Hereditary Spastic Paraplegia Due to a Novel Mutation in SPG11 Gene Presenting as Dopa-Responsive Dystonia.

Subhashie Wijemanne, MD, MRCP; Joseph Jankovic, MD

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

BACKGROUND

- Hereditary spastic paraplegia (HSP) is clinically and genetically heterogeneous group of neurodegenerative disorders characterized by progressive weakness and spasticity of the lower limbs.[1]
- HSP due to *SPG11* mutations is a common cause of autosomal recessive HSP. To date, at least 127 distinct mutations in the *SPG11* gene have been reported. *SPG11* (MIM610844) maps to chromosome 15q13–15 and encodes spatacsin, a protein of unknown function
- *SPG11* mutation typically presents with spasticity, cognitive impairment, and peripheral neuropathy; Radiologically SPG11 is characterized by thinning of the corpus callosum and periventricular white matter changes.
- We describe a case of dopa-responsive dystonia (DRD) associated with HSP due to *SPG11* gene mutations, diagnosed using whole exome sequencing (WES).

CASE REPORT

- An 11 year old boy was born full term but his birth was complicated by fetal distress and bilateral pneumothorax and had some delay motor development which improved over time.
- At 8 years developed abnormal posturing of the legs and then arms suggestive of dystonia. His gait became stiff and he developed postural instability and near falling. Over time he became dependent on a wheelchair and had urinary incontinence.
- He had marked diurnal variation of his symptoms.
- In 2011 at the age of 9 years he was suspected to have DRD and his motor symptoms responded markedly to a trial of carbidopa/levodopa (25/100 mg three times a day).
- However, within a few months he experienced wearing off, requiring increased frequency of levodopa dose up to four times a daily.
- Examination in 2013 at the age of 11 years.
- **Levodopa "ON" state:** He had dystonia in both arms, worse on the left with flexion of wrist and fingers and extension of fingers on the right. There was extension of the left leg with eversion and slight extension of the foot, especially at rest. Irregular head tremor and rest and action tremors in both arms suggestive of dystonic tremors. Fine finger movements were slow and deliberate without decrementing amplitude.
- **Levodopa "OFF" state**: Marked worsening of dystonia with moderate left torticollis and retrocollis at rest. He also had mild intermittent opisthotonic extension of the trunk, which limited his gait and resulted in near falls in the absence of support. Dystonic tremor was more pronounced when off medications. Reflexes were brisk particularly in the lower extremities with transient ankle clonus and bilateral extensor plantar response. There was no ataxia or dysmetria. Sensory examination was normal.
- He developed disabling levodopa induced choreiform peak-dose dyskinesia when the dose of the carbidopa/levodopa was further increased.
- A neuropsychologic tests were within average range. MRI brain (Figure 1 A-D) and a DaTscan (Figure 1 D) were done. WES was requested to determine the genetic etiology.

RESULTS

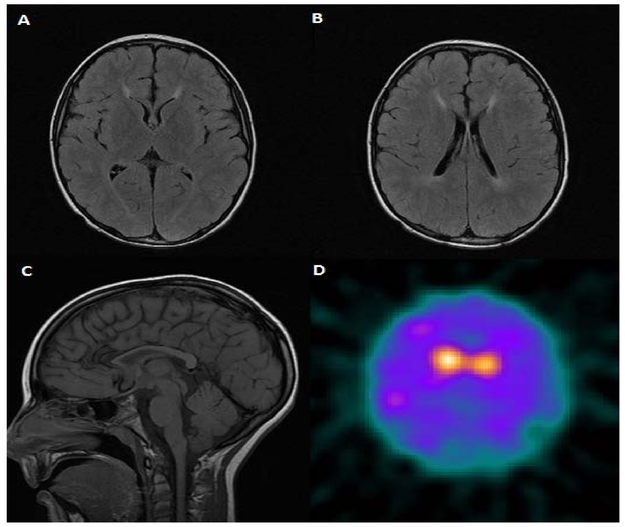

Figure 1:

A- B- Axial T2 FLAIR- showing increased T2 signal in the periventricular white matter.
C- Sagittal T1- Marked thinning of the anterior half of the corpus callosum.
D- ^{123}I-ioflupane single photon emission coupled tomography showing essentially absent tracer activity in bilateral putamina and reduced uptake in caudate with slightly greater reduction in left caudate nucleus compared to the right.

Cerebrospinal fluid (CSF) neurotransmitter assessment

- Homovanilic acid (HVA) low at 204 nmol/L (218-852 nmol/L) and tetrahydrobipterin (BH4) is low at 7 nmol/L (9-40 nmol/L),
- Normal levels of 5-methyltetrahydrofolate 70 nmol/L (40-128 nmol/L), 5-hydroxyindoleacetic acid 133 nmol/L (66-338 nmol/L), 3-O-methyldopa 12 nmol/L (<100 nmol/L) and neopterin 16 nmol/L (7-40 nmol/L).

Genetic analysis

- Mutation, **c.4888G>T (p.E1630X**), in *SPG11* gene on chromosome 15:4881468, predicted to introduce a premature STOP within exon 28, and consistent with a pathogenic allele based on established guidelines .
- A second heterozygous variant in *SPG11* **c.6899T>G (p. L2300R**) at chromosome 15: 44858152 was also discovered. This is a rare missense variant within exon 38, predicted to result in a leucine to arginine change at position 2300.
- Targeted *SPG11* sequencing of both parents showed that E1630X and L2300R alleles were inherited from the father and mother, respectively.
- Although the L2300R change is classified as a variant of unknown clinical significance (VUS) based on ACMG guidelines, it is predicted to be damaging by SIFT (Sorting Intolerant From Tolerant) technique[2] and probably damaging by PolyPhen-2,[3] two validated algorithms for predicting the consequences of protein amino acid substitutions.[2]

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DISCUSSION

- Compound heterozygous genotype at the *SPG11* gene, discovered by WES, is the most likely cause of the clinical phenotype in our patient.[2]
- Of the two *SPG11* allelic variants identified, the premature nonsense variant (E1630X) is a potentially truncating mutation and is pathogenic based on ACMG guidelines.[4]
- While the L2300R variant by contrast is formally classified as a VUS, this rare missense change is found to be deleterious based on two independent algorithms.
- This new compound heterozygous mutation in our patient broadens the potential allelic spectrum in *SPG11*-associated HSP.
- The mean age at onset of HSP due to *SPG11* mutations is 12 years (range 2–23) with initial presentation of difficulty with ambulation (57%), which may be preceded by intellectual disability in up to 19% of patients. Parkinsonism is unusual but there are reported cases presenting predominantly as juvenile-onset parkinsonism[5] or combination of spasticity, dystonia and parkinsonism.
- Our patient's presentation with DRD is unique, and is further distinguished by a comparatively rapidly progressive course and the occurrence of levodopa-induced dyskinesia.
- DRD was classically attributed to *GTP cyclohydrolase* deficiency, but it is now recognized that mutations in *TH* and *SPR* can also cause this syndrome. There are other rare causes of DRD which include 6-pyruvoyl-tetrahydropterin synthase deficiency, *PARK2*, *SCA3* and *ATM*.
- Prior studies have also found abnormalities in CSF neurotransmitter metabolite in *SPG11*. In one study, three out of four patients showed low concentration of HVA, the main metabolite in the catabolic pathway of dopamine; and low levels of BH4 similar to our patient.[6]
- The brain MRI showed characteristic thinning of the corpus callosum (Figure 1 D) and periventricular white matter changes (Figure 1 A,B).[7]
- To better control his motor symptoms and fluctuations the patient has been scheduled to undergo brain stimulation surgery targeting bilateral globus pallidus interna.

CONCLUSIONS

- HSP due to *SPG11* mutation should be considered in the differential diagnosis of a patient presenting with DRD.
- This unusual case expands the clinical phenotypes associated with this form of HSP, and further adds to the heterogeneous genetic causes of DRD.

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