off' the immune system. Ther Adv Neurol Disord. 2018;11, http://dx.doi.org/10.1177/1756286418799864.
7. Yshii LM, Hohlfeld R, Liblau RS. Inflammatory CNS disease caused by immune checkpoint inhibitors: status and perspectives. Nat Rev Neurol. 2017;13:755—63.
8. Kolb NA, Trevino CR, Waheed W, Sobhani F, Landry KK, Thomas AA, et al. Neuromuscular complications of immune checkpoint inhibitor therapy. Muscle Nerve. 2018, http://dx.doi.org/10.1002/mus.26070.
9. Suzuki S, Ishikawa N. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. Neurology. 2017;89:1127—34.
10. Astaras C, de Micheli R, Moura B, Hundsberger T, Hottinger AF. Neurological adverse events associated with immune checkpoint inhibitors: diagnosis and management. Curr Neurol Neurosci Rep. 2018;18:3.
11. Makarious D, Horwood K, Coward JIG. Myasthenia gravis: an emerging toxicity of immune checkpoint inhibitors. Eur J Cancer. 2017;82:128—36.
12. Menzies AM, Johnson DB. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol. 2017;28:368—76.
13. Cooper DS, Meriggioli MN, Bonomi PD, Malik R. Severe exacerbation of myasthenia gravis associated with checkpoint inhibitor immunotherapy. J Neuromuscul Dis. 2017;4:169—73.
14. Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, et al. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. N Engl J Med. 2019;380:2377—9.

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A Spanish family with a compound heterozygous mutation in *SPG7*: From uncertainty to clinical reality

Familia española portadora de una mutación en heterocigosis compuesta en el gen *SPG7*: de la incertidumbre a la realidad clínica

Spastic paraplegia type 7 (SPG7; OMIM #607259) is an autosomal recessive disorder caused by mutations in the *SPG7* gene, which encodes the mitochondrial metalloprotease paraplegin.[1] It accounts for approximately 5%-12% of all autosomal recessive forms and up to 7% of sporadic cases in adults. It has also been associated with symptoms of cerebellar ataxia,[2] which may constitute the most relevant clinical manifestation. However, phenotypic variations are more complex; the literature includes cases of chronic progressive external ophthalmoplegia,[3] primary lateral sclerosis,[4] and parkinsonism.[5]

Over 131 pathogenic variants have been described (Human Gene Mutation Database, accessed 14 July 2019). We report the cases of 3 sisters from a Spanish family, who presented ataxia and spasticity and were carriers of 2 single nucleotide variants of uncertain significance in the *SPG7* gene.

We studied a family of 7 siblings born to non-consanguineous parents and with no family history of neurological disease. Three of them (3 women) reported progressive difficulty walking, with instability and dysarthria appearing in the third decade of life. A clinical examination performed after 20 years of disease progression revealed multidirectional nystagmus, dysarthria, global hyperreflexia with bilateral extensor plantar reflex, and marked spasticity of the lower limbs, with the patients requiring bilateral support to walk. The eldest of the 3 sisters also presented cognitive impairment, ophthalmoparesis, upper limb dysmetria, and wide-based gait. All 3 showed cerebellar atrophy on MR images (Fig. 1). The remaining siblings were not affected (Fig. 2A).

After ruling out secondary causes and the mutations most frequently associated with ataxia and spastic paraparesis in the proband, we conducted a genetic study of the *SPG7* gene. We detected 2 missense mutations, and decided to perform the genetic study in the remaining siblings.

Peripheral blood samples were collected and we performed DNA amplification by PCR and traditional DNA sequencing with the ABI 3730® analyser (Applied Biosys-

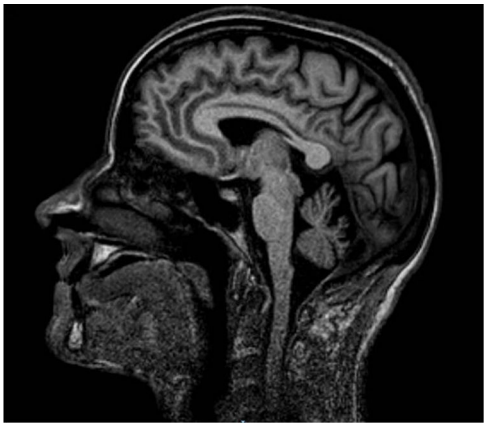

Fig 1 T1-weighted sagittal brain MRI scan showing cerebellar atrophy.

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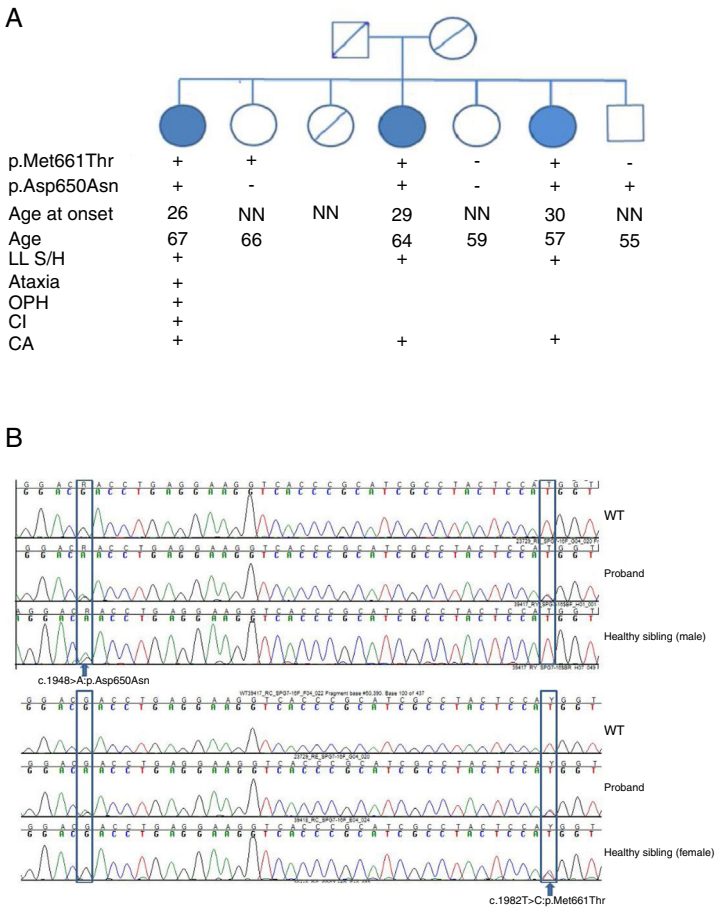

Fig 2 *SPG7* mutations and clinical correlations. (A) Pedigree chart of the family. CA: cerebellar atrophy; CI: cognitive impairment; LL S/H: lower limb spasticity/hyperreflexia; NN: neurologically normal; OPH: ophthalmoparesis; +: present; —: absent. (B) Sanger sequencing of the *SPG7* gene. Heterozygous mutations are indicated with arrows.

tems; Foster City, CA, USA). We studied all coding exons and exon-intron boundaries. We also analysed small deletions/insertions and point mutations in the coding regions and splice sites of *SPG7*.

We detected 2 compound missense mutations (NM_003119.3:c.1982T>C:p.Met661Thr and NM_003119.3:c.1948G>A:p.Asp650Asn) in heterozygosis in the 3 siblings affected. Two unaffected siblings carried one of the mutations each, and another carried neither (Fig. 2B).

The clinical and genetic significance of the variants was established by studying population frequencies, conservation scores (GERP, Phylophen, SiPhy), and prediction scores (SIFT, Polyphen, Mutation Taster, Mutation Assessor, LRT, CADD, DANN) for each variant. We reviewed the available information on *SPG7* variants previously associated with the disease (published articles, OMIM®, GeneReviews®, ClinVar, Human Gene Mutation Database). We also studied family segregation, although no samples were available from either of the parents.

In silico predictions and the clinical and genetic criteria studied support the pathogenic potential of both variants. Variant p.Met661Thr is not included in population frequency databases, and was found in compound heterozygosity in a patient with suspected pure spastic paraparesis.[6] Variant p.Asp650Asn, in turn, presents a population frequency of 0.001% and had previously been detected in a sporadic case in a patient with ataxia as the main symptom and who also presented symptoms of upper motor neuron involvement.[7] In both cases, all conservation and prediction algorithms signalled a functional impact on the protein.

The patients presented here show the characteristic clinical features, with some exceptions. The patient with the longest disease progression time presented more severe ataxia and less common symptoms, including ophthalmoparesis and cognitive impairment.

These phenotypic differences may be explained by the accumulation of symptoms over the period of disease progression; however, we lack prospective follow-up data.

Both mutations have been classified as variants of uncertain significance, and have previously been described in only 2 cases. The clinical and genetic data presented here support the pathogenic role of these mutations. However, further research is necessary to evaluate their pathogenicity.

To our knowledge, this is the first study to report the occurrence of both variants in a single family with spastic ataxia. Although no samples were available from the parents, the segregation of both variants in different affected and non-affected siblings suggests that each variant comes from one parent.

References

1. Casari G, De Fusco M, Ciarmatori S, Zeviani M, Mora M, Fernández P, et al. Spastic paraplegia and OXPHOS impairment caused by mutations in Paraplegin, a nuclear-encoded mitochondrial metalloprotease. Cell. 1998;93:973—83.
2. Yahikozawa H, Yoshida K, Sato SH, Hanyu N, Doi H, Miyatake S, et al. Predominant cerebellar phenotype in spastic paraplegia 7 (SPG7). Hum Genome Var. 2015;26:15012.
3. Pfeffer G, Gorman GS, Griffin H, Kurzawa-Akanbi M, Blakely EL, Wilson I, et al. Mutations in the SPG7gene cause chronic progressive external ophthalmoplegia through disordered mitochondrial DNA maintenance. Brain. 2014;137:1323—36.
4. Yang Y, Zhang L, Lynch DR, Lukas T, Ahmeti K, Sleiman PM, et al. Compound heterozygote mutations in SPG7 in a family with adult-onset primary lateral sclerosis. Neurol Genet. 2016;2:e60.
5. Pedroso JL, Vale TC, Bueno FL, Marussi VHR, Amaral LLFD, França MC Jr, et al. SPG7 with parkinsonism responsive to levodopa and dopaminergic deficit. Parkinsonism Relat Disord. 2018;47:88—90.
6. Sánchez-Ferrero E, Coto E, Beetz C, Gámez J, Corao AI, Díaz M, et al. PG7 mutational screening in spastic paraplegia patients supports a dominant effect for some mutations and a pathogenic role for p.A510V. Clin Genet. 2013;83:257—62.
7. Fogel BL, Lee H, Deignan JL, Strom SP, Kantarci S, Wang X, et al. Exome sequencing in the clinical diagnosis of sporadic or familial cerebellar ataxia. JAMA Neurol. 2014;71:1237—46.

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Associated posterior reversible encephalopathy syndrome (PRES) to SARS-CoV-2. Case report

Síndrome de encefalopatía posterior reversible (PRES) asociado a SARS-CoV-2. Reporte de caso

Dear Editor:

Since the beginning of the COVID-19 pandemic, a wide range of manifestations, particularly respiratory symptoms, have been associated with SARS-CoV-2 infection. However, due to the neurotropic and neuroinvasive potential of the virus, cases have also been observed of such neurological symptoms as anosmia, dysgeusia, headache, cerebrovascular accidents, seizures, Guillain-Barré syndrome, and encephalitis.[1—3]

We present the case of a patient with posterior reversible encephalopathy syndrome (PRES) associated with SARS-CoV-2 infection.

Our patient was a 46-year-old man (clinical characteristics and medical history are shown in Table 1) who visited the emergency department with a 4-day history of muscle pain, cough, hyposmia, dysgeusia, and fever. The initial examination revealed dyspnoea, fever (39.0°C), arterial blood pressure of 130/70 mm Hg, and oxygen saturation of 85%. Chest CT revealed multiple subpleural and peribronchovascular areas of ground-glass opacification, predominantly in the inferior lobes, as well as subpleural consolidation (Fig. 1A). Reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal exudate returned positive results for SARS-CoV-2. We started treatment with hydroxychloroquine, azithromycin, and cefuroxime. Three days later, the patient presented exacerbation of dyspnoea, with oxygen saturation of 60%, and required invasive mechanical ventilation (IMV) and admission to the intensive care unit. From admission, he presented poorly controlled blood pressure imbalance, with a mean arterial pressure (MAP) of 120-130 mm Hg. He was extubated 9 days later (22 days after symptom onset), and presented disorientation, psychomotor agitation, and disconnection from his surroundings. A contrast-enhanced MRI scan revealed bilateral subcortical and white matter hyperintensities in the occipital and frontal lobes on T2-weighted and FLAIR sequences; the lesions were hypointense on T1-weighted sequences and showed no diffusion restriction or contrast uptake (Fig. 1 B and C). An EEG study revealed no alterations. However, 48 hours after extubation, the patient required orotracheal intubation; IVM was maintained for a further 7 days. After the second extubation, the patient continued to present disorientation, which improved progressively. He reported no visual impairment, and presented quadriparesis predominantly affecting the lower limbs; quadriparesis improved and the patient was able to walk with assistance at discharge. He was discharged 34 days later, presenting no alterations in cognitive function; lower limb weakness persisted. A follow-up MRI scan performed 15 days after the initial scan revealed resolution of the hyperintense lesions in the frontal and occipital lobes; these findings are compatible with PRES (Fig. 1D).

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