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## Camptocormia as the main manifestation of a mutation in the *POLG* gene<sup>☆</sup>



## Camptocormia como principal manifestación de mutación en el gen *POLG*

Dear Editor:

The term camptocormia refers to marked flexion of the thoracolumbar spine, which resolves with supine positions, in the absence of fixed deformity.<sup>1</sup> This symptom may have multiple aetiologies, including parkinsonian syndromes, paraspinal myopathies, dystonia, motor neuron diseases, and functional disorders.<sup>1–3</sup> In exceptional cases, it can also be associated with *POLG* mutations.

We present the case of a 52-year-old man with history of mild psychomotor retardation since childhood; his father had late-onset Parkinson's disease and his mother had essential tremor. His 2 older siblings were asymptomatic. The patient was referred to our department due to progressive anteroflexion of the trunk of 4 years' progression, which hindered walking and was associated with poor coordination and slow movement, mainly affecting the right side; these symptoms were highly disabling. He displayed no signs of dysautonomia, with the exception of constipation.

Neurological examination revealed hypomimia, moderate bilateral bradykinesia, mainly affecting the right side, and low-amplitude right-sided resting tremor. Eye movement was not restricted. When standing, the patient displayed forced anteroflexion of the trunk, with the waist at an angle of approximately 70° (Fig. 1). In the decubitus

position, he was able to correct his posture, lying flat on the bed.

A complete blood analysis including copper metabolism, muscle enzymes, and lactate detected no abnormalities; serology results for syphilis and HIV were negative. A brain MRI study detected no relevant alterations. A DaTSCAN study revealed dopamine transporter inactivity in both putamina and reduced uptake in the left caudate nucleus.

In the light of these findings, treatment was started with levodopa at increasing doses of up to 250 mg/6 hours, with a suboptimal response. After a 350 mg loading dose, he presented an improvement of over 30% on the UPDRS part III motor examination, with his posture improving and stabilising. The extreme anteroflexion of the trunk (Fig. 1) resolved, and he was able to carefully walk over 20 metres unassisted.

Given the history of psychomotor delay and the atypical parkinsonian symptoms, we requested an exome sequencing study, which identified a heterozygous missense mutation in exon 20 of the *POLG* gene (C.3218C>T; p [Pro1073Leu]), located on chromosome 15. The mutation is listed on the ClinVar and HGMD databases as a pathogenic variant. Functional studies have shown that this variant also affects mitochondrial DNA replication.<sup>4</sup>

Despite the lack of clear symptoms, we performed further diagnostic testing. An electromyoneurography study yielded normal results, and a multidisciplinary evaluation identified mild bilateral cataracts and predominantly sensorineural mixed hearing loss.

The *POLG* gene encodes the catalytic subunit of DNA polymerase gamma, which is responsible for the replication of the mitochondrial genome.<sup>5</sup> Mutations of the gene are associated with a broad spectrum of neurological syndromes, with age of onset ranging from infancy to adulthood; manifestations include epilepsy, psychiatric disorders, polyneuropathy, myopathy, ataxia, and progressive external ophthalmoplegia, and may be associated with such non-neurological conditions as cataracts, sensorineural hearing loss, and premature ovarian failure.<sup>5,6</sup>

More rarely, *POLG* mutations may be associated with parkinsonism,<sup>7</sup> often preceded for several years by classical

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**Figure 1** The patient before (A) and one hour after (B) a 350 mg dose of levodopa, showing a clear improvement in the anteroflexion of the trunk.

phenotypes: usually progressive external ophthalmoplegia,<sup>8</sup> but also sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO).<sup>9</sup> In these patients, parkinsonism tends to be asymmetrical, with onset occurring around the age of 40 years and good response to levodopa.<sup>8,10</sup> Our patient developed an atypical parkinsonian syndrome, with no evidence of other neurological characteristics associated with *POLG* mutations; prominent camptocormia was the most striking symptom. Additional tests performed after diagnosis identified bilateral cataracts and mild sensorineural hearing loss; these findings are associated with the mutation. This form of presentation, in which the parkinsonian syndrome is not preceded by ophthalmoparesis, has only been described in 2 patients also presenting peripheral neuropathy<sup>11</sup> and in a patient with another pathogenic mutation in the *GBA* gene.<sup>12</sup> We believe that the cause of camptocormia in our patient was parkinsonism itself, as he presented severe anteroflexion of the trunk and absence of abnormal postures in the head and neck (as would be the case for dystonic camptocormia), and posture improved (albeit suboptimally) with levodopa. Furthermore, the electromyography study showed no myopathic changes.

In conclusion, our patient presented a unique phenotype of *POLG* mutation, presenting with camptocormia secondary to atypical parkinsonism not preceded by SANDO or progressive external ophthalmoplegia, which has rarely been described in the literature.<sup>13</sup> *POLG* mutations should be considered in the differential diagnosis of atypical parkinsonism, even in patients without ophthalmoparesis or polyneuropathy.

### Conflicts of interest

The authors have no conflicts of interest to declare.

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## Idiopathic hypereosinophilic syndrome presenting as mononeuritis multiplex. Lessons learned after 18-months of follow-up<sup>☆</sup>



### Mononeuritis múltiple como forma de presentación de un síndrome hipereosinofílico idiopático. Lecciones aprendidas tras 18 meses de seguimiento

Dear Editor:

Hypereosinophilic syndrome (HS) is a rare systemic disease included in the group of myeloproliferative disorders. It is diagnosed in patients presenting elevated eosinophil counts below 1500 cells/ $\mu$ L for over 6 consecutive months and eosinophilic infiltration of tissues and organs after excluding such secondary causes of eosinophilia as drug reactions, infections, immune disorders, or allergies.<sup>1</sup>

Several subtypes have been described, including a myeloproliferative and a lymphoproliferative form; diagnosis of these subtypes is based on the detection of genetic mutations (in *BCR-ABL* and *FIP1L1/PDGFR* fusion genes) and expression of eosinophil membrane proteins. However, idiopathic HS does not meet these diagnostic criteria.<sup>2</sup>

From a neurological viewpoint, idiopathic HS is characterised by involvement of both the central nervous system (venous thrombosis and encephalopathy) and the peripheral nervous system (peripheral neuropathy).<sup>3,4</sup> The pathogenic mechanism of peripheral neuropathy is unclear. Although nearly all affected tissues present eosinophil infiltration, histopathology studies of the damaged nerves do not reveal direct infiltration, inflammation, or vasculitis. The role of eosinophils as secretory cells and mediators of the cytotoxic response seems to explain the pathophysiology of peripheral neuropathy, particularly major basic protein and eosinophil-derived neurotoxin, which are responsible for neuropathic

axonal damage through disruption of vasa vasorum permeability and perineuronal oedema, respectively.<sup>5,6</sup>

We present the case of a 49-year-old woman with no relevant medical history who presented mononeuritis multiplex as the initial manifestation of idiopathic HS. She consulted due to one month's history of acute pain beginning in the left forearm, and subsequently affecting the right elbow and the anterior aspect of the right thigh. Pain progressed to persistent paraesthesia and weakness in the areas previously mentioned. The examination confirmed mild motor weakness in the left arm (flexor digitorum profundus muscle of the fourth and fifth digits, adductor minimi digiti, first dorsal interosseous, and adductor pollicis) and right leg (posterior tibialis, triceps surae, flexor digitorum longus, and flexor digitorum brevis); absent right Achilles reflex; and hypoaesthesia and hypalgesia in the territories of the left ulnar and saphenous nerves and the posterior aspect of the right leg.

A complete blood count revealed an elevated eosinophil count (2100 cells/ $\mu$ L), mild thrombocytopenia (99 000 platelets/ $\mu$ L), and a white blood cell differential with 26% eosinophils. A possible adverse drug reaction was ruled out; serology studies for Epstein Barr virus, cytomegalovirus, hepatitis C virus, HIV, *Borrelia*, and syphilis yielded negative results, and stool examination detected no parasites. Antibody testing detected a low titre of antinuclear antibodies with a homogeneous pattern, and normal immunoglobulin levels (IgE: 2.45 kU/L; normal range, < 100 kU/L); the patient tested negative for the remaining parameters (complement, anti-dsDNA, anti-RNP, anti-Scl-70, anti-SN, anti-Ro, anti-La, ANCA, anti-CCP, cryoglobulins, antineuronal antibodies). Cytochemical analysis and a monoclonal antibody study of the CSF yielded normal results. Electromyography revealed multiple mononeuropathy, with mild involvement of the left ulnar nerve and extremely severe involvement of the right peroneal and posterior tibial nerves. Bone marrow biopsy yielded normal results. Cytogenetic testing of the *BCR-ABL* and *PDGFR* genes revealed no pathological alterations. Peripheral nerve biopsy was not performed.

Suspecting idiopathic HS as the cause of mononeuritis multiplex, we started treatment with high-dose corticosteroids (methylprednisolone dosed at 1 g/day) for 5 days, which improved our patient's symptoms and laboratory parameters within weeks. We subsequently started treatment with prednisone, tapering the dose to 15 mg/day. A follow-up examination at 6 months revealed no motor or sensory impairment, with the patient presenting a normal blood eosinophil count. At 18 months, a decrease in the dose

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