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Cranial dystonia as an isolated presentation of *DJ-1* disease: Case report and literature review

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Disease-causing variants in the *DJ-1* gene (formerly *PARK7*) are the third commonest cause of autosomal recessive early-onset parkinsonism after *PRKN* and *PINK1* variants. Due to the small number of cases hitherto reported, the phenotype of *DJ-1*-associated disorder remains poorly characterized. Despite often being described as a ‘Parkin-like’ parkinsonism, preliminary evidence suggests that the phenotypic spectrum of *DJ-1* related diseases is much broader, encompassing lower motor neuron pathology, oculogyric crises, and various non-motor features [1-6].

Dystonia, usually involving the foot, is a common feature of young-onset recessive parkinsonian syndromes, often presenting prior to overt parkinsonism. In contrast, focal dystonia involving the facial region alongside parkinsonism is an uncommon juxtaposition which invokes rarer disorders such as Wilson’s disease, neuroacanthocytic disorders, brain iron accumulation disorders and multiple system atrophy, often as a levodopa-related manifestation.

Herein, we report a case of *DJ-1*-related disease manifesting with isolated, levodopa-responsive orofacial dystonia preceding the onset of parkinsonism by over 7 years. To our knowledge, isolated orofacial dystonia in dopamine-naïve patients has never been reported as a presenting feature of monogenic Parkinson’s disease (PD). Besides reviewing dystonic features in *DJ-1*-related disorders reported so far (Table 1), we put forth the suggestion that orofacial dystonia may be a clinical hint to *DJ-1*-related parkinsonism.

Case report

A 27-years-old right-handed female of South Asian ancestry, born to non-consanguineous parents, was referred to the neurology clinic for evaluation of abnormal jaw movements. Her parents reported they had sought an ophthalmological opinion about her excessive eye blinking at age 17, but no diagnosis was made. Two years later, she noticed progressive difficulty in closing her mouth when speaking and eating. At age 24, she developed walking difficulty and slowness of movement. Her cognitive functions and mood were normal. She had no constipation, anosmia, or features suggestive of REM sleep behavior disorder. There was no family history of neurological disorders nor history of current or previous exposure to dopamine receptor blockers.

Examination revealed blepharospasm and jaw-opening dystonia (video-segment 1). Assessment of cranial nerves was unremarkable, including normal eye movements, speech and swallowing function. There was facial hypomimia, an action and postural jerky limb tremor, and asymmetrical bradykinesia on finger- and foot-tapping (video-segment 2). She had no resting tremor, rigidity, hyperreflexia, or cerebellar signs were detected. There was no gait abnormality. Her jaw-opening dystonic spasms resolved 30 minutes after administration of levodopa.

Serum copper and caeruloplasmin, iron profile, three blood smears for the detection of acanthocytes, and brain MRI were all normal. Whole-genome sequencing identified a homozygous NM_007262.5:c.487G>A (p. Glu163Lys) variant in *DJ-1*. This variant has one heterozygous and no homozygous entries in the population dataset gnomAD v.3.1.2 (<https://gnomad.broadinstitute.org/>; accessed on 27/02/2022), has a CADD score of 23.4, is predicted pathogenic by *in silico* prediction tools (including PolyPhen2, PROVEAN, and MutationTaster), and affects an amino acid residue highly conserved across species. It has

previously been reported in the homozygous state and along with another homozygous variant in the promoter region of *DJ-1* in three Italian siblings with early-onset parkinsonism, cognitive decline, and motor neuron disease.

The patient received botulinum toxin injections for jaw-opening dystonia and was started on levodopa 100/25mg three times daily with dramatic improvement of dystonia. Peak-dose dyskinesia developed after one year of treatment, requiring the addition of amantadine 100mg twice daily.

Discussion

Disease-causing biallelic variants in *DJ-1* were first reported to account for early-onset Parkinson's disease (EOPD) in Italian and Dutch consanguineous families in 2003[1]. Since then, a total of 37 cases belonging to 24 families have been described, with the most frequent presenting clinical phenotype being young-onset levodopa-responsive parkinsonism (mean age of onset 32 years, range 25-40). Nevertheless, atypical presentations are increasingly recognized. These include amyotrophic lateral sclerosis, voice changes and oculogyric crises (Table 1).

Isolated orofacial dystonia in early adulthood carries a relatively limited differential diagnosis, which should include monogenic dystonia syndromes (e.g., those caused by mutations in the *KMT2B* or *THAP1* genes), metal accumulation disorders (in particular, Wilson's disease and neurodegeneration with brain iron accumulation), inborn errors of metabolism and neuroacanthocytosis. In older age, this differential diagnosis expands further to include tardive syndromes, idiopathic (or indeed secondary edentulous) oromandibular dystonia and

complications of dopamine replacement therapy in both typical and atypical neurodegenerative parkinsonian disorders. In cases as the one herein presented, the absence of parkinsonian features at the time of clinical presentation may lead to inappropriate omission of recessive PD-causing genes from the differential diagnosis.

Conclusion

This case further expands the clinical phenotype of *DJ-1*-related disorder and suggests that *DJ-1* related disease should be included in the diagnostic workup of early isolated orofacial dystonia. Taken alongside other cases in the literature, it suggests that orofacial dystonia may be a clinical pointer towards a diagnosis of *DJ-1*-related disorder, and may precede the appearance of parkinsonism by many years.

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Author contribution

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

IR: 1A, 1B, 1C, 2A, 2B, 3A

EM: 1B, 1C, 2C, 3B

FM: 1B, 1C, 3B

CM: 1C, 3B

KB: 1C, 3B

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Ethical compliance statement

The authors confirm that the approval of an institutional review board was not required for this work and the informed written consent obtained from the patient. 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.

References

1. Van Duijn CM, Dekker MC, Bonifati V, et al. Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. *Am J Hum Genet* 2001;69:629–634.
2. Bonifati V, Rizzu P, Squitieri F, et al. DJ-1(PARK7), a novel gene for autosomal recessive, early onset parkinsonism. *Neurol Sci* 2003;24:159–160.
3. Bonifati V, Rizzu P, van Baren MJ, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science* 2003;299:256–259.
4. Abou-Sleiman PM, Healy DG, Quinn N, et al. The role of pathogenic DJ-1 mutations in Parkinson's disease. *Ann Neurol* 2003;54:283– 286.
5. Annesi G, Savettieri G, Pugliese P, et al. DJ-1 mutations and parkinsonism-dementia-amyotrophic lateral sclerosis complex. *Ann Neurol* 2005;58:803–807.
6. Desai K, Agrawal S, Walzade P, Ravat SH, Agarwal PA. Atypical, Early-Onset Dystonia-Parkinsonism with Oculogyric Crises and Anterior Horn Cell Disorder Due to a Novel DJ-1 Mutation. *Mov Disord Clin Pract*. 2021 Sep 3;8(Suppl 1).

7. Djarmati A, Hedrich K, Svetel M, et al. Detection of parkin (PARK2) and DJ1 (PARK7) mutations in early-onset Parkinson disease: parkin mutation frequency depends on ethnic origin of patients. *Hum Mutat* 2004;23:525.
8. Hering R, Strauss KM, Tao X, et al. Novel homozygous p. E64D mutation in DJ1 in early onset Parkinson disease (PARK7). *Hum Mutat* 2004;24:321–329.
9. Tarantino P, Civitelli D, Annesi F, et al. Compound heterozygosity in DJ-1 gene non-coding portion related to parkinsonism. *Parkinsonism Relat Disord* 2009;15:324–326.
10. Jose M. Bras, Rita J. Guerreiro, James T.H. Teo, Lee Darwent, Jenny Vaughan, Sophie Molloy, John Hardy, Susanne A. Schneider, Atypical Parkinsonism-Dystonia Caused by a Novel DJ1 Mutation; *Mov Disord Clin Pract*. 2014 Apr 10;1(1)
11. Changrui Xiao, Thomas Markello, Wadih M. Zein, Rachel Bishop, Catherine Groden, William Gahl, Camilo Toro; PARK7-Related Early Onset Parkinson Disease in the Setting of Complete Uniparental Isodisomy of Chromosome 1, *Neurology genet*;2021 Aug; 7(4): e606.
12. Taipa, Ricardo; Pereira, Conceição; Reis, Inês; Alonso, Isabel; Bastos-Lima, António; Melo-Pires, Manuel; Magalhães, Marina (2016). DJ-1 linked parkinsonism (PARK7) is associated with Lewy body pathology. *Brain*, (), aww080–. doi:10.1093/brain/aww080
13. Stephenson SE, Djaldetti R, Rafehi H, Wilson GR, Gillies G, Bahlo M, Lockhart PJ. Familial early onset Parkinson's disease caused by a homozygous frameshift variant in PARK7: Clinical features and literature update. *Parkinsonism Relat Disord*. 2019 Jul;64:308-311. doi: 10.1016/j.parkreldis.2019.03.013.
14. Lesage S, Lunati A, Houot M, Romdhan SB, Clot F, Tesson C, Mangone G, Toullec BL, Courtin T, Larcher K, Benmahdjoub M, Arezki M, Bouhouche A, Anheim M, Roze E,

Viallet F, Tison F, Broussolle E, Emre M, Hanagasi H, Bilgic B, Tazir M, Djebara MB, Gouider R, Tranchant C, Vidailhet M, Le Guern E, Corti O, Mhiri C, Lohmann E, Singleton A, Corvol JC, Brice A; French Parkinson Disease Genetics Study Group. Characterization of Recessive Parkinson Disease in a Large Multicenter Study; *Ann Neurol*. 2020 Oct;88(4):843-850. doi: 10.1002/ana.25787.

15. Kasten M, Hartmann C, Hampf J, et al. . Genotype-phenotype relations for the Parkinson's disease genes parkin, PINK1, DJ1: MDSGene systematic review. *Mov Disord*. 2018;33(5):730-741.
16. Derek P. Narendra, MD, PhD, Risa Isonaka, PhD, Diana Nguyen, BS, Alice B. Schindler, MS, CGC, Angela D. Kokkinis, BSN, RN, Debra Ehrlich, MD, MS, Tanya M. Bardakjian, MS,CGC,David S. Goldstein, MD, PhD, Tsao-Wei Liang, MD, and Pedro Gonzalez-Alegre, MD, PhD: Peripheral synucleinopathy in a DJ1 patient with Parkinson disease, cataracts, and hearing loss ; *Neurology* 2019 Jun 4;92(23):1113-1115. Epub 2019 Apr 26.

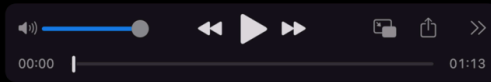
Legends

Video: Segment 1: showing blepharospasm and jaw-opening dystonia, Segment 2: facial hypomimia, showing action postural jerky tremor, asymmetrical bradykinesia on finger and foot tapping. She has no resting tremor and her gait appears normal.

Supplementary material: Table 1: Summary of DJ1 cases reported in the literature

Accepted Article

Segment 1



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