ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

CASO CLÍNICO

Spinocerebellar Ataxia Type 27B (SCA27B): A Hereditary Ataxia in Portugal

Ataxia Espinocerebelosa Tipo 27B (SCA27B): Uma Ataxia Hereditária em Portugal

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Acta Med Port (In Press) ▪ https://doi.org/10.20344/amp.22232

ABSTRACT

Spinocerebellar ataxia type 27B (SCA27B) is a recently discovered hereditary disease caused by $(GAA)_{\geq 250}$ repeat expansion in the fibroblast growth factor 14 (*FGF14*) gene, and multiple studies have recognized it as one of the most common causes of autosomal dominant ataxia in the European population. We present the case of a 62-year-old Portuguese patient who developed a slowly progressive gait impairment associated with wide-base ataxic gait, dysarthria, left upper limb dysmetria, and dysdiadochokinesia. This pure cerebellar phenotype had an episodic worsening induced by intense physical activity and alcohol intake. The patient had an older brother with a late-onset cerebellar ataxia of unknown cause. Genetic testing detected a heterozygotic intronic *FGF14* repeat expansion with complete penetrance (> 360 repeats), confirming the diagnosis of SCA27B. To our knowledge, we present the first reported case of SCA27B in the Portuguese population.
Keywords: Spinocerebellar Ataxias/diagnosis; Spinocerebellar Ataxias/genetics; Portugal

RESUMO

A ataxia espinocerebelosa tipo 27B (SCA27B) é uma doença hereditária descoberta recentemente, provocada por expansões $(GAA)_{\geq 250}$ no gene do fator de crescimento de fibroblastos 14 (*FGF14*), e vários estudos sugerem ser uma das causas mais comuns de ataxia de transmissão autossómica dominante na população europeia. Apresentamos o caso de um doente português de 62 anos que iniciou um quadro de desequilíbrio da marcha lentamente progressivo, associado a marcha atáxica, disartria, dismetria e disdiadococinesia do membro superior esquerdo, que apresentava um agravamento paroxístico induzido pela atividade física intensa e consumo de álcool. O doente tinha um irmão mais velho diagnosticado com ataxia cerebelosa de início no adulto de causa indeterminada. A pesquisa de expansões patogénicas no gene *FGF14* detetou uma expansão intrónica em heterozigotia com penetrância completa (> 360 repetições), confirmando o diagnóstico de SCA27B. Tanto quanto sabemos, apresentamos o primeiro caso reportado de SCA27B na população portuguesa.
Palavras-chave: Ataxias Espinocerebelosas/diagnóstico; Ataxias Espinocerebelosas/genética; Portugal

INTRODUCTION

Late-onset cerebellar ataxias (LOCA) are a group of heterogeneous neurodegenerative diseases characterized by progressive cerebellar dysfunction after the age of 30.[1] In recent decades, advances in molecular and genetic techniques have allowed the detection of new causative genes and genetic variants. Nonetheless, more than half of patients with LOCA remain without a diagnosis.[1-3] Recently, a new cerebellar autosomal dominant (AD) ataxia caused by $(GAA)_{\geq 250}$ repeat expansion in intron 1 of the fibroblast growth factor 14 (*FGF14*) gene was identified as a cause of slowly progressive cerebellar ataxia, designated spinocerebellar ataxia type 27B (SCA27B).[1] The *FGF14-SCA27B* repeat locus has highly variable lengths, with the level of pathogenicity classified as follows: $(GAA)_{<200}$ repeats – normal; $GAA)_{200\text{-}249}$ repeats – uncertain pathogenicity; $(GAA)_{250\text{-}300}$ repeats – pathogenic with incomplete penetrance, so a diagnosis should only be made in patients with a compatible phenotype and AD transmission; $(GAA)_{>300}$ repeats – pathogenic with complete penetrance.[1,2] Multiple population studies across Europe showed that SCA27B is a common cause of AD ataxia in this population. To our knowledge, we present the first reported case of SCA27B in the Portuguese population.

CASE REPORT

A 62-year-old male patient of European ancestry presented with a five-year history of slowly progressive gait and balance impairment. The patient reported a paroxysmal worsening induced by intense physical activity and alcohol ingestion, even in small quantities. Medical history was, otherwise, unremarkable.

The neurological examination revealed impaired smooth ocular pursuit without nystagmus, wide-base ataxic gait with tandem gait impairment, mild dysarthria, mild left upper limb dysmetria, and dysdiadochokinesia – Scale for the Assessment and Rating of Ataxia (SARA) of 5.5 points (maximum score of 40 points, with higher scores indicating more severe ataxia). There were no pyramidal, extrapyramidal, or sensory signs. Extensive blood work including auto-immune, paraneoplastic, and toxic causes of ataxia was unremarkable. Brain magnetic resonance imaging (MRI) revealed mild atrophy of the cerebellar vermis (Fig. 1).

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Recebido/*Received*: 25/08/2024 - **Aceite/*Accepted*:** 07/10/2024 - **Publicado *Online*/*Published Online*:** 11/10/2024

A therapeutical trial with riluzole resulted in a worsening of the cerebellar symptoms, that resolved after drug interruption. During the three-year follow-up, the patient remained clinically stable, without significant progression of the cerebellar syndrome (SARA 5.5 points at three years of follow-up). However, he reported paroxysmal episodes of oscillopsia and dizziness.

Regarding family history, his older brother had been diagnosed with late-onset pure cerebellar ataxia of unknown cause at the age of 70, characterized by slowly progressive gait impairment with wide-base gait, accompanied by episodic dysarthria and diplopia. Brain MRI revealed mild chronic ischemic microangiopathy with mild diffuse cerebral atrophy. Genetic evaluation, including common causes of hereditary ataxias (*ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *ATXN8*, *ATN1*, *TBP*, *FXN*, *PGN* genes) was unremarkable. A more extensive exome sequencing ataxia genetic panel revealed two heterozygotic variants of uncertain significance (VUS) in *CAMTA1* and *KIF5A* genes. The patient's brother died of medical complications at 77 years old. Assuming a common etiology between both siblings, our patient initially performed a *CAMTA1* and *KIF5A* genetic testing that was negative, without the previously mentioned VUS. Subsequently, *FMR1* and *RFC1* gene pathogenic expansions were also excluded. Due to paroxysmal symptoms and slow disease progression, *FGF14* intronic expansion testing was performed and detected a heterozygotic repeat expansion with complete penetrance (> 360 repeats), confirming the diagnosis of SCA27B.

DISCUSSION

Spinocerebellar ataxia type 27B is a recently discovered AD hereditary ataxia, and as such, its epidemiologic data and phenotypic spectrum are yet to be fully clarified.[1] The current literature suggests that this diagnosis should be considered in patients with a pure late-onset cerebellar ataxia, typically presenting in the fifth to seventh decade of life with a slowly progressive course and a pan-cerebellar phenotype.[2,3]

The presence of episodic symptoms, either at disease onset or throughout disease progression, appears to be one of the main distinguishing factors from other hereditary ataxias.[1-3] Up to now, alcohol consumption, intense physical exercise, and caffeine intake have been identified as the most common triggers.[2] The most common clinical features by range of frequency are gait ataxia (95% - 100%); cerebellar oculomotor signs, including pursuit impairment, dysmetric saccades, and nystagmus (80% - 96%); episodic symptoms (13% - 80%); cerebellar dysarthria (12% - 74%); upper limb ataxia (44% - 71%); diplopia, oscillopsia, and visual blurring (40% - 68%); vertigo and dizziness (21% - 67%); postural tremor of upper limbs (10% - 27%).[3-7] Dysautonomic symptoms are classically absent, an important feature for distinguishing this condition from multiple system atrophy type C (MSA-C), another common form of LOCA.[8] We present a case of SCA27B with onset in the fifth decade that presented with a slowly progressive gait and balance impairment. In our patient, the disease had a slowly progressive clinical course of pure cerebellar ataxia as it has been previously described. In our case, although cerebellar oculomotor signs are one of the most common findings in SCA27B, with downbeat nystagmus being particularly mentioned in previous cohorts, we only identified impaired ocular pursuit. We did not identify pyramidal signs, extrapyramidal signs, sensory signs, or dystonia, which seem to be uncommon in SCA27B. The cerebellar symptoms were exacerbated by physical exertion and alcohol intake, but not caffeine (another common trigger).[3-7] Brain MRI revealed cerebellar atrophy that was more evident in the cerebellar vermis without brainstem atrophy, which concurs with what is documented in the literature, in which 60% - 97% of SCA27B patients have mild to moderate cerebellar atrophy, more pronounced in the cerebellar vermis.[3]

Riluzole has been used off-label for the treatment of hereditary cerebellar ataxias, with several trials showing clinical improvement.[9] In our literature review, we did not find any reports of riluzole use in SCA27B patients. However, in our case this drug led to a worsening of the cerebellar symptoms, which the patient described as exacerbated dysarthria, gait imbalance, and upper limb ataxia, comparable to what was observed with the previously mentioned triggers. This led to the early discontinuation of the drug. The knockdown of *FGF14* in cerebellar granule cells has been demonstrated to reduce calcium currents and vesicular recycling, suggesting that SCA27B may, at least in part, stem from dysregulation of calcium channel function.[10] Additionally, riluzole inhibits N-type and P/Q-type calcium channels, resulting in decreased calcium influx at presynaptic terminals, which may account for the exacerbation of symptoms observed with riluzole treatment in our patient.[10,11] On the other hand, initial findings from observational case series suggest that 4-aminopyridine (also known as fampridine) may be beneficial for SCA27B patients, reducing the severity and frequency of cerebellar symptoms. Even though randomized placebo-controlled trials are needed to validate these findings, it seems to be an effective symptomatic therapy.[2]

To our knowledge, this is the first reported case of SCA27B in Portugal, and this report should encourage not only neurologists but also ophthalmologists and otolaryngologists to consider this new entity when approaching cases of

adult-onset cerebellar ataxia, as it appears to be a common cause of LOCA in the European population. Furthermore, and given its high prevalence and potential treatment, it should be considered as one of the main causes of genetic ataxias to investigate during the initial evaluation of these patients.

AUTHOR CONTRIBUTIONS

VMF: Study design, writing of the manuscript.
MM, BM, RB: Data interpretation, critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

RB has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boston Scientific; received support for attending meetings and/or travel from Medtronic.

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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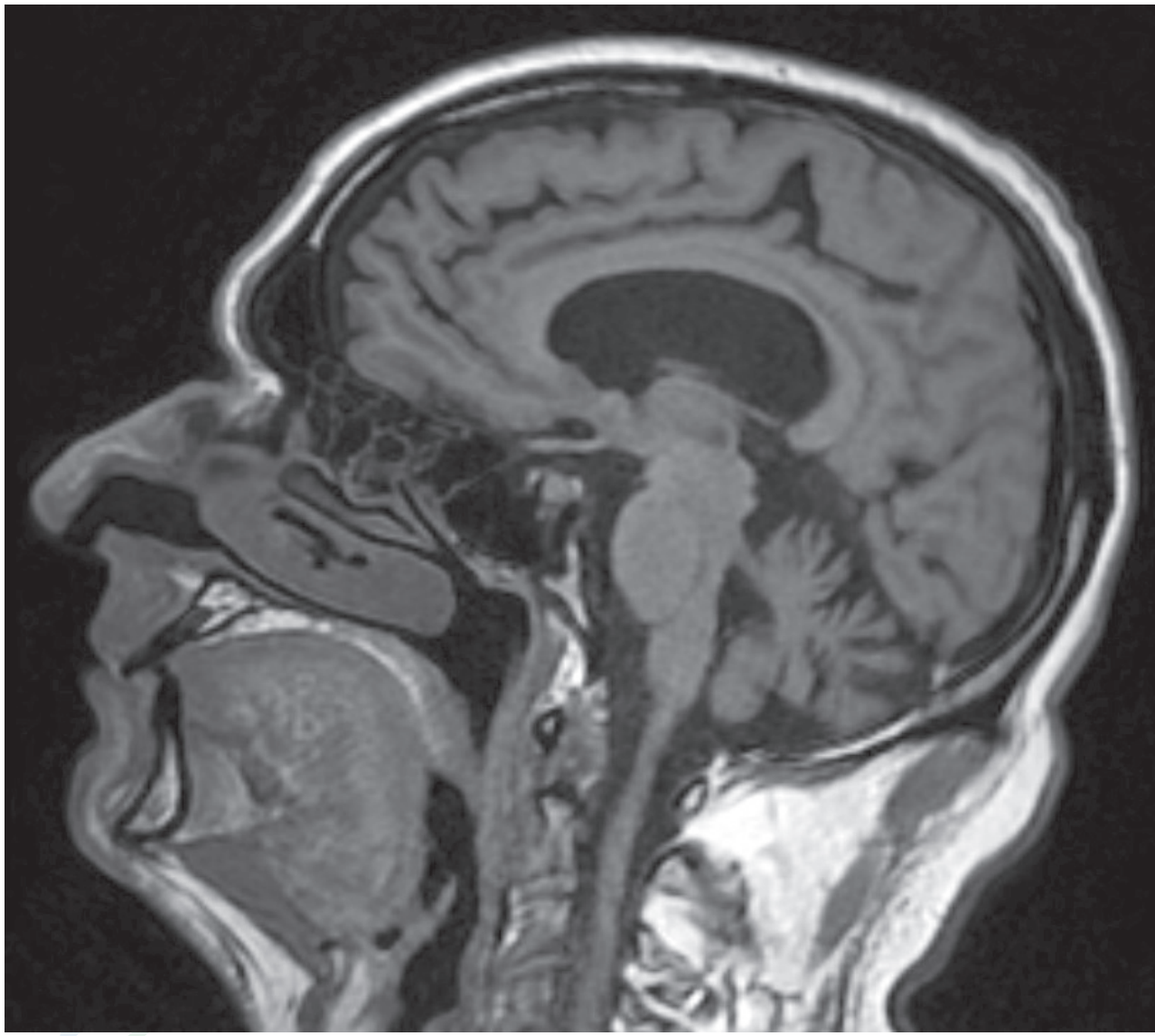

Figure 1 – Mild cerebellar atrophy most pronounced in the cerebellar vermis