Levodopa Induced Dyskinesias in Neurodegeneration with Brain Iron Accumulation due to a Heterozygous Mutation in C19orf12

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Background

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 function1. The NBIA's present at variable ages with a combination of movement disorders, cognitive decline, and other symptoms that usually do not respond to levodopa. Mutations in C19orf12 have recently been identified in patients with an NBIA phenotype2. This gene codes for a mitochondrial membrane protein, hence the term “mitochondrial membrane protein-associated neurodegeneration” (MPAN). MPAN typically presents in childhood or adolescence with progressive dystonia-parkinsonism, optic atrophy, axonal motor neuronopathy and iron deposition in globus pallidus and substantia nigra. MPAN is an autosomal recessive disorder leading to NBIA and prominent, widespread Lewy body pathology3. In reported cases of MPAN, levodopa response is variable and no levodopa-induced dyskinesias have been reported.

Case Presentation

A 34 year old male with a family history of neurodegenerative disorders presented with a rapid progression of slowness, stiffness, gait imbalance, action tremors, and cognitive decline.

Imaging

MRI brain: T2 hypointensities in the globus pallidus, especially on the left.

DaTscan: Severe loss of dopaminergic neuronal function in the bilateral dorsal striata.

References

Case Presentation

This 34-year-old previously healthy right-handed man, a sales representative with a family history of neurodegenerative disorders, presented with one-year history of gait imbalance. His symptoms progressed rapidly to marked motor slowness and shuffling gait, and tremors in both arms. He developed new onset anxiety including panic attacks. He also described severe muscle spasms at night disrupting sleep.

Neurologic examination showed intact cranial nerves, hypomimia, hypokinetic dysarthria and hypophonia, moderate right sided predominant bradykinesia and rigidity, bilateral postural and kinetic hand tremor, decreased right arm swing, stooped posture and shuffling gait.

His MRI brain revealed T2 hypointensities in the globus pallidus, especially on the left. His DatScan revealed severe loss of dopaminergic neuronal function in the bilateral dorsal striata.

References


Conclusions

MPAN should be considered in the differential diagnosis of young-onset parkinsonism.

Results

Whole exome sequencing revealed a mutation in C19orf12, consistent with MPAN. The patient's parkinsonism significantly improved with levodopa but was complicated by the development of levodopa-induced dyskinesias.
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Whole exome sequencing revealed a pathogenic variant in C19orf12 (c. 194_204 del or p.M65fs) without a second pathogenic variant. 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 three generations, suggesting an autosomal dominant inheritance.

Carbidopa/levodopa 25/100mg 2 tablets three times daily provided initial symptomatic improvement in his parkinsonism. There was also improvement of nocturnal spasms and alleviation of anxiety as he was able to return to work. He soon developed motor fluctuations and levodopa-induced dyskinesias manifested as moderate generalized chorea when his carbidopa/levodopa was increased to 25/250mg tablets taken 2 tablets each morning, 2 tablets each afternoon, and 1 tablet in the evening.

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Conclusions

Defects in C19orf12 are the cause of mitochondrial membrane protein-associated neurodegeneration (MPAN), a form of Neurodegeneration with Brain Iron Accumulation (NBIA). In reported cases of MPAN, levodopa response is variable and no levodopa-induced dyskinesias have been reported.

Our patient with documented familial MPAN presented with progressive parkinsonism that initially responded well to carbidopa/levodopa therapy. He later developed both motor fluctuations and levodopa-induced dyskinesias manifesting as generalized chorea. A trial of levodopa is warranted in patients with parkinsonism due to MPAN with consideration that motor fluctuations and levodopa-induced dyskinesias may complicate therapy. MPAN should be considered in the differential diagnosis of young-onset parkinsonism.

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