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Mutation in the *GCH1* gene with dopa-responsive dystonia and phenotypic variability

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Dopa-responsive dystonia (DRD) is an autosomal dominant neurologic disorder characterized by incomplete penetrance and high variability of its phenotypic expression.[1] The usual phenotype is defined by early-onset isolated dystonia, predominant in the lower limb, with marked diurnal fluctuations and a dramatic and sustained response to low doses of L-DOPA.[2] We report 2 members of the same family (mother and daughter) with a nonsense heterozygous mutation (*c.706G>T; p.Glu236**) in the *GCH1* gene and having DRD with phenotypic variability.

Case (Index case)

A 23-year-old woman presented 10 months ago with severe cervical dystonia. At the age of 19 years, she had transient right lower limb dystonia that appeared immediately after physical effort and lasted 18 months. At the age of 22 years, she presented with left cervical dystonia lasting 2 weeks. Neurologic examination showed severe cervical dystonia with right laterocollis associated with a moderate retrocaput (video segment 1, links.lww.com/NXG/A40). The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS[3]) score was 49/85, with a severity score of 19/35, a disability score of 24/30 and a pain score of 6/20. Standard biological testing and brain MRI were normal. Levodopa/carbidopa 125 mg per day led to the complete regression of symptoms within 2 months (video segment 2). After 4 months of therapy, she decided to stop her medication. After 30 months of follow-up, her symptoms had not reappeared (video segment 3).

Her mother is 54 years old. At the age of 15 years, she had dystonia in the left foot during exercise, and at the age of 20 years, she had right upper limb dystonia. Diurnal fluctuations and task-specific dystonia appeared progressively over time. Indeed, she has writer's cramp and experiences left lower limb dystonia during prolonged walking. However, she refused to be treated. A molecular study revealed a nonsense mutation in exon 6 of the *GCH1* gene (*c.706G>T; p.Glu236**) in both of these patients.

Discussion

We report a novel DYT-5a mutation in exon 6 of the *GCH1* gene (*c.706G>T, p.Glu236**) manifesting as DRD with phenotypic variability, including cervical dystonia. This change is predicted to replace a glutamic acid residue by a stop codon. To date, 214 mutations have been reported in the gene (The Human Gene Mutation Database: hgmd.cf.ac.uk/ac/gene.php?gene=GCH1). A mutation in the *GCH1* gene is found in most patients with DRD. It encodes GTP cyclohydrolase 1, an enzyme that catalyzes the first step in the biosynthesis of

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tetrahydrobiopterin. The latter is an essential cofactor for tyrosine hydroxylase, which is the rate-limiting enzyme for dopamine synthesis.[4] As reported in the literature, there is a female-dominant penetration[4] but no clear anticipation phenomenon.

The clinical presentations and evolution of our cases were uncommon compared with the phenotypes usually recognized.[5] Indeed, our index case initially had severe cervical dystonia, and her mother presented with writer's cramp. However, clinical presentations of DRD can be heterogeneous and encompass a wide variety of symptoms including focal-task dystonia[6] and parkinsonism[7] or share some clinical similarities with cerebral palsy.[8] The time course of symptoms was also very unusual for DRD. Although cervical dystonia quickly and completely abated after levodopa therapy, no relapse occurred after medication withdrawal during the 30 months of follow-up. This is surprising but could potentially be explained by corticostriatal synaptic homeostatic practice-dependent plasticity over time in patients with subtle dopaminergic alterations linked to the *GCH1* mutation.[9]

These 2 patients presented with DRD. Focal dystonia is usually idiopathic with no clear genetic background or relation to basal ganglia lesions.[1,10] However, clinicians should be aware of the fact that patients exhibiting focal dystonia can present a *GCH1* mutation and dopa responsiveness. This new mutation could potentially explain the unusual phenotype presented by our patients throw further light on the pathophysiology of dystonia.

Author contributions

E.K.: acquisition of data and writing of the first draft of the manuscript. J.A.: writing of the first draft of the manuscript and critical revision of the manuscript for intellectual content. F.C. and M.B.: acquisition of data and critical revision of the manuscript for intellectual content. P.B.: study supervision and critical revision of the manuscript for intellectual content. D.G.: acquisition of data, study concept and design, and critical revision of the manuscript for intellectual content.

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