A woman with a novel mutation of THAP1 with a prominent response to deep brain stimulation of the globus pallidus internus

Jung E. Park, MD; Nora Vanegas-Arroyave, MD; Mark Hallett, MD; Codrin Lungu, MD

A 27-year-old woman presented with generalized dystonia that began at age 15 years as dystonic posturing of the right hand when writing. She was diagnosed with cervical dystonia and botulinum toxin injections were tried, providing minimal pain relief and no improvement of the dystonia. The cervical dystonia was partially responsive to sensory tricks (Video, A). She was most bothered by her cervical dystonia, and disability was 6 on Part II of the Toronto Western Spasmonic Torticollis Rating Scale (TWSTRS).

On examination, she had increased rate of eye blinking and occasional spasms involving the lower face, mouth, and jaw, and mild dysarthria. Severe right torticollis and an intermittent head tremor were present. Dystonic posturing of the right upper extremity and increased handgrip were observed while writing. Mild left foot inversion was present while walking. The Fahn-Marsden Scale score was 16, and TWSTRS Part I score was 20. A trial of carbidopa/levodopa did not provide benefit.

Deep brain stimulation (DBS) surgery targeting the globus pallidus internus (GPi) was performed, resulting in moderate improvement 1 month after the procedure, prior to initial programming (TWSTRS Part I = 18, Fahn-Marsden = 8.5) (Video, B). She experienced further benefit 2 months after initial programming (TWSTRS Part I = 13, Fahn-Marsden = 3). Whole-exome sequencing revealed a frameshift mutation, confirmed as a novel 2-base pair deletion mutation in exon 3 of the THAP1 gene (heterozygous exon 3 c.377_378delCT, p.Pro126Arg*2) via full sequencing analysis of DYT6.

Discussion

DBS dystonia is a autosomal dominant form of isolated dystonia, presenting in adolescence or adulthood. Symptoms are variable, commonly affecting the cranio-cervical region. The locus has been identified on chromosome 8p21-q22 and the gene is designated THAP1 (Thanatos-associated protein 1).

Deep brain stimulation of the GPi in patients with primary generalized or segmental dystonia can result in significant improvement during long-term follow-up. Patients with DYT6 dystonia generally have a relatively modest response, but response varies with percentages of improvement of dystonia rating scale scores from 16% to 55%.

Jech et al reported a patient with generalized dystonia and a THAP1 mutation located on exon 2, who had an excellent response to GPi DBS. Our case is another example of a novel THAP1 mutation expressed as a phenotype that responded well. Different mutations may not only have different clinical presentations, but also variable response patterns to DBS. Sorting this out may help with preoperative decisions.