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Asymmetrical leg atrophy in Dopa Responsive Dystonia due to a novel GTP cyclohydrolase mutation

E Mulroy, MB, BCh¹, A McCarthy, MRCPI^{1,*}, D Costello, MRCPI², OA Ross, PhD³, and T Lynch, BSc, MB, FRCPI, FRCP(Lond)¹

¹Dublin Neurological Institute at the Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland. ²Cork University Hospital, Wilton, Cork, Ireland. ³Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA.

Case report

A 33 year old man was referred by orthopaedics for assessment of a progressive gait disturbance since childhood. At 11 years he developed in-turning of his left foot. Between the ages of 12 to 28 years of age he underwent spinal exploratory surgery, triple arthrodesis of his left ankle, repeat left ankle arthrodesis, elongation of his achilles tendon and wedge osteotomy. A paediatric neurologist recorded pes cavus, wasting of the left lower limb and brisk reflexes at 12 years. Wasting and shortening of the left leg was noted prior to any orthopaedic operations and subsequently a diagnosis of cerebral palsy was made. A sister (one of six siblings) never walked normally from childhood and was unable to run. She did not have limb wasting and was also diagnosed with cerebral palsy.

At the age of 33 he was noted to have bilateral leg wasting, especially on the left side with an inverted champagne bottle appearance, and bilateral pes cavus (Figure 1). Legs were spastic with brisk knee jerks but plantars were flexor. He had an awkward scissor gait with flexed hips and knees. There was no bradykinesia. MRI brain was normal. Neurophysiology revealed mild slowing of the right sural nerve only (35m/s). One week following initial assessment, he was started on a trial of sinemet 62.5mgs three times daily, resulting in dramatic improvement in gait and lower limb function within days. His sister was simultaneously undergoing investigation in a US hospital. Their mother visited and insisted she try the 'same pills' as her brother. She also experienced dramatic improvement on levodopa.

*Corresponding authors contact information: Dr. Allan McCarthy, Dublin Neurological Institute at the Mater Misericordiae University Hospital, 57 Eccles Street, Dublin 7, Ireland. Tel: +353857204651, amaccarthy@gmail.com.

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Genetic Result

A novel single T>A base pair substitution in exon 5 of the guanosine triphosphate cyclohydrolase 1 (*GCHI*; OMIM 128230) gene (c. 578 T>A, p. I193N;) was found. Both siblings were heterozygous for this novel mutation, it is absent from the public databases and was not observed in the exome variant server data (<http://evs.gs.washington.edu/EVS/>).

Discussion

Dopa responsive dystonia (DRD), described by Segawa¹, displays both genetic and phenotypic heterogeneity. A large cohort of GTPCH1-deficient DRD patients revealed four main phenotypes: young onset classic disease, young onset mild, young-onset with severe initial hypotonia and adult-onset.² Particular care is required to distinguish it from cerebral palsy, spastic paraparesis and young-onset parkinsonism.^{3, 4} Lack of an accurate diagnosis may lead to unnecessary investigations, surgeries and delayed effective treatment. Leg atrophy is uncommon, but can rarely occur in DRD and in parkinsonian syndromes, with the underlying mechanism unknown.⁵ It has been postulated that an asymmetric deficit in dopaminergic transmission may lead to asymmetric limb atrophy.⁵ Interestingly the sibling with the later onset and milder phenotype was the one with the associated atrophy. Finally we describe a new mutation in the *GCHI* gene that is likely pathogenic.

Our findings demonstrate the importance of a clear and accurate diagnosis for DRD. The signs and symptoms described in our family should alert neurologists to consider DRD as a diagnostic possibility in patients with paediatric limb disorders associated with atrophy and any patient with 'cerebral palsy'.

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Figure 1.