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Case Report

Gerstmann-Sträussler-Scheinker Disease: A Case with Unusual Presentation in Association with Anti-GAD Antibodies

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Abstract

Introduction: Prion diseases have an incidence of 1/1,000,000. Familial, acquired or sporadic forms are described, the latter being the most frequent. Gerstmann-Sträussler-Scheinker syndrome (GSS) is a familial variant of prion diseases, whose symptoms usually manifest around the fifth decade of life, with cerebellar ataxia and dementia with a mean disease duration of 49 to 57 months. The most frequent mutation is found in the prion protein gene (PRNP) at residue 102 (P102L). Three families with GSS have been reported in Argentina. We report the fourth family, with an early age of onset.

Clinical Case: A 22-year-old woman who began 2 years earlier with progressive symptoms of emotional lability, mood swings, memory failures, delirious ideas and insomnia. She evolves with gait instability, falls, constipation and speech disorders. In the second year of evolution, she progresses to prostration, global aphasia and pyramidal syndrome. Her father had died at the age of 40 years with neuropsychiatric disorder interpreted as alcoholic cirrhosis by the family, which evolved to death in two years and her 27-year-old brother had cerebellar syndrome of 10 months of evolution. The cerebrospinal fluid study was normal, the electroencephalogram (EEG) showed slowing of background activity and periodic sharp waves, the magnetic resonance imaging (MRI) of the cerebellum was normal. Genetic test showed P102L mutation in the PRNP gene.

Conclusion: GSS is a rare cause of rapidly progressive dementia. Few families with early onset of symptoms have been reported in Argentina.

Keywords: *Prion Disease – Gerstmann-Sträussler-Scheinker - Early Onset - Antibodies - Anti GAD - Immune-Mediated Encephalopathies*

Introduction

Gerstmann-Sträussler-Scheinker syndrome (GSS) is a rare autosomal dominant progressive neurodegenerative prion disease with onset in the late fourties and an average illness duration of 49-57 months.

GSS typically starts with prominent ataxia and gait disturbances followed by cognitive decline and dementia at later stages. A common clinical finding is the presence of hyporeflexia or even absence of deep tendon reflexes with spasticity in the lower limbs. Other manifestations are painful dysesthesias, and less commonly, visual disturbances, dystonia, myoclonus, fasciculations, fibrillations, amyotrophy and progressive supranuclear palsy. Phenotypic variability is frequent and it is thought to result, in part, from genetic heterogeneity. Classically, the GSS has been divided into two major phenotypic groups.

The first corresponds to the initial description of GSS and can be divided into three subtypes: typical GSS, GSS with areflexia and paresthesia, described as a late-onset picture of ataxia and dementia, and GSS with pure dementia, characterized by early onset, early dementia, late ataxia and slow disease progression. The second main phenotype is known as Creutzfeldt-Jakob-like disease defined by late onset with early dementia and ataxia and rapid disease progression. [1,2,3,4,11]

GSS is associated with point mutation (P102L) in the human prion protein gene (PRNP), premature stop codon mutations and changes in the number of octapeptide repeat insertions (OPRI) in the unstructured region of the N-terminal domain. [1]

We report a patient with GSS disease with an early age of onset, some atypical clinical features and serum anti-GAD antibodies.

Case Presentation

A 22 years-old woman started in 2012 with emotional lability, delusional ideas, anosognosia and falls. A few months later she developed severe insomnia and rapidly progressive cognitive impairment. Within the first year the patient was demented, unable to walk, and presented sphincter incontinence. A brain MRI was performed at that time and the result was normal. In May 2014 she was admitted to our hospital. Personal medical history was unremarkable and family history was positive for alcoholic dementia in her father, who died at 40 years-old.

On physical examination we found serious cognitive impairment, unintelligible speech with some echolalia and severe trunk ataxia which prevented her to walk or remain standing. Deep tendon reflexes were brisk in four limbs with bilateral Babinski and Hoffman signs and bilateral ankle clonus. However, no spasticity was evident. Routine laboratory test, B12 vitamin, folic acid, thyroid hormones, cupremia, cupruria, ceruloplasmin and a rheumatologic screening were tested resulting in normal. Serology for HIV, VDRL, anti-peroxidase and anti-thyroglobulin antibodies were negative. She was evaluated by the gynecology service who also performed a gynecological ultrasound where no pathological findings were found. A computed tomography (CT) scan of the chest, abdomen and pelvis with intravenous contrast were performed and found to be normal.An electroencephalogram (EEG) was carried out and showed slow alpha background activity and periodic sharp waves (Figure 1). Cerebrospinal fluid analysis ruled out the presence of 14-3-3 protein. Serum anti-NMDA antibodies were normal while anti-GAD antibodies levels were increased (17.91 U/ml; normal value: < 1 U/ml).

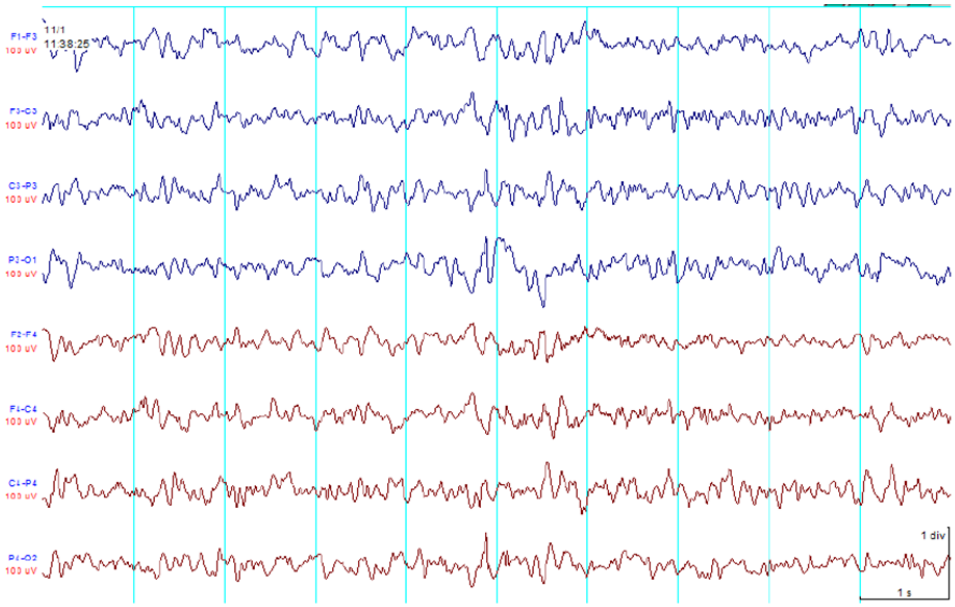

Figure 1. *EEG showing slowing generalized background activity and periodic sharp waves.*

Considering the possibility of immune-mediated encephalitis a trial with methylprednisolone 1 g/day with subsequent taper was conducted, but failed to achieve any improvement. A course of intravenous hyperimmune gamma globulin was also performed with negative results.A new brain MRI showed cortico-subcortical atrophy and hypointensities in FLAIR sequence in pallidum, thalamus, red nucleus and substantia nigra (Figure 2). Further inquiring about his father made us suspect that it was a familiar disease and that he was misdiagnosed. He had begun at 38 years-old with aggressive behavior, dysarthria and gait instability, followed by rapidly progressive dementia, dying 2 years later. Grandparents' history did not reveal neurological disease (Figure 3). Genetic analysis of the coding region of PRNP by PCR-sequencing showed a proline-to-leucine substitution within the N-terminal region of the PrP at codon 102 (P102L), supporting GSS diagnosis.

Two years later, her older brother of 28 years-old started with progressive trunkal and appendicular ataxia and cognitive impairments. He worsened rapidly and had to be institutionalized. Genetic test demonstrated the same mutation as in his sister, but anti GAD antibodies were < 1 U/ml. The patient developed generalized tonic-clonic seizures, which usually occur at night with a frequency of about twice a week. She ended up dying 10 years after the onset of the disease.

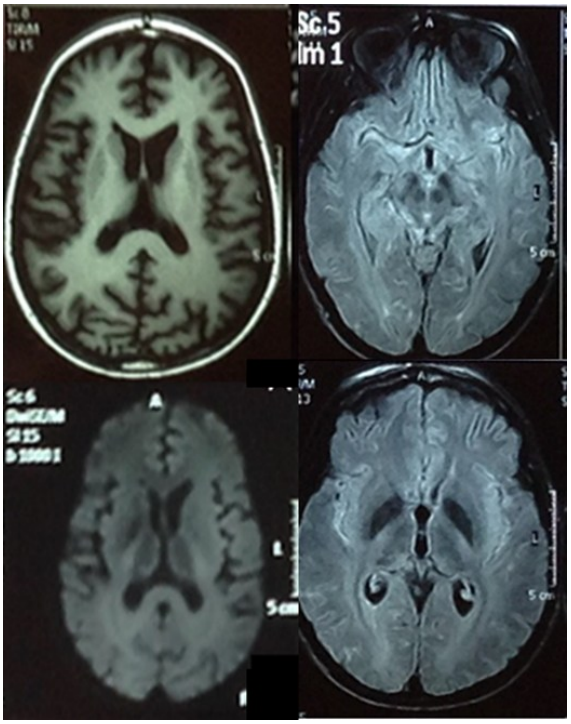

Figure 2. *MRI showing cortico-subcortical atrophy and hypointensities in FLAIR sequence in pallidum, thalamus, red nucleus and substantia nigra.*

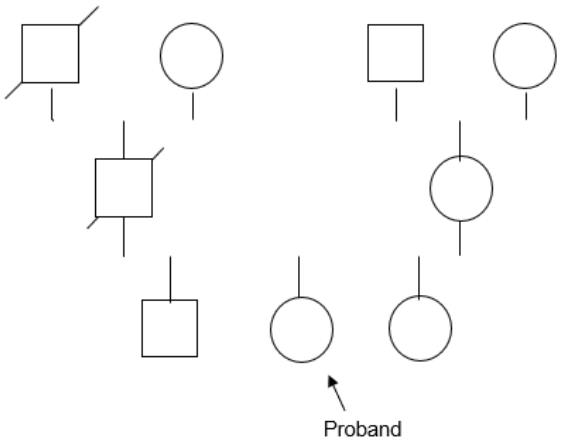

Figure 3

Discussion

This GSS case presents some unusual clinical features such as the early onset of the disease, the rapid development of dementia, the presence of hyperreflexia without spasticity in lower limbs, the occurrence of seizures, a long survival and the association with anti-GAD antibodies. Symptoms in our patient developed at an early age, and to our knowledge this is the youngest age of onset reported up today for a GSS patient, beginning when she was 22 years old. [12]

Cognitive decline is typically present in GSS, but is usually mild and occurs late in the course of the disease. Our patient presented delusional ideas and anosognosia in the first months of the disease followed by severe dementia within a year. Another atypical finding was anti-GAD antibodies, which have not been previously reported in GSS. [1-4]

There are a few reported cases where the patients initially were assumed to have prion diseases and they turned out to be immune-mediated encephalitis; and others where the opposite occurred, in which the initial diagnosis was an immune-mediated encephalitis and at last a prion disease was demonstrated.

There is a case in the literature of a woman with a rapidly progressive cerebellar ataxia and some cognitive complaints with elevated levels of 14-3-3 protein in CSF that turned out to be an anti-GAD65 cerebellar ataxia with cognitive impairment. Rare cases of patients with antibodies against voltage gated potassium channel (VGKC) mimicking dementing process similar to frontotemporal dementia or prionic dementia have been described. Conversely, two patients with autopsy-confirmed sporadic CJD with low titers of N-methyl-D-aspartate receptor antibodies (NMDAR Abs) were reported; other patient with post-mortem-confirmed CJD who had both kind of antibodies, against VGKC and glycine receptors, and a patient with GSS disease with high titers of Abs VGKC. As in our case, patients reported in the literature with prion diseases and positive antibodies failed to respond to immune-suppressive therapy. The presence of these antibodies in prion diseases is unknown, and could be induced by neuronal degeneration [5,6,7,8,9,10].

Conclusion

GSS is a rare cause of rapidly progressive dementia. Few families with early onset of symptoms have been reported in Argentina. Although cognitive decline typically presents in late states, it can manifest earlier as in our patient. The presence of GAD antibodies in low titers may be present but it's not common, thus it can be a challenge to arrive at the correct diagnosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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