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Int J Case Rep Images 2024;15(2):53–57.
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Spinocerebellar ataxia type 7: A case report

Roberto Monteiro Leitão, Marco Orsini, Mariana Pontes do Nascimento Mateus, Renan Falconi, Antônio Marcos da Silva Catarino, Gilberto Canedo Martins Jr

ABSTRACT

Introduction: Spinocerebellar ataxia type 7 is part of a rare group of neurodegenerative diseases, characterized by lesions in the brainstem, cerebellum, spinal cord, and retina, manifesting as motor disturbances associated with signs of pyramidal involvement and amaurosis. The dysfunction is caused by autosomal dominant genetic alterations, with disease severity and the age of symptom onset being directly linked to the patient's genetic expression.

Case Report: We present the case of a 24-year-old woman, previously healthy, who denied smoking, drinking alcohol, or taking any other drugs. She reported that approximately nine months, she had experienced a decline in dexterity for tasks requiring fine motor skills. She also exhibited impaired gait, frequent falls, and difficulties in performing basic activities of daily living (ADLs). On neurological examination, she presented with an ataxic and staggering gait, tremor during movement, dysmetria, dysdiadochokinesia, movement decomposition, dysarthria (scanning speech), dysphagia, dystasia, dysbasia, and nystagmus, all of which are indicative of cerebellar impairment. A genetic panel revealed the presence of 44 cytosine-adenine-guanine nucleotide repeat expansions on allele 2 of the ATXN7 gene, confirming the diagnosis of spinocerebellar ataxia type 7.

Conclusion: In this case report, the diagnosis of spinocerebellar ataxia was established through a comprehensive assessment of the patient's clinical history, neurological examination, imaging studies, and genetic profiling, all of which are essential for reaching a definitive diagnosis. The prognosis for this disease varies due to ongoing research into its pathophysiology. Furthermore, discussions within the scientific community regarding potential cures for this condition continue.

Keywords: Ataxias, Cerebellar degeneration, Spinocerebellar ataxia type 7

How to cite this article

Leitão RM, Orsini M, do Nascimento Mateus MP, Falconi R, da Silva Catarino AM, Martins Jr GC. Spinocerebellar ataxia type 7: A case report. Int J Case Rep Images 2024;15(2):53–57.

Article ID: 101470Z01RL2024

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doi: 10.5348/101470Z01RL2024CR

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Received: 05 May 2024
Accepted: 13 August 2024
Published: 12 September 2024

INTRODUCTION

Spinocerebellar ataxias (SCAs) constitute a group of diverse neurodegenerative ataxic disorders affecting the cerebellum, brainstem, and spinal cord [1]. They arise from autosomal dominant genetic mutations [2]. The classification of these ataxias has evolved over time and was initially divided into three groups: type 1 (ADCA-I), type 2 (ADCA-II), and type 3 (ADCA-III). With the advancement of biotechnologies, positional genetic

cloning techniques have been employed to identify the genes that are responsible for the mutations found in SCAs. Consequently, ADCA-II was then renamed spinocerebellar ataxia type 7 (SCA-7) [1].

The genetic origin of the disease is based on expanded repeats [3] of the cytosine-adenine-guanine (CAG) trinucleotide in the coding region of the ATXN7 gene, responsible for encoding the ataxin-7 protein. These repetitions lead to an uninterrupted series of glutamine residues, resulting in an abnormal polyglutamine (polyQ) tract and, consequently, the accumulation of the synthesized protein [4, 5]. The clinical phenotype is dependent on the number of nitrogen base repeats, with higher expression leading to a faster disease progression and earlier symptom onset [1, 4]. The resulting disorder, stemming from the degeneration of neurons in the brainstem and cerebellum, clinically presents as progressive cerebellar ataxia with signs of pyramidal tract involvement [6]. Additionally, ophthalmoplegia and progressive amaurosis are observed due to cone and rod dystrophy in the macular region of the retina [7]. Spinocerebellar ataxia type 7 is a rare disorder, with a prevalence of 0.3 to 2 per 100,000 individuals [4], showing a higher incidence in Finland, Sweden, Scandinavia, the United States, and China [3, 4]. Among genetically confirmed diseases, SCA-7 represents approximately 1–11.7% of cases, with diagnostic confirmation often hindered by limited access to genetic screening, which is crucial given the various potential differential diagnoses [7]. In light of the above, the objective of this study is to present a case report of SCA-7 and provide a genetic foundation related to the disease, along with its implications not only for the patient but also for those within their hereditary lineage.

CASE REPORT

NM, 24-years-old, woman, teacher, with no comorbidities. She denied using illicit and legal substances, such as cigarettes and alcohol. It was reported that approximately nine months ago, she started a decline in dexterity for tasks that requires fine motor skills and walking impairments. Initially, the issue was treated as a possible psychiatric condition. In February, she looked for assistance from the Neurology department due to frequent falls and difficulties/incapacities in basic and instrumental activities of daily living. *Family History*: Although she had no direct contact with her father, she mentioned that he had difficulties walking, appearing intoxicated. On inspection, proptosis was observed. During the neurological examination, she exhibited a staggering ataxic gait, tremors during movement, dysmetria, dysdiadochokinesia, movement decomposition, scanning speech (dysarthria), dysphagia, dystasia, dysbasia, and nystagmus. All of these findings are indicative of cerebellar impairment. However, she did not present muscle weakness or sensory deficits suggestive of space occupying lesions in cord. Cranial magnetic resonance imaging (MRI): Atrophy of the posterior fossa structures (cerebellum and pons) was observed, along with tapering of the upper and middle cerebellar peduncles. There was a reduction in the thickness of the pons (Figures 1 and 2). Additionally, there was marginal widening of the cingulate gyrus sulcus, reflecting a reduction in bilateral parietal cortical thickness (Figure 3). *Genetic Panel*: Molecular testing identified an ATXN7 allele with approximately 44 CAG repeats (Figure 4). This expansion is responsible for the SCA7 form of spinocerebellar ataxia.

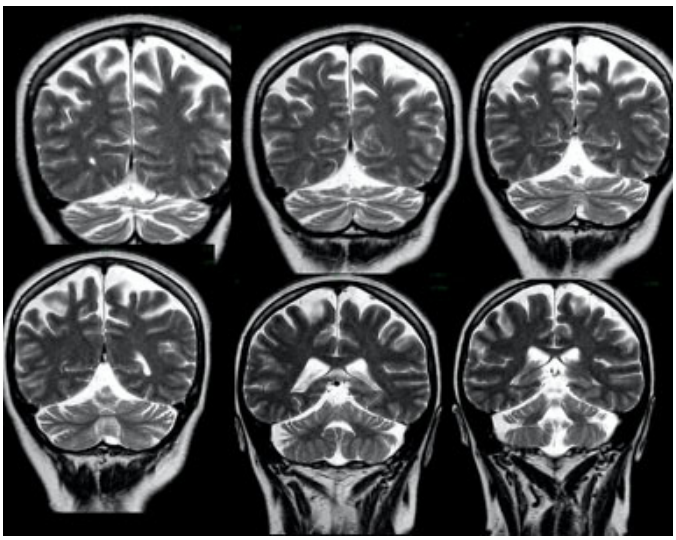

Figure 1: Atrophy of the structures in the posterior fossa, including the cerebellum and pons, is observed. There is also thinning of the upper and middle cerebellar peduncles, and a reduction in the thickness of the pons.

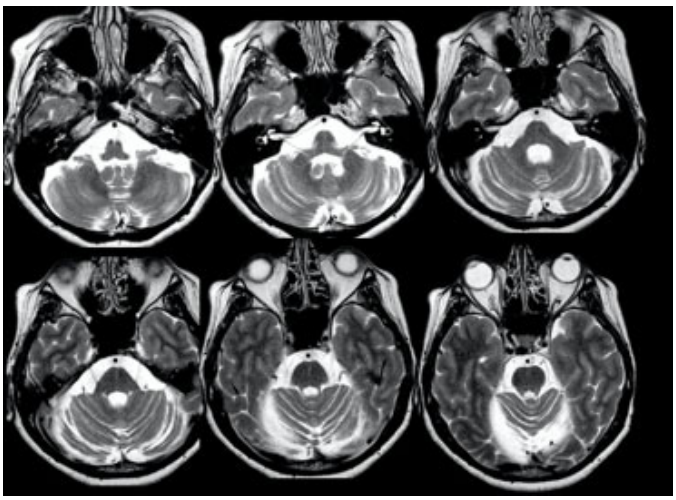

Figure 2: Atrophy of the structures in the posterior fossa, specifically the cerebellum and pons, is noted. Additionally, there is tapering of the upper and middle cerebellar peduncles and a reduction in the thickness of the pons.

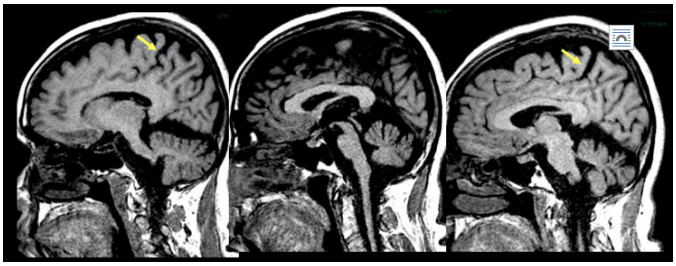

Figure 3: Widening of the marginal branch of the cingulate sulcus, translating to a reduction in bilateral parietal cortical thickness—Koedam 2.

Resultado:

			PACIENTE*		Valores de referência*	
GENE	FORMA	OMIM #	alelo 1	alelo 2	normal	alterado
ATXN1	SCA1	164400	28	29	menor ou igual a 36	maior ou igual a 39
ATXN2	SCA2	183090	22	22	menor ou igual a 31	maior ou igual a 32
ATXN3	SCA3	109150	20	27	menor ou igual a 44	maior ou igual a 52
CACNA1A	SCA6	183086	11	13	menor ou igual a 18	maior ou igual a 20
ATXN7	SCA7	164500	10	**44**	menor ou igual a 19	maior ou igual a 36

*Número de repetições de trinucleotídeos
Erro: mais ou menos 1 repetição para alelos normais e mais ou menos 3 repetições para alelos alterados.

Interpretação: O teste molecular identificou um alelo de *ATXN7* com aproximadamente 44 repetições de CAG. Esta expansão é responsável pela forma SCA7 de ataxia espinocerebelar.

Figure 4: Genetic panel results show an allele of ATXN7 with approximately 44 CAG repeats, responsible for the SCA7 form of spinocerebellar ataxia.

DISCUSSION

Spinocerebellar ataxia type 7 (SCA7) is a rare, late-onset, and slowly progressive autosomal dominant neurodegenerative disease. It is caused by an expanded CAG (CAGexp) repeat in the ATXN7 gene located on chromosome 3, resulting in the insertion of an elongated polyglutamine (polyQ) protein ataxin-7 [8]. Affected individuals typically have an allele with 36 to 460 CAG repeats [9]. As a differential diagnosis, the most common are other types of ACS, such as SCA1, SCA2, SCA3, ischemic vascular accident (CVA) in the cerebellum or brain stem, hemorrhage in the brain, multiple sclerosis, and Wernicke–Korsakoff syndrome [10]. In the case presented, the patient has 44 CAG repeats, which confirms the diagnosis of SCA7. The diagnosis is typically confirmed through the ATXN7/SCA7 gene expansion test. As a result, individuals with SCA7 develop alterations that affect the functioning of cerebellar, spinal cord, and retinal cells [11]. Symptoms of SCA7 typically emerge in early adulthood, around the ages of 20–30 [12]. In this case, the patient is 24 years old, which falls within the expected age range. The age at diagnosis and symptom onset is crucial in SCA7 patients, as younger onset is associated with faster disease progression [13]. Clinical manifestations are characterized by pyramidal tract signs, ophthalmoplegia, Parkinsonism, slow saccadic eye movements, and muscle weakness [3]. The patient exhibits alterations in proprioception, gait, eye motility, and visual acuity, manifesting nystagmus and exophthalmos. In MRI, it is possible to observe brainstem atrophy in SCA7 patients, suggesting that the pons is the most affected structure in the central nervous system, preceding the involvement of the cerebellum and supratentorial regions [14]. This is consistent with the imaging findings in the patient, showing atrophy of brainstem structures. Being a genetic disease, it is essential to investigate the family history, checking if grandparents, parents, and siblings, if any, exhibit any features, signs, or symptoms of the disease. Moreover, genetic testing for spinocerebellar ataxias should ideally be performed in all family members to facilitate screening and early diagnosis. There is currently no specific treatment for this disease; however, gene silencing studies are underway to prevent the development of SCA7. Allele-specific silencing of the polyglutamine mutation in SCA7 models is being explored in research [2]. The prognosis of the disease involves the loss of vision due to the degeneration of photoreceptor cones and motor impairments, such as dysphagia and dysarthria [5].

CONCLUSION

Based on the patient's genetic panel combined with the clinical history of frequent falls, neurological examination showing ataxic gait, movement tremor, dysmetria, dysdiadochokinesia, nystagmus, and the imaging findings of pontine atrophy, the diagnosis of spinocerebellar ataxia type 7 has been confirmed. The prognosis varies, but improvement in the condition is unlikely. The mechanisms of this disease are not well understood, and there is a low probability of significant interventions that can improve the prognosis. Despite robust therapeutic evidence, there is no cure for this condition, only treatment aimed at managing some of the symptoms.

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Author Contributions

Roberto Monteiro Leitão – Conception of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Marco Orsini – Conception of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mariana Pontes do Nascimento Mateus – Conception of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Renan Falconi – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Antônio Marcos da Silva Catarino – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Gilberto Canedo Martins Jr – Conception of the work, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.