CASO CLÍNICO/CASE REPORT

A *KIF5A* Motor Domain Pathogenic Variant Associated with Spastic Paraplegia Type 10 and Demyelination

Variante Patogénica do Domínio Motor do Gene *KIF5A* Associada a Paraparésia Espástica Tipo 10 e Desmielinização

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Abstract

Spastic paraplegia type 10 is an autosomal dominant disease caused by *KIF5A* gene pathogenic variants. It commonly presents as pure spastic paraplegia but occasionally appears associated with polyneuropathy, cognitive impairment, parkinsonism, cerebellar ataxia, retinitis pigmentosa or deafness. The gene *KIF5A* codifies the kinesin-1 heavy chain, a protein with three main parts (globular motor domain, alfa-helical stalk and C-terminal tail). Its complete genotype-phenotype is still unclear however, some degree of correlation has been seen between motor domain variations and SPG10 and Charcot-Marie-Toth type 2. The other domains are mainly associated with amyotrophic lateral sclerosis and neonatal intractable myoclonus. We present a case of a *KIF5A* gene motor domain disease-causing variant with white matter lesions and SPG10. Unlike the other parts of the protein, pathogenic variants of the motor domain have not been associated with white matter lesions. We believe this case contributes to further uncover the phenotypical spectrum of *KIF5A* related disorders.

Resumo

A paraplegia espástica tipo 10 é uma doença autossómica dominante causada por variantes patogénicas do gene *KIF5A*. Geralmente, manifesta-se como paraplegia espástica pura, porém outros sinais podem estar associados como polineuropatia, défice cognitivo, parkinsonismo, ataxia cerebelosa, retinite pigmentosa ou surdez. O gene *KIF5A* codifica a cadeia pesada da cinesina-1, uma proteína com três partes principais (domínio motor globular, haste alfa-helicoidal e cauda C-terminal). O seu genótipo-fenótipo completo não está totalmente esclarecido; contudo, foi observada alguma correlação entre variantes no domínio motor e SPG10 e Charcot-Marie-Tooth tipo 2. Os outros domínios estão associados à esclerose lateral amiotrófica e mioclonia neonatal intratável. Apresentamos um caso de variante patogénica no domínio motor do gene *KIF5A* com lesões na substância branca e SPG10. Ao contrário das outras partes, variantes patogénicas no domínio motor não foram associadas a lesões na substância branca. Acreditamos que este caso contribui para ampliar o espectro fenotípico das variantes do gene *KIF5A*.

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Introduction

Spastic paraplegia type 10 (SPG10) is a rare, autosomal dominant, hereditary spastic paraplegia associated with pathogenic variants in the *KIF5A* gene. SPG10 commonly presents as pure spastic paraplegia, however, there is evidence in the literature of less frequently associated complex phenotypes, including additional neurological signs besides spastic paraplegia. In these cases, the most frequently associated is sensitive and motor polyneuropathy, which can be subclinical and only detected in neurophysiological studies.[1,2] Less commonly associated features are cognitive impairment, parkinsonism, cerebellar ataxia, *retinitis pigmentosa* and deafness.[1-3]

Case Report

We present a case of a female patient first seen at our Movement Disorders outpatient clinic at 61 years of age. At 26 years old, she developed acute severe weakness in both her lower limbs that compromised standing up and walking unassisted. After a prolonged hospitalization, she recovered partially and was able to walk with crutches. After an initial partial recovery, during the following years, there was a slow progressive worsening of paraparesis. At 38 years old she was bound to a wheelchair. The patient denied sensitive changes, sphincter disturbances, cognitive impairment, or previous episodes suggestive of demyelinating disease, such as optic neuritis or other related symptoms. She had previous medical history of high blood pressure, dyslipidemia and smoking. She was the only child of non-consanguineous parents. The patient was raised by her paternal aunt following the death of her father during her childhood, attributed to complications from alcohol-associated diseases. She lost contact with her biological mother. Although she knew her mother exhibited a similar gait disturbance starting at age 50, she was never seen by a neurologist and the patient had limited information on further clinical details. The patient has one estranged son, now 40 years old, who remains asymptomatic. Therefore, segregation studies in the relatives were not possible. Current physical examination revealed severe spastic paraparesis, grade 2/5 muscle strength at hip adduction and grade 0/5 at remaining lower limb segments (Medical Research Council scale), hyperreflexia, bilateral inextinguishable clonus and bilateral Babinski sign. There were no superficial or deep sensitive abnormalities. Blood studies, including autoimmunity screening, serologic tests for infectious diseases and metabolic panels, were normal. Brain magnetic resonance imaging (MRI), done at 55 years of age, revealed multiple white matter T2/FLAIR hyperintense lesions with periventricular, subcortical and *corona radiata* distribution (**Fig. 1**), some of which hypointense in T1, suggestive of a demyelinating disease. These lesions were deemed out of proportion to be explained solely by microvascular disease. There were no optic nerve anomalies.

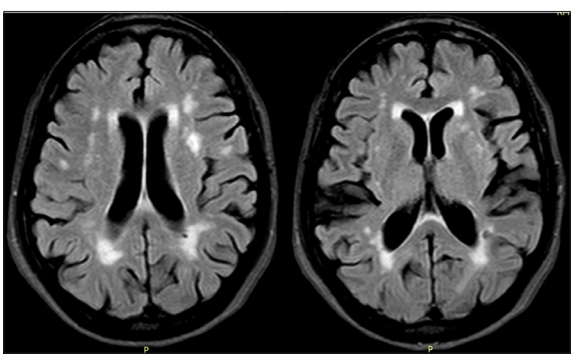

Figure 1. Brain MRI, FLAIR. Multiple periventricular, subcortical and corona radiata white matter lesions suggestive of a demyelinating disease.

To exclude for a central nervous system inflammatory disease, a complete medullar MRI and cerebrospinal fluid analysis, including oligoclonal band screening, were performed which did not reveal any abnormalities. Genetic tests revealed a heterozygous pathogenic variant on the *KIF5A* gene (c.610<T[p.(Arg204Trp]), previously reported as associated with SPG10.

The gene *KIF5A* codifies the heavy chains subunits of kinesin-1, a protein involved in fast anterograde axonal transport and composed of four subunits, two heavy chains and two light chains. Kinesin-1 heavy chains, coded by *KIF5A*, are divided in three main parts, a globular motor domain (from amino acid residues [aa]9-327), an alfa-helical stalk (aa331-906) and a C-terminal tail domain (aa907-1032).[4] Most of the pathogenic variants resulting in SPG10 are in the highly preserved motor domain, although some rarer pathogenic variants were found in the tail and stalk domains.[5] The complete genotype-phenotype correlation of the gene *KIF5A* is still not completely understood, mainly because of its rarity and few cases reported. Nonetheless, there is an apparent genotype-phenotype correlation in the *KIF5A* gene, especially on motor unit pathogenic variants which are clearly associated with SPG10 and Charcot-Marie-Tooth type 2. Disease-causing variants on the tail domain are mainly associated with

amyotrophic lateral sclerosis (ALS) and neonatal intractable myoclonus (NEIMY), a condition associated with severe progressive leukoencephalopathy. Stalk pathogenic variants are more heterogeneous and can present as either one of these diseases.[5]

Discussion

Interestingly, neuropathological studies have demonstrated that multiple sclerosis (MS) patients have a reduced white matter expression of *KIF5A* in all phases of the disease, suggesting the involvement of this protein in the pathophysiology of an inflammatory demyelinating disease.[6] Several genome-wide association studies have identified single nucleotide polymorphisms (SNP) on the *KIF5A* gene that confer susceptibility to MS.[7] Furthermore, there is a case reported in the literature of a patient diagnosed with primary progressive MS and a pathogenic variant on the gene *KIF5A* (p.Ala361Val), in the stalk domain of *KIF5A*.[8]

The disease-causing variant in our case is located on the motor domain of the *KIF5A* gene, not previously clearly associated with white matter lesions, unlike the other domains of the protein. In our review, we could only identify one case of SPG10 associated with severe white matter lesions in a patient presenting a *KIF5A* gene pathogenic variant in the motor domain (c.768_770delCAA, p.Asn256del). However, the association with a demyelinating phenotype was unclear as there was evidence of active demyelinating disease in this patient (immunoreactive CSF, partially contrast-enhancing lesions and corticoid responsiveness).[1] In our case, the white matter lesions seem to be caused by a neurodegenerative process, since a demyelinating disease was ruled out. These lesions might also have a role in the very severe clinical course observed, unlike most other cases described which were not wheelchair-bound even after a very long disease duration.[2]

We believe our case represents a possible association between SPG10-related pathogenic variants in the *KIF5A* motor domain and a central nervous system demyelinating process, contributing to further uncovering the phenotypical spectrum of *KIF5A*-related disorders. More reports are needed to further support this possible association.

Prémios e Apresentações Prévias / Presentations and Awards:

Este caso foi apresentado na forma de cartaz no Congresso Anual da Sociedade Portuguesa de Doenças do Movimento em 2023.

This case was presented in the form of poster at the Annual Congress of the Portuguese Movement Disorders Society in 2023. ■

Contributorship Statement / Declaração de Contribuição

Data collection: TJ, AP, LCG. Data analysis and interpretation: TJ, AP, VC, LCG. Review of literature: TJ, LCG. Writing of the first draft: TJ. Critical review and critique: AP, VC, LCG. All authors approved the final version to be published.

Colheita de dados: TJ, AP, LCG. Análise e interpretação de dados: TJ, AP, VC, LCG. Revisão da literatura: TJ, LCG. Escrita do primeiro rascunho: TJ. Revisão e crítica: AP, VC, LCG. Todos os autores aprovaram a versão final a ser publicada.

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