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Generalized dystonia without Parkinsonism in an *LRRK2* carrier

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Occasionally, carriers of Parkinson's disease (PD)-related genes can present as pure dystonic syndrome. We report a case of pure dystonic syndrome in an *LRRK2* gene carrier.

A 45-year-old male presented to our outpatient clinic with a 10-year history of a progressive abnormal movements of both legs, trunk, cervical spine, and, finally, both arms. He denied slowness, loss of dexterity, tremor, or loss of postural reflexes.

A baseline examination in 2014 revealed generalized dystonia involving the cervical spine, trunk, and lower and upper limbs. The patient did not present bradykinesia, rest tremor, or loss of dexterity. His gait was unusual, with twisting of both feet while walking (Video 1). He maintained normal cognition. His mother (deceased) was diagnosed with Parkinsońs disease.

Initial treatment with anticholinergics (trihexyphenidyl) and botulinum toxin partially relieved his symptoms. The results of the MRI and a full battery of tests (blood and laboratory) were normal, and the genetic tests for dystonia and dystonia plus syndromes were negative, including the following genes:

ACTB, ANO3, ARSA, ATN1, ATP13A2, ATP1A3, ATP7B, BCKDHA, BCKDHB, BCS1L, BTD, CBS, CLN3, CLN5, CLN6, CLN8, COL6A3, COX10, COX15, CP, CTSD, D2HGDH, DBT, DCAF17, DNAJC5, DRD5, FA2H, FOXG1, FOXRED1, FUCA1, GALC, GALT, GAMT, GATM, GCDH, GCH1, GLB1, GM2A, GRN, HPRT1, HTT, IVD, JPH3, KCTD7, MCEE, MECP2, MFSD8, MMAA, MMAB, MMADHC, MR1, MTFMT, NDUFA10, NDUFA12, NDUFA2, NDUFA9, NDUFAF6, NDUFS1, NDUFS3, NDUFS4, NDUFS7, NDUFS8, NPC1, NPC2, PAH, PANK2, PCCA, PCCB, PDGFB, PDGFRB, PLA2G6, PLP1, PNKD, POLG, PPT1, PRRT2, RAX, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SCP2, SDHA, SERAC1, SGCE, SLC19A3, SLC20A2, SLC2A1, SLC30A10, SLC6A19, SLC6A3, SLC6A8, SPR, SUCLA2, SURF1, TAF1, TH, THAP1, TIMM8A, TOR1A, TPP1, TREX1, VPS13A,WDR45, XK.

Over the following 6 years, his dystonia progressively worsened. Treatment with levodopa produced clear but partial improvement without side effects (this improvement was confirmed after temporal withdrawal of levodopa with subjective and objective impairment). Currently, the patient exhibits mild generalized dystonia especially noticeable with ambulation, as well as absence of bradykinesia, tremor and loss of postural reflexes.

Due to the positive response to levodopa and despite a normal DAT-SPECT scan, a genetic panel study was carried out. The panel contains the coding region + 50-bp splice-junction for the following genes:

ANKK1, ATP13A2, ATP6AP2, ATP7B, COQ2, DNAJC13, DNAJC6, EIF4G1, FBXO7, GBA, GCH1, HTRA2, LRRK2, NR4A2, PARK2, PARK7, PINK1, PLA2G6, SLC6A3, SMPD1, SNCA, SYNJ1, UCHL1, VPS35.

Unexpectedly, he was found to have a leucine-rich repeat kinase 2 (*LRRK2*) p.G 2019S mutation. The results have been confirmed by two independent laboratories.

This *LRRK2* carrier (p.G2019S mutation) presented mild generalized dystonia, with positive but partial levodopa response, in absence of bradykinesia (confirmed up to the present).

Mutations in leucine-rich repeat kinase 2 (*LRRK2*) (PARK8) are associated with both familial and sporadic forms of Parkinson's disease (PD) [1]. A common mutation (G2019S) has been reported across most ethnic populations and is quite prevalent in the south of Europe [1,2]. The pathologic and clinical characteristics of symptomatic *LRRK2* carriers are quite variable [3]. According with some authors, patients carrying the G2019S mutation have more gait disorders [1,2] and dystonia [4] compared to non-carriers. In summary, we described the case of a G2019S carrier with generalized persistent dystonia as the only manifestation, and probably this may be the case with some others *LRRK2* carriers. This fact is very well known with Parkin carriers [5], but in our knowledge, highly unusual in LRRK2 carriers.

Certainly, dystonia in this particular case may be coincidental and other genetic factors may be present, but the objective improvement with levodopa is intriguing and not typical of other genetic dystonias, save dopa-responsive dystonia. Finally, it is also possible that this patient will manifest Parkinsońs disease or just remain a carrier since the *LRKK2* penetrance is far from complete. Despite these drawbacks, it seems logical to attribute the dystonic symptoms to a single verified genetic finding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Dr. Javier Del Val: Review and critique
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Competing interests

Drs. Cici Feliz-Feliz, Almudena Ávila-Fernández, Isabel Lorda-Sanchez and Javier Del Val have nothing to disclosure.

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Ethical compliance

The authors confirm that the approval of an institutional review board was not required for this work. Informed consent was obtained for this publication.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2022.100157.

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