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Letter to the Editor

Gerstmann-Sträussler-Scheinker syndrome in an Argentinean family due to mutation at codon 117 of the Prion Protein Gene (PrPA117V)

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1. Introduction

Prion Diseases or Transmissible Spongiform Encephalopathies (TSEs) constitute rare neurodegenerative diseases, the most common being Creutzfeldt–Jakob disease (CJD). Fifteen percent (15%) of the cases worldwide are considered to be of the familial type and the remainder (85%) present as a sporadic disorder (sCJD) [1]. The familial (or genetic) type includes: genetic CJD (gCJD), fatal familial insomnia (FFI), and Gerstmann–Sträussler–Scheinker syndrome (GSS) [2]. Here we present the clinical findings of an Argentinean family with GSS due to mutation at codon 117 of the prion protein gene (PrPA117V), the first in Argentina and in Latin America.

2. Case 1

A 36 year old woman, number eight of the thirteen children in the family, was brought by her relatives complaining of dysarthria, dysphagia a right hemiparesis and ipsilateral movement disorders. The family history was relevant because her mother had a similar disorder featuring language and gait disturbances with a progressive course that led her to death two years after onset. Three siblings (two brothers and one sister) and the maternal grandfather had also died at a young age, but there was no more information about them and the cause of death remained unknown. She was descendant of Argentine indigenous both from maternal and paternal branch.

She had started two years before with right upper limb paresthesias, followed by recurrent falling and a right hemiparesis that led her bedridden in five months. At this point she developed rapidly progressive dysarthria. One year before, she had developed dysphagia leading to the loss of 15 kg. In the last months she developed movement disorders in the right hemibody and the family decided to bring her to our center.

At examination mental functions were difficult to assess due to dysarthria and the right hemiparesis but they seemed to be relatively preserved as we only could find mild defects in calculation and abstraction. Ocular movements revealed difficulty in initiating saccades. She had severely diminished gag reflex and myoclonic jerks in right arm and leg, predominating in the leg. Myoclonus was easily evoked by tactile stimuli or when she attempted to move. Plantar responses were extensor bilaterally and there were no sensory disturbances. The remainder of the examination was normal.

Laboratory studies were unremarkable. An electroencephalogram (EEG) was normal too. Magnetic Resonance Imaging (MRI) showed global atrophy most severe in the left hemisphere, special sequences including diffusion did not reveal additional information.

2.1. Case 2

Her brother, the sixth of the thirteen children in the family, is a 38 year-old patient who started one year ago with paresthesias in the right arm and subsequently developed progressive dysarthria that became very severe. Physical examination revealed severe dysarthria and mild cognitive deficits such as disorientation in time and a slight defect in working memory. A neuropsychological evaluation was consistent with mild cognitive impairment. There were no alterations in cranial nerves, motor and sensory systems were also normal and the remainder of the examination was normal.

Ancillary investigations including blood count, electrolytes, glucose, creatinine, urea, liver function test and lactic acid were unremarkable. EEGs were normal and the MRI showed similar findings as those observed in the previous case, with global atrophy more severe in the left hemisphere and without restriction at diffusion.

Analysis of PRNP gene coding region by PCR-Sanger sequencing by capillary electrophoresis in both siblings reported a mutation at codon 117 (PrPA117V). Both patients were heterozygous for the polymorphism c.385A > G; p.Met129Val and also had a heterozygous variant of uncertain pathogenic significance in codon 165 (c.494C > A;p.Arg165His). Clinical findings in conjunction with the reported mutation were consistent with Gerstmann–Sträussler–Scheinker syndrome. The family received genetic counseling. Symptomatic treatment was prescribed. (Fig. 1).

3. Discussion

The incidence of GSS is considered to be 1 in 100 million of population per year [3]. A local epidemiology of Creutzfeldt–Jakob disease surveillance performed in Argentina between 1997 and 2008 reported that out of the 517 patients referred to the surveillance center, 211 (40.8%) had CJD or other transmissible spongiform encephalopathies (TSEs). Eighty-three percent of TSE cases were sporadic CJD, 17% were genetic, the most common being (15.6%) a missense mutation resulting in the substitution of glutamate by lysine at codon 200 (E200K); the remaining 1.4% included an octarepeat insertion and two GSS cases with the proline to leucine point mutation at codon 102 (P102L).

In our cases, both patients presented an alanine to valine point mutation at codon 117 of the prion protein gene (PrPA117V) (Fig. 2), this mutation has not been previously reported in Argentina but is known to be present in few cases in France, Germany and in the United Kingdom with respect to European countries [2]. The relevance to mention the distribution of this mutation in European countries is that Argentina is known to be one of the main receptor countries of

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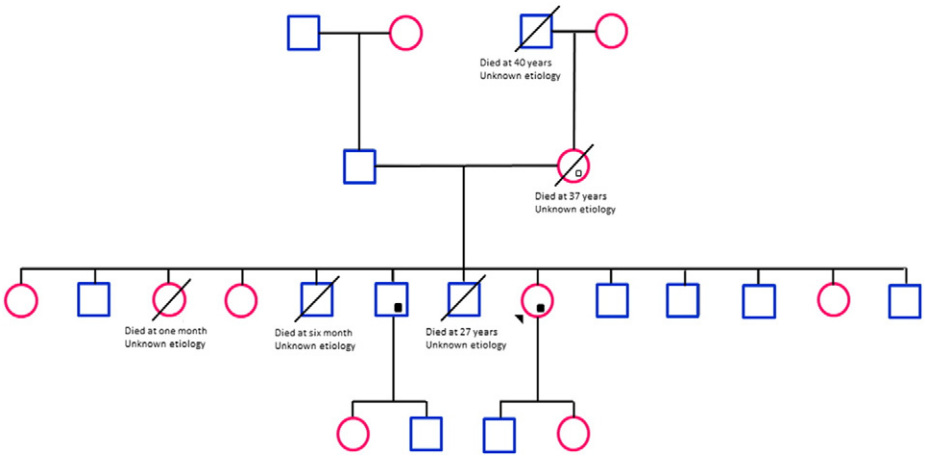

Fig. 1. Pedigree of the Argentinean family. Circles represent females and squares represent males. Symbols with lines through them represent deceased individuals (none of them had a diagnosis or the cause of death). Arrow represents the proband. Symbols with a shading square inside represent affected individuals with a genetic diagnosis, symbol with a square inside without shading represent an individual suspected to be affected but without a genetic diagnosis.

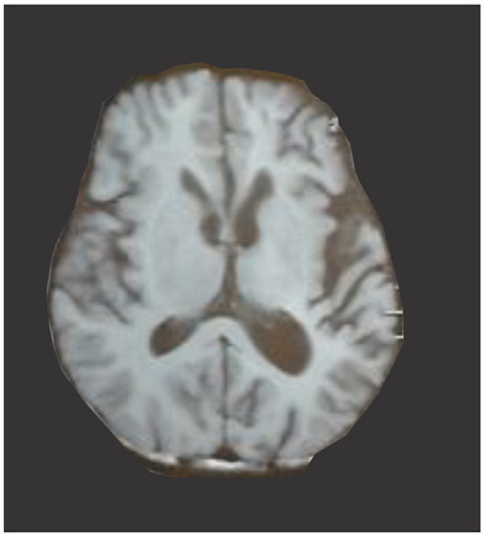

Fig. 2. Axial T1 showing global atrophy that is severe in the left hemisphere.

European emigration but our patients are from argentine indigenous descent.

Ancillary studies in our patients resulted normal (EEG) or nonspecific (MRI) (Fig. 3). In the EUROCJD neither the EEG nor the 14-3-3 tests helped in the clinical diagnosis of GSS and FFI. In the mentioned study MRI brain scan was positive in about 30% of GSS [2].

As treatment for prion diseases remains supportive this was the conduct with our patients, we prescribed rehabilitation and levetiracetam for myoclonus with partial response; promising gene therapy-based approaches are still under investigation [4].

4. Conclusion

To the best of our knowledge, this is the first case of a Latin American, Argentinean family with Gerstmann–Sträussler–Scheinker syndrome due to mutation at codon 117 of the prion protein gene (PrPA117V).

Competing interest statement

Michel Saenz Farret has no competing interest.

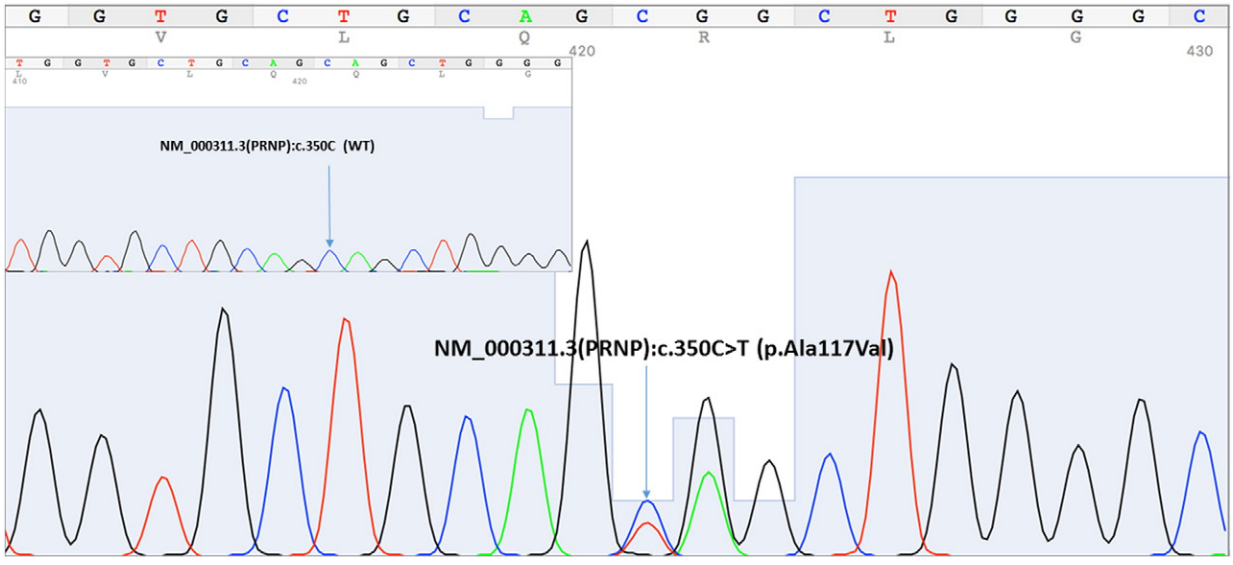

Fig. 3. Analysis of PRNP gene coding region of both siblings by PCR-Sanger sequencing by capillary electrophoresis reported an alanine to valine point mutation at codon 117 of the prion protein gene (PrPA117V).

Carolina Candelaria Ramirez-Gomez has no competing interest.
Natalia Araoz-Olivos has no competing interest.
Heidi Carrillo-Canedo has no competing interest.
Victoria Aldinio has no competing interest.
Veronica Gisela Montilla-Uzcategui has no competing interest.
Marcelo Kauffman served in the editorial board of Neurologia Argentina.
Federico Micheli has no competing interest.

Contributorship statement

Michel Saenz Farret conducted, planned, reported and revised the work.
Carolina Candelaria Ramirez-Gomez conducted and planned the work.
Natalia Araoz-Olivos conducted the work.
Heidi Carrillo-Canedo conducted the work.
Victoria Aldinio conducted the work.
Veronica Gisela Montilla-Uzcategui conducted the work.
Marcelo Kauffman conducted the work.
Federico Micheli planned, conducted and revised the work.

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Michel Saenz-Farret
Carolina Candelaria Ramirez-Gomez
Natalia Araoz-Olivos
Heidi Carrillo-Canedo
Victoria Aldinio
Veronica Gisela Montilla-Uzcategui
Parkinson's Disease and Movement Disorders Unit, Neurology Department, Hospital de Clinicas "Jose de San Martin", Buenos Aires University, Buenos Aires, Argentina

Marcelo Kauffman
Neurogenetics Unit, Neurology Department, Hospital J. M. Ramos Mejia and IBCN Eduardo de Robertis, University of Buenos Aires-CONICET, Argentina

Federico Micheli
Parkinson's Disease and Movement Disorders Unit, Neurology Department, Hospital de Clinicas "Jose de San Martin", Buenos Aires University, Buenos Aires, Argentina
Corresponding author at: Juncal 1695 Piso 5 J, Zip code 1062 Buenos Aires, Argentina.
E-mail address: Fmicheli@fibertel.com.ar.

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