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CASE REPORT

Late diagnosis and multidisciplinary treatment of autosomal recessive spastic paraplegia type 35 in an adolescent: a case report

Diagnóstico tardio e tratamento multiprofissional de paraplegia espástica autossômica recessiva tipo 35 em adolescente

Livia Justino Figueiredo[1], Natália Karine Sumida Vaz[1], Tainara Maria de Souza Abrão[1], Vitor Emanuel de Lima Nunes[1], Flávia Linhares Martins[1]

ABSTRACT

Introduction: Autosomal recessive spastic paraplegia type 35 (SPG35) is a rare disease characterized by central nervous system involvement, leading to spasticity, mixed movement disorders, and ocular findings. As the disease progresses, intellectual impairment and seizures may also develop. This report describes a case of late diagnosis of SPG35 in an adolescent and examines the impact of multidisciplinary treatment on the quality of life of the patient and her family. **Case Report**: JAB, a 16-year-old female, presented with toe walking at the age of 4 years and 8 months. Her condition progressively worsened, resulting in significant mobility limitations and wheelchair dependence. She also developed dysarthria, reduced visual acuity, and spasticity. Her diagnosis was confirmed at age 14 via genetic testing, following years of treatment based on misdiagnoses such as cerebellar atrophy and epilepsy. Since the age of 9, she has been receiving multidisciplinary treatment—including physical, respiratory, and speech therapy; neurological and physiatric care; nutrition; psychology; and music therapy—through a municipal disability association. This approach has led to an improvement in her quality of life. **Discussion:** Although SPG35 is a debilitating and progressive disease, no specific curative treatments exist. Current interventions focus on improving quality of life through multidisciplinary care, such as physiotherapy, botulinum toxin injections, and transcranial magnetic stimulation. Early diagnosis is essential to mitigate functional impairments. **Conclusion:** Further studies with larger cohorts are needed to explore specific treatments. In the meantime, early diagnosis and multidisciplinary management remain crucial to improving outcomes for both patients and their families.

Keywords: Hereditary spastic paraplegia; Late diagnosis; Therapeutics.

[1] Pontifícia Universidade Católica de Minas Gerais, Poços de Caldas, Minas Gerais, Brazil.

Responsible Editor:
Cássio da Cunha Ibiapina
Faculdade de Medicina da Universidade Federal de Minas Gerais.
Belo Horizonte/MG, Brazil.

Corresponding Author:
Lívia Justino Figueiredo
E-mail: livia.fdj@gmail.com

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RESUMO

Introdução: A paraplegia espástica autossômica recessiva do tipo 35 (SPG35) é uma doença rara caracterizada pelo envolvimento do sistema nervoso central, resultando em sintomas como espasticidade, distúrbios de movimento misto e achados oculares. Conforme a doença progride, também ocorre comprometimento intelectual progressivo e convulsões. O objetivo deste artigo foi relatar um caso de diagnóstico tardio da SPG35 em adolescente e como o tratamento multiprofissional impacta na qualidade de vida da paciente em questão e seus familiares. **Relato de Caso:** JAB, feminino, 16 anos, teve como primeira manifestação da patologia a dificuldade de deambulação com marcha na ponta dos pés aos 4 anos e 8 meses. Teve progressão no quadro e atualmente deambula pouco, com dificuldade e necessitando de apoio, e faz uso de cadeira de rodas. Apresenta, ainda, disartria, baixa acuidade visual e espasticidade de adutores do quadril e tríceps sural. Teve seu diagnóstico firmado aos 14 anos por um exame genético, sendo, anteriormente, submetida a tratamentos medicamentosos incoerentes com o diagnóstico, em decorrência das hipóteses diagnósticas levantadas, como atrofia cerebelar e encefálica, síndrome de liberação piramidal e epilepsia. Realiza tratamento multiprofissional na associação dos deficientes físicos do município de residência desde os nove anos de idade com os setores de fisioterapia motora, respiratória, nutrição, neurologia, fisiatria, terapia ocupacional, musicoterapia, fonoaudiologia e psicologia, onde os pais e os profissionais da instituição notam melhorias na qualidade de vida da paciente. **Discussão:** Apesar da SPG35 ser uma doença progressiva e debilitante, ainda não há estudos grandes que comprovem uma medida terapêutica específica, apenas tratamentos que melhoram a qualidade de vida, como fisioterapia, estimulação magnética transcraniana repetitiva e injeção de toxina botulínica para a espasticidade. Sendo assim, é fundamental um diagnóstico precoce para reduzir déficits funcionais. **Conclusão:** Novos estudos com maior contingente de participantes são necessários para a descoberta de um tratamento específico para a patologia. Enquanto isso, o tratamento multidisciplinar desde o diagnóstico melhora a qualidade de vida do paciente e sua família.

Palavras-chave: Paraplegia espástica hereditária; Diagnóstico tardio; Terapêutica.

Introduction

Hereditary Spastic Paraplegia (HSP) is characterized by being a heterogeneous group of neurodegenerative pathologies that manifest with spasticity and progressive loss of strength in the extremities, most often affecting the lower limbs[1]. This group is divided into uncomplicated or pure HSP, when the involvement is limited to neurological signs and symptoms; or complicated SHP, which progresses with muscle atrophy, ataxia, and seizures[2]. Within the group of complicated HSP, there is autosomal recessive spastic paraplegia type 35 (SPG35), caused by a mutation in the fatty acid 2-hydroxylase (FA2H) gene, with a prevalence of 1-10/100,000 births, considered a rare disease[3]. The first clinical manifestations can occur from the neonatal period to adulthood[4]. SPG35 is characterized by central nervous system involvement, resulting in symptoms such as spasticity and mixed movement disorders (ataxia/dystonia), in addition to ocular findings (optic atrophy, oculomotor abnormalities). As the disease progresses, there is also progressive intellectual impairment and seizures, and it is considered a subtype of neurodegeneration with cerebral iron accumulation[5]. Thus, pathophysiological involvement, involving the degeneration of axons in the corticospinal tract and dorsal column, can affect other parts of the central and peripheral nervous system[4].

This case report describes a 16-year-old female patient who began follow-up at a specialized rehabilitation institution in a city in the south of Minas Gerais in 2015 due to progressive cognitive and motor impairment. Later, she was referred to another specific association for children with disabilities after failing to make a diagnosis. Only in 2021, at the age of 14, was she diagnosed with SPG35 through a genetic test.

This study was approved by the Research Ethics Committee (CEP) of the Pontifical Catholic University of Minas Gerais (PUC-MG), under protocol CAAE No. 80705124.7.0000.5137. Institutional authorization was obtained through the signing of the Institutional Agreement Form. The patient provided assent by signing the Assent Form, and the legal guardians consented by signing the Informed Consent Form.

This case is particularly relevant due to the complexity of the initial diagnosis and the time from the onset of the first symptoms to the end of diagnosis, even though the adolescent is under multidisciplinary follow-up. Thus, the objective of this case report is to provide an in-depth analysis of the clinical presentation, diagnostic investigation and multidisciplinary treatment of this patient in order to increase knowledge about the pathology.

Case Report

Clinical history

Patient, female, currently 16 years old was taken to the pediatrician by her mother at 4 years and 8 months, in 2011, because she had difficulty walking, presenting walking on tiptoe, loss of balance, falls, speech alteration (with reduced volume and speed), in addition to cognitive delay, all symptoms that she had never presented before. In addition, the mother reported that the patient started speaking but stopped for a while and stared for a few seconds, then speaking again with difficulty. Due to the symptoms presented, she was referred to a neurologist and orthopedist, and an X-ray of the lower limbs was requested — which showed no alteration —, as well as an MRI of the brain which showed the presence of signs of diffuse and symmetrical volume reduction of the cerebellum, as well as a brainstem associated with thinning of the corpus callosum.

Regarding the prenatal history, the mother denied any alcohol or drug use during pregnancy. The delivery was vaginal at term, with a birth weight of 3.430 g and length of 51 cm, and Apgar scores of 8 and 10 at one and five minutes, respectively. The patient did not present jaundice and underwent all recommended neonatal screening tests, which yielded negative results. The developmental history was reported as normal until four years and eight months of age, with no similar cases in the family. The patient's father has asthma with no other relevant comorbidities, and the patient is an only child. There is no history of consanguinity between the parents.

The treatment, at first, was done with the hypothesis of ataxia, starting her follow-up in a specialized institution, however, because the diagnosis was not closed, in one year she was disconnected from the institution.

In 2015, at eight years old, the patient resumed multidisciplinary treatment at another specialized rehabilitation institution, where she received follow-up care from motor and respiratory physical therapy, nutrition, neurology, physiatry, occupational therapy, music therapy, speech therapy, and psychology departments. The institution in question is a non-governmental, non-profit organization located in southern Minas Gerais, linked to primary health care. Through a municipal regulatory board, patients diagnosed with or suspected of having physical disabilities are referred to this service, to which the patient remains affiliated to date. During this period, she was also referred to a public hospital in the interior of São Paulo, where she continues multidisciplinary follow-up. The neurogeneticist maintained the hypothesis of spinocerebellar ataxia and continued to monitor her. The multidisciplinary team at the São Paulo institution also considered differential diagnoses such as cerebellar and cerebral atrophy, pyramidal release syndrome, and epilepsy. Accordingly, the patient was treated with sodium valproate 250 mg every 8 hours for approximately four years, from 8 to 12 years of age (2015 to 2019), as well as ethosuximide 50 mg/mL administered in 2015.

In 2016, at age 10, she experienced worsening motor skills and loss of gait, requiring the use of a wheelchair, and concurrently, her speech slowness worsened. The diagnosis of SPG35 was confirmed in 2021, at age 14, through genetic testing using a panel of epilepsies and ataxias from DNA extracted from a buccal swab. This test identified homozygosity for the FA2H gene, requested by the referral hospital where the patient receives care, as shown in the timeline of clinical events in Figure 1. In addition, she was diagnosed with progressive dysphagia by the speech therapist at the same hospital, and was already at nutritional risk due to low caloric intake and loss of appetite.

Physical examination and complementary tests

The previous physical examination in 2015, at 8 years of age, showed no cardiac, respiratory or abdominal changes. The patient had a scissor gait with the aid of third parties and orthoses, reduced speed, forward trunk projection, slight knee flexion during the swing phase, and knee hyperextension in the stance phase. She also presented dysmetria and horizontal nystagmus, as well as strabismus divergent to the left, global grade 5 strength, exhaustible alonus in Achilles, spasticity of hip adductors and bilateral triceps sural. The current physical examination showed good general condition: she is ruddy, hydrated, eupneic, anicteric and acyanotic, lucid and oriented in time and space. Cardiorespiratory examination showed no abnormalities. In the evaluation of the upper limbs, she did not present fixed deformities, makes key forceps, with the right upper limb being dominant, but with incoordination of movement. In

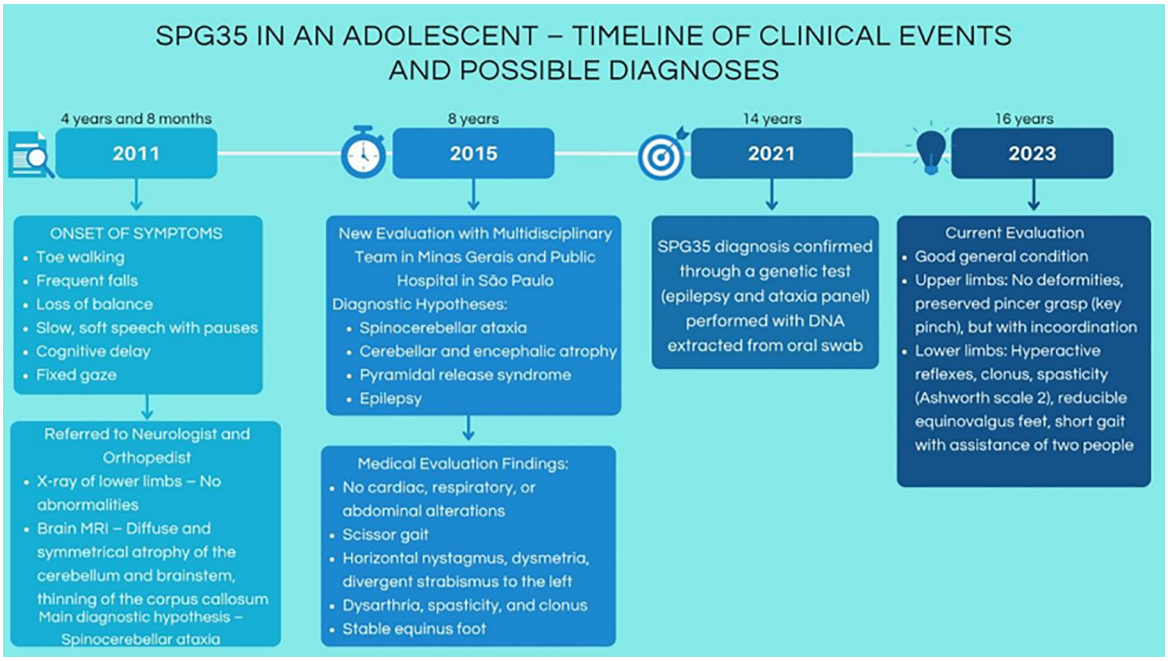

Figure 1. Timeline of clinical events and possible diagnoses. Source: Prepared by authors, 2025

the lower limbs, she had hyperactive patellar and Achilles reflexes, a positive Galeazzi sign on the left, clonus aquileus present, bilateral adductor spasticity classified as 2 on the modified Ashworth scale, equinus valgus feet reducible to a neutral position, and a short gait due to fatigue with the support of only 2 people. An MRI of the skull was performed in June 2021, which showed signs of diffuse and symmetrical volume reduction of the cerebellum, as well as brainstem associated with thinning of the corpus callosum, as well as thoracolumbar scoliosis and lumbar rectification. She also presented normal electroencephalograms for 2020 and 2021.

Treatment

The patient has been undergoing multidisciplinary treatment since she was four years old in order to improve her quality of life. In motor physical therapy, currently, the objective is to control the trunk, change steps, favor manual function in feeding activities and preserve gait and orthostatism through an exercise bike and playful activities with the use of music and activities that the patient likes, such as makeup and painting. In physical education and music therapy, during the pandemic, she carried out the activities prescribed by the physical educator and music therapist at home with distance monitoring and with the help of her mother. Currently, she does face-to-face monitoring and works on her motor function by playing instruments such as the ukulele for trunk control, in addition to rhythmic movements to strengthen her muscles. When singing, the patient works on vowels but has been presenting progressive speech loss — others have had difficulty understanding her. In respiratory physical therapy, the therapist emphasized the importance of maintaining vital capacity with the objectives of improving/maintaining thoracic mobility and diaphragmatic strength, preventing pulmonary hypoventilation.

In the nutrition sector, the professional advised a healthy and hypercaloric diet due to the patient's low caloric intake, in addition to pasty and moist foods due to the dysphagia presented. Due to her clinical condition, gastrostomy was indicated to assist the patient's nutritional intake.

In the speech-language pathology sector, aspects related to expressive language and speech were worked on so that she can better articulate sounds and be understood despite dysarthria, in addition to respiratory physical therapy associated with the objective of pneumophonoarticulatory coordination, laryngeal elevation and anteriorization, and breathing exercises associated with phonation and articulation. She has slow, pasty and unintelligible speech in most activities. In addition, from 2021 onwards, she presented worsening in speech with greater slowness and difficulty in articulation. At the moment, she continues to be monitored by the speech therapist.

In psychology, there is therapy combined with the patient's speech therapist, in addition to welcoming the family into the institution's family group due to the emotional demand, family organization and financial difficulties, through dynamics and conversation circles.

In the follow-up with the pedagogue, the patient had help to carry out her schoolwork when she attended school. However she stopped going to school due to the fatigue she felt. She currently performs daily practical group activities combined with occupational therapy. She has completed elementary school, but the family chose not to continue with high school. At the moment, she no longer follows up with a pedagogue at home because of her age.

Medical follow-up continues to be carried out according to the patient's demand. In continuity with a neurologist,

she presented grade 5 distal upper limb strength, patellar and Achilles hyperreflexia, did not make any sounds but smiled and obeyed simple commands. The patient presented worsening of dysarthria, increased diuresis with the use of diapers, and appetite and sleep without alterations. She is not currently taking any continuous medication.

The nursing team is responsible for coordinating care within the institution, providing guidance for home care, integrating treatment plans proposed by the various multidisciplinary teams, and offering support and counseling to the patient's family.

Discussion

Autosomal recessive spastic paraplegia is a rare diagnosis, which is made by exclusion, especially when there is no history and family consanguinity[6]. A clinical history of progressive weakness is a common finding for many neurological diseases that make a differential diagnosis with PEH, such as spinocerebellar ataxia. The most prevalent spinocerebellar ataxia is Machado-Joseph disease, which should be considered a differential diagnosis of pure PEH if there is a family history of neurodegenerative diseases; there may still be an overlap of the two pathologies in the same individual[7]. The symptomatology is similar; the difference is due to the result of the molecular test.

Other differential diagnoses for PGS35 are the other complicated autosomal recessive HEPs, such as SGS11, SPG15, SPG21, SPG48 and SPG54. This is similar in imaging findings to the presence of thinning of the corpus callosum and/or white matter lesions and/or in clinical manifestations such as mental retardation. In a cohort study with DNA samples, it was noted that SPG48 is the closest to SPG35 clinically and can be overlapping: both have a broad clinical spectrum with the presence of thinning of the corpus callosum, intellectual impairment and lesions in the white matter, but cerebellar atrophy was documented only in patients who had SPG35[8]. Therefore, for a specific diagnosis of the described pathology, in addition to the clinical findings, genetic testing, such as the epilepsy and ataxia panel that was performed by the patient, is necessary.

Autosomal recessive spastic paraplegia type 35 is characterized by weakness and spasticity of the lower limbs, with symptoms of variable intensity and often delayed diagnosis. Affected individuals typically present with delayed walking milestones, paresthesia in the lower limbs, urinary urgency, and, in more severe cases, dementia, ataxia, intellectual disabilities, seizures, and cerebral dysfunction[6]. The impairment of the lower limbs results from distal axonal degeneration of the corticospinal tracts[9].

Similarly, the diagnosis of progressive oropharyngeal dysphagia presented by the patient is commonly observed in the complicated forms of hereditary spastic paraplegia (HSP)[10]. This condition may impair swallowing, increase the risk of aspiration of saliva and food due to a reduced gag reflex, contribute to the development of pneumonia, and negatively affect the patient's nutritional status, often requiring specific dietary management[11].

Currently, scientific evidence indicates that there is still no targeted treatment proven to be effective in reversing the described condition. Thus, despite the degenerative nature and lack of curative therapies for autosomal recessive spastic paraplegia type 35, early diagnosis is crucial to enable interventions aimed at minimizing functional deficits, delaying symptom progression, and contributing to the patient's overall well-being. Accordingly, the therapies available to date focus on relieving the main symptoms and improving the patient's quality of life, as it is still not possible to prevent, slow down, or reverse the progressive disability caused by HSP[9].

Furthermore, the literature emphasizes that systematic monitoring of child growth and development — outlined in public health policies such as the Child Health Handbook and the Child Health Program of the Brazilian Ministry of Health — is essential for the early identification of neurological warning signs[12,13]. In the present case report, a four-year period without specialized interventions represented a lost therapeutic window during which early implementation of physical therapy, speech therapy, and educational strategies could have mitigated motor impairments and contributed to a more favorable functional prognosis[14,15]. In addition, the role of primary healthcare and multidisciplinary teams is crucial in the surveillance of developmental milestones and in ensuring timely diagnosis and referral for early stimulation. Even in rare and difficult diagnostic conditions such as SPG35, early and coordinated healthcare interventions can provide therapeutic and emotional support to families, as well as guide appropriate referrals and diagnostic procedures. This underscores the importance of training healthcare teams to recognize early atypical developmental signs and to provide longitudinal, humanized care to children with chronic and neurological conditions[16,14].

In addition, a small-scale study demonstrated the effects of repetitive transcranial magnetic stimulation (rTMS) in reducing lower limb weakness and spasticity in cases of SPG35. The results varied depending on the type of stimulation applied and the patient's clinical presentation. rTMS represents a non-invasive brain stimulation treatment option, though further studies with larger sample sizes are needed to confirm its therapeutic efficacy[17]. Therefore, despite the availability of some treatment alternatives, there are still no guidelines or strong evidence-based recommendations to guide professionals in selecting a gold-standard intervention.

Patient and guardian perspective

In view of the clinical condition of the patient, who has difficulty in expressing herself verbally, the case in question was discussed with some limitations, as it relied on the veracity of the data obtained from the young woman's physical record and the information provided by the

patient's parents and by the professionals who work on her care plan. However, this document is indispensable in the scenario of a disease with such progression and symptomatic manifestations in the individual who presents the issue.

The patient, due to dysarthria, was unable to communicate verbally, only by nods. Despite the difficulties, she feels very happy to undergo treatment at the specialized rehabilitation institution and to be able to count on this support network.

In addition, the parents are extremely grateful for the help and welcome of the association and for the assurance that their daughter will be well taken care of, performing multiple treatments that directly reflect on her quality of life. They also mention how the diagnosis process was difficult for the family, because it took them many years to close it, previously carrying out measures that were not effective. They also reported that they did not know how to take care of their own daughter at first, but that with the support of the team they feel more confident. Finally, they reinforced the importance of reporting their daughter's case as study material to help other patients, family members and health professionals.

Conclusion

PGS35 is a rare pathology that affects an individual in several ways and still has a restricted scientific advance. The diversity of symptoms, together with the numerous differential diagnoses, hinders closing a diagnosis, hence, there is a need to increase theoretical and practical experiments for better management and prognosis. The search for appropriate treatments will ensure an improvement in the quality of life of patients with this disease, benefiting the family and helping the professionals who are working on the care plan.

Therefore, it is possible to conclude that the early diagnosis of autosomal recessive spastic paraplegia type 35, as well as multidisciplinary treatment, changes the prognosis by placing the patient at the center of care in various areas. In this manner, family members feel welcomed, and treatment promotes an improvement in quality of life.

Authors' Contributions:

We describe contributions to the papers using the taxanomy (CRediT) provided above: *Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing*: NKS Vaz; TM de S Abrão; VE de L Nunes. *Project administration, Supervision & Writing – original draft*: LJ Figueiredo; FL Martins. *Data curation & Formal Analysis*: LJ Figueiredo; FL Martins.

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