6. Ferrante MA, Wilbourn AJ. Lesion distributions among neuralgic amyotrophy patients. Muscle Nerve. 2008;38:1372.
7. Lindgren B, Rivers D, Clark J. Bilateral Parsonage-Turner syndrome after initial unilateral presentation: a case report. Cureus. 2019;11:e6422, http://dx.doi.org/10.7759/cureus.6422.
8. van Alfen N, van Eijk JJ, Ennik T, Flynn SO, Nobacht IE, Groothuis J, et al. Incidence of neuralgic amyotrophy (Parsonage Turner syndrome) in a primary care setting — a prospective cohort study. PLoS One. 2015;10:e0128361, http://dx.doi.org/10.1371/journal.pone.0128361.
9. Gstoettner C, Mayer JA, Rassam S, Hruby LA, Salminger S, Sturma A. Neuralgic amyotrophy: a paradigm shift in diagnosis and treatment. J Neurol Neurosurg Psychiatry. 2020;91:879—88, http://dx.doi.org/10.1136/jnnp-2020-323164.
10. Seror P. Neuralgic amyotrophy. An update. Joint Bone Spine. 2017;84:153—8, http://dx.doi.org/10.1016/j.jbspin.2016.03.005.
11. Ferrante MA, Wilbourn AJ. The timing and distribution of triggers among 268 bouts of neuralgic amyotrophy. Neurology. 2010;74 Suppl. 2:A529.
12. Nagano A. Spontaneous anterior interosseous nerve palsy. J Bone Joint Surg Br. 2003;85:313—8, http://dx.doi.org/10.1302/0301-620x.85b3.14147.
13. Lundborg G. Commentary: hourglass-like fascicular nerve compressions. J Hand Surg Am. 2003;28:212—4, http://dx.doi.org/10.1053/jhsu.2003.50040.
14. Arányi Z, Csillik A, Dévay K, Rosero M, Barsi P, Böhm J, et al. Ultrasonographic identification of nerve pathology in neuralgic amyotrophy: enlargement, constriction, fascicular entwinement, and torsion. Muscle Nerve. 2015;52:503—11, http://dx.doi.org/10.1002/mus.24615.

G. Rusin[a,*], R. Morga[b], M. Spaczyńska-Boczar[a], W. Rudnicki[c], B.M. Kwinta[d], E. Luczynska[c], A. Słowik[a,e], J. Antczak[a,e]

[a] *Department of Neurology, University Hospital in Krakow, Jakubowskiego 2, Krakow, Poland*
[b] *Department of Neurosurgery, University Hospital in Krakow, Jakubowskiego 2, Krakow, Poland*
[c] *Electroradiology Department, Jagiellonian University Medical College, Jakubowskiego 2, Krakow, Poland*
[d] *Department of Neurosurgery and Neurotraumatology, Jagiellonian University Medical College, Jakubowskiego 2, Krakow, Poland*
[e] *Department of Neurology, Jagiellonian University Medical College, Jakubowskiego 2, Krakow, Poland*

* Corresponding author.
E-mail address: grusin@su.krakow.pl (G. Rusin).

https://doi.org/10.1016/j.nrleng.2022.11.002

Hereditary spastic paraparesis due to SPG5/CYP7B1 mutation with potential therapeutic implications

Paraparesia espástica hereditaria por mutación en SPG5/CYP7B1 con potenciales implicaciones terapeúticas

Dear Editor:

Spastic paraplegia type 5 (SPG5) is an extremely rare disease caused by mutations to the *CYP7B1* gene, with prevalence estimated at 1 case per 1 000 000 population.[1] To date, 56 families with SPG5 have been described worldwide. While one epidemiological series reports the presence of the disease in Spain (5 cases),[2] no study published to date has described the clinical phenotype or specific molecular findings. The first symptoms tend to appear during childhood or adolescence, with patients losing the ability to walk independently within approximately 23 years of disease onset. Patients usually present pure phenotypes, although some cases of complex forms have been reported.

DOI of refers to article: https://doi.org/10.1016/j.nrl.2023.05.001

We present the cases of 2 siblings with SPG5, born to consanguineous parents, with no direct family history of neurological disease (Fig. 1). Both patients have been under follow-up by the neurology department since adolescence, when they developed a gait disorder. Patient 1 presented difficulty walking at 16 years of age, subsequently devel-

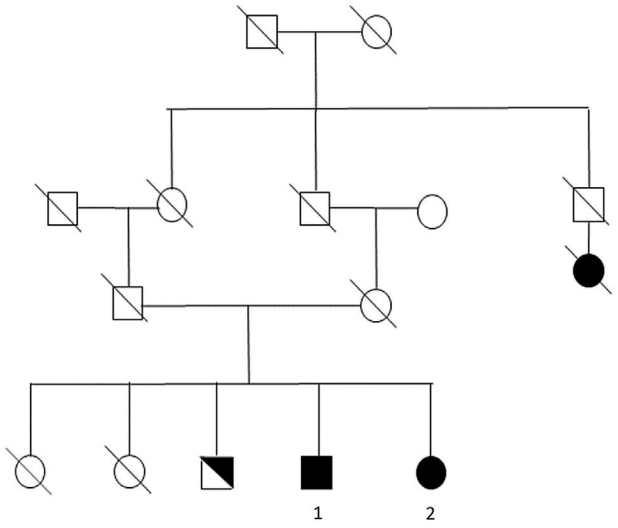

Figure 1 Pedigree chart of our patients' family. Affected individuals are filled in black. The patients reported in this study are labelled 1 and 2. The third brother, an asymptomatic carrier, is shown in black and white.

oping signs of lower limb spasticity around the age of 20. Symptoms progressed, and he needed support to walk by the age of 30 years, and a wheelchair by 55 years of age. Patient 2 (the sister of patient 1) presented similar disease progression, with onset at 17 years of age, and needed to use crutches at 22 years and a wheelchair at 59 years of age. In both patients, the clinical syndrome was considered to be a form of pure spastic paraplegia (no complementary neurological symptoms were detected). Currently, both patients also present urological symptoms (urinary urgency).

In a neurological examination, both patients presented normal cognitive test scores. Both patients displayed symptoms of spastic paraplegia with predominantly lower limb involvement, with muscle weakness (4/5 by muscle group), pyramidal signs (overactive reflexes in the lower limbs with bilateral extensor plantar reflex, persistent bilateral Achilles clonus, and pes cavus), and reduced positional and vibration sensitivity in the lower limbs.

Of 5 siblings, the 2 eldest sisters were deceased, with one dying within days of birth and the other at one year of age; the causes of death were unknown. The other living brother presented no neurological symptoms. A cousin of our patients' parents (not evaluated) presented similar symptoms, with a gait disorder of childhood onset, and died at 60 years of age. Imaging studies (brain and cervical spine MRI), an electromyography study including nerve conduction velocities, and complete blood count detected no major alteration in either patient.

With the patients' informed consent, DNA samples were taken for massive parallel sequencing analysis of the coding regions of a panel of 109 genes associated with spastic paraplegia; results were analysed using the Imegen Data Genomics software. All variants classified as pathogenic were confirmed with Sanger sequencing. The analysis detected the c.825T>A variant of *CYP7B1* in homozygosis. This change causes a premature stop codon at position 275 (p.Tyr275*), resulting in absence or alteration of the protein product. The healthy older brother was also tested, and was found to be a heterozygous carrier of the same variant, confirming the segregation of the mutation. The remaining family members were not available for analysis. Functional analysis of the protein was not performed. In silico analysis using the ClinVar and Varsome programs determined that the variant identified was pathogenic. Both patients started treatment with atorvastatin and ezetimibe.

The *CYP7B1* gene encodes the enzyme oxysterol 7α-hydroxylase, which is involved in the degradation of cholesterol into primary bile acids. Deficiency of the enzyme is associated with accumulation of neurotoxic oxysterols that may play a key role in SPG5, with potential therapeutic implications.[2,3]

Short-term treatment with atorvastatin has been shown to significantly reduce levels of the toxic metabolite 27-OHC in the serum of patients with SPG5, suggesting a treatment strategy targeting the cause of the disease.[4,5] Therefore, diagnosis of the disease is relevant due to the availability of a potentially efficacious treatment alternative, although to date this has only been validated using surrogate markers in a small series. In our patients, the short duration of follow-up after onset of statin treatment prevents us from drawing conclusions regarding this question; in the long term, controlled trials are needed to more comprehensively study this type of treatment.

Funding

This study has received no specific funding from any public, commercial, or non-profit organisation.

References

1. Schule R, Wiethoff S, Martus P, Karle KN, Otto S, Klebe S, et al. Hereditary spastic paraplegia: clinicogenetic lessons from 608 patients. Ann Neurol. 2016;79:646—58.
2. Ortega Suero G, Abenza Abildúa MJ, Serrano Munuera C, Rouco Axpe I, Arpa Gutiérrez FJ, Adarmes Gómez AD, et al. Epidemiology of ataxia and hereditary spastic paraplegia in Spain: a cross-sectional study. Neurologia (Engl Ed). 2021;25, http://dx.doi.org/10.1016/j.nrl.2021.01.006. S0213-4853(21)00021-9.
3. Heverin M, Meaney S, Lütjohann D, Diczfalusy U, Wahren J, Björkhem I. Crossing the barrier: net flux of 27-hydroxycholesterol into the human brain. J Lipid Res. 2005;46:1047—105.
4. Schöls L, Rattay TW, Martus P, Meisner C, Baets J, Fischer I, et al. Hereditary spastic paraplegia type 5: natural history, biomarkers and a randomized controlled trial. Brain. 2017;140:3112—27, http://dx.doi.org/10.1093/brain/awx273.
5. Mignarri A, Malandrini A, Del Puppo M, Magni A, Monti L, Ginanneschi F, et al. Hereditary spastic paraplegia type 5: a potentially treatable disorder of cholesterol metabolism. J Neurol. 2014;261:617—9, http://dx.doi.org/10.1007/s00415-014-7253-7.

P. Pérez-Torre[a], E. García Galloway[b], J.L. López-Sendón Moreno[a,*]

[a] *Servicio de Neurología, IRYCIS, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[b] *Servicio de Genética, Hospital Universitario Ramón y Cajal, Madrid, Spain*

* Corresponding author.
E-mail address: jlsendonmoreno@salud.madrid.org (J.L. López-Sendón Moreno).

https://doi.org/10.1016/j.nrleng.2023.10.005