REVISTA NEUROCIÊNCIAS

Relato de Caso

Juvenile amyotrophic lateral sclerosis: case report

Esclerose lateral amiotrófica juvenil: relato de caso

Esclerosis lateral amiotrófica juvenil: reporte de caso

Caroline Frucci[1], Paola Peres Freire[1], Lucas Porto Ferreira[2], Ana Clara Rodrigues Santos[3], Luiza Serafini Balestrassi[2]

1.Students at the Itajubá School of Medicine. Itajubá-MG, Brazil.
2.Neurologist and Professor at the Itajubá School of Medicine. Itajubá-MG, Brazil.
3.Resident Physician in Neurology at the Itajubá Clinical Hospital. Itajubá-MG, Brazil.

Resumo

Introdução. A esclerose lateral amiotrófica (ELA) juvenil é uma doença neurodegenerativa rara que acomete o neurônio motor superior (NMS) e/ou o neurônio motor inferior (NMI) antes dos 25 anos de idade. O desenvolvimento clínico e prognóstico da doença estão diretamente relacionados ao gene acometido, sendo de progressão lenta e curso indolente, na maioria dos casos. **Relato de Caso**. Neste estudo, descreveu-se o caso de uma paciente que apresentou dificuldade para deambular e fraqueza muscular a partir dos quatro anos de idade, evoluindo com discreta piora aos 14 anos, tendo o diagnóstico confirmado por teste genético com mutação no gene SETX. O objetivo foi fornecer o relato de uma doença pouco comum, evidenciando os sintomas característicos relacionados ao tipo de mutação e sua progressão. **Conclusão**. A ELA juvenil deve ser lembrada como diagnóstico diferencial, pois implica na necessidade de uma abordagem multidisciplinar para manutenção da qualidade física, psíquica e social do paciente.

Unitermos. Doenças do Sistema Nervoso; Degeneração neural; Esclerose Lateral Amiotrófica

Abstract

Introduction. Juvenile amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease that affects the upper motor neuron (UMN) and/or the lower motor neuron (LMN) before the age of 25. The clinical development and prognosis of the disease are directly related to the affected gene, with slow progression and an indolent course in most cases**. Case Report**. This study describes the case of a patient who presented difficulty walking and muscle weakness from the age of four, progressing with slight worsening at the age of 14, and whose diagnosis was confirmed by genetic testing for a mutation in the SETX gene. The objective was to report an uncommon disease, highlighting the characteristic symptoms related to the type of mutation and its progression. **Conclusion**. Juvenile ALS should be considered as a differential diagnosis, as it implies the need for a multidisciplinary approach to maintain the patient's physical, psychological and social well-being.

Keywords. Diseases of the Nervous System; Neural Degeneration; Amyotrophic lateral sclerosis

Resumen

Introducción. La esclerosis lateral amiotrófica juvenil (ELA) es una enfermedad neurodegenerativa rara que afecta a la motoneurona superior (SMN) y/o a la motoneurona inferior (LMN) antes de los 25 años. El desarrollo clínico y pronóstico de la enfermedad está directamente relacionado con el gen afectado, con progresión lenta y curso indolente, en la mayoría de los casos. **Reporte de Caso**. En este estudio se describió el caso de una paciente que presentó dificultad para caminar y debilidad muscular desde los cuatro años, evolucionando con ligero empeoramiento a los 14 años, confirmándose el diagnóstico mediante prueba genética con mutación en el gen SETX. El objetivo era brindar un informe sobre una enfermedad poco común, destacando los síntomas característicos relacionados con el tipo de mutación y su progresión. **Conclusión**. La ELA juvenil debe recordarse como un

diagnóstico diferencial, ya que implica la necesidad de un abordaje multidisciplinar para mantener la calidad física, psicológica y social del paciente.
Palabras clave. Enfermedades del Sistema Nervioso; Degeneración neuronal; Esclerosis lateral amiotrófica

Research developed at Hospital das Clínicas de Itajubá. Itajubá-MG, Brazil.

Conflict of interest: no Received in: 03/13/2024 Accept in: 06/05/2024

Corresponding address: Luiza S Balestrassi. Hospital das Clínicas de Itajubá. R. Miguel Viana 420. Morro Chic. Itajubá-MG, Brazil. CEP 37500-080. Email: lbalestrassi@hotmail.com

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurological disease resulting from the degeneration of upper (UMN) and lower (LMN) motor neurons that typically develops during the sixth or seventh decade of life and is diagnosed based on standard clinical criteria. The disease may occur more frequently within certain families, often in association with specific genomic mutations, while some sporadic cases have been associated with environmental toxins or trauma[1].

Treatment consists of supportive measures based on controlling the main symptoms, such as sialorrhea, emotional lability, sleep disorders, fatigue, muscle spasticity, constipation, laryngospasm, respiratory failure[2], dysphagia[3] and anarthria[4]. Approximately 30% of individuals may also present cognitive alterations, mainly related to deficits in fluency, language, executive function and memory[5]. Several medications are being studied, but their use is still in the experimental phase. However, the only specific drug approved actually is Riluzole, whose expected result is a delay in use of a ventilator or tracheostomy, increasing survival by three to five months[6].

Juvenile ALS is a subtype of classical ALS, with few cases described in the medical literature, which makes it difficult to quantify its incidence and prevalence. Thus, juvenile ALS can be defined as a rare neurodegenerative disorder that begins before the age of 25 and causes degeneration of the UMN and LMN. Its clinical development and prognosis are directly related to theaffected gene, with slow progression and an indolent course in most cases[7].

The most common genetic mutations associated with juvenile ALS are: FUS; SETX; and ALS2. In familial cases, FUS and ALS2 gene mutations are mainly autosomal recessive, whereas SETX mutations are autosomal dominant[7]. A heterozygous pathogenic variant of the SETX4 gene has the following clinical features: initially, slowly progressive weakness and atrophy of the muscles of the upper and lower extremities. In addition, hyperreflexia, clonus, and plantar extension cutaneous reflexes may be present. To date, sensory disturbances have been reported in a few patients. Thus, the aim of this article was to report a clinical case of juvenile ALS associated with a mutation in the SETX gene, with early onset of symptoms.

CASE REPORT

CEP#6.252.320; Plataforma Brasil CAAE #67166622.8.0000.5559. The Informed Consent Form was signed by the participant's legal guardians, and the Assent Form was signed by the participant herself, ensuring her

understanding and agreement to collaborate with the study.

A 14-year-old white female student from Itajubá, Minas Gerais, who came from Maria da Fé, Minas Gerais, sought care at the neurology clinic reporting difficulty walking for approximately 10 years. She reported that at the age of four she began to experience weakness in her lower limbs, more intense on the right, associated with falls, especially when running and performing physical exertion. She began to walk on tiptoe and avoid such activities. The patient denies any progression of symptoms until the age of 12, when falls became more frequent. In addition, she denies diplopia, dysphagia, weakness in the upper limbs, dyspnea, or any other associated symptoms.

The patient was born at term, exclusively breastfed until six months of age, with no perinatal complications and normal neuropsychomotor development. There is no personal history of serious illnesses, trauma, adverse reactions to vaccination, muscle pain or hospitalizations.

Family history shows that his mother, aged 43, has had a similar clinical condition of difficulty walking since she was seven years old, with no worsening to date. His father, aged 45, is healthy. He has two paternal sisters, one of whom died at the age of 18 from external causes and the other, aged three, with no comorbidities. There are no reports of neuromuscular symptoms or neurological diseases in grandparents, uncles, and first cousins on his mother's or father's side, and there is no consanguinity in the family.

Neurology Dr. Lucas Porto Ferreira was the doctor directly involved with the reported case. The general physical examination showed no abnormalities. On neurological examination, the patient was awake, alert, lucid and oriented in time and space, with preserved cortical functions. Pupils were isochoric and photoreactive. There were no abnormalities in fundoscopy, visual campimetry or color changes. Extrinsic eye movement was unchanged. Facial sensitivity and mimicry were preserved. Palate and tongue movement were unchanged. Speech and language were unchanged. On strength examination, the patient presented tetraparesis, with distal crural predominance according to the Medical Research Council (MRC) scale, grade IV+ in upper limbs and proximal lower limbs, grade IV- in distal lower limbs, and grade III in bilateral dorsiflexion of the foot. Mild atrophy of the bilateral hypothenar muscles. The deep tendon reflexes were lively and symmetrical. The plantar cutaneous reflex in bilateral flexion. Balance was unchanged. Regarding coordination, the index-nose maneuver showed bilateral intentional tremor. Tactile and deep sensitivity were unchanged. No fasciculations were observed. Presence of talon gait. An electroneuromyography examination of four limbs was requested, which was performed in September 2020 and showed signs of neurogenic abnormality in multiple myotomes of the cervical/lumbosacral segment, with active denervation and chronic reinnervation, indicating preganglionic motor axonal impairment, which

may correspond to multiradiculopathy or lesion of the anterior horn of the spinal cord. General laboratory examination showed increased CPK (397), without other alterations.

Based on the patient's electroneuromyographic findings and clinical/family history, genetic testing with whole exome sequencing was requested to investigate hereditary neuromuscular disease. This test was performed on August 2, 2021, and revealed a heterozygous mutation in the SETX gene (Senataxin, OMIM*608465), variant chr 9:132.330.431 T>G, promoting the replacement of the amino acid leucine at codon 389 by phenylalanine (p.Leu389Phe). From this, the diagnosis of juvenile ALS type 4 was confirmed. The same variant was investigated and is present in her mother.

After diagnosis, the patient was advised about the prognosis and probable progression of the pathology and did not need periodic medical monitoring. In addition, counseling was provided on motor rehabilitation with physiotherapy and muscle strengthening, without the need for the use of specific or symptomatic medications. During all the guidance given to the patient, his mother was present.

DISCUSSION

The clinical and genetic profile of juvenile ALS is quite complex and heterogeneous in Brazil, with predominant forms linked to the FUX, SETX and ALS2 genes[7-9]. The SETX

gene (senataxin) is an RNA/DNA helicase that has been implicated in the regulation of transcription and in the response to DNA damage through the resolution of R-loop structures. Mutations in SETX result in two distinct neurodegenerative disorders: i) dominant mutations result in a juvenile form of ALS type 4, called ALS4; and ii) recessive mutations are responsible for ataxia, called ataxia with oculomotor apraxia type 2 (AOA2)[9]. In familial cases, genetic mutations are mainly inherited in an autosomal recessive pattern and mutations in SETX are the only ones inherited in an autosomal dominant manner[7].

The patient's genetic testing revealed a mutation in the SETX gene (Senataxin, OMIM* 608465), compatible with the diagnosis of ALS4, with onset of symptoms from an average age of 16 years and, as in the patient in this report, it has a slow progression, with initial symptoms of lower distal weakness and difficulty in locomotion, which may progress to proximal weakness in the upper extremities (e.g., in the hands), sparing the bulbar, respiratory and sensory systems. Studies reveal a possible dysmetria in the index-nose test, and there are cases with a greater symptomatic predisposition in men than in women[7]. The occurrence of a positive family history of ALS or other neurodegenerative conditions is possible in the setting of juvenile ALS, both in dominant and recessive forms, but is not mandatory for diagnostic purposes[8].

Juvenile ALS presents typologies with specific clinical and genetic characteristics. Juvenile ALS represented by

the SOD1 gene (type 1) has symptoms that begin in the second decade of life and presents asymmetric tetraparesis, with a predominance of lower motor neurons and rapid clinical progression[10]. The ALS2 gene (type 2) manifests in the first decade of life and presents spastic paraparesis/tetraparesis, facial spasticity and signs of UMN involvement that are more prominent than those of LMN[11]. Mutations caused by the SETX gene (type 4) appear in the second decade of life, with progressive distal amyotrophy in the upper and lower limbs and signs of pyramidal release[12]. The SPG11 gene (type 5) manifests symptoms in the second or third decade of life and presents in spastic paraparesis/tetraparesis, cognitive and psychiatric dysfunction and cortical atrophy[13]. Type 6, caused by mutations in the FUS gene, has symptoms from the first to the third decade of life and presents in ALS with a predominance of LMN, rapid progression and early bulbar symptoms[14]. Finally, the mutation in the UBQLN2 gene (type 15) manifests in the second decade of life and presents signs of LMN impairment, including muscle weakness and atrophy, which progress slowly over time[15].

When investigating the pathophysiology of juvenile ALS, it is essential to pay attention to genetic causes and differential diagnoses that may be treatable or that have specific therapeutic options under development[16], such as in cases of distal hereditary motor neuropathies with pyramidal tract signs, juvenile primary lateral sclerosis (PLS), distal spinal amyotrophies, pure and complicated

hereditary spastic paraparesis, non-5q forms of spinal muscular atrophy (SMA) and hereditary metabolic diseases[17].

Currently, there are sporadic or familial cases of juvenile ALS associated with more than 20 distinct gene loci, including SETX, ALS2, SPG11, FUS, SIGMAR1 and other monogenic bases[8]. There are no disease-modifying therapies specific for young people with ALS, and researches about the topic are limited[18]. Thus, treatment is centered on a multidisciplinary approach that includes physical, occupational and speech therapies, nutritional and psychological support, while maintaining patient functionality and quality of life. In cases with identified genetic mutations, targeted therapies, such as antisense oligonucleotides, are being explored, although still in the early stages of research[18]. The use of Riluzole, a drug that acts on the cellular pathways that stimulate neurodegeneration, treating glutamate excitotoxicity, has also been an option[19].

The main challenges of current clinical trials are: ethical aspects related to consent and assent; the delay in diagnosis; family involvement in treatment; the specialist approach focused on pediatric care; and the rarity of juvenile ALS[20]. Another challenge is the transition from pediatric care to adult health services. This transition must be planned in advance, involving the patient, family and health teams[21]. It is essential to promote the young person's autonomy by providing education about the

disease, self-management skills and emotional support[21].

CONCLUSÃO

Based on the information provided, we can conclude that juvenile ALS is a rare neurodegenerative disease, with onset before the age of 25 and which presents in a sporadic or familial form. The clinical development and prognosis of the disease are directly related to the affected gene, so that the most common genetic mutations associated with this disease are: FUS; SETX; and ALS2.

In general, although they share some clinical and pathological features, such as motor neuron degeneration, juvenile ALS is distinct from classical ALS in that it is a rarer disease with an earlier onset and a different genetic pattern of inheritance. While classical ALS is usually sporadic, juvenile ALS can be inherited in an autosomal dominant or recessive manner, depending on the genetic mutation involved.

Treatment is multidisciplinary and aims to ensure the patient's quality of life by controlling symptoms and monitoring the progression of the disease. Early diagnosis, identification of the gene, and immediate intervention can reduce juvenile ALS progression. Scientific research is needed to broaden our understanding of the pathophysiology of the disease, in addition to seeking new therapeutic approaches to improve the prognosis of patients with juvenile ALS. Therefore, it is extremely important to remember this pathology as a differential diagnosis in

young patients who present symptoms of lower and upper motor neuron disease, aiming to ensure better evolutionary control of the disease, as well as the development of appropriate genetic counseling.

REREFÊNCIAS

1.Alfahad T, Avindra N. Retroviruses and amyotrophic lateral sclerosis. Antiviral Res 2013;99:180-7. https://doi.org/10.1016/j.antiviral.2013.05.006

2.Statland JM, Barohn RJ, McVey AL, Katz JS, Dimachkie MM. Patterns of weakness, classification of motor neuron disease, and clinical diagnosis of Sporadic Amyotrophic Lateral Sclerosis. Neurol Clin 2015;33:735-48. https://doi.org/10.1016/j.ncl.2015.07.006

3.Fattori B, Grosso M, Bongioanni P, Nacci A, Cristofani R, AlSharif A, *et al*. Assessment of swallowing by oropharyngoesophageal scintilografy in patients with amyotrophic lateral sclerosis. Dysphasia 2006;21:280-6. https://doi.org/10.1007/s00455-006-9052-5

4.Makkonen T, Ruottinen H, Puhto R, Helminen M, Palmio J. Speech deterioration in Amyotrophic Lateral Sclerosis (ALS) after manifestation of bulbar symptoms. Int J Lang Commun Disord 2018;53:385-92. https://doi.org/10.1111/1460-6984.12357

5.Branco LMT, Zanao T, Rezende TJ, Casseb RF, Balthazar MF, Woolley SC, *et al*. Transcultural validation of the ALS-CBS Cognitive Section for the Brazilian population. Amyotr Lat Scler Frontotemp Deg 2017;18:60-7. https://doi.org/10.1080/21678421.2016.1211147

6.Albuquerque KMF, Pernambuco L, Lopes LW. Impacto do tratamento medicamentoso na voz, fala e deglutição de pacientes com esclerose lateral amiotrófica: revisão sistemática. Audiol Commun Res 2022;27:1-9. https://doi.org/10.1590/2317-6431-2021-2599

7.Lehky T, Grunseich C. Juvenile Amyotrophic Lateral Sclerosis: A Review. Genes (Basel) 2021;12:1-16. https://doi.org/10.3390/genes12121935

8.Souza PVS. Análise clínica e genética de pacientes com Esclerose Lateral Amiotrófica Juvenil (Dissertation). São Paulo: Universidade Federal de São Paulo; 2022. https://hdl.handle.net/11600/65322

9.Richard P, Feng S, Tsai YL, Li W, Rinchetti P, Muhith U, *et al*. SETX (senataxin), the helicase mutated in AOA2 and ALS4, functions in autophagy regulation. Autophagy 2021;17:1889-906. https://doi.org/10.1080/15548627.2020.1796292

10.Pansarasa O, Bordoni M, Diamanti L, Sproviero D, Gagliardi S, Cereda C. SOD1 in Amyotrophic Lateral Sclerosis: "Ambivalent" Behavior Connected to the Disease. Int J Mol Sci 2018;19:1345. https://doi.org/10.3390/ijms19051345

11.Hadano S, Yanagisawa Y, Skaug J, Fichter K, Nasir J, Martindale D, *et al*. Cloning and characterization of three novel genes, ALS2CR1,

ALS2CR2, and ALS2CR3, in the juvenile amyotrophic lateral sclerosis (ALS2) critical region at chromosome 2q33-q34: candidate genes for ALS2. Genomics 2001;71:200-13. https://doi.org/10.1006/geno.2000.6392
12.Hadjinicolaou A, Ngo KJ, Conway DY, Provias JP, Baker SK, Brady LI, *et al*. De novo pathogenic variant in SETX causes a rapidly progressive neurodegenerative disorder of early childhood-onset with severe axonal polyneuropathy. Acta Neuropathol Commun 2021;9:194. https://doi.org/10.1186/s40478-021-01277-5
13.Orlacchio A, Babalini C, Borreca A, Patrono C, Massa R, Basaran S, *et al*. SPATACSIN mutations cause autosomal recessive juvenile amyotrophic lateral sclerosis. Brain 2010;133:591-8. https://doi.org/10.1093/brain/awp325
14.Bäumer D, Hilton D, Paine SML, Turner MR, Lowe J, Talbot K, *et al*. Juvenile ALS with basophilic inclusions is a FUS proteinopathy with FUS mutations. Neurology 2010;75:611-8. https://doi.org/10.1212/WNL.0b013e3181ed9cde
15.Deng HX, Chen W, Hong ST, Boycott KM, Gorrie GH, Siddique N, *et al*. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature 2011;477:211-5. https://doi.org/10.1038/nature10353
16.Johnson JO, Chia R, Miller DE, Li R, Kumaran R, Abramzon Y, *et al*. Association of variants in the SPTLC1 gene with juvenile Amyotrophic Lateral Sclerosis. JAMA Neurol 2021;78:1236-48. https://doi.org/10.1001/jamaneurol.2021.2598
17.Sabatelli M, Marangi G, Conte A, Tasca G, Zollino M, Lattante S. New ALS-related genes expand the spectrum paradigm of Amyotrophic Lateral Sclerosis. Brain Pathol 2016;26:266-75. https://doi.org/10.1111/bpa.12354
18.Souza PVS, Serrano PL, Farias IB, Machado RIL, Badia BML, Oliveira H, *et al*. Clinical and genetic aspects of juvenile amyotrophic lateral sclerosis: a promising era emerges. Genes 2024;15:311. https://doi.org/10.3390/genes15030311
19.Cappella M, Pradat PF, Querin G, Biferi MG. Beyond the traditional clinical trials for Amyotrophic Lateral Sclerosis and the future impact of gene therapy. J Neuromuscul Dis 2021;8:25-38. https://doi.org/10.3233/JND-200531
20.Kliest T, Van Eijk RPA, Al-Chalabi A, Albanese A, Andersen PM, Amador MDM, *et al*. Clinical trials in pediatric ALS: a TRICALS feasibility study. Amyotr Lat Scler Frontotemp Degener 2022;23:481-8. https://doi.org/10.1080/21678421.2021.2024856
21.Zhou H, Roberts P, Dhaliwal S, Della P. Transitioning adolescent and young adults with chronic disease and/or disabilities from paediatric to adult care services – an integrative review. J Clin Nursing 2016;25:3113–30. https://doi.org/10.1111/jocn.13326