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LETTER TO THE EDITOR

SPG46 spastic paraplegia due to GBA2 mutation: description of the first case in Spain

Paraparesia espástica SPG-46 por mutación de GBA2: a propósito del primer caso descrito en España

Hereditary spastic paraplegia refers to a group of neurodegenerative diseases presenting great heterogeneity both in clinical and genetic terms, which makes their diagnosis a challenging process. The true prevalence of hereditary spastic paraplegia in Spain is currently unknown; however, a recent study has estimated a rate of 2.24 cases per 100 000 population. In Spain, the most frequent autosomal dominant hereditary spastic paraplegias are SPG4 and SPG17, and SPG7 and SPG11 are the most frequent autosomal recessive forms.[1] Autosomal dominant, autosomal recessive, X-linked, and mitochondrial forms have been identified.

At least 86 genetic types have been described. There are pure and complex forms, which are accompanied by neurological or non-neurological symptoms. The first classification was established by Harding in 1983.[2]

Advances in the field of genomics represent a revolution in this disease, contributing to their diagnosis and the discovery of new variants.[3] We present the clinical case of a patient diagnosed with SPG46, a recessive form caused by a variant of the gene encoding the beta-glucosidase 2 enzyme (*GBA2*).

Our patient, a 57-year-old white woman, was referred to the neurology department due to a gait disorder progressing for several years. She presented no family history of neurodegenerative diseases, and her parents were non-consanguineous. The first motor symptoms (difficulty running) manifested during childhood, accompanied by poor performance at school. She was diagnosed with mild intellectual disability. Motor symptoms progressed slowly, becoming more apparent in the fifth decade of life, when she presented frequent falls. By the age of 54, she required a wheelchair.

The neurological examination revealed a Mini—Mental State Examination score of 26/30. The patient presented hypometric horizontal saccades, without nystagmus. Motor symptoms included dystonia of the hands, predominantly distal spastic tetraplegia, mainly affecting the lower limbs (proximal and distal muscle strength 4/5 in all 4 limbs), pyramidal signs (overactive tendon reflexes, bilateral extensor plantar reflex, and bilateral Achilles clonus), and pes cavus and equinus. Sensory symptoms included impaired positional sensitivity in the lower limbs. These symptoms were accompanied by such cerebellar symptoms as bradylalia, dysarthria, bilateral dysmetria on the finger-to-nose test and heel-to-knee test, and ataxic-spastic gait. An examination by the ophthalmology department diagnosed bilateral cataracts. A complete blood analysis (including thyroid hormones and vitamins, lactic and pyruvic acid, copper and ceruloplasmin, muscle enzymes, amino acids, sterols, and branched chain fatty acids) revealed no remarkable findings. The cerebrospinal fluid (CSF) study revealed elevated protein levels (77.9 mg/dL, normal range: 15—45) together with intrathecal IgG synthesis (oligoclonal in CSF and polyclonal in serum) with CSF IgG values of 4.75 mg/dL (normal range: 1—4), an IgG index of 0.00036, and a CSF albumin level of 27.7 mg/dL (normal range: 13.9—24.6).

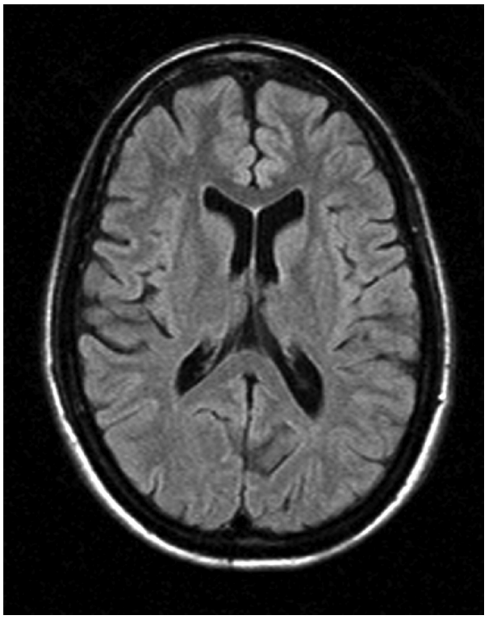

Figure 1 Brain MRI scan.

Somatosensory evoked potentials in the lower limbs showed increased latencies bilaterally, suggesting demyelination. A peripheral nerve study identified mixed (motor and sensory), mainly demyelinating neuropathy (probable secondary demyelination) of distal predominance. A brain (Fig. 1 and 2) and cervical spine MRI scan; a chest, abdomen, and pelvis CT scan; and a biopsy of the deltoid muscle and

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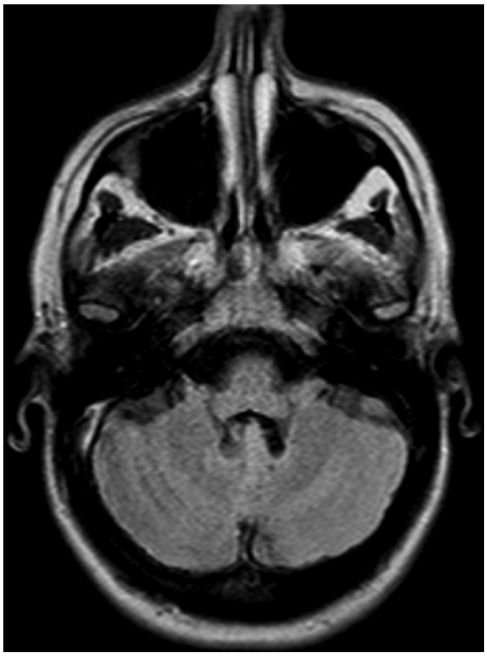

Figure 2 Cerebellar MRI scan.

sural nerve all showed normal results. A polymerase chain reaction (PCR) study of spinocerebellar ataxias (*SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *SCA12*, *SCA17*, *DRPLA*) revealed no alterations.

Lastly, we conducted a genetic study of spastic paraplegias (*NPC1*, *NPC2*, *GBA*, *GBA2*, *PSAP*, *POLG*, *APTX*, *HFE*, *CYP27A1*, and *ATP7A* genes), taking into account the genotype-phenotype correlation, using massive DNA sequencing (AmpliSeq and ultrasequencing with the Ion PGM platform). The study revealed the homozygous deletion of 2 nucleotides in exon 9 of the *GBA2* gene: Nm_020944:exon9:c.1475_1476del, predicted to result in a frameshift from codon 492 (NP_065995.1:p.T492fs). This variant was not found in a search of population and pathogenic variant databases.

Furthermore, a genetic study of the patient's brother (asymptomatic) revealed that he was a heterozygous carrier of the variant. No family segregation studies were performed (the parents and grandparents were deceased, and her only brother had no children). Results were confirmed by PCR and bidirectional Sanger sequencing, and a diagnosis of SPG was established.

The *GBA2* gene is located on chromosome 9, and has 17 exons.[4] It encodes the beta-glucosidase 2 enzyme, which catalyses the conversion of glucosylceramide to free glucose and ceramide.[5] Glucosylceramide is a precursor of sphingolipids, which are abundantly found in the cell membranes of the central nervous system. They have been observed to increase in number throughout growth and to change with axonal development and differentiation, and are important for the development of these neuronal structures.[6] The first cases of *GBA2* variants were described in 2013, in 3 families from Tunisia.[7] Since then, patients with *GBA2* variants have been described in Italy, China, Japan, Germany, and India,[8—13] both with the classic phenotype of pyramidal signs in the lower limbs accompanied by cerebellar symptoms and progressive cognitive impairment, and with such other symptoms as dystonia.[12,13]

In conclusion, we present the first case of SPG46 described to date in Spain. An unusual feature in our patient is the elevated CSF protein level, which has not been described in the reviewed literature. Advances in genomic sequencing have led to a revolution in hereditary spastic paraplegias. We would underscore the relevance of continuing to implement methods for genomic diagnosis in the field of neurology, as we believe that this will lead to findings in diseases not currently linked to a specific gene, and will open new pathways for possible therapies.

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Conflicts of interest

None.

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Neuroleptic malignant syndrome induced by aripiprazole depot

Síndrome neuroléptico maligno por aripiprazol depot

Dear Editor:

Aripiprazole is a second-generation antipsychotic drug indicated for schizophrenia. Extended-release injectable (ERI) formulations of aripiprazole were approved by the European Medicines Agency in 2013-2015.[1]

Neuroleptic malignant syndrome (NMS) is an infrequent but severe complication of first- and second-generation antipsychotics. It represents a neurological emergency[2]; diagnostic criteria include administration of an antipsychotic in the prior 72 hours, hyperthermia, rigidity, and altered level of consciousness (major criteria), and the presence of at least 3 of the following signs: tachycardia, diaphoresis, urinary incontinence, tachypnoea, blood pressure fluctuations, elevated creatine kinase (CK) level, and leukocytosis, after exclusion of other causes. NMS manifests 24-72 hours after the intake of antipsychotics, although it may take several days to present. It presents a monophasic course, with duration ranging from one to 44 days.[3]

NMS is less frequent and severe when caused by second-generation antipsychotics, and ERI formulations are not associated with increased frequency or mortality.[4,5]

We present an atypical case of NMS after the administration of ERI aripiprazole.

Our patient is a 37-year-old man with history of a psychotic episode of unknown origin 14 years earlier, who attended the emergency department due to delusional symptoms. The patient started treatment with antipsychotics and benzodiazepines, but due to suspicion that he was not taking the medication, 800 mg of ERI aripiprazole were administered.

At 30 days after the injection, the patient developed parkinsonian symptoms with severe rigidity and bradykinesia. He started treatment with oral diazepam, showing little response. At 4 days, he presented diaphoresis, tachypnoea, fever of up to 39°C, leukocytosis, and CK elevation of up to 630 U/L; level of consciousness was preserved. After diagnosis of possible NMS, he was transferred to the ICU and started treatment with dantrolene (60 mg/6 h intravenously) and bromocriptine (5 mg/8 h), after lumbar puncture ruled out focal systemic or central nervous system infection. Progression at the ICU was favourable, with good control of body temperature, improvement in parkinsonian symptoms, and normalisation of CK levels; at 10 days, he was transferred to the neurology ward. Subsequent progression was torpid, with fever of up to 40°C and exacerbated rigidity, but no CK elevation; a full-body CT scan yielded normal results. The patient was eventually transferred back to the ICU, where hyperthermia was managed with intravenous dantrolene. After showing good progression, he was transferred once more to the neurology ward.

Oral treatment with dantrolene (100 mg/8 h) had to be maintained, and dopaminergic agonists were replaced with levodopa to minimise psychiatric complications. We requested a blood analysis including antineuronal antibodies, and brain MRI and DaTSCAN studies; all tests showed normal results. The patient's condition improved progressively over the 3 following weeks, although strange utterances and obsessive thought persisted. Parkinsonian symptoms remitted at 6 weeks.

Given the good subsequent progression, no such therapeutic options as amantadine or electroconvulsive therapy were considered.

NMS is a neurological emergency, with incidence ranging from 0.02% to 3% of patients treated with antipsychotic drugs.[5,6]

ERI formulations are useful in avoiding relapses in patients with schizophrenia,[5] although they are less frequently used than oral formulations due to their higher cost and the fear of such adverse effects as NMS. However, there is no evidence showing a higher risk of NMS with ERI than with oral formulations.[3] There is evidence that the clinical course of NMS associated with ERI formulations is more severe.[5]

This case is an example of NMS associated with ERI aripiprazole. The delayed onset and the prolonged, biphasic course of NMS in our patient are atypical features with respect to classical descriptions of the disease.

NMS cases associated with aripiprazole present fewer motor complications and shorter duration due to the drug's pharmacodynamics (partial dopaminergic/serotonergic agonism).[7] However, the initial symptom in our patient was generalised rigidity, and lasted weeks.

These peculiarities in the progression of NMS may be due to the complex pharmacodynamics of ERI aripiprazole[8,9] and the doses used. Although NMS is an idiosyncratic reaction,