Levodopa-induced dyskinesias in mitochondrial membrane protein–associated neurodegeneration

Daniel Savitt, DO, and Joseph Jankovic, MD

Neurology: Clinical Practice February 2019 vol. 9 no. 1 e7-e9 doi:10.1212/CPJ.0000000000000577

Correspondence

Dr. Jankovic
josephj@bcm.edu

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of disorders caused by mutations in genes involved in iron metabolic pathways, phospholipid metabolism, and lysosomal function. The NBIA disorders present at variable ages with a combination of movement disorders, cognitive decline, and other features that usually do not respond to levodopa or other pharmacologic therapies.¹ Mutations in *C19orf12*, a gene that codes for mitochondrial membrane protein, hence the term “mitochondrial MPAN”, have been recently identified in patients with an NBIA phenotype.² In reported cases of MPAN, levodopa response is variable, and no levodopa-induced dyskinesias (LID) have been reported. Here, we describe a unique case of MPAN and LID.

PRACTICAL IMPLICATIONS

Parkinsonism may be the presenting feature of neurodegeneration with brain iron accumulation, such as “mitochondrial membrane protein–associated neurodegeneration” (MPAN), caused by mutations in *C19orf12*. Levodopa therapy may be complicated by development of motor fluctuations and dyskinesias.

Case report

A 34-year-old right-handed man, with a family history of neurodegenerative disorders, presented with 1-year history of progressive gait slowness with reduced right arm swing and impaired balance. Gait imbalance emerged rather abruptly with rapid progression of motor slowness, shuffling gait, tremors in both arms, and low speech volume over a 2- to 3-year period. Within 5 months of symptom onset, he developed anxiety, including panic attacks, and short-term memory difficulties.

Neurologic examination showed normal extraocular movements without nystagmus, hypometric saccades, hypomimia, hypokinetic dysarthria and hypophonia, moderate right-sided predominant rigidity without cogwheeling, bradykinesia, postural and kinetic tremor in both hands, and no cerebellar incoordination. He had a shuffling gait with decreased right arm swing and stooped posture (video 1). His brain MRI revealed T2 hypointensities in each globus pallidus (figure 1), and DaTscan revealed evidence of marked dopaminergic deficit in the bilateral dorsal striata (figure 2).

Whole-exome sequencing revealed a heterozygous c.194_204del (p.M65fs) pathogenic variant in the *C19orf12* gene. The patient was subsequently identified as a first cousin once removed from the proband of a family in which a single *C19orf12* mutation segregates with disease through 3 generations, suggesting an autosomal dominant inheritance.

Carbidopa/levodopa 25/100 mg 2 tablets 3 times daily provided initial symptomatic improvement in his parkinsonism and anxiety. Approximately 1 year after levodopa initiation, he developed motor fluctuations and peak-dose LID manifested as moderate, symmetric, generalized chorea when his carbidopa/levodopa was increased to 25/250 mg tablets taken 2 tablets each morning, 2 tablets each afternoon, and 1 tablet in the evening (video 2). There was moderate improvement of the patient’s dyskinesias with amantadine 100 mg taken twice daily.

MORE ONLINE

► Videos

Department of Neurology, Parkinson's Disease and Movement Disorders Clinic, Baylor College of Medicine, Houston, TX.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

T2-weighted (A) and T2-FLAIR (B) MRI showing hypointensities in the globus pallidus on the left more than right side. T1-weighted (C) and T2-FLAIR (D) MRI showing a normal-appearing midbrain.

Discussion

The most common causes of NBIA are genetic defects in *PANK2* (MIM 606157) causing pantothenate kinase-associated neurodegeneration (PKAN) and *PLA2G6*; both genes encode mitochondrial proteins.³ The responsible genes have not yet been identified in approximately 30% of patients with clinically and radiographically diagnosed NBIA. Mutations in *C19orf12* were first described in 2011 in a homogenous cohort in Poland comprised mainly of patients homozygous for a founder mutation.³

MPAN is an autosomal recessive disorder leading to NBIA, manifested by movement disorders, including parkinsonism, tremor, dystonia, and gait impairment. At autopsy, there is prominent, widespread Lewy body pathology.⁴ There are also documented cases with possible autosomal dominant pattern of inheritance.⁴ This family with a single *C19orf12* mutation causing disease suggests that a single mutant allele is sufficient to cause the MPAN phenotype in some cases. De novo dominant mutations might account for this inheritance pattern. Incomplete penetrance or variable expressivity may explain the

lack of symptoms in some family members, including this patient's parents.

MPAN typically presents in the first decade of life with progressive dystonia-parkinsonism, optic nerve atrophy, and axonal motor neuropathy.^{3,4} Onset in early adulthood has also been described, although the initial presentation in these cases is more variable. Typical manifestations include cognitive and behavioral changes, parkinsonism, and gait disorders.⁵ MRI usually shows iron accumulation with hypointensity in the globus pallidus and substantia nigra on T2/T2*-weighted images, not to be confused with the “eye of the tiger” sign, characteristic of PKAN, hyperintense streaking of the internal medullary lamina of the globus pallidus, and white matter lesions.^{4,6} The yield of testing for the *C19orf12* mutation is very low in patients without signs of iron accumulation on MRI.⁶ Levodopa responsiveness and the presence of LID suggest predominantly nigrostriatal degeneration rather than striatal or pallidal pathology, also supported by the abnormal DaTscan (figure 2). Treatment of NBIA is mainly symptomatic because there are no pathogenesis-targeted or disease-modifying therapies, although iron chelation and enzyme

Figure 2 DaTscan

DaTscan showing severe loss of dopaminergic neuronal function in the bilateral dorsal striata.

replacement therapies are currently being investigated in PKAN and other NBIA⁷.

Our patient presented with progressive parkinsonism and gait disorder who initially responded well to carbidopa/levodopa therapy with subsequent development of motor fluctuations and LID (video 2). MPAN should be considered in the differential diagnosis of young-onset, levodopa-responsive parkinsonism.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication history

Received by *Neurology: Clinical Practice* June 12, 2018. Accepted in final form September 6, 2018.

Appendix 1 Author contributions

Name	Location	Role	Contribution
Daniel Savitt, DO	Baylor College of Medicine, Houston	Author	Drafted the manuscript for intellectual content
Joseph Jankovic, MD	Baylor College of Medicine, Houston	Author	Revised the manuscript for intellectual content

References

1. Wiethoff S, Houlden H. Neurodegeneration with brain iron accumulation. *Handb Clin Neurol* 2017;145:157–166.
2. Gagliardi M, Annesi G, Lesca G, et al. C19orf12 gene mutations in patients with neurodegeneration with brain iron accumulation. *Parkinsonism Relat Disord* 2015; 21:813–816.
3. Hartig MB, Iuso A, Haack T, et al. Absence of an orphan mitochondrial protein, c19orf12, causes a distinct clinical subtype of neurodegeneration with brain iron accumulation. *Am J Hum Genet* 2011;89:543–550.
4. Hogarth P, Gregory A, Krueger MC, et al. New NBIA subtype: genetic, clinical, pathologic, and radiographic features of MPAN. *Neurology* 2013;80:268–275.
5. Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. *J Mov Disord* 2015;8:1–13.
6. Dušek P, Školoudík D, Roth J, Dušek P. Mitochondrial membrane protein-associated neurodegeneration: a case report and literature review. *Neurocase* 2018;24:161–165.
7. Elbaum D, Beconi MG, Monteagudo E, et al. Fosmetpantotenate (RE-024), a phosphopantothenate replacement therapy for pantothenate kinase-associated neurodegeneration: mechanism of action and efficacy in nonclinical models. *PLoS One* 2018;13:e0192028.