4. Maguire M, Singh J, Marson A. Epilepsy and psychosis: a practical approach. Prac Neurol. 2018;18:106—14, http://dx.doi.org/10.1136/practneurol-2017-001775.
5. Hilger E, Zimprich F, Pataraia E, Aull-Watschinger S, Jung R, Baumgartner C, et al. Psychoses in epilepsy: a comparision of postictal and interictal psychoses. Epilepsy Behav. 2016;60:58—62, http://dx.doi.org/10.1016/j.yebeh.2016.04.005.
6. Elliot B, Joyce E, Shorvon S. Delusions, illusions and hallucinations in epilepsy: 2. complex phenomena and psychosis. Epilepsy Res. 2009;85(2—3):172—86, http://dx.doi.org/10.1016/j.eplepsyres.2009.03.017.
7. Werner F-M, Coveñas R. Classical neurotransmitters and neuropeptides involved in generalized epilepsy in a multineurotransmitter system: how to improve the antiepileptic effect? Epilepsy Behav. 2015, http://dx.doi.org/10.1016/j.yebeh.2015.01.038.
8. Picard F. Epileptic feeling of multiple presences in the frontal space. Cortex. 2010;46:1037—42, http://dx.doi.org/10.1016/j.cortex.2010.02.002.
9. Brugger P, Regard M, Landis T. Unilaterally felt 'presences': the neuropsychiatry of one's invisible doppelganger. Neuropsychiatry Neuropsychol Behav Neurol. 1996;9:114—22.
10. Persinger MA, Bureau YR, Peredery OP, Richards PM. The sensed presence as right hemispheric intrusions into the left hemispheric awareness of self: an illustrative case study. Percept Mot Skills. 1994;78:999—1009.

A. Moreno-Estébanez[a,*], A. Marinas Alejo[a], S.J. Ontiveros Navarro[b], I. Bilbao Villabeitia[a]

[a] *Servicio de Neurología, Hospital Universitario de Cruces, Barakaldo, Vizcaya, Spain*
[b] *Servicio de Neurofisiología, Hospital Universitario de Cruces, Barakaldo, Vizcaya, Spain*

* Corresponding author.
E-mail address: anamorenoest@hotmail.com
(A. Moreno-Estébanez).

5 February 2019

https://doi.org/10.1016/j.nrleng.2019.05.005
2173-5808/

Parkinson's disease secondary to 2 mutations of genes involved in lysosomal protein degradation*

Enfermedad de Parkinson por sendas mutaciones en 2 genes relacionados con la degradación por lisosomas

Dear Editor,

The precise mechanisms of neuronal degeneration in Parkinson's disease (PD) are yet to be determined. We already know of several cellular alterations that contribute to neuronal damage to differing degrees. These include alterations in protein processing, oxidative stress, mitochondrial dysfunction, inflammatory and excitotoxic mechanisms, or intracellular vesicular transport alterations. Impaired neuronal autophagy is currently considered one of the main mechanisms related to PD; specifically, primary lysosomal defects may promote the formation of Lewy bodies.[1]

We present the case of a 71-year-old man diagnosed with PD at the age of 68, who presented mild, predominantly right-sided parkinsonian syndrome and resting tremor in the right hand. He showed good response to treatment with low doses of levodopa (300 mg/day) and dopaminergic agonists (extended-release pramipexole at 1.05 mg/day). Cognitive performance was consistent with his age and level of education. Regarding non-motor symptoms, he reported frequent nightmares and sleep talking, associated with a probable REM sleep behaviour disorder; however, he did not present hyposmia or hypogeusia. His sister, living in Venezuela, was diagnosed with PD at the age of 75.

A genetic study of the patient revealed 2 mutations in genes associated with familial PD. The patient was a heterozygous carrier of a variant of the *GBA* gene, causing the amino acid isoleucine to be replaced by valine at codon 445 (1333A>G, Ile445Val). This is a novel mutation that may affect messenger RNA splicing mechanisms. The patient was also a heterozygous carrier of a variant of the *ATP13A2* gene, causing the amino acid methionine to be replaced by lysine at codon 210 (629T>A, Met210Lys).

Neurons are extremely sensitive to alterations in protein degradation pathways. α-Synuclein is the main component of Lewy bodies. It is degraded by both the ubiquitin-proteasome system and the lysosomal system. While α-synuclein accumulation may partly be caused by dysfunction of proteolytic systems, it may also cause this dysfunction, as it is known to reduce the activity of these systems.[2] Furthermore, mutations in PD-associated genes such as *LRRK2*, *parkin*, and *PINK1* have been associated with decreased autophagic degradation.

Some genes coding for such lysosomal proteins as glucocerebrosidase (*GBA*) and *ATP13A2* (encoding a lysosomal type 5 P-type ATPase), have been associated with familial PD.[3] *GBA* mutations in homozygosis or compound heterozygosis are responsible for Gaucher disease, the most frequent disorder of lysosomal storage. Heterozygous mutations cause partial loss of the enzyme's function, leading to a reduction in the lysosomal degradation of α-synuclein. These heterozygous mutations are currently the most sig-

* Please cite this article as: Fernández-Pajarín G, Sesar A, Ares-Pensado B, Castro A. Enfermedad de Parkinson por sendas mutaciones en 2 genes relacionados con la degradación por lisosomas. Neurología. 2020;35:611—612.

nificant known genetic risk factor in PD, multiplying the risk of developing PD by 20 with respect to non-carriers.[4] Mutations in the *ATP13A2* gene are responsible for severe parkinsonism with good response to levodopa (Kufor-Rakeb syndrome or PARK9). Heterozygous mutations of this gene have been associated with greater predisposition to PD due to the loss of enzyme function, which causes alterations to intracellular zinc homeostasis.[5] The resulting lysosomal dysfunction leads to greater accumulation of α-synuclein.[6] Furthermore, the function of cathepsin D, a protease active in the lysosomal degradation of α-synuclein, is also diminished in the context of *ATP13A2* mutation.[7] In both enzyme defects, PD phenotype is undistinguishable from that of sporadic PD.

Our patient presented 2 mutations in genes associated with lysosomal enzyme activity that cause an impairment of lysosome-mediated autophagy and accumulation of α-synuclein in neurons. This pathogenic mechanism is an area of increasing interest in PD, not only because of its pathogenic role but also because it may represent a line of research for neuroprotective treatment.[1] We suggest that both mutations may even have a synergistic effect for the patient; the genetic study of the patient's sister would confirm the pathogenicity of both mutations; however, this was not possible.

Bibliografía

1. Dehay B, Martinez-Vicente M, Caldwell GA, Caldwell KA, Yue Z, Cookson MR, et al. Lysosomal impairment in Parkinson's disease. Mov Disord. 2013;28:725—32.
2. Martinez-Vicente M, Talloczy Z, Kaushik S, Massey AC, Mazzulli J, Mosharov EV, et al. Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy. J Clin Invest. 2008;118:777—88.
3. Sato S, Li Y, Hattori N. Lysosomal defects in ATP13A2 and GBA associated familial Parkinson's disease. J Neural Transm (Vienna). 2017;124:1395—400.
4. Murphy KE, Gysbers AM, Abbott SK, Tayebi N, Kim WS, Sidransky E, et al. Reduced glucocerebrosidase is associated with increased a-synuclein in sporadic Parkinson's disease. Brain. 2014;137:834—48.
5. Park JS, Blair NF, Sue CM. The role of ATP13A2 in Parkinson's disease: clinical phenotypes and molecular mechanisms. Mov Disord. 2015;30:770—9.
6. Usenovic M, Tresse E, Mazzulli JR, Taylor JP, Krainc D. Deficiency of ATP13A2 leads to lysosomal dysfunction, alpha-synuclein accumulation, and neurotoxicity. J Neurosci. 2012;32:4240—6.
7. Matsui H, Sato F, Sato S, Koike M, Taruno Y, Saiki S, et al. ATP13A2 deficiency induces a decrease in cathepsin D activity, fingerprint-like inclusion body formation, and selective degeneration of dopaminergic neurons. FEBS Lett. 2013;587:1316—25.

G. Fernández-Pajarín*, A. Sesar, B. Ares-Pensado, A. Castro

Unidad de Trastornos del Movimiento, Servicio de Neurología, Hospital Clínico Universitario de Santiago, Santiago de Compostela, La Coruña, Spain

* Corresponding author.
E-mail address: gferpaj@gmail.com
(G. Fernández-Pajarín).

https://doi.org/10.1016/j.nrleng.2019.09.003
2173-5808/

A new case of CAPOS/CAOS syndrome☆

Un nuevo caso de síndrome CAPOS/CAOS

Dear Editor:

CAPOS/CAOS syndrome (cerebellar ataxia, areflexia, with/without pes cavus, optic atrophy, and sensorineural hearing loss)[1] is a rare autosomal dominant genetic disorder, with only 29 reported cases according to our literature search on PubMed. It is associated with heterozygous missense mutation c.2452G>A (p.Glu818Lys) of the *ATP1A3* gene, and is characterised by episodes of neurological impairment associated with encephalopathy and weakness. The syndrome usually manifests at an early age following an acute episode of fever.[2]

We present a new case of de novo CAPOS/CAOS syndrome associated with the previously mentioned *ATP1A3* mutation, and review the available literature on the topic.

Our patient is a 46-year-old woman, the first of 2 siblings (the other sibling is a 40-year-old man, who is asymptomatic); she was born to non-consanguineous parents. She had no relevant personal history. She came to our hospital due to optic atrophy with bilateral amaurosis, sensorineural hearing loss, and gait ataxia, developing progressively from childhood.

At 22 months of age, the patient had presented 3 episodes of fever within a 6-month period, with no associated infectious disease identified; she also presented partially reversible gait instability. The results of a muscle biopsy performed at the time were normal. At 5 years of age, she developed progressive hearing loss; sural nerve biopsy revealed no abnormalities. Around the age of 10 years, she presented another episode of high fever with no apparent focus of infection, associated with muscle weakness and worsening of balance, which prevented her from walking and performing fine motor tasks. She partially recovered from this episode, remaining stable until the present time. Lastly, at age 12 she presented progressive loss of visual acuity, associated with bilateral optic atrophy.

☆ Please cite this article as: González Plata A, Marcos Toledano MM, Correa Martínez L, Fernández-Burriel Tercero M. Un nuevo caso de síndrome CAPOS/CAOS. Neurología. 2020;35:612—614.