OSJI OPEN SCIENCE JOURNAL

CASE REPORT

Novel Missense Variant in SPTBN2 Possibly Associated with Spinocerebellar Ataxia Type 5 Presenting as Parkinson's Disease

Natalia Gonzalez Rojas[1*], Javier Enrique Ziliani[1]

[1]Fundacion Dr. Cesar R. Burry, Argentina

*Corresponding author: Natalia Gonzalez Rojas: natigonzalezrojas@hotmail.com

OPEN ACCESS

Citation: Gonzalez Rojas N., Ziliani J.E. (2022) Novel Missense Variant in SPTBN2 Possibly Associated with Spinocerebellar Ataxia Type 5 Presenting as Parkinson's Disease. Open Science Journal 7(4)

Received: 13th July 2022

Accepted: 6th December 2022

Published: 22nd December 2022

Funding: The author(s) received no specific funding for this work

Competing Interests: The authors have declared that no competing interests exists.

Abstract:

Spinocerebellar ataxias are a heterogeneous group of neurodegenerative diseases. There are more than 40 subtypes described so far, being spinocerebellar ataxia type 5 (SCA5) a rare autosomal-dominant ataxia with pure cerebellum involvement. The gene responsible is the non-erythrocyte beta 2 spectrin gene (SPTBN2), encoding β-III spectrin, highly expressed in Purkinje cells. Onset is usually before 30 years, although it ranges from infancy to 70 years. The main clinical manifestations are limb and gait ataxia (> 90%); however, some patients also show trunk ataxia, sensory deficits, abnormal eye movements, dysarthria, and hyperactive deep tendon reflexes (25–90%)

Keywords: Spinocerebellar ataxias, Parkinson's Diseas.

Introduction

Spinocerebellar ataxias are a heterogeneous group of neurodegenerative diseases. The underlying mechanisms include triplet CAG expansion in coding and no coding regions or conventional mutations leading to production and accumulation of abnormal proteins towards neurodegeneration, although many other mechanisms were identified, including toxic RNA gain-of-function, mitochondrial dysfunction, channelopathies, autophagy and transcription dysregulation. It is currently considered a rare disease with a worldwide prevalence of <1/1,000,000 [1].

There are more than 40 subtypes described so far, being spinocerebellar ataxia type 5 (SCA5) a rare autosomal-dominant ataxia with pure cerebellum involvement.

The gene responsible for SCA5 is the non-erythrocyte beta 2 spectrin gene (SPTBN2), encoding β-III spectrin, highly expressed in Purkinje cells. Its function

is to stabilize membrane proteins such as the receptor of glutamate. To date, more than 20 associated SPTBN2 mutations have been described [2].

Onset is usually before 30 years, although it ranges from infancy to 70 years. The main clinical manifestations are limb and gait ataxia (> 90%); however, some patients also show trunk ataxia, sensory deficits, abnormal eye movements, dysarthria, and hyperactive deep tendon reflexes (25–90%) [3]. We performed bibliographic research of the last 5 years through PubMed, finding a total of 9 publications between reviews and case reports.

Here we describe the clinical, genetic and neuroradiological features of a SCA5 case first diagnosed with Parkinson's disease.

Case report

A 44-year-old male of non-consanguineous parents, started 4 years ago with motor clumsiness in the right side of the body associated with ipsilateral akinetorigid symptoms. He was first treated as Parkinson´s disease with ropinirole with no response, switched after that to levodopa/carbidopa 250/25 mg tablets every four hours.

On physical examination, he revealed a right akinetorigid syndrome, as well as cerebellar ataxia in the right side of the body with moderate dysarthria, impaired gait with increased base of support and heightened generalized osteotendinous reflexes. Eye examination showed saccadic intrusions in pursuit eye movements and hypermetric saccades (Video 1, 2). He had a positive family history, as his father started with falls and gait problems at the age of 60.

Levels of vitamin B12 and thyroid function were normal. Celiac disease was ruled out. Abdominal ultrasound did not reveal any relevant findings. Brain MRI showed cerebellar atrophy with foliar accentuation. (Fig 1, 2) Electromyography (EMG) informed a sensory neuropathy.

Mini-Mental State Examination (MMSE) score was 22 and Montreal Cognitive Assessment (MoCA) score was 19.

Taking into account the paternal family history, a genetic test for hereditary ataxias was performed, finding a heterozygous variant of uncertain clinical significance in the SPTBN2 gene (p.Arg883Cys). Pathogenic variants in heterozygosity in the mentioned gene, with an autosomal dominant inheritance mechanism, are associated with Spinocerebellar Ataxia type 5 (SCA 5).

He started symptomatic treatment with gabapentin 300 mg three times a day and amantadine 100 mg three times a day with partial improvement.

Mutation analysis

We detected a heterozygous transition from cytosine to thymine in exon 15 of the STPBN2 gene (c.2647C>T), generating an amino acid change at position 883 in the protein (p. Arg883Cys). This variant of the missense type has been observed in a control population in relatively low frequency (GnomAD rs761263852 0.006%). In-silico predictors classify this variant as deleterious, and functional studies are necessary to define the true impact on the protein. Due to the above and following the ACMG international rules, the variant in the SPTBN2 c.2647C>T gene has been classified as clinically uncertain (PM2 PP3). (Table 1)

Discussion

SCA5 is an uncommon disease characterized by pure cerebellar limb and trunk ataxia, associated to uncoordinated eye movements, slurred speech and dysarthria. Onset can be very wide from infancy to adulthood, with the majority of cases within the 3rd or 4th decade [4]. In this case, we verified a novel heterozygous variant in SPTBN2 (c.2647C>T) by targeted next generation sequencing. The patient presented an asymmetric akinetorigid syndrome, progressively added walking instability, limb ataxia and dysarthria; confirming cerebellar involvement in the MRI.

Spectrins are a group of cytoskeletal membrane proteins composed of two main alpha subunits (SPTA1, SPTAN1) and five beta subunits (SPTB, SPTBN1-5) [5]. The non-erythrocytic beta spectrin 2 subunit (beta-III spectrin) is a 2391-amino acid protein encoded by SPTBN2 (11q13.2) and expressed throughout the soma and dendritic tree of cerebellar Purkinje cells, playing a role in maintaining dendritic architecture, trafficking and stabilization of several membrane proteins. Its malfunction reduces sodium currents and alters glutamatergic neurotransmission [6].

The causative gene was mapped in 1994 by Ranum and colleagues to the centromeric region of chromosome 11 in a single family descending from the grandparents of president of the United States, Abraham Lincoln [7].

To date, 20 variants of SPTBN2 have been reported for SCA5 [8,9]: 16 missense variants, two three-nucleotide in-frame deletion and two larger in-frame deletions. Through our research of the last 5 years we found 12 case reports associated with different missense mutations of the SPTBN2 gene around the world, mainly Europe, North America, and China. Despite the different reported ages of presentation, all emphasize the clinical homogeneity of the pathology, with clear pure cerebellar involvement. Despite this, there are childhood cases associated with psychomotor retardation or cerebral palsy in children [10]. In adults, the clinical manifestations are more predictable, with pure cerebellar and pyramidal involvement. To our knowledge, there is an infantile case reported in May 2022 by Benevides et al in Latin America, this being the first adult presentation along the continent.

Here, we identified a novel variant of SPTBN2 responsible for SCA5 in an Argentinean male with onset on the fifth decade resulting in extrapyramidal signs such as parkinsonian features and severe ataxia outlining the correlation between the genotype and phenotype of SCA5. We believe that this case is important and worthy of being reported, taking into account its atypical presentation, which opens the possibilities of considering this pathology within the range of differential diagnoses in Parkinson's disease. Continuous reports of possible pathogenic variants of the disease-causing gene should be further researched, as they may help to develop genetic counselling and investigate targeted pharmaceutical interventions.

References

1.Sullivan R, Yau WY, O'Connor E and Houlden H. Spinocerebellar ataxia: an update. Journal of Neurology (2019) 266:533–544 https://doi.org/10.1007/s00415-018-9076-4

2.Klockgether T, Mariotti C, Paulson HL (2019) Spinocerebellar ataxia. Nat Rev Dis Primers 5:24

3.Dick KA, Ikeda Y, Day JW, Ranum LP (2012) Spinocerebellar ataxia type 5. Handb Clin Neurol 103:451–459

4.Liquori C, Schut LJ, Clark HB et al. (2002). Spinocerebellar ataxia type 5 (SCA5). In: M Pandolfo (Ed.), Cerebellar Ataxias. Cambridge University Press, Cambridge, pp. 445–450.

5.Machnicka B, Czogalla A, Hryniewicz-Jankowska A et al. Spectrins: a structural platform for stabilization and activation of membrane channels, receptors and transporters. Biochim Biophys Acta. 2014;1838:620-634.

6.Efimova N, Korobova F, Stankewich MC et al. βIII Spectrin is necessary for formation of the constricted neck of dendritic spines and regulation of synaptic activity in neurons. J Neurosci. 2017;37:6442-6459.

7.Ranum LP, Schut LJ, Lundgren JK, Orr HT, Livingston DM(1994) Spinocerebellar ataxia type 5 in a family descended from the grandparents of President Lincoln maps to chromosome 11. Nat Genet 8:280–284

8.Nuovo S,Micalizzi A, D'Arrigo S, Ginevrino M, Biagini T, Mazza T, Valente EM(2018) Between SCA5 and SCAR14: delineation of the SPTBN2 p.R480W-associated phenotype. Eur J HumGenet 26:928–929

9.Accogli A, St-Onge J, Addour-Boudrahem N, Lafond-Lapalme J, Laporte AD, Rouleau GA, Riviere JB, Srour M (2020) Heterozygous missense pathogenic variants within the second spectrin repeat of SPTBN2 lead to infantile-onset cerebellar ataxia. J Child Neurol 35:106–110

10.Rea G, Tirupathi S, Williams J, Clouston P, Morrison PJ. Infantile onset of Spinocerebellar Ataxia Type 5 (SCA-5) in a 6 month old with ataxic cerebral palsy. The Cerebellum (2020) 19:161–163. https://doi.org/10.1007/s12311-019-01085-7