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Letter to the Editor

Pure hypotonia in a four-year-old patient: An atypical presentation of Dopa-responsive dystonia

Dear Editors,

Dopa-responsive dystonia (DRD) was first described in a Japanese family with a hereditary progressive dystonia [1]. Three hallmarks of the disease were subsequently identified – progressive dystonia with childhood or adolescent onset, a diurnal fluctuation of symptoms, and alleviation of symptoms as a result of treatment with low-dose oral levodopa [2].

The most common cause of DRD is an autosomal dominant mutation in guanosine triphosphate (GTP) cyclohydrolase 1 (GCH-1). GCH-1 is the first rate-limiting step in the biosynthesis of tetrahydrobiopterin (BH4) [3]. Atypical presentations of DRD include the core symptoms of DRD but have additional features such as infantile or neonatal onset, truncal hypotonia, bulbar weakness, Parkinsonism, seizure, myoclonus, developmental delay, intellectual disability, cerebral palsy, and autonomic dysfunction [4–6]. DRD and DRD-plus can be caused by other mutations of the dopamine synthetic pathway including autosomal recessive (AR) GCH-1, tyrosine hydroxylase (TH), sepiapterin reductase (SR), 6-pyruvoyltetrahydropterin synthase (PTPS), dihydropteridine reductase (DHPR), and aromatic L-amino acid decarboxylase (AADC) [5]. SR mutations are especially associated with hypotonia and cognitive delay prior to emergence of diurnal dystonia which can be delayed in onset by several years [7]. The case below illustrates a case of pure hypotonia that was eventually diagnosed as DRD.

We present a 3.5 year-old girl with progressive gait instability that was first recognized at the 3 year well visit. The patient first rolled over at 4 months, sat without support at 6 months, and started walking at 14 months with a gait that was unsteady but resembled other children her age. Over time, the patient's gait remained unbalanced with frequent falls due to tripping over her feet and with knees and hips bending inward on ambulation. Gait instability and fall frequency worsened with fatigue. The patient met all other gross, fine, and language milestones per patient's father. The patient had an uncomplicated delivery without NICU stay and no other past medical history. Family history was remarkable for a paternal great-aunt with dopa-responsive dystonia (DRD) and a father with ulcerative colitis that was well controlled.

Neurologic examination at 3 years and 6 months of age was remarkable for decreased strength, predominantly axial, with the neck flexors and abdominal muscles most markedly affected. The patient had ligamentous laxity with foot inversion and ankle dorsiflexion weakness. Gower's sign was present. Gait examination was remarkable for frequent locking of the legs to support the patient's weight, bilateral foot drop contributing to frequent falls, decreased hip flexion, and fluctuation between wide and narrow base. Reflexes were 2+, sensation, and the remainder of the neurologic examination was normal.

Myopathy was considered and a hypotonia workup including creatine kinase, lactate, thyroid stimulating hormone, erythrocyte sedimentation rate, C-reactive protein was normal. MRI brain and spine and nerve conduction study (NCS) was normal. Repeat examination at 3 years and 9 months of age by neurology remained unchanged with preserved reflexes, coordination, and sensation. Pyruvate, carnitine, acylcarnitine, and plasma amino acids were normal. The patient underwent a genetic panel for hypotonia and three variants of undetermined significance were noted including c.6559C > T in DYNC1H1, c.1528C > T in MFN2, and c.212T > C in TCAP. These genes more typically contribute to hereditary sensory and motor neuropathy and were not considered significant.

At 4 years and 2 months of age, the examination was remarkable for mild flexed and pronated posturing of the bilateral upper extremities with ambulation. At 4 years and 8 months of age, patient's father noted more persistent arm posturing with ambulation and left more than right foot inversion with leg extension. Repeat examination showed increased right more than left flexed dystonic arm posturing with ambulation. The patient was started on an empiric trial of Sinemet 12.5/50 twice daily and genetic testing was expanded to whole exome sequencing. Examination on Sinemet showed improvement in hypotonia with only mild truncal hypotonia, negative Gower's sign, resolution of falls, improved axial and appendicular strength to 5/5, and a new ability to run and jump. The patient developed mild dyskinesias in all 4 extremities which were not distressing or disruptive to the patient. Whole exome sequencing was positive for a GCH1 mutation c.607G > A (p.G203R).

To our knowledge, hypotonia without dystonia, spasticity, and hyperreflexia is a rare and under-recognized presentation of GCH-1 DRD. The only other similar reported case is by Kong et Al. Their patient also underwent a similar myopathy workup as well as additional testing including muscle biopsy and MRI of the limb and trunk muscles, all of which did not yield a diagnosis. Their patient's younger sister was affected starting at age 5. Eventually the siblings' symptoms were noted to have a diurnal variation and both were trialed on Sinemet 6.25/25 twice daily with significant improvement in ambulation, scapular winging, handwriting, and speech but with persistent hypotonia. Genetic testing revealed a Gly203Arg mutation at exon 5 of the GCH-1 gene [8]. Our case differs from the above due to the marked improvement in hypotonia with Sinemet; however our patient was given a higher dose of the medication. This is the second report of the Gly203Arg GCH-1 mutation presenting as pure hypotonia.

Trender-Gerhard et al. described 34 DRD patients with confirmed GCH-1 mutations and an atypical group consisting of two siblings with truncal hypotonia in the first year of life who developed a significant delay in motor development and rapid progression of severe generalized dystonia with oropharyngeal involvement [9]. It is not clear whether these patients presented with pure hypotonia or whether additional abnormal examination findings existed at the time of presentation. Intellectual and language development were preserved throughout the course of illness. Both siblings improved with treatment but the older sibling remained limited by joint contractures. Both had

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compound heterozygosity with maternally and paternally inherited GCH-1 gene mutations [9].

This case illustrates the importance of serial examinations in cases of undiagnosed hypotonia. Emergence of subtle and progressive dystonia was informative in diagnosing the patient. There are a myriad of causes of hypotonia and the workup is extensive and often inconclusive. While it is important to address common or potentially catastrophic causes of hypotonia with the initial workup, rare causes that are sensitive to treatment should be considered as well. Compared to the other cases of DRD presenting as pure hypotonia, our patient was treated before chronic sequellae such as joint contractures developed and had a superior outcome. Given that DRD is a rare but highly treatable condition, patients with unexplained hypotonia may benefit from early GCH-1 testing or an empiric trial of Sinemet.

Disclosures

This work represents the sole opinion of the authors and does not necessarily represent the opinion of the United States Department of Defense or US Government.

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