doenças Neuromusculares**Tipo do trabalho** Trabalhos Originais**Forma de apresentação:** Pôster

## Título do Trabalho: **FREQUENCY OF SCA27B IN A LARGE BRAZILIAN COHORT OF SPINOCEREBELLAR ATAXIAS**

**Autores:** DIAS, Amanda Jesus Araujo<sup>1</sup>; SILVEIRA, Cynthia<sup>1</sup>; VINAGRE, Adriana Mendes<sup>1</sup>; BONADIA, Luciana Cardoso<sup>1</sup>; FRANÇA JR, Marcondes Cavalcante<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Estadual de Campinas - Campinas - SP - Brasil;

### **Resumo do trabalho:**

Introduction: Spinocerebellar Ataxias (SCAs) are monogenic conditions that share cerebellar ataxia as the core feature and an autosomal dominant mode of transmission. SCA27B is a recently described SCA subtype caused by intronic GAA expansions at FGF14. It is prevalent in European cohorts with frequencies ranging from 5.4% to 31% of all SCAs. In French-Canadians, it is even more frequent (61% of all SCAs). So far, little is known about its frequency in Latin America. Objectives: to investigate the frequency of SCA27B in a large Brazilian single center cohort. Methods: Between 1997 and 2024, 749 index-patients with suspected SCA were seen at the neurogenetics outpatient clinic at the State University of Campinas, a reference center in Brazil. Patients underwent genetic screening for polyQ SCAs (SCA1, SCA2, SCA3, SCA6, SCA7, and SCA8). Patients who tested negative for the most common SCAs, as well as those with clinical phenotype specific for the disease, were tested for SCA27B. For the detection of the most common SCAs, conventional PCR was used, and the amplified products were analyzed by capillary electrophoresis. The technique used for SCA27B, due to the number of repeats, was long-range PCR followed by capillary electrophoresis. Results: Among the 749 patients analyzed, 244 (32.58%) were diagnosed with known SCAs. Considering this subgroup with positive testing, we found the following proportions - SCA3: 62.71%, SCA1: 15.28%, SCA2: 10.66%, SCA7: 6.15%, SCA27B: 4.10% and SCA6: 0.82%. Mean age of patients with SCA27B was 55 years, ranging from 30 to 70 years. Ataxia was the key feature in all patients with SCA27B, but additional features were also found: downbeat nystagmus, resting tremor and vestibulo-ocular reflexes alteration. Discussion: This is one the largest studies looking at the relative frequency of SCA27B in Brazilian patients with SCAs. We found this new condition to be rare relative to the other polyQ SCAs. Additional surveys including patients from other Brazilian regions are still needed to further understand the relevance and geographic distribution of SCA27B beyond the Southeastern region of our country.

**Palavras-Chave do trabalho:** FREQUENCY; GAA-FGF14; NEURODEGENERATIVE DISORDERS; SCA27B;

**ID do trabalho:** 259**Área Técnica do trabalho:** Transtornos do movimento**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## Título do Trabalho: **GENETIC CLUES TO GAIT AND GAZE: A CASE OF ATAXIA WITH OCULOMOTOR APRAXIA TYPE 4**

**Autores:** NUNES GALVAO, Heloisy Maria<sup>1</sup>; PEREIRA DE MOURA, Raissa Josefa<sup>1</sup>; DA SILVA LIMA QUEIROZ, Danielle Cleide<sup>2</sup>; CARVALHO SOARES, Miriam<sup>1</sup>; AMARAL ANDRADE DE MENDONÇA, Renata<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Pelopidas Silveira - Recife - PE - Brasil; (2) Real Hospital Portugues de Beneficiencia - Recife - PE - Brasil;

### **Resumo do trabalho:**

Case presentation: A 21-year-old female patient presented to an outpatient neurology center with severe progressive gait impairment, dysarthria, dysphagia, and a history of involuntary movements. Her symptoms began at six months of age, initially manifesting as hypotonia and choreiform movements. She experienced neurodevelopmental delays, walking at 17 months and developing language skills at 18 months. During infancy, she had seizures that resolved in childhood. Neurological examination revealed severe oculomotor apraxia, flaccid tetraparesis with distal predominance, globally absent reflexes, superficial and deep hypoesthesia in a gradient pattern, and global ataxia. She had been obese since early childhood despite multiple unsuccessful weight-loss attempts. There was no reported family history of similar conditions, but consanguinity was noted between her maternal grandparents. Brain magnetic resonance imaging (MRI) demonstrated global cerebellar atrophy. Electroneuromyography findings were consistent with severe sensorimotor axonal polyneuropathy. Laboratory tests revealed hypercholesterolemia, while alpha-fetoprotein levels were within the normal range. Whole-exome sequencing identified a pathogenic homozygous variant in the PNKP gene, confirming the diagnosis of ataxia with oculomotor apraxia type 4 (AOA4). Discussion: AOA4 is a rare autosomal recessive cerebellar ataxia caused by mutations in the PNKP gene, which plays a crucial role in DNA repair. The disease typically manifests in the first decade of life with progressive cerebellar ataxia, oculomotor apraxia, sensorimotor axonal polyneuropathy, and extrapyramidal signs such as dystonia and chorea. Most patients develop distal muscle weakness and areflexia, eventually becoming wheelchair-bound by the third decade. In this case, the patient exhibited an earlier onset than typically reported, with symptoms beginning at six months of age. Seizures were an initial feature, although they are not a hallmark of AOA4. Despite the early onset, disease progression was similar to that of other

reported cases, with the patient requiring a wheelchair by age 21 (Freitas et al.). Obesity is a commonly observed feature in patients with AOA4. Thus, brain MRI findings of global cerebellar atrophy and electrophysiological evidence of severe sensorimotor axonal polyneuropathy further supported the diagnosis. Final comments: AOA4 remains an untreatable, progressive neurodegenerative disorder, underscoring the need for further research into disease-modifying therapies. Previous studies have shown that AOA2 and AOA4 are the most common AOA subtypes in Brazil (Da Costa et al.). Given its autosomal recessive inheritance, genetic counseling is crucial, especially in populations with a high prevalence of consanguinity. Early recognition through genetic testing can facilitate diagnosis, supportive management, and potential future therapeutic interventions.

**Palavras-Chave do trabalho:** Ataxia with oculomotor apraxia type 4; Genetic ataxia; PNKP;

**ID do trabalho:** 260

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: METABOLIC SYNDROME IN DUCHENNE MUSCULAR DYSTROPHY PATIENTS**

**Autores:** BRITO, Mariana Rabelo<sup>1</sup>; MIYATA, Marcela Misao<sup>1</sup>; REZENDE, Thiago Junqueira Ribeiro<sup>1</sup>; FRANÇA JR., Marcondes Cavalcante<sup>1</sup>;

**Instituição dos Autores:** (1) UNICAMP - Campinas - SP - Brasil;

### **Resumo do trabalho:**

**BACKGROUND:** Duchenne muscular dystrophy (DMD) is the most prevalent muscular dystrophy in children, caused by loss-of-function mutations in the X-linked DMD gene. Disease progression leads to significant lean body mass loss, severe motor impairment, and prolonged corticosteroid therapy, all contributing to an increased risk of metabolic syndrome (MS) even in childhood. Despite this, few studies have explored MS in DMD, particularly in Brazilian cohorts. **OBJECTIVE:** To determine the prevalence and associated risk factors for MS in individuals with DMD from a Brazilian cohort. **METHODS:** This cross-sectional study included 49 DMD patients under regular follow-up at UNICAMP. Clinical assessments encompassed blood pressure, body mass index (BMI), and motor function, while laboratory evaluations included serum glucose, HbA1C, cholesterol, and triglyceride levels. Demographic, genetic, and steroid usage data (cumulative dose) were also collected. MS was diagnosed based on the International Diabetes Federation criteria for pediatric populations. Hypothalamic volume was measured and compared to healthy controls using the HypAST pipeline developed at UNICAMP. **RESULTS:** The mean age of participants was 11.1 years, with 60.8% being wheelchair users. Four individuals met the full diagnostic criteria for MS. However, metabolic alterations were common, including obesity in 41.8%, BMI above the 85th percentile in 62.7%, central obesity in 65.9%, and elevated blood pressure in 18.2%. While HbA1C levels were normal for all participants, one individual had elevated glucose levels. Age-adjusted cholesterol and/or triglyceride levels were elevated in 65.2% of patients. Hypothalamic volume in DMD patients was significantly larger than in healthy controls ( $p = 0.02$ ), adjusted by ETIV. Textural analysis revealed significant differences in mean ( $p = 0.004$ ), variance ( $p = 0.01$ ), and skewness ( $p = 0.02$ ). Corticosteroid use was associated with increased BMI and central obesity, supporting literature findings that prednisone and deflazacort contribute to weight gain. **CONCLUSION:** Metabolic abnormalities are highly prevalent in DMD and should be systematically monitored. Current MS diagnostic criteria may not fully apply to this population, potentially leading to underdiagnosis. The increased hypothalamic volume represents an unexpected finding, suggesting neuroplastic or pathological responses. These results highlight the need for further studies on long-term metabolic and neurological implications in DMD, which could contribute to the development of new therapeutic strategies.

**Palavras-Chave do trabalho:** Duchenne muscular dystrophy; Hypothalamus; metabolic syndrome;

**ID do trabalho:** 261

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: CLINICAL AND GENETIC FEATURES OF MUSK-RELATED CONGENITAL MYASTHENIC SYNDROME: A CASE SERIES AND A PROPOSAL FOR CLINICAL CLASSIFICATION**

**Autores:** CAMELO-FILHO, Antonio Edvan<sup>1</sup>; BEZERRA, Henrique Alves<sup>2</sup>; MACHADO, Nicole Lopes Cavalcante<sup>2</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; STEPHAN, Eduardo de Paula<sup>3</sup>; SGOBBI, Paulo Victor<sup>4</sup>; ROCHA, Maria Sheila<sup>2</sup>; MORENO,

*Cristiane Araujo Martins<sup>3</sup>; Nóbrega, Paulo Ribeiro<sup>1</sup>;*

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Hospital Santa Marcelina - São Paulo - SP - Brasil; (3) Universidade de São Paulo - São Paulo - SP - Brasil; (4) Universidade Federal de São Paulo - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Background: MUSK-related congenital myasthenic syndrome (MUSK-CMS) is a rare neuromuscular disorder caused by pathogenic variants in the MUSK gene. The phenotypic spectrum is broad, ranging from mild, fatigable muscle weakness to severe neonatal presentations with respiratory failure. Objective: This study aims to describe the clinical and genetic features of MUSK-CMS through a case series of six patients, alongside a literature review, to highlight diagnostic challenges and treatment responses. Methods: We conducted a clinical and genetic analysis of six patients diagnosed with MUSK-CMS from three tertiary centers in Brazil. Comprehensive clinical assessments included muscle strength, respiratory function, and bulbar symptoms. Genetic testing was performed using next-generation sequencing. Treatment responses to salbutamol and pyridostigmine were documented. Results: Patients ranged in age from 19 to 58 years, with symptom onset varying from congenital to 32 years of age. All but one patient exhibited bilateral ptosis, extraocular muscle weakness, and gaze limitations. Muscle weakness predominantly affected the lower limbs, with varying degrees of severity. MUSK-CMS demonstrates considerable phenotypic and genetic heterogeneity, with symptom onset ranging from birth to the third decade of life. Conclusion: We suggest a clinical classification framework for recognizing distinct clinical phenotypes: an early-onset severe phenotype, a ptosis-dominant phenotype, and a late-onset limb-girdle phenotype. The response to salbutamol and pyridostigmine was generally favorable, but variability in treatment efficacy emphasizes the need for personalized therapeutic approaches. Early recognition and genetic testing are critical for optimal patient outcomes, especially in atypical or adult-onset cases

**Palavras-Chave do trabalho:** MUSK; Neuromuscular Disease; Neuromuscular Junction;

**ID do trabalho:** 263

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: INTRAVENOUS APPLICATION OF HUMAN DENTAL PULP STEM CELL DERIVED EXOSOMES LESSEN MOTONEURON LOSS AND SLOWS ILLNESS PROGRESSION IN AN ALS MURINE MODEL**

**Autores:** NUNES GONÇALVES, João Pedro<sup>1</sup>; DE MATOS, Alexandre Hilário Berenguer<sup>1</sup>; DE OLIVEIRA, Alexandre Leite Rodrigues<sup>1</sup>; KERKIS, Irina<sup>2</sup>; ARALDI, Rodrigo Pinheiro<sup>3</sup>; WENCESLAU, Cristiane Valverde<sup>4</sup>; FRANÇA JR., Marcondes Cavalcante<sup>1</sup>;

**Instituição dos Autores:** (1) UNICAMP - CAMPINAS - SP - Brasil; (2) INSTITUTO BUTANTÃ - SÃO PAULO - SP - Brasil; (3) BIODECISION ANALYTICS - SÃO PAULO - SP - Brasil; (4) CELLAVITA SCIENTIFIC RESEARCH - SÃO PAULO - SP - Brasil;

**Resumo do trabalho:**

Background: Amyotrophic lateral sclerosis (ALS) is a devastating condition for which treatment still represents an unmet need. Exosomes derived from human dental pulp stem cell (hDPSCs) secrete neurotrophic factors and have shown positive therapeutic results in some neurodegenerative disease models, but not yet properly explored in ALS. Objective: To evaluate the potential therapeutic effect of hDPSC-derived exosomes in the ALS SOD1G93A transgenic mice model. Methods: Seventy-day-old transgenic mice were treated intravenously (IV) either with exosomes (n=5) or saline (n=5) for 5 weeks and were sacrificed at the age of 15 weeks. A 3rd third group of wild type mice was also used for comparison. The next steps included quantifying motor neurons in the ventral horns of lumbar spinal cord using Nissl staining and glial components labeling for quantitative assessment of integrated density of pixels. Between-group comparisons were accomplished with ANOVA followed by post-hoc Tukey test. Results: At 15 weeks, neuronal survival was significantly different across experimental groups. Neuronal loss was significantly higher in non-treated SOD1 G93A mice compared to the other two groups ( $p < 0.001$ , CI:95% for both groups). In contrast, there was a noticeable variance in neuronal survival between treated and wild type mice. ( $p < 0.05$ , CI:95%). When compared to wild-type animals, both treated and non-treated mice showed greater levels of astrogliosis; however, glial fibrillary acid protein expression was lower on treated mice ( $p < 0.05$ , CI:95%). Transgenic mice exhibited increased microglial activation, with no discernible therapeutic effect ( $p = 0.95$ , CI:95%). Immunolabeling quantification of synaptophysin, a marker of presynaptic terminals, showed that in 15-week-old mice, hDPSC-derived exosomes application maintained synaptophysin levels close to wild type mice, while in saline application group labeling was reduced to half ( $p < 0.001$ , CI:95%). Mice treated with hDPSC-derived exosomes also showed symptoms' onset attenuation when compared with non-treated mice. Discussion: While still in the early stages, our findings show that spinal cord motor neuron survival in this ALS mouse model is preserved by repeated IV injections of hDPSC-derived exosomes, though they still vary from wild-type animals. Additionally, our results point to a decrease in treatment-related astrogliosis without affecting microglia, preserved synaptic transmission and delayed onset of symptoms. Further studies are needed to understand the mechanisms underlying such therapeutic effects.

**Palavras-Chave do trabalho:** ALS; Gliosis; motor neuron survival;

**ID do trabalho:** 264

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: PHENOTYPIC AND GENETIC SPECTRUM OF A BRAZILIAN COHORT OF PATIENTS WITH SCN4A CHANNELOPATHIES

**Autores:** BUENO, Manoella Guerra de Albuquerque<sup>1</sup>; PEREIRA, Mariana Ribeiro<sup>1</sup>; FREZATTI, Rodrigo Siqueira Soares<sup>1</sup>; WILSON, Lindsay<sup>2</sup>; REILLY, Mary M<sup>2</sup>; HANNA, Michael<sup>2</sup>; TOMASELLI, Pedro Jose<sup>3</sup>; JUNIOR, Wilson Marques<sup>3</sup>; SOBREIRA, Claudia Ferreira da Rosa<sup>3</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - FMRP-USP - Ribeirão Preto - SP - Brasil; (2) University College London - United Kingdom; (3) Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo - FMRP-USP - Ribeirão Preto - SP - Brasil;

### Resumo do trabalho:

Background: Skeletal Muscle Channelopathies (SMC) are a group of rare genetic neuromuscular disorders caused by pathogenic variants within genes encoding ion channel subunits. These ion channels perform an important role in modulating muscle membrane electrical activity. Based on the main clinical symptom, SMCs manifest predominantly with periodic paralysis (PP - hyper or hypokalemic and Andersen Tawil Syndrome) or myotonia (myotonia congenita - MC -, paramyotonia congenita - PMC -, and sodium-channel myotonia). One of the genes responsible for SMC is the SCN4A gene, which can manifest as a range of phenotypes, except ATS. Objective: To evaluate the clinical and genetic profile of a cohort of patients with SCN4A variants from a single centre. Methods: Clinical and genetic data were retrospectively collected using a standardized proforma. Probandes were tested with WES and/or WGS. Relatives at risk were tested using direct Sanger sequencing. Results: Fifteen patients from ten different families were included. Twelve (80%) patients were male. Four cases were sporadic. Based on clinical presentation, five (33%) patients presented with CM, five (33%) with PMC and five (33%) with PP. Disease onset was in the first two decades in the majority of cases (86% - 12/14). Eight-seven percent of patients (13/15) recurrent symptoms within days and 46% symptoms lasted up to minutes. As described in the literature, triggers were stress, cold, carbohydrate intake, rest after exercise, and the menstrual period. There was no history of seizures and only one patient had delayed motor milestones. Myotonia was observed on 92% of patients (11/12) and the "warm-up phenomenon" was identified on five patients. Eleven patients had fixed weakness with myopathic pattern in the majority of cases (proximal weakness). On the physical examination, most patients had normal reflexes. As to lab work, potassium level was abnormal on three cases, with one of them being low on the symptomatic period. CK level was above normal interval in 66% of cases and the highest value was 3845 (ref.: 46-171 U/L). WES was performed in 80% of patients and the following variants were identified: c.1333G>A, c.1762A>G, c.1921G>T, c.2111C>T, c.3466 G>A, c.3917G>A, c.3917G>T, c.3917G>C, c.3938C>T. When analysing each variant, most of them are considered pathogenic in public databases; SCN4A - c.1762A>G pathogenicity was proven by functional analysis in a previous study; SCN4A c.1921G>T is likely pathogenic with strong in-silico predictors, but waiting to confirm its pathogenicity. Conclusion: Despite improvement in genetic testing and in the understanding of the etiopathogenesis of SMC, the phenotypic diversity still represents a challenge to the diagnosis and management of these patients. Therefore, this study brings some new insights on our Brazilian SMC patients and hopefully opens to new discoveries regarding genotypic-phenotypic correlations.

**Palavras-Chave do trabalho:** Muscle channelopathies; SCN4A; WES;

**ID do trabalho:** 265

**Área Técnica do trabalho:** Pesquisa translacional, modelos celulares e animais

**Tipo do trabalho:** Trabalhos Originais

**Forma de apresentação:** Pôster

## Título do Trabalho: DEVELOPMENT OF 3D MODELS FOR GLIOBLASTOMA CELL CULTURE

**Autores:** GARCIA, Larissa Suellen Amorim<sup>1</sup>; LING, Ma Hui<sup>1</sup>; FERREIRA, Raiane Oliveira<sup>1</sup>; ZATZ, Mayana<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil;

### Resumo do trabalho:

Glioblastoma (GBM) is the most common and aggressive brain tumor, with an average survival rate of less than 15 months. The complexity of GBM arises from its cellular heterogeneity, invasive capacity, and uncontrolled angiogenesis, leading to therapeutic resistance. Two-dimensional (2D) cell culture models are widely used but fail to replicate the three-dimensional (3D) structure of the tumor microenvironment, limiting their clinical relevance. To address these challenges, 3D in vitro models, such as spheroids and hydrogel-based cell cultures, have been explored. Spheroids are multicellular aggregates formed under specific conditions, creating oxygen, nutrient, and metabolite gradients, while promoting cell-cell interactions. Nevertheless, the lack of a structural extracellular matrix (ECM) and the inability to control mechanical properties, such as stiffness and porosity,

compromise their biomimicry, making them inadequate for detailed studies of tumor behavior. In this study, we developed a 3D model using gelatin methacrylate (GelMA), a collagen-derived hydrogel containing the RGD tripeptide sequence, essential for cell adhesion, due to its biocompatibility and tunable mechanical properties. The U87 glioblastoma cells were cultured in 6% GelMA hydrogels, polymerized with violet light using 0.3% lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) as a photoinitiator. Scanning electron microscopy (SEM) and ImageJ analysis revealed pores with an approximate diameter of  $14 \pm 3.6 \mu\text{m}$  providing an ideal environment for cell adhesion and proliferation. As a result, through immunofluorescence for f-actin and DAPI nuclear staining by using confocal microscopy, we observed that cells efficiently adhered and grew in GelMA hydrogel, organizing similarly to in vivo conditions, with uniform distribution and preserved cell-matrix interactions. In conclusion, these results demonstrate that the GelMA-based 3D model replicates the architecture and functionality of the tumor microenvironment, offering a versatile and highly biomimetic tool for glioblastoma studies that overcomes the limitations of traditional models. Additionally, the ability to control the hydrogel's mechanical properties and structure makes this model particularly efficient for drug testing, enabling the evaluation of therapeutic responses in a more physiological and predictive environment.

**Palavras-Chave do trabalho:** 3D cell culture; Glioblastoma; Hydrogels; Tumor Microenvironment;

**ID do trabalho:** 266

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: "CONGENITAL MYASTHENIC SYNDROME WITH LIMB-GIRDLE PHENOTYPE: REPORT OF A RARE MUTATION IN THE AGRIN GENE."**

**Autores:** FREITAS, Lorena<sup>1</sup>; MEDEIROS, Alex<sup>1</sup>; ARAGÃO, Ademir<sup>1</sup>;

**Instituição dos Autores:** (1) HU UFPI - teresina - PI - Brasil;

### **Resumo do trabalho:**

Background: Congenital myasthenic syndromes are a group of disorders caused by genetic defects that impair neuromuscular transmission, resulting in muscle weakness exacerbated by exertion. They are classified into: alterations in the presynaptic compartment, the synaptic basal lamina, or the postsynaptic compartment. The reported case involves an alteration in the AGRIN gene, meaning it results from a defect in the conformation of the synaptic basal lamina. Objective: To report a case of congenital myasthenic syndrome caused by a mutation in the AGRIN gene. Methods: Case report based on a retrospective analysis through a review of the medical records of a patient seen at the neurology outpatient clinic of the University Hospital of the Federal University of Piauí. Results: The patient presented with progressive weakness since childhood and was initially diagnosed with muscular dystrophy, with no response to pyridostigmine. Electroneuromyography exams revealed a pattern consistent with neuromuscular junction impairment, later confirmed by the identification of a homozygous mutation in the AGRN gene. Conclusion and Case Presentation: A 48-year-old female patient presented with progressive weakness since the age of 9. At 12 years old, she began experiencing frequent falls. Weakness fluctuated throughout the day, worsening with exertion, mimicking limb-girdle dystrophy, and leading to a diagnosis of muscular dystrophy in 2001, with no response to pyridostigmine. Family history: consanguinity (parents are first cousins). Physical examination: Short-step gait. Proximal muscle strength grade III and distal grade V in all four limbs. Global hyporeflexia. Complementary exams: Electroneuromyography (2001): Short, low-amplitude polyphasic potentials with early and complete proximal recruitment in all four limbs, suggesting moderate myopathy. Histopathological examination of striated muscle (2001): No alterations. Electroneuromyography (2023): Signs of postsynaptic neuromuscular junction impairment. Genetic testing was a key step for diagnosis: Mendelics result (2022): Congenital myasthenic syndrome 8 – mutation in the AGRN gene (position chr1:1,050,763, consequence P.Val1727Phe, two copies in homozygosity); OMIM 103320. Discussion: A PubMed database search using the terms "myasthenia" and "agrin" resulted in 22 articles, of which only three reported clinical cases, and none described the same alteration identified in this patient. The rarity of this mutation justifies the presentation of this case, contributing to knowledge and future research on the disease. Final comments: This report expands the phenotypic characterization of congenital myasthenic syndrome associated with the AGRN gene, reinforcing the relevance of genetic investigation in atypical cases of chronic muscle weakness. The identification of this mutation may assist in differential diagnosis and the definition of therapeutic approaches for patients with similar profiles.

**Palavras-Chave do trabalho:** AGRIN; CONGENITAL MYASTHENIC SYNDROME; Neuromuscular Junction;

**ID do trabalho:** 267

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: **EXPANSIONHUNTER IN CLINICAL PRACTICE: PINPOINTING ATXN2 GENE EXPANSION IN SPINOCEREBELLAR ATAXIA TYPE 2 (SCA2) THROUGH INTEGRATED CLINICAL AND NEUROIMAGING INSIGHTS**

**Autores:** MOURA, Eder Alencar<sup>1</sup>; CASTRO, Matheus Augusto Araújo<sup>2</sup>; SAKAI, Eric Oneda<sup>3</sup>; MARCARINI, Bruno Guimaraes<sup>3</sup>; BARBOSA, Renata Montes Garcia<sup>3</sup>; DA SILVA, Sergio Roberto Pereira<sup>3</sup>; CRUZ, Patricia Pontes<sup>3</sup>; FREUA, Fernando<sup>3</sup>; KOK, Fernando<sup>3</sup>;

**Instituição dos Autores:** (1) HCFMUSP - SÃO PAULO - SP - Brasil; (2) HCFMUSP - SÃO PAULO - SP - Brasil; (3) HCFMUSP - São Paulo - SP - Brasil;

### Resumo do trabalho:

The proband is a 49-year-old male with a history of herpetiform dermatitis and celiac disease, both controlled with a gluten-free diet. Since the age of 33, he has been monitored for progressive neurological symptoms, including tremors, coordination difficulties, dysarthria, dysphagia, and global ataxia with axial predominance. He reports a significant family history of similar neurological conditions, allegedly Huntington's disease and Parkinson's disease, with multiple relatives having died from these conditions. Currently, he presents with an ataxic gait, dysphagia for solids, and mild postural tremors, without evident chorea. Brain MRI revealed cerebellar and pontine atrophy, with the presence of the "hot cross bun" sign. Laboratory tests showed normal levels of vitamin D, B12, electrolytes, and liver function, with no immunological or infectious alterations. Genetic testing was performed, and PCR ruled out Spinocerebellar Ataxia (SCA) types 1, 2, 3, and 6. Exome sequencing revealed no candidate single nucleotide variants. However, due to a strong clinical suspicion of SCA2, ExpansionHunter was performed on exome sequencing data and suggested an expansion in the ATXN2 gene, with one allele with 23 repeats and the other allele with 37 repeats, consistent with SCA2. PCR was performed again, confirming the expanded allele, missed in the first reaction. The clinical picture, along with neuroimaging findings, raised suspicion of a progressive cerebellar ataxia, likely of genetic origin, given the patient's family history of degenerative neurological diseases. The cerebellar atrophy observed in the MRI, combined with the "hot cross bun" sign, is indicative of a spinocerebellar ataxia or multiple system atrophy, though the latter is less likely due to the absence of other suggestive features. Despite negative results from genetic testing for SCA types 1, 2, 3, and 6, further genetic investigation using Expansion Hunter bioinformatics analysis revealed a noteworthy finding in the ATXN2 gene, consistent with Spinocerebellar Ataxia type 2 (SCA2). The abnormal CAG trinucleotide repeat expansion in ATXN2 is characteristic of this condition, and affected individuals typically present with alleles containing 33 or more CAG repeats. This case underscores the significance of a thorough diagnostic workup in patients with progressive neurological symptoms, particularly when there is a strong family history of similar conditions. The combination of clinical, neuroimaging, and genetic findings, including the use of advanced bioinformatics tools like ExpansionHunter, ultimately led to the diagnosis of SCA2. Despite the negative initial genetic tests, the molecular analysis provided the critical evidence for a definitive diagnosis. This highlights the evolving role of genetic testing and bioinformatics in the diagnosis of rare neurodegenerative diseases, offering better insight into patient care, prognosis and genetic counseling.

**Palavras-Chave do trabalho:** brain MRI; ExpansionHunter; spinocerebellar ataxia;

**ID do trabalho:** 269

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: **MIGRAINE WITH BRAINSTEM AURA, MULTIFOCAL SEIZURES AND ELECTRICAL STATUS EPILEPTICUS IN SLEEP WITHOUT COGNITIVE REGRESSION: A COMPLEX PHENOTYPE DUE TO A KCNA1 VARIANT**

**Autores:** BUENO, Manoella Guerra de Albuquerque<sup>1</sup>; PEREIRA, Mariana Ribeiro<sup>1</sup>; FREZATTI, Rodrigo Siqueira Soares<sup>1</sup>; WILSON, Lindsay<sup>2</sup>; REILLY, Mary M<sup>2</sup>; HANNA, Michael<sup>2</sup>; TOMASELLI, Pedro Jose<sup>3</sup>; JUNIOR, Wilson Marques<sup>3</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - FMRP-USP - Ribeirão Preto - SP - Brasil; (2) University College London - United Kingdom; (3) Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo - FMRP-USP - Ribeirão Preto - SP - Brasil;

### Resumo do trabalho:

Case presentation: We present a case of a 12 year-old boy who complained of migraine since the age of five. He was born full-term after one complicated event during pregnancy (threatened preterm labor reversed with tocolytics). He had steady gains of motor milestones and said his first words at one year and two months of age. He was previously healthy and there was no seizure history. Migraine episodes were preceded by diplopia and vertigo, classifying it as migraine with brainstem aura, and were recurrent multiple times during the week. Associated with this, he also had somnambulism and somniloquy daily. There was a partial response in frequency to flunarizine. However, at the age of seven, he had two episodes of impaired awareness that lasted 2 minutes and were followed by mental confusion that lasted 2 minutes. There were no other seizure symptoms. His treatment was modified to valproic acid and he hadn't recurred for months. His family history is remarkable for a mother with

episodic ataxia, myokymia, focal epilepsy since the neonatal period and hemiplegic migraine. Brain MRI at age of seven was normal and his firsts EEGs were characterized by multifocal spikes with correlation with self-limited epilepsy with centrotemporal spikes, since there was no regression on development and spikes were markedly on the centrotemporal region bilaterally. He then started feeling dizziness at eleven years old. His treatment was changed to topiramate (with an excellent response) and a new EEG showed electrical status epilepticus in sleep (medium activation of epileptiform activity in NREM sleep of 83%) with 12 years old. He still has no developmental regression, but is showing some difficulties in learning new subjects in school. Since his family history was distinctive for epilepsy and hemiplegic migraine, WES was done and revealed a heterozygous KCNA1 gene variant (c.902G>A; p.Arg301Lys), which was also present in his mother. Discussion: The KCNA1 gene encodes Kv1.1 voltage-gated potassium channel  $\alpha$  subunits and mutations in the KCNA1 gene can cause several neurological disorders, including episodic ataxia type 1 (EA1) and epilepsy. The range of clinical presentations related to this gene hampers the simple genotype–phenotype correlation. This variant was already described in the literature (his mother) and is located on the S4 domain of the KCNA1 related protein. Its pathogenicity was proved by functional analysis, but, at that time, the ESES was not present. One recently published article identified a de novo KCNA1 gene variant (KCNA1:c.1214C>T; p.Pro405Leu) located on the S6 domain, that presented with encephalopathy related to status epilepticus during slow sleep (ESES). Final comments: This finding adds to the spectrum of phenotypes associated with this KCNA1 variant. It also highlights the need for clinical suspicion for ESES in cases of patients with KCNA1 variants or other epilepsy-related channelopathies presenting mild school difficulties.

**Palavras-Chave do trabalho:** Developmental and Epileptic Encephalopathy; epilepsy; KCNA1 gene;

**ID do trabalho:** 270

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho:** Made in Brazil

**Forma de apresentação:** Apresentação Oral

## Título do Trabalho: FURTHER DESCRIPTION OF THE PHENOTYPIC SPECTRUM OF NEURONAL CEROID LIPOFUSCINOSIS TYPE 11

**Autores:** Nóbrega, Paulo Ribeiro<sup>1</sup>; PAIVA, Anderson Rodrigues Brandão<sup>2</sup>; AMORIM JUNIOR, Antonio Duarte<sup>2</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; CABRAL, Katiane Sayão Souza<sup>2</sup>; BARCELOS, Isabella Peixoto<sup>2</sup>; PESSOA, André Luiz Santos<sup>3</sup>; SOUZA-LIMA, Carlos Frederico Leite<sup>4</sup>; CASTRO, Matheus Augusto Araújo<sup>2</sup>; FREUA, Fernando<sup>2</sup>; SANTOS, Emerson de Santana<sup>5</sup>; ROCHA, Margleice Marinho Vieira<sup>5</sup>; MAIA, Rayana Elias<sup>6</sup>; ARAÚJO, Rodrigo Santos<sup>5</sup>; RAMOS, Juan David Guevara<sup>7</sup>; RESENDE, Rosane Guazi<sup>8</sup>; CARVALHO, Gerson da Silva<sup>9</sup>; VALENÇA, Luciana Patrizia Andrade<sup>10</sup>; CARVALHO JR, José Ronaldo Lima de<sup>10</sup>; MELO, Eduardo Sousa<sup>10</sup>; PEDROSO, José Luiz<sup>11</sup>; BARSOTTINI, Orlando Graziani Povoas<sup>11</sup>; HOULDEN, Henry<sup>12</sup>; KOK, Fernando<sup>2</sup>; LYNCH, David S<sup>12</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Universidade de São Paulo - São Paulo - SP - Brasil; (3) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil; (4) Universidade Estadual de Pernambuco - Recife - PE - Brasil; (5) Universidade Federal de Sergipe - Aracaju - SE - Brasil; (6) Universidade Federal da Paraíba - João Pessoa - PB - Brasil; (7) Fundación Hospital pediátrico de la Misericordia - Colombia; (8) Instituto de Olhos Carioca - Rio de Janeiro - RJ - Brasil; (9) Centro de Referência em Doenças Raras do Distrito Federal - Brasília - DF - Brasil; (10) Universidade Federal de Pernambuco - Recife - PE - Brasil; (11) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (12) UCL Institute of Neurology - United Kingdom;

### Resumo do trabalho:

**Background:** Neuronal ceroid lipofuscinosis (CLN) is a group of rare, inherited neurodegenerative disorders characterized by the accumulation of autofluorescent lipopigments in tissues. CLN11 is a specific form of this condition, with varied clinical manifestations including visual impairment, cerebellar ataxia, seizures, and cognitive decline. **Objective:** The objective of this study was to analyze the clinical and epidemiological characteristics of patients with CLN11, identifying common patterns and variations in disease presentation. **Methods:** Patients with biallelic pathogenic or likely pathogenic variants were recruited. The attending physicians for each patient were contacted and invited to participate in the study. Clinical charts were reviewed, and additional information was collected and organized in a database containing epidemiological data, age of onset, symptoms at onset, disease duration, loss of ambulation, visual impairment, visual hallucinations, cognitive decline, seizures, myoclonus, and the age of onset of each symptom. All magnetic resonance imaging scans were reviewed by an experienced neuroradiologist. Data extracted from participants were summarized using descriptive statistics. **Results:** We identified 11 individuals with CLN11, of which 2 were excluded due to insufficient clinical data. Therefore, 9 patients with CLN11 were analyzed. The age of onset varied between 3 to 17 years. The most common findings were visual impairment and cerebellar ataxia, present in all patients. Generalized seizures were found in 8 cases and myoclonus in 7 patients. Cognitive decline was reported in 7 cases. Visual hallucinations were present in 5 cases and pyramidal signs were found in 4. Five of the 9 patients (56%) were able to walk unassisted at the last follow-up visit after an average of 14.2 years from disease onset. Loss of ambulation occurred in 4 patients, on average 7.25 years after symptom onset. **Conclusion:** CLN11 presents a wide range of clinical manifestations, with visual impairment and cerebellar ataxia being the most common findings. The variability in age of onset and symptom progression highlights the need for early diagnosis and continuous follow-up to improve the quality of life for patients.

**Palavras-Chave do trabalho:** CLN11; Neurodegenerative Diseases; Neuronal Ceroid Lipofuscinosis;

**ID do trabalho:** 271**Área Técnica do trabalho:** Neurodesenvolvimento**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: FROM THE DIAGNOSTIC CHALLENGE TO THE PROGNOSTIC CHALLENGE IN MULTIDISORDERS CASE: CASE REPORT OF MYH10 GENE VARIANT AND BOSCH-BOONSTRA-SCHAAF OPTIC ATROPHY**

**Autores:** MAIA, Rayana Elias<sup>1</sup>; LEAL, Suenia Timotheo Figueiredo<sup>2</sup>;**Instituição dos Autores:** (1) UFPB - João Pessoa - PB - Brasil; (2) HULW - João Pessoa - PB - Brasil;**Resumo do trabalho:**

Case presentation: Patient, male, was referred due to congenital hypotonia, hearing and visual deficits. He is the second child of a non-consanguineous and young couple, mother 36 years old and father 33 years old. There was polyhydramnios during pregnancy and he was born by cesarean section, with an Apgar score of 8/9, weighing 2716g, and measuring 48cm. He progressed with good weight gain but with neurodevelopmental delay. On examination, in addition to global hypotonia, he has brachycephaly, unilateral convergent strabismus and a bulging forehead. Brain resonance was normal, but he has low visual acuity, interatrial communication and mild bilateral hearing loss. Exome sequencing showed pathogenic variants in heterozygosity in MYH10 c.1189delA p.Met397\* and NR2F1 c.421T>C p.Cys141Arg. Discussion: In this case, the neurodevelopmental disorder related with the MYH10 gene is still poorly understood and is associated with Bosch-Boonstra-Schaaf optic atrophy. Both compromise neurodevelopment in addition to other associated comorbidities. The burden of morbidity is aggravated by the combination of pathologies. Clinical complexity increases, compromising results and management. Final comments: Technological advances have allowed the definition of complex clinical pictures, especially in the diagnosis of concurrent conditions. However, determining the correct prognosis is still challenging and requires individualized clinical monitoring.

**Palavras-Chave do trabalho:** Bosch-Boonstra-Schaaf optic atrophy; MYH10 gene; neurodevelopment disorder;**ID do trabalho:** 272**Área Técnica do trabalho:** Doenças Neuromusculares**Tipo do trabalho** Relatos de Caso**Forma de apresentação:** Pôster

## **Título do Trabalho: DIAGNOSTIC CHALLENGES IN KEARNS-SAYRE SYNDROME: A CASE REPORT OF SEVERE CARDIAC COMPLICATIONS WITH NEGATIVE MITOCHONDRIAL DNA TESTING**

**Autores:** LOPES, Jessica Vargas<sup>1</sup>; SABADIN, Caroline Dresch<sup>2</sup>; FINK, Isabela Alicia<sup>1</sup>; CARRILHO, Paulo Eduardo Mestrinelli<sup>2</sup>; DOS SANTOS, Marcius Benigno Marques<sup>2</sup>;**Instituição dos Autores:** (1) UFCSPA - Porto Alegre - RS - Brasil; (2) UNIOESTE - Cascavel - PR - Brasil;**Resumo do trabalho:**

Case Report: A 24-year-old female was admitted due to complete atrioventricular block (CAVB). She presented with syncope, after an episode of malaise and weakness. At the referring service, CAVB with a heart rate (HR) of 36 bpm was found, and during transport she developed cardiorespiratory arrest (CRA), reversed after one minute of resuscitation. She had another CRA in ventricular fibrillation (VF) at the hospital, reversed with defibrillation. She had a previous diagnosis of mild mitral valve prolapse. A transvenous pacemaker was placed, and subsequently, an implantable cardioverter-defibrillator (ICD) was implanted. ECGs showed CAVB and ventricular paced rhythm. Echocardiograms showed preserved left ventricular ejection fraction (LVEF), mild mitral valve prolapse. Tilt-test was positive (vasodepressor and cardioinhibitory). Electromyography showed a non-specific myopathic pattern. Ophthalmological evaluation suggested pigmentary retinopathy. Genetic testing for a panel of mitochondrial diseases was negative, although the clinical presentation raised suspicion for KSS. Family history included deaths from AMI at young ages and a nephew with developmental delay and cardiac abnormalities. On follow-up, she presented with mild bilateral ptosis, external ophthalmoparesis, and mild gait ataxia. Discussion: This case illustrates the diagnostic challenges of KSS, especially when routine genetic tests for mtDNA deletions are negative. The patient presented a clinical picture highly suggestive of KSS, with severe cardiac manifestations, including CAVB requiring ICD implantation, and clinical signs such as probable pigmentary retinopathy, ophthalmoparesis, and ptosis. The occurrence of CAVB in young patients reinforces the suspicion of KSS. Despite the strong clinical suspicion, the genetic test for a panel of mitochondrial diseases did not detect alterations. This raises the possibility that the patient has an atypical mtDNA deletion not covered by the panel, a rare point variant, somatic mosaicism, or heteroplasmy. Differential diagnoses include CPEO plus, MELAS, MERRF, and NARP syndromes, although the presentation is more consistent with KSS. Non-mitochondrial neuromuscular diseases

could also be considered, but the presence of CAVB is a strong indicator of mitochondrial disease. The family history suggests a possible hereditary disease. The management of CAVB was essential for the patient's survival. Final Comments: This case highlights the importance of considering the clinical suspicion of KSS even when routine genetic tests for mtDNA deletions are negative. The negative test does not rule out the diagnosis, and more comprehensive tests, such as complete mtDNA sequencing or muscle biopsy, should be considered. Multidisciplinary management, with an emphasis on rigorous cardiological follow-up, is crucial. Early detection and appropriate management of complications are essential to improve quality of life and prognosis.

**Palavras-Chave do trabalho:** ; Cardiac Complications; Diagnosis; Kearns-Sayre Syndrome; Mitochondrial Disease;

**ID do trabalho:** 273

**Área Técnica do trabalho:** Testes Genéticos e Medicina genômica

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: DIAGNOSTIC YIELD OF EXOME SEQUENCING FOR INTELLECTUAL DISABILITY AT HOSPITAL DE CLÍNICAS DE PORTO ALEGRE**

**Autores:** SIMÃO MEDEIROS, Leonardo<sup>1</sup>; WOYCINCK KOWALSKI, Thayne<sup>1</sup>; RODRIGUES BOTTON, Mariana<sup>1</sup>; ARTIGALÁS, Osvaldo Alfonso<sup>1</sup>; SPERB LUDWIG, Fernanda<sup>2</sup>; SALES LUIZ VIANNA, Fernanda<sup>2</sup>; FERREIRA RODRIGUES, Nureyev<sup>1</sup>; MACHADO XAVIER, Ricardo<sup>1</sup>; MATTE, Ursula<sup>1</sup>; FELIX, Temis Maria<sup>1</sup>; SAUTE, Jonas Alex Morales<sup>2</sup>;

**Instituição dos Autores:** (1) Hospital de Clínicas de Porto Alegre - Porto Alegre - RS - Brasil; (2) Universidade Federal do Rio Grande do Sul - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Background: Genomic medicine has greatly advanced clinical practice, improving diagnosis, prognosis, and treatment. Exome Sequencing (ES), a key technique, is recommended for investigating Intellectual Disability (ID) under SUS guidelines. As HCPA is a Reference Service in Rare Diseases, adopting this technology became crucial. Starting in 2021 through an institutional project, ES was fully established as an institutional exam by 2024. Objective: To evaluate the diagnostic yield of ES for patients with ID in the period of implementation of this exam in Hospital de Clínicas de Porto Alegre. Methods: ES reports released in 2023 and 2024 were evaluated and data from the variants reported was collected. A case was considered as conclusive if there was detection of Pathogenic or Likely Pathogenic (P/LP) variants that explain the phenotype in the zygosity and context compatible with the disorder and its inheritance. For cases with Variants of Uncertain Significance (VUS) reported, parental segregation analysis was recommended when useful to potentially reclassify the variants and determine the diagnosis. Secondary findings were reported for P/LP variants in genes of the ACMG SF v3.2 list. The results are presented in absolute and relative frequencies, calculated in R language. Results: Sixty-three report exams were released in 2023 and 2024. Of these, 23 (36.5%) were considered conclusive. Of the remaining reports, there were 22 (34.9%) VUS reports and 18 (28.6%) negative reports. In 8 cases with a VUS report, parents' segregation is recommended to possibly reclassify the variant, potentially increasing the diagnostic yield of ES up to 49.2%. Secondary findings were reported in 4 cases (6.3%), including 3 with RYR1 variants associated with malignant hyperthermia susceptibility and 1 with the TTR V142I variant. Conclusions: According to a recent literature review, the diagnostic yield of ES for patients with ID ranged from 21% to 63%, demonstrating that the yield registered in HCPA is satisfactory. Despite the challenges in ES interpretation, this advanced technology represented a significant diagnostic resolutivity. This may help reduce the burden of the diagnostic odyssey and enhance the accuracy of prognosis, patient management, and genetic counseling for patients and their families.

**Palavras-Chave do trabalho:** Diagnosis; exome; genomic medicine; Intellectual Disability;

**ID do trabalho:** 275

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: CEROID LIPOFUSCINOSIS TYPE 5: NOVEL PATHOGENIC VARIANTS AND UNEXPECTED PHENOTYPIC FINDINGS**

**Autores:** PAIVA, Anderson Rodrigues Brandão<sup>1</sup>; PESSOA, André Luiz Santos<sup>2</sup>; Nóbrega, Paulo Ribeiro<sup>3</sup>; MORENO, Cristiane Araujo Martins<sup>1</sup>; LYNCH, David S<sup>4</sup>; TANIGUTI, Lucas Mitsuo<sup>5</sup>; KITAJIMA, João Paulo<sup>5</sup>; FREUA, Fernando<sup>1</sup>; DELLARIPA, Bruno<sup>1</sup>; CUNHA, Paulina<sup>1</sup>; BARCELOS, Isabella Peixoto<sup>1</sup>; MACEDO-SOUZA, Lúcia Inês<sup>1</sup>; TAKEUCHI, Carlos Augusto<sup>6</sup>;

GARCIA, Antônio Milton Silva<sup>7</sup>; NARDES, Flávia<sup>8</sup>; FONTÃO, Ramiro<sup>9</sup>; ANTONIUK, Sérgio Antônio<sup>10</sup>; TRONCOSO, Monica<sup>11</sup>; SPÉCOLA, Norma<sup>12</sup>; DURAND, Consuelo<sup>13</sup>; MADEIRO, Bianca de Aguiar Coelho Silva<sup>14</sup>; DORIQUEI, Maria Juliana Rodvalho<sup>15</sup>; VERGARA, Diane<sup>16</sup>; HOULDEN, Henry<sup>4</sup>; KOK, Fernando<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade de São Paulo - São Paulo - SP - Brasil; (2) Hospital Infantil Albert Sabin - Fortaleza - CE - Brasil; (3) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (4) UCL Queen Square Institute of Neurology - United Kingdom; (5) Mendelics Genomic Analysis - São Paulo - SP - Brasil; (6) Sabará Hospital Infantil - São Paulo - SP - Brasil; (7) Hospital Regional Dom Moura - Garanhuns - PE - Brasil; (8) Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ - Brasil; (9) Penna Hospital, Bahía Blanca - Argentina; (10) Universidade Federal do Paraná - Curitiba - PR - Brasil; (11) Pediatric Neurology Department - Chile; (12) Hospital de Niños Sor María Ludovica - Argentina; (13) Laboratorio de Neuroquímica Dr. N.A. Chamoles - Argentina; (14) Hospital Universitário Oswaldo Cruz - Recife - PE - Brasil; (15) Universidade Federal do Maranhão - São Luis - MA - Brasil; (16) Hospital Clínico San Borja Arriarán - Chile;

#### Resumo do trabalho:

**Background:** Ceroid lipofuscinosis type 5 (CLN5) is a neurodegenerative disorder belonging to the group of neuronal ceroid lipofuscinoses, characterized by progressive cognitive decline, motor impairment, and seizures. The clinical presentation can vary significantly among patients, and genetic factors play a crucial role in the disease's manifestation. **Objective:** This study aims to report on 16 additional cases of CLN5 from South America, focusing on novel pathogenic variants and unexpected phenotypic findings to enhance the understanding of this disorder's clinical and genetic landscape. **Methods:** A retrospective analysis was performed on 18 patients from 17 families diagnosed with CLN5 through molecular analysis using next-generation sequencing. Clinical data, including age of onset, presenting symptoms, and neuroimaging findings, were collected. Genetic variants were classified and analyzed for their pathogenicity. **Results:** The cohort included 15 childhood-onset patients (ages 1-10 years) and one adult-onset patient (age 61). Common clinical features observed were global cerebellar ataxia, severe dysarthria, cognitive decline, and seizures, with epilepsy being the initial symptom in eight patients. Fundoscopic examinations indicated retinitis pigmentosa in some cases. Neuroimaging revealed global cortical and cerebellar atrophy, with no white matter involvement. Genetic analysis identified six missense mutations (three novel), two frameshift variants (one novel), two nonsense variants, and one new splicing site variant. Notably, the p.Arg63Cys variant was found in a homozygous state in six patients, suggesting a potential founder effect in the Brazilian population. **Conclusion:** This study expands the understanding of CLN5 by documenting additional cases and novel genetic variants in South America. The findings highlight the clinical heterogeneity of CLN5, with a predominant presentation of language impairment and seizures in the late infantile variant. The identification of novel pathogenic variants contributes to the genetic landscape of CLN5, emphasizing the importance of genetic testing for accurate diagnosis and management of affected individuals.

**Palavras-Chave do trabalho:** Ceroid Lipofuscinosis Type 5 (CLN5); epilepsy; NEURODEGENERATIVE DISORDERS; neurogenetics;

**ID do trabalho:** 277

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: LONG DIAGNOSTIC JOURNEY OF SPINAL MUSCULAR ATROPHY: THE ROLE OF LONG-READ SEQUENCING IN A CHALLENGING CASE

**Autores:** MENDONCA, Rodrigo Holanda<sup>1</sup>; KOK, Fernando<sup>1</sup>; ZANOTELI, Edmar<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina da USP - Sao Paulo - SP - Brasil;

#### Resumo do trabalho:

**Case description:** Female patient, a 39-year-old, exhibited early-onset motor impairment, never achieving independent crawling or walking. She was able to sit at 7 months of age, and at 1.5 years, an electroneuromyography suggested a diagnosis of spinal muscular atrophy (SMA). Throughout childhood, she experienced recurrent pneumonias and progressive muscle weakness, developing severe scoliosis, which was never surgically corrected due to her restrictive ventilatory disorder (FVC: 25%). Currently, she requires non-invasive ventilation (BiPAP) nightly and intermittently during the day. Neurological examination reveals global areflexia, diffuse muscle atrophy, contractures in major joints (shoulders, elbows, hips, knees), and a characteristic bulbar phenotype of SMA type 2, with jaw-opening difficulty, nasal speech, fasciculations, and dysphagia, which began in adolescence. Despite a clinical presentation consistent with SMA type 2, multiple molecular investigations failed to confirm the diagnosis. In 2000, a PCR-based deletion test for SMN1 yielded a normal result, ruling out the common homozygous deletion. In 2021, MLPA analysis identified two copies of SMN1, further complicating the diagnosis. Seeking alternative explanations, whole-exome sequencing (WES) in 2023 did not reveal pathogenic variants associated with SMA or other neuromuscular disorders. Given the strong clinical suspicion, in 2024, third-generation long-read sequencing (Oxford Nanopore Technologies®) was performed, successfully identifying a homozygous nonsense variant in SMN1 (chr5:70.942.740 C>G; c.497C>G; p.Ser166\*), confirming the diagnosis of SMA. **Discussion** This case underscores the limitations of conventional molecular testing in detecting SMA when point mutations are involved. While most SMA cases result from homozygous SMN1 deletions, rare homozygous point mutations can be missed by standard PCR, MLPA, or even exome sequencing. Long-read sequencing provides a comprehensive genetic analysis, capturing complex variants that escape traditional methods. Given that SMA is a treatable disease with approved therapies (nusinersen, risdiplam, gene therapy), a precise and timely diagnosis is

crucial. Conclusion Long-read sequencing is a powerful tool for diagnosing atypical SMA cases, particularly when standard molecular techniques yield inconclusive results. This case highlights the need for broader accessibility of advanced sequencing methods in neurogenetic diseases, ensuring that all patients receive appropriate diagnosis and treatment.

**Palavras-Chave do trabalho:** Long read sequencing; SMN1; Spinal Muscular Atrophy;

**ID do trabalho:** 278

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: MYOPATHY WITH FLUCTUATING MUSCLE ENZYMES AND ARTHRALGIA ASSOCIATED WITH PATHOGENIC MYL2 VARIANTS: A CASE REPORT**

**Autores:** SANTANA, FABIANO FERREIRA<sup>1</sup>; NASCIMENTO, MONIQUE EVELYN MENDONÇA<sup>1</sup>; ALVES, LUCAS VICTOR<sup>2</sup>; MENEZES, ANA CECÍLIA<sup>3</sup>; FILHO, JOSELITO SOBREIRA<sup>3</sup>; CARDOSO, MARIA EDUARDA MOREIRA<sup>3</sup>;

**Instituição dos Autores:** (1) HOSPITAL DA RESTAURAÇÃO GOVERNADOR PAULO GUERRA - Recife - PE - Brasil; (2) INSTITUTO DE MEDICINA INTEGRAL FERNANDO FIGUEIRA - Recife - PE - Brasil; (3) INSTITUIÇÃO DE MEDICINA INTEGRAL FERNANDO FIGUEIRA - Recife - PE - Brasil;

### **Resumo do trabalho:**

Case presentation: A 17-year-old male patient with significant progressive heart disease diagnosed as restrictive cardiomyopathy with no other reported comorbidities. He underwent heart transplantation in 2016 at the age of nine. After surgery and immunosuppressive therapy, at the age of 15, the patient began to present with intermittent episodes of migratory polyarthritides of large and medium-sized joints, myalgia, and intermittent increases in muscle enzymes (Aldolase and Creatine-kinase). During the pain crises, the CPK level varied between 900 and 3470 and the aldolase variation was between 7.5 and 21. The hypothesis of graft rejection was raised, but was ruled out after clinical examination. The initial symptoms could have been suggestive of viral myositis, but the patient evolved with a new increase in muscle enzymes unrelated to infection or increased physical activity. On physical examination, the patient had preserved cognition and no skin lesions suggestive of dermatomyositis. When not in crisis, he engages in normal physical activity and denies muscle weakness. Past medical history: no neuropsychological developmental delay. Mother denies consanguinity and fetal loss. Therefore, in 2024, following an investigation with the departments of pediatrics, rheumatology, and cardiology, the patient was referred to the neurogenetics outpatient clinic for evaluation. Further diagnostic testing was requested, including a complete exome. Two variants in compound heterozygosity were identified in The myl2 gene (myosin light chain 2, OMIM\* 160781), classified as type 03 (variant of uncertain significance), and chr12:110.913.097 T>G (or alternatively c.401 A>C - ENST0 0000228841) is associated with the substitution of the amino acid glutamate in codon 134 with alanine (p.Glu134ala). Discussion: Two heterozygous variants were identified in the MYL2 (myosin light chain 2, OMIM\* 160781) gene, classified as variants of uncertain significance according to ACMG criteria: c.278C>A; p.(Ala93Glu) and c.401A>C; p.(Glu134Ala). The MYL2 gene is associated with two clinical phenotypes, including infant-onset myofibrillar myopathy with cardiomyopathy 12. This is an autosomal recessive myopathy that affects both skeletal and cardiac muscle tissue, becoming apparent within the first weeks of life. Affected children may present with tremors or clonus at birth, followed by the onset of rapidly progressive generalized muscle weakness, dilated cardiomyopathy, and heart failure. Final comments: Genetic neuromuscular diseases that result in intermittent elevation of muscle enzymes, such as creatine kinase (CK), encompass a range of metabolic and genetic myopathies. These conditions exhibit genetic heterogeneity and can manifest with variable symptoms, complicating diagnosis. These variants may contribute to the patient's clinical condition, who is currently under observation and awaiting further tests for a more comprehensive diagnosis.

**Palavras-Chave do trabalho:** Genetic diseases; Muscular weakness; Neuromuscular Diseases;

**ID do trabalho:** 279

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Pôster

## **Título do Trabalho: EXPANDING THE PHENOTYPIC SPECTRUM OF CLCN2-RELATED LEUCOENCEPHALOPATHY AND ATAXIA**

**Autores:** Nóbrega, Paulo R<sup>1</sup>; PAIVA, Anderson R B<sup>2</sup>; SOUZA, Katiane S<sup>3</sup>; DE SOUZA, Jorge Luiz B<sup>4</sup>; LIMA, Pedro Lucas G S B<sup>1</sup>; DA SILVA, Delson José<sup>5</sup>; PITOMBEIRA, Milena Sales<sup>6</sup>; BORGES, Vivienne K<sup>7</sup>; DIAS, Daniel A<sup>8</sup>; BISPO, Luciana M<sup>2</sup>;

SANTOS, Carolina F<sup>9</sup>; FREUA, Fernando<sup>10</sup>; SILVA, Paulo Diego S<sup>11</sup>; ALVES, Isabela S<sup>11</sup>; PORTELLA, Leonardo B<sup>11</sup>; CUNHA, Paulina R<sup>12</sup>; SALOMAO, Rubens Paulo A<sup>13</sup>; PEDROSO, José Luiz<sup>13</sup>; MIYAJIMA, Veridiana P<sup>14</sup>; MIYAJIMA, Fábio<sup>15</sup>; CALI, Elisa<sup>16</sup>; WADE, Charles<sup>16</sup>; SUDARSANAM, Annapurna<sup>17</sup>; O'DRISCOLL, Mary<sup>18</sup>; HAYTON, Tom<sup>19</sup>; BARSOTTINI, Orlando G P<sup>20</sup>; KLEBE, Stephan<sup>21</sup>; KOK, Fernando<sup>22</sup>; LUCATO, Leandro Tavares<sup>22</sup>; HOULDEN, Henry<sup>23</sup>; DEPIENNE, Christel<sup>24</sup>; LYNCH, David S<sup>16</sup>; BRAGA-NETO, Pedro<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) University of Sao Paulo - São Paulo - SP - Brasil; (3) University of Sao Paulo School - São Paulo - SP - Brasil; (4) Universidade Estadual do Ceará - Fortaleza - CE - Brasil; (5) Universidade Federal de Goiás - Goiânia - GO - Brasil; (6) Hospital Geral de Fortaleza - Fortaleza - CE - Brasil; (7) Universidade Federal de Uberlândia - Uberlândia - MG - Brasil; (8) Federal University of Ceara - Fortaleza - CE - Brasil; (9) Universidade de Fortaleza - Fortaleza - RO - Brasil; (10) Universiade de São Paulo - São Paulo - SP - Brasil; (11) Prevent Senior - São Paulo - SP - Brasil; (12) Paris Brain Institute (ICM) - France; (13) Universidade Federal de São Paulo - São Paulo - SP - Brasil; (14) Haematology and Haemotherapy Centre of Ceara (HEMOCE) - Fortaleza - CE - Brasil; (15) Oswaldo Cruz Foundation (Fiocruz) - Fortaleza - CE - Brasil; (16) UCL Queen Square Institute of Neurology - United Kingdom; (17) Birmingham Children's Hospital - United Kingdom; (18) Birmingham Women's Hospital - United Kingdom; (19) University Hospital Birmingham - United Kingdom; (20) Universidade Federal de São paulo - São Paulo - SP - Brasil; (21) University of Würzburg - Germany; (22) Universidade de São Paulo - São Paulo - SP - Brasil; (23) UCL Queen Square Institute of Neurology - São Paulo - SP - Brasil; (24) University Hospital Essen, University Duisburg-Essen - Germany;

#### Resumo do trabalho:

Background: CLCN2-related leucoencephalopathy and ataxia (LKPAT) is a rare genetic disorder associated with biallelic pathogenic variants in the CLCN2 gene, which encodes the CIC-2 chloride channel. The clinical presentation of LKPAT is heterogeneous, often including neurological symptoms such as ataxia, cognitive decline, and seizures. Despite previous reports, the phenotypic spectrum of this condition remains inadequately characterized. Objective: This study aims to delineate the clinical, radiological, and molecular features of 12 patients with biallelic CLCN2 variants, thereby expanding the understanding of LKPAT and its associated phenotypes. Methods: A total of 12 patients from 11 unrelated families (9 from Brazil, 2 from the UK, and 1 from Germany) were recruited. Informed consent was obtained in accordance with the Declaration of Helsinki, and the study was approved by the local ethical committee. Whole exome sequencing (WES) was performed on DNA extracted from oral swab samples. Clinical histories, physical examinations, and MRI findings were reviewed. The presence of restricted diffusion on MRI was assessed through visual analysis of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps. Results: The cohort comprised 7 males and 5 females, with an age of onset ranging from 6 months to 62 years (mean 25.95 years). The most prevalent clinical finding was ataxia, observed in 75% of patients, followed by cognitive decline in 42%. Seizures were reported in 25% of cases. MRI findings revealed hyperintense foci in the putamina, indicative of facilitated diffusion, with no enhancement noted on post-contrast imaging. A total of 110 articles were reviewed, leading to the identification of 48 relevant studies, which included 15 case reports and 33 research papers. Conclusion: This study provides a comprehensive characterization of the clinical and imaging profiles of patients with CLCN2-related leucoencephalopathy and ataxia. The findings underscore the variability in clinical presentation and highlight the importance of genetic testing in diagnosing this condition. Further research is warranted to elucidate the underlying mechanisms and to establish standardized diagnostic criteria for LKPAT.

**Palavras-Chave do trabalho:** ATAXIA; CIC-2 chloride channels; LEUCOENCEPHALOPATHY; MRI;

**ID do trabalho:** 281

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## Título do Trabalho: CASE REPORT: SEVERE EPILEPSY IN A PATIENT WITH BAINBRIDGE-ROPER'S SYNDROME (ASXL3 MUTATION)

**Autores:** NAGATA, Glauco Kody<sup>1</sup>; FERNANDES, Eduarda Rosa<sup>1</sup>; HAUBRICH, Carolina Heck<sup>1</sup>; VERZA, Caroline Schiochet<sup>1</sup>; DEVENS, Leticia Bassani<sup>1</sup>; KRUM, Vitória<sup>1</sup>; FUSSIGER, Helena<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital São Lucas da PUCRS - Porto Alegre - RS - Brasil;

#### Resumo do trabalho:

Case presentation: This case report describes a female patient with severe epilepsy and Bainbridge-Ropers Syndrome caused by a mutation in the ASXL3 gene. The patient's epilepsy began on the second day of life, presenting with focal seizures characterized by ocular and cervical version. She was started on phenobarbital during the first month of life. Over the years, the seizure semiology evolved, with the patient exhibiting hypotonia and developing seizures frequently triggered by head trauma. These episodes often required hospitalization and treatment with hydantoins, as they escalated to recurrent tonic-clonic seizures. A transition to carbamazepine provided partial seizure control, with episodes occurring mainly during infectious illnesses. However, switching to valproate led to status epilepticus, necessitating a change in the treatment regimen. Approximately nine years ago, the patient was started on oxcarbazepine, which she continues to use. Seizures are now predominantly triggered by traumatic brain injury (TBI) or non-febrile infections. The patient has experienced significant neurodevelopmental delays, including severe psychomotor delay, hypotonia, ataxia, lack of speech development, and stereotypic behaviors. Magnetic resonance imaging (MRI) revealed cerebellar atrophy, and video-electroencephalography (VEEG) showed left posterior temporal paroxysms. Seizures occur more frequently during winter months, averaging one

episode per month during this time. The patient's therapeutic history includes trials of multiple antiepileptic drugs. Given the refractory nature of the seizures and the patient's clinical complexity, vagus nerve stimulation (VNS) has been proposed as a therapeutic strategy. The current treatment plan includes maintaining oxcarbazepine at 600 mg in the morning and 900 mg at night, continuing clobazam (10 mg once daily). Discussion: Heterozygous, de novo loss-of-function mutations in ASXL3, which underlie Bainbridge-Ropers syndrome (BRPS; OMIM #615485), have been scarcely described. The major phenotypic features reported in most patients include failure to thrive, global developmental delay, feeding difficulties, hypotonia, dysmorphic features, profound speech delay, and intellectual disability. Seizures and structural malformations of internal organs, including the brain and kidneys, do not appear to be predominant features of the phenotype. However, this may be subject to revision or expansion as more cases of BRPS are identified and described. Final Comments: This case highlights the challenges of managing epilepsy in patients with neurodevelopmental syndromes, particularly in the context of refractory seizures, multiple AED intolerances, and significant comorbidities. Bainbridge-Ropers Syndrome adds complexity to the clinical picture, necessitating a multidisciplinary approach to optimize seizure control and improve quality of life.

**Palavras-Chave do trabalho:** Antiepileptic; Cerebellar atrophy; epilepsy;

**ID do trabalho:** 283

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## **Título do Trabalho: DIAGNOSTIC CHALLENGE: CADASIL OR MYOTONIC DYSTROPHY TYPE 1?**

**Autores:** BANDEIRA, Gustavo Marques<sup>1</sup>; FUSSINGER, Helena<sup>1</sup>; HENRICH, Katyaline Gustavo<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade do Vale do Rio dos Sinos - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

**ABSTRACT:** A 60-year-old female patient initially diagnosed with CADASIL (variant c.3691C>T in exon 22 of the NOTCH3 gene) presented with clinical features inconsistent with the disease. She exhibited mild facial weakness, muscle atrophy, and alopecia, with a family history suggestive of myotonic dystrophy type 1 (DM1). Her brother had a confirmed DM1 diagnosis, myotonic discharges on electromyography, and a history of cataract surgery. The patient's own electromyography revealed widespread myotonic discharges. However, molecular testing for DM1 and DM2 was negative, raising questions about the correct diagnosis. Although the patient's MRI findings were suggestive of CADASIL, she lacked key clinical features such as ischemic strokes, migraines, or dementia. White matter hyperintensities in the anterior temporal lobes, common in CADASIL, have also been documented in DM1, complicating the differentiation. Literature from the Hospital de Clínicas de Porto Alegre (HCPA) supports that MRI abnormalities in DM1 are more common than previously thought. Given her clinical presentation—facial weakness, family history, and electromyographic findings—DM1 remained the most plausible diagnosis. Additionally, the NOTCH3 variant initially classified as pathogenic was later reclassified as benign, emphasizing the importance of genetic reassessment in complex cases. Neuroimaging alone is not sufficient to distinguish between CADASIL and DM1, as both may present with anterior temporal white matter lesions. Electromyographic findings are crucial for diagnosing DM1, even when genetic testing is inconclusive. Genetic reclassification can impact diagnosis, as seen in this case with the NOTCH3 variant. A thorough clinical evaluation remains essential in distinguishing CADASIL from DM1, preventing misdiagnosis and ensuring appropriate management. Reference: Liu B, Yang CL, Li XL, Zhang M, Li YB, Duan RS. CADASIL-like leukodystrophy and symptomatic cerebral infarction in myotonic dystrophy type 1. *CNS Neurosci Ther.* 2022 Oct;28(10):1655-1657. doi: 10.1111/cns.13908. Epub 2022 Jul 3. PMID: 35785420; PMCID: PMC9437229.

**Palavras-Chave do trabalho:** CADASIL; Electromyography; genetic diagnosis; Myotonic Dystrophy Type 1; White Matter Hyperintensities;

**ID do trabalho:** 284

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Relatos de Caso

**Forma de apresentação:** Pôster

## **Título do Trabalho: HETEROZYGOUS PRKN FRAMESHIFT VARIANT IN EARLY-ONSET PARKINSON'S DISEASE: UNRAVELING DIAGNOSTIC COMPLEXITY AND THERAPEUTIC SUCCESS WITH STN-DBS**

**Autores:** NEPOMUCENO, Camila Rodrigues<sup>1</sup>; LEATI, Maria Fernanda Hamamoto<sup>1</sup>; MENDES FILHO, Antonio Avelino<sup>1</sup>; DE LUCENA, Larissa Neves<sup>1</sup>; MESIAS, Andre Vinicio Cruz<sup>1</sup>; SENTO-Sé NETO, Heitor Nunes de Oliveira<sup>1</sup>; MORENO, Cristiane de

Araujo Martins<sup>1</sup>; DE FREITAS, Julian Leticia<sup>1</sup>; ROCHA, Maria Sheila Guimaraes<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital Santa Marcelina - São Paulo - SP - Brasil;

**Resumo do trabalho:**

Case Report: A 30-year-old woman with no significant medical history presented with a progressive neurological disorder manifesting at age 23. Initial symptoms included a left-sided resting tremor, followed by development of lower limb rigidity and gait disturbances. By age 27, she has first episode of freezing of gait (FOG), accompanied by recurrent falls over subsequent weeks. Neurological examination at presentation demonstrated bradykinesia, asymmetric rigidity and postural instability, consistent with parkinsonism. A therapeutic trial of levodopa elicited marked motor improvement, supporting a provisional diagnosis of early-onset Parkinson's disease (EOPD). Brain MRI revealed no evidence of basal ganglia abnormalities or iron accumulation, and metabolic panels ruled out secondary causes. Whole-exome sequencing identified a heterozygous pathogenic frameshift variant in the PRKN gene (NM\_004562.2: c.155delA, p.[Asn52Metfs\*29]), confirming molecular diagnosis of PRKN-associated EOPD. The variant was absent in population databases (gnomAD), and no consanguinity or family history of neurodegenerative disorders was reported. At age 30, due to wearing-off motor fluctuations and medication-refractory FOG, the patient underwent bilateral subthalamic nucleus deep brain stimulation (STN-DBS) resulting in significant resolution of tremor, dystonia, and FOG. Discussion: The PRKN-associated EOPD is a recessive form of parkinsonism linked to impaired ubiquitin-mediated proteolysis and mitochondrial dysfunction. Frameshift mutations in PRKN typically result in premature protein truncation, consistent with loss-of-function mechanisms observed in parkin-related disease. While biallelic PRKN mutations are classically associated with early-onset, levodopa-responsive parkinsonism, our patient's heterozygous variant raises questions about potential digenic inheritance or unmasked recessive alleles, warranting further parental segregation analysis. The patient's robust levodopa response aligns with the characteristic phenotype of PRKN-EOPD, which often demonstrates sustained dopaminergic sensitivity compared to idiopathic PD. TN-DBS efficacy in PRKN carriers remains debated, with some studies reporting superior motor outcomes compared to LRRK2-PD. Our patient's postoperative improvement supports recent evidence that DBS benefits in PRKN-EOPD correlate with preserved cortical-basal ganglia-thalamocortical loop integrity. The reduction in levodopa requirements post-DBS further aligns with reports of reduced dyskinesia risk in monogenic PD subtypes. Final Comments: PRKN screening is warranted in patients with onset <40 years, asymmetric levodopa-responsive parkinsonism even without family history. PRKN carriers may derive durable benefit from DBS, particularly when medication-refractory FOG impacts quality of life. Further studies are needed to clarify the pathogenicity of heterozygous PRKN variants and optimize neuromodulation strategies in monogenic PD.

**Palavras-Chave do trabalho:** Early-onset Parkinson's disease; PRKN; Subthalamic Nucleus Deep Brain Stimulation;

**ID do trabalho:** 285

**Área Técnica do trabalho:** Outros

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: WHEN SIMPLICITY WORKS: THE IMPACT OF QUALITATIVE TESTING ON ACUTE INTERMITTENT PORPHYRIA DETECTION IN PIAUÍ**

**Autores:** KARPEJANY, Natalia Rebeca Alves de Araújo<sup>1</sup>; PEREIRA, Ester Miranda<sup>2</sup>; DA COSTA, Renato Fernandes<sup>2</sup>; NETO, José Tibúrcio do Monte<sup>2</sup>; SOUSA, Ian Jhemes Oliveira<sup>2</sup>; DA SILVA, Adalberto Socorro<sup>2</sup>; DO MONTE, Semiramis Jamil Hadad<sup>2</sup>;

**Instituição dos Autores:** (1) Hospital Universitário da Universidade Federal do Piauí - Teresin - PI - Brasil; (2) Universidade Federal do Piauí - Teresina - PI - Brasil;

**Resumo do trabalho:**

BACKGROUND: Rare diseases affect approximately 13 million people in Brazil. They are mostly genetic, progressive, and difficult to diagnose, leading to severe complications and significant emotional and financial impacts. The National Policy for Comprehensive Care for People with Rare Diseases aims to improve access to diagnosis and treatment but faces challenges such as a lack of specialized centers and trained professionals, especially in states like Piauí and Maranhão. Biochemical screening and early diagnosis are essential to prevent complications. In Piauí, the implementation of PBG detection at Biology Laboratory of the Federal University of Piauí (LIB-UFPI) represents progress in diagnosing Acute Intermittent Porphyria and other rare diseases. OBJECTIVE: To describe the implementation and standardization of the qualitative porphobilinogen (PBG) test at LIB-UFPI, aimed at diagnosing Acute Intermittent Porphyria (AIP). METHODS: The Ehrlich test for detecting PBG in urine was standardized and implemented by optimizing the Ehrlich reagent and validating the protocol to ensure specificity and reproducibility. To minimize false positives caused by urobilinogen, a confirmatory step with chloroform was incorporated, improving test reliability. Meetings were held with healthcare professionals to raise awareness about AIP, its symptoms, and management. Informational materials were distributed, and a workflow was established for sample collection, storage, and transport to the laboratory. The test was implemented with results available within 48 hours, enabling prompt interventions. This study was approved by the ethics committee. RESULTS: In five months, the test was crucial in diagnosing six patients with AIP, representing 42.8% of the 14 individuals referred for testing. All positive cases exhibited typical symptoms, and there was evidence of previously undiagnosed familial cases. Family screening proved essential, as one patient reported the death of a sister with compatible symptoms who had not been diagnosed during her lifetime. Additionally, 57.2% of those tested had negative results, reinforcing the test's role not only in confirming AIP but also in ruling out the disease, guiding further

investigation into other possible causes. The impact of this initiative extends beyond individual diagnosis, promoting genetic screening, early management. **CONCLUSION:** The standardization of the Ehrlich test enabled the provision of an accessible diagnostic tool in a region with limited resources.

**Palavras-Chave do trabalho:** acute intermittent porphyria; Diagnosis; Neuromuscular Disease;

**ID do trabalho:** 286

**Área Técnica do trabalho:** Neurodesenvolvimento

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## **Título do Trabalho: NEW PHENOTYPE AND DISEASE MACHANISM ASSOCIATED WITH ATAD3A GENE?**

**Autores:** KRUM, Vitoria<sup>1</sup>; FERNANDES, Eduarda Rosa<sup>1</sup>; NAGATA, Glauco<sup>1</sup>; HAUBRICH, Carolina Heck<sup>1</sup>; DEVENS, Leticia Bassani<sup>1</sup>; VERZA, Caroline Schiochet<sup>1</sup>; FUSSIGER, Helena<sup>1</sup>;

**Instituição dos Autores:** (1) Hospital São Lucas da PUCRS - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

Case Report: A 31-year-old woman was born with congenital cataracts, which required multiple surgeries. Symptoms, such as imbalance and difficulty walking, were first noted at 8 years old, and at 29, she developed cerebellar ataxia syndrome, starting with dysphagia, followed by speech and gait ataxia. These symptoms gradually progressed to the point where she was unable to walk without support. Her brother also exhibited similar neurological symptoms, suggesting autosomal recessive inheritance. Neurological examination revealed mild dysarthria, spontaneous and multidirectional nystagmus, hyperreflexia with clonus, a positive Babinski sign on the left, palatal myoclonus, dysidiadochokinesia and dysmetria. Brain magnetic resonance imaging (MRI) showed hyperintensity with an expansile effect in the inferior olive nuclei, suggesting hypertrophic olivary degeneration. Recessive ataxia panel testing identified a likely pathogenic variant in the POLG gene, but exome sequencing of both siblings revealed two variants in the ATAD3A gene: a nonsense loss-of-function variant (c.731G>A p.(Trp224\*)) and a missense variant of uncertain significance (c.229C>G p.(Leu77Val)). These were found in compound heterozygous form. The same POLG variant was present in both siblings and their asymptomatic mother. Discussion: Mitochondrial disorders are caused by mutations in mitochondrial DNA or nuclear genes, leading to various diseases, including neurodegenerative, cardiovascular, and neurometabolic disorders. ATAD3 is a mitochondrial protein involved in membrane dynamics, though its full function remains unclear. Mutations in ATAD3A are linked to neurodevelopmental disorders, including developmental delay, hypotonia, cardiomyopathy, cataracts, and cerebellar atrophy. The ATAD3A gene is linked to both autosomal recessive diseases, caused by the absence of gene product (two loss-of-function variants in trans), and autosomal dominant diseases. In this case report, we describe a unique phenotype, including congenital cataracts, infantile walking difficulties, and adult-onset spinocerebellar ataxia, not typically associated with ATAD3A mutations. Whole exome sequencing identified a compound heterozygous variant with a loss-of-function mutation and a missense variant, p.Leu77Val, which partially affects protein function. This variant, though present in healthy individuals, was found in combination with another loss-of-function mutation, leading to a phenotype similar to the one described. Final Comments: This report brings more evidence to the possibility of a different phenotype related to the ATAD3A gene due to a different disease mechanism. Mitochondrial disorders, particularly those associated with mutations in the ATAD3A gene, reveal significant complexities both in clinical manifestations and in the pathological pathways involved. A detailed understanding of these mutations and their consequences is critical for advancing the diagnosis and treatment of mitochondrial diseases.

**Palavras-Chave do trabalho:** ATAD3; mitochondrial diseases; spinocerebellar ataxia;

**ID do trabalho:** 287

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: LATE-ONSET GM2 GANGLIOSIDOSIS DUE TO MUTATIONS IN GM2A GENE MIMICKING SPINAL MUSCULAR ATROPHY TYPE 3**

**Autores:** MENDONCA, Rodrigo Holanda<sup>1</sup>; GURGEL-JIANETTI, JULIANA<sup>2</sup>; GRATIVVOL, RONNYSON<sup>3</sup>; ZANOTELI, Edmar<sup>4</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas da Faculdade de Medicina da USP - Sao Paulo - SP - Brasil; (2) Departamento de Pediatria Universidade Federal de Minas Gerais - Belo Horizonte - MG - Brasil; (3) Universidade Federal do Espírito Santo - Vitória - ES - Brasil; (4) Hospital das Clínicas da Faculdade de Medicina da USP - Sao Paulo - SP - Brasil;

**Resumo do trabalho:**

**Introduction:** Non-5q Spinal Muscular Atrophy (SMA) presents a diversity of genes described in the literature. Previously, GM2 gangliosidosis mimicking spinal muscular atrophy (related to mutations in the HEXA gene) was described. However, motor neuron disease related to mutations in the GM2A gene, which encodes a ganglioside activator protein, has not yet been described. Here, we describe a late-onset motor neuron disease phenotype mimicking SMA type 3 or 4, whose genetic investigation resulted in the finding of GM2A gene mutations. **Results:** Case 1 is a male, 36 years old, history of parental consanguinity. He started progressive proximal muscular weakness in lower limbs at ten years old—weakness presented with slow progression over the years to the scapular girdle. Clinical evaluation at that time with 15 years old showed a motor neuron disease, being diagnosed as Kugelberg Welander disease (SMA type 3). At that time, neurological evaluation was remarkable for the presence of preserved tendon reflexes in 4 limbs. Weakness progressed slowly, and the patient lost his gait around the third decade of life. At the age of 35, he presented proximal and distal muscle atrophy, and tendon reflexes are now abolished, with exuberant polyminimyoclonus on examination. Cognitive is normal. Molecular investigation for deletions in the SMN1 gene ruled out that it was 5q SMA - it had 02 SMN1 copies and 00 SMN2 copies. Exome sequencing revealed a homozygous missense mutation at position c.428G>A (p.Gly143Glu) in the GM2A gene. Case 2 is a female, 43 years old, started muscle weakness of proximal predominance, exclusively affecting the lower limbs, around ten years ago and with electroneuromyography indicating a neurogenic process restricted to the quadriceps femoris and gastrocnemius muscles bilaterally. MRI of the thighs and legs showed exclusive involvement of the quadriceps femoris and gastrocnemius muscles, with a neurogenic pattern. Exome NGS showed two variants in compound heterozygosity (p.Gly143Glu and p.Gly166Arg) in the GM2A gene. Case 3 is a male, 40 years old, adult-onset muscle weakness of the lower limbs, mimicking SMA type 3, and investigation with NGS also showed two variants in the GM2A gene (p.Gly166Arg and p.Asp116His). **Conclusion:** The three cases presented here have in common a late-onset motor neuron disease mimicking SMA 3, with preferential involvement of the quadriceps and recessive mutations in the GM2A gene.

**Palavras-Chave do trabalho:** GM2 Gangliosidosis; Motor neuron disease; Spinal Muscular Atrophy;

**ID do trabalho:** 288

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: SPINOCEREBELLAR ATAXIA TYPE 2 (SCA2) WITH CLINICAL ONSET IN CHILDHOOD: A CASE SERIES**

**Autores:** RIBEIRO, Giovana Barros e Silva<sup>1</sup>; COAN, Ana Carolina<sup>1</sup>; DE BORBA, Fabrício Castro<sup>1</sup>; JÚNIOR, Marcondes Cavalcante França<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade Estadual de Campinas - Campinas - SP - Brasil;

**Resumo do trabalho:**

**BACKGROUND:** Clinical features of Spinocerebellar Ataxia Type 2 (SCA2) usually begin in the fourth decade of life. However, a wide range of clinical presentations has been reported, from infancy to the eightieth decade of life. Infantile and juvenile onset of SCA2 symptoms are associated with larger trinucleotide (CAG) repeat sizes. **OBJECTIVE AND METHODS:** This study aimed to describe the clinical features of three patients with clinical onset of SCA2 in childhood. **RESULTS:** The patients began experiencing symptoms at the ages of 3, 4 and 7 years old, and the number of CAG repeats was 66, 78, and 58, respectively. Gait ataxia was the first clinical feature in two patients, while cerebellar tremor was the first symptom reported in the other. All patients developed loss of ambulation and dysphagia. Myoclonus was a prominent clinical feature in all patients; however, correlated epileptiform discharges were observed in only one individual. Sensory axonal neuropathy was observed in one patient. Cerebellar Cognitive Affective Syndrome (CCAS) was reported in one patient, and autism spectrum disorder (ASD)-associated behavior was observed in another one. All of the patients developed a progressive and severe cognitive impairment. Olivopontocerebellar atrophy (OPCA) was observed in one individual, while global cerebellar atrophy was described in the other two. All patients inherited the condition through paternal transmission. **CONCLUSION:** The phenotype of SCA2 is broad and anticipation is more prominent in paternal transmissions. Here, we describe three cases of paternal inheritance with beginning of symptoms in childhood and clinical features that include ataxia, nonepileptic and epileptic myoclonus, sensory axonal neuropathy and cognitive and behavioral impairment.

**Palavras-Chave do trabalho:** Myoclonus; SCA2; spinocerebellar ataxia;

**ID do trabalho:** 289

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Made in Brazil

**Forma de apresentação:** Pôster

## Título do Trabalho: **MARKED NEUROPSYCHIATRIC INVOLVEMENT AND DYSMORPHIC FEATURES IN NEMALINE MYOPATHY**

**Autores:** Nóbrega, Paulo Ribeiro<sup>1</sup>; DE SOUZA, Jorge Luiz de Brito<sup>2</sup>; MAURÍCIO, Rebeca Bessa<sup>2</sup>; DE PAIVA, Anderson Rodrigues Brandão<sup>3</sup>; DIAS, Daniel Aguiar<sup>1</sup>; LIMA, Pedro Lucas Grangeiro Sá Barreto<sup>1</sup>; CAMELO, Clara Gontijo<sup>3</sup>; ZANOTELLI, Edmar<sup>3</sup>; SCHLESINGER, David<sup>4</sup>; BRAGA-NETO, Pedro<sup>1</sup>; MORENO, Cristiane Araujo Martins<sup>3</sup>;

**Instituição dos Autores:** (1) Universidade Federal do Ceará - Fortaleza - CE - Brasil; (2) Universidade Estadual do Ceará - Fortaleza - CE - Brasil; (3) Universidade de São Paulo - São Paulo - SP - Brasil; (4) Mendelics Genomic Analysis - São Paulo - SP - Brasil;

### Resumo do trabalho:

Background: Nemaline myopathy is a neuromuscular disorder characterized by muscle weakness and developmental delays. Genetic mutations and cognitive impairments are often associated with this condition. Objective: To describe the clinical features, genetic findings, and cognitive assessments of two patients with nemaline myopathy. Methods: Clinical evaluations, genetic testing, electromyography (EMG), creatine kinase (CK) levels, forced vital capacity (FVC), and brain magnetic resonance imaging (MRI) were performed. Cognitive assessments included the Montreal Cognitive Assessment (MoCA) and the Childhood Autism Rating Scale (CARS). Results: Patient 1 was a 32-year-old male with no prenatal symptoms and no neonatal interventions. He started walking at 3 years with frequent falls and had delayed language development. His school performance was poor, and he had difficulty with basic mathematical calculations. MoCA score was 20/30, indicating impairment in attention, executive functions, and language domains. He was partially dependent for basic activities of daily living. Physical examination revealed short stature, brachydactyly, brachymetatarsia, pes cavus, rigid spine, myopathic face, high arched palate, and atrophic tongue. Genetic findings included NEB: c.2943G > A (synonymous) and c.8889 + 1G > A (splice donor). Patient 2 was a 7-year-old male with polyhydramnios and decreased fetal movements. He required tracheostomy and gastrostomy at 1 month. He achieved head support at 2 years, trunk support at 2.5 years, and walked unsupported at 4 years after foot deformity correction. He had instrumental language at 2 years but could not speak. His school performance was poor, and he could not recognize colors or numbers, nor read or write. MoCA score was 21/30, and CARS score was 41/60, indicating severe autism. He was dependent for basic activities of daily living. Physical examination showed scoliosis, myopathic face, high arched palate, and atrophic tongue. Genetic findings included ACTA1: c.169G > C (p.Gly57Arg). Conclusion: Both patients exhibited significant neuromuscular and cognitive impairments associated with nemaline myopathy. Genetic mutations in NEB and ACTA1 were identified, contributing to the understanding of the clinical manifestations and aiding in the diagnosis and management of the disorder.

**Palavras-Chave do trabalho:** Cognitive impairment; Genetic mutations; Nemaline myopathy;

**ID do trabalho:** 290

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## Título do Trabalho: **DIAGNOSTIC CHALLENGE: CADASIL OR MYOTONIC DYSTROPHY TYPE 1?**

**Autores:** BANDEIRA, Gustavo Marques<sup>1</sup>; FUSSINGER, Helena<sup>1</sup>; HENRICH, Katyaline<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade do Vale do Rio dos Sinos - Porto Alegre - RS - Brasil;

### Resumo do trabalho:

**ABSTRACT:** A 60-year-old female patient initially diagnosed with CADASIL (variant c.3691C>T in exon 22 of the NOTCH3 gene) presented with clinical features inconsistent with the disease. She exhibited mild facial weakness, muscle atrophy, and alopecia, with a family history suggestive of myotonic dystrophy type 1 (DM1). Her brother had a confirmed DM1 diagnosis, myotonic discharges on electromyography, and a history of cataract surgery. The patient's own electromyography revealed widespread myotonic discharges. However, molecular testing for DM1 and DM2 was negative, raising questions about the correct diagnosis. Although the patient's MRI findings were suggestive of CADASIL, she lacked key clinical features such as ischemic strokes, migraines, or dementia. White matter hyperintensities in the anterior temporal lobes, common in CADASIL, have also been documented in DM1, complicating the differentiation. Literature from the Hospital de Clínicas de Porto Alegre (HCPA) supports that MRI abnormalities in DM1 are more common than previously thought. Given her clinical presentation—facial weakness, family history, and electromyographic findings—DM1 remained the most plausible diagnosis. Additionally, the NOTCH3 variant initially classified as pathogenic was later reclassified as benign, emphasizing the importance of genetic reassessment in complex cases. Neuroimaging alone is not sufficient to distinguish between CADASIL and DM1, as both may present with anterior temporal white matter lesions. Electromyographic findings are crucial for diagnosing DM1, even when genetic testing is inconclusive. Genetic reclassification can impact diagnosis, as seen in this case with the NOTCH3 variant. A thorough clinical evaluation remains essential in distinguishing CADASIL from DM1, preventing misdiagnosis and ensuring appropriate management. Reference: Liu B, Yang CL, Li XL, Zhang M, Li YB, Duan RS. CADASIL-like leukodystrophy and symptomatic cerebral infarction in myotonic dystrophy type 1. CNS Neurosci Ther. 2022 Oct;28(10):1655-1657. doi: 10.1111/cns.13908. Epub 2022 Jul 3. PMID: 35785420; PMCID: PMC9437229.

**Palavras-Chave do trabalho:** CADASIL; Electromyography; genetic diagnosis; Myotonic Dystrophy Type 1; White Matter Hyperintensities;

**ID do trabalho:** 291

**Área Técnica do trabalho:** Doenças Neuromusculares

**Tipo do trabalho** Trabalhos Originais

**Forma de apresentação:** Pôster

## **Título do Trabalho: GENE THERAPY FOR SPINAL MUSCULAR ATROPHY WITH ONASEMNOGENE ABEPARVOVEC: A 4-YEAR REAL-LIFE FOLLOW-UP STUDY**

**Autores:** MENDONCA, Rodrigo Holanda<sup>1</sup>; ORTEGA, Adriana Banzato<sup>2</sup>; VAN DER LINDEN, Vanessa<sup>3</sup>; ZANOTELI, Edmar<sup>4</sup>;

**Instituição dos Autores:** (1) Hospital das Clínicas Faculdade de Medicina da USP - Sao Paulo - SP - Brasil; (2) Hospital Pequeno Príncipe - Curitiba - PR - Brasil; (3) Hospital Maria Lucinda - Recife - PE - Brasil; (4) Hospital das Clínicas da Faculdade de Medicina da USP - Sao Paulo - SP - Brasil;

### **Resumo do trabalho:**

**Introduction:** Gene therapy with Onasemnogene Apeparvovec (OA) has revolutionized the treatment of spinal muscular atrophy (SMA), marking a significant advancement in monogenic neuromuscular diseases. While its short-term efficacy is well established through randomized clinical trials and real-world studies, data on long-term effectiveness and late-onset adverse events remain limited. This study provides a 4-year follow-up of patients who underwent gene therapy in Brazil and were previously reported in an earlier study. **Objectives:** To evaluate the long-term efficacy, late complications, and the frequency of combination therapies (nusinersen or risdiplam) following gene therapy. **Methodology:** A retrospective, observational, non-interventional study was conducted. Statistical analysis was performed to identify factors associated with the initiation of combination therapy after gene therapy. **Results:** A total of 41 SMA patients were included, with 58.5% females and 80.1% diagnosed with SMA type 1. The mean age at gene therapy administration was  $18 \pm 6.4$  months. Prior to gene therapy, 87.8% (n=36) of patients were receiving nusinersen, and 24.4% (n=10) continued nusinersen post-gene therapy. A subset of patients maintained combination therapy for an average of 1 to 2 years post-infusion. No specific factor was identified as predictive of combination therapy use. Over the 4-year follow-up period, no new adverse events were reported, aside from transient transaminase elevations during the initial post-treatment period. Gene therapy demonstrated sustained efficacy in SMA patients, and the addition of nusinersen post-gene therapy did not appear to provide further motor function gains. **Conclusion:** This 4-year real-world study confirms the long-term effectiveness of gene therapy in SMA. No late-onset adverse events were identified beyond those already expected in the early post-infusion phase. Additionally, combination therapy with nusinersen did not show a significant impact on motor function outcomes, suggesting that gene therapy alone may be sufficient for long-term disease management.

**Palavras-Chave do trabalho:** Gene therapy; SMN1; Spinal Muscular Atrophy;

**ID do trabalho:** 292

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## **Título do Trabalho: DIAGNOSTIC CHALLENGE: CADASIL OR MYOTONIC DYSTROPHY TYPE 1?**

**Autores:** BANDEIRA, Gustavo Marques<sup>1</sup>; FUSSINGER, Helena<sup>1</sup>; HENRICH, Katyaline<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade do Vale do Rio dos Sinos - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

**ABSTRACT:** A 60-year-old female patient initially diagnosed with CADASIL (variant c.3691C>T in exon 22 of the NOTCH3 gene) presented with clinical features inconsistent with the disease. She exhibited mild facial weakness, muscle atrophy, and alopecia, with a family history suggestive of myotonic dystrophy type 1 (DM1). Her brother had a confirmed DM1 diagnosis, myotonic discharges on electromyography, and a history of cataract surgery. The patient's own electromyography revealed widespread myotonic discharges. However, molecular testing for DM1 and DM2 was negative, raising questions about the correct diagnosis. Although the patient's MRI findings were suggestive of CADASIL, she lacked key clinical features such as ischemic strokes, migraines, or dementia. White matter hyperintensities in the anterior temporal lobes, common in CADASIL, have also been documented in DM1, complicating the differentiation. Literature from the Hospital de Clínicas de Porto Alegre (HCPA) supports that MRI abnormalities in DM1 are more common than previously thought. Given her clinical presentation—facial weakness,

family history, and electromyographic findings—DM1 remained the most plausible diagnosis. Additionally, the NOTCH3 variant initially classified as pathogenic was later reclassified as benign, emphasizing the importance of genetic reassessment in complex cases. Neuroimaging alone is not sufficient to distinguish between CADASIL and DM1, as both may present with anterior temporal white matter lesions. Electromyographic findings are crucial for diagnosing DM1, even when genetic testing is inconclusive. Genetic reclassification can impact diagnosis, as seen in this case with the NOTCH3 variant. A thorough clinical evaluation remains essential in distinguishing CADASIL from DM1, preventing misdiagnosis and ensuring appropriate management. Reference: Liu B, Yang CL, Li XL, Zhang M, Li YB, Duan RS. CADASIL-like leukodystrophy and symptomatic cerebral infarction in myotonic dystrophy type 1. *CNS Neurosci Ther.* 2022 Oct;28(10):1655-1657. doi: 10.1111/cns.13908. Epub 2022 Jul 3. PMID: 35785420; PMCID: PMC9437229.

**Palavras-Chave do trabalho:** CADASIL; Electromyography; genetic diagnosis; Myotonic Dystrophy Type 1; White Matter Hyperintensities;

**ID do trabalho:** 293

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## **Título do Trabalho: DIAGNOSTIC CHALLENGE: CADASIL OR MYOTONIC DYSTROPHY TYPE 1?**

**Autores:** BANDEIRA, Gustavo Marques<sup>1</sup>; FUSSINGER, Helena<sup>1</sup>; HENRICH, Katyaline<sup>1</sup>;

**Instituição dos Autores:** (1) Universidade do Vale do Rio dos Sinos - Porto Alegre - RS - Brasil;

### **Resumo do trabalho:**

**ABSTRACT:** A 60-year-old female patient initially diagnosed with CADASIL (variant c.3691C>T in exon 22 of the NOTCH3 gene) presented with clinical features inconsistent with the disease. She exhibited mild facial weakness, muscle atrophy, and alopecia, with a family history suggestive of myotonic dystrophy type 1 (DM1). Her brother had a confirmed DM1 diagnosis, myotonic discharges on electromyography, and a history of cataract surgery. The patient's own electromyography revealed widespread myotonic discharges. However, molecular testing for DM1 and DM2 was negative, raising questions about the correct diagnosis. Although the patient's MRI findings were suggestive of CADASIL, she lacked key clinical features such as ischemic strokes, migraines, or dementia. White matter hyperintensities in the anterior temporal lobes, common in CADASIL, have also been documented in DM1, complicating the differentiation. Literature from the Hospital de Clínicas de Porto Alegre (HCPA) supports that MRI abnormalities in DM1 are more common than previously thought. Given her clinical presentation—facial weakness, family history, and electromyographic findings—DM1 remained the most plausible diagnosis. Additionally, the NOTCH3 variant initially classified as pathogenic was later reclassified as benign, emphasizing the importance of genetic reassessment in complex cases. Neuroimaging alone is not sufficient to distinguish between CADASIL and DM1, as both may present with anterior temporal white matter lesions. Electromyographic findings are crucial for diagnosing DM1, even when genetic testing is inconclusive. Genetic reclassification can impact diagnosis, as seen in this case with the NOTCH3 variant. A thorough clinical evaluation remains essential in distinguishing CADASIL from DM1, preventing misdiagnosis and ensuring appropriate management. Reference: Liu B, Yang CL, Li XL, Zhang M, Li YB, Duan RS. CADASIL-like leukodystrophy and symptomatic cerebral infarction in myotonic dystrophy type 1. *CNS Neurosci Ther.* 2022 Oct;28(10):1655-1657. doi: 10.1111/cns.13908. Epub 2022 Jul 3. PMID: 35785420; PMCID: PMC9437229.

**Palavras-Chave do trabalho:** CADASIL; Electromyography; genetic diagnosis; Myotonic Dystrophy Type 1; White Matter Hyperintensities;

**ID do trabalho:** 294

**Área Técnica do trabalho:** Transtornos do movimento

**Tipo do trabalho** Casos Clínicos Desafiadores

**Forma de apresentação:** Apresentação Oral

## **Título do Trabalho: LIPODYSTROPHY AND LATE-ONSET DYSTONIA – SOLVING AN OCCAM'S RAZOR RIDDLE**

**Autores:** SILVA, ELIS VANESSA DE LIMA<sup>1</sup>; SOARES, MARCONE CRUZ MORENO<sup>2</sup>; PESSOA, BIANCA PORTELA TELES<sup>3</sup>; DA SILVA, MARI-NILVA MAIA<sup>3</sup>;

**Instituição dos Autores:** (1) HOSPITAL INFANTIL DR. JUVÊNCIO MATTOS - São Luís - MA - Brasil; (2) iNeuron - Referência em Cérebro e Coluna - São Luís - MA - Brasil; (3) HOSPITAL NINA RODRIGUES - SÃO LUÍS - MA - Brasil;

**Resumo do trabalho:**

**Case Presentation:** A 21-year-old female with a prior clinical diagnosis of lipodystrophy and normal neuropsychomotor development, began experiencing blepharospasm and oromandibular dyskinesia after a traumatic event at 18 years old. She was initially referred for a psychiatric evaluation, however her symptoms progressively worsened, leading to severe blepharospasm, jaw opening and tongue dystonia, choreic movements, parkinsonian gait, and malnutrition. She is the only child of non-consanguineous parents, with no family history of lipodystrophy or dystonia. Laboratory tests, including lipid profile, glucose, and insulin, were all within normal ranges. Brain MRI revealed diffuse brain atrophy. After attempts to clarify the neurological condition as a complication of lipodystrophy, malnutrition, and possible hypovitaminosis, the patient was referred for genetic evaluation, and underwent a hypertriglyceridemia NGS panel, which revealed two presumed compound heterozygous variants in BSCL2: the pathogenic chr11:62.694.680 G>GT (c.517dup) and a likely pathogenic intragenic deletion encompassing exon 11 and 3'UTR, with breakpoints chr11:62.689.681–chr11:62.690.523. **Discussion:** BSCL2 pathogenic variants are associated with several phenotypes, including Seipinopathies, Berardinelli-Seip syndrome, and Progressive Encephalopathy, with or without lipodystrophy (PELD) or Celia's encephalopathy. PELD is an ultra-rare, autosomal recessive neurodegenerative disease characterized by neurological regression, spasticity, ataxia, tremors, dystonia, and sometimes lipodystrophy. It typically begins in the first years of life, progresses rapidly, and results in death during the first decade of life. PELD was first described in 2013, with fewer than 30 published cases. It is classically caused by the c.985C>T variant in exon 7 of the BSCL2 gene, although other variants, such as 974dupG, 1076dupC, 1048C>T, and 566T>A, have also been reported. The proposed pathophysiological mechanism involves a gain of toxic seipin function, leading to endoplasmic reticulum dysfunction. Some reports suggest that neurological symptoms may respond to metreleptin treatment; however, treatment was not initiated in this patient due to severe malnutrition. **Final comments:** This report highlights the diagnostic challenge posed by the combination of lipodystrophy and late-onset encephalopathy, initially presenting with orofacial dystonia, in an atypical case of PELD. Additionally, the identification of a novel BSCL2 variant with an unclear pathogenic mechanism further complicates the diagnosis, emphasizing the need for further research into the RNA and protein assembly of BSCL2 to enhance our understanding of this disorder.

**Palavras-Chave do trabalho:** BSCL2; Celia Encephalopathy; Lipodystrophy; Orofacial Dystonia; PELD;

**ID do trabalho:** 295

**Área Técnica do trabalho:** Epilepsia

**Tipo do trabalho:** Casos Clínicos Desafiadores

**Forma de apresentação:** Pôster

## **Título do Trabalho: WHEN IN A DIAGNOSTIC DEAD END, GO BACK TO SQUARE ONE: A CASE OF EPILEPTIC ENCEPHALOPATHY, METABOLIC ACIDOSIS AND NEGATIVE WES**

**Autores:** SILVA, ELIS VANESSA DE LIMA<sup>1</sup>; ALMEIDA, BIANCA ALVARES<sup>2</sup>; DORIQUEI, MARIA JULIANA RODOVALHO<sup>1</sup>;

**Instituição dos Autores:** (1) HOSPITAL INFANTIL DR. JUVÊNCIO MATTOS - SÃO LUÍS - MA - Brasil; (2) HOSPITAL UNIVERSITÁRIO DA UNIVERSIDADE FEDERAL DO MARANHÃO - UNIDADE MATERNO-INFANTIL - SÃO LUÍS - MA - Brasil;

**Resumo do trabalho:**

**Case Presentation:** A 4-year-old girl with developmental delay noticed at 3 months and refractory epilepsy starting at 6 months required ICU admission at 8 months for seizure management. Blood gas analysis showed metabolic acidosis with an increased anion gap. Brain CT was normal, EEG showed a burst suppression pattern, and metabolic evaluation was unavailable. She is the only child of consanguineous parents, with no family history of epilepsy, and was born at term after an uneventful pregnancy. Initial whole exome sequencing (WES) was negative. She was discharged with partially controlled seizures on sodium bicarbonate for acidosis management. During follow-up, her mother noted that temperatures >36.5°C triggered seizures, while immersion in cool water improved symptoms. Brain MRI at 1 year revealed brain atrophy, diffuse corpus callosum thinning, and hippocampal volume reduction. Metabolic evaluation, including acylcarnitine and urine organic acid profiles, was normal. Exam showed profound developmental delay, hypotonia, normal deep tendon reflexes, achilles clonus, myoclonic jerks, and dyskinetic movements. Physical examination revealed profound developmental delay, hypotonia, normal deep tendon reflexes, achilles tendon clonus, and myoclonic jerks with dyskinetic movements. After two years, WES reanalysis identified a homozygous, likely pathogenic variant in FGF12 (NM\_004113.6: c.124+1G>T). The epilepsy remains refractory to all tested antiepileptic drugs, including valproic acid, phenobarbital, levetiracetam, topiramate, clobazam and phenytoin. Valproate treatment worsened seizure and there was a brief response to cannabidiol for 6 months. **Discussion:** FGF12 encodes fibroblast growth factor homologous factor 1 (FHF1), a voltage-gated sodium channel (Nav)-binding protein, essential for neuronal function. Navs have been linked to severe genetic epileptic encephalopathies, as well as heterozygous gain-of-function variants in FGF12 have been associated with early-onset epileptic encephalopathies with refractory seizures and progressive neurological deterioration. However, biallelic loss-of-function variants have only recently been linked to intractable seizures and profound developmental delay in just two case reports (Otori et al., 2023). In this report, we describe a novel homozygous, likely pathogenic, loss-of-function FGF12 variant, and provide further clinical description for the biallelic loss of function phenotype. **Final Comments:** This case underscores the importance of WES reanalysis and literature review in solving diagnosis in epilepsy. Since the FGF12 c.124+1G>T variant preserves the reading frame, further RNA studies and functional assays would be valuable to confirm the biallelic loss-of-function mechanism. Additionally, this case raises significant discussion regarding the treatment of refractory epilepsies.

**Palavras-Chave do trabalho:** Epileptic Encephalopathy; FGF12; Seizures; WES reanalysis;