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Clinician's Corner
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An 8-year-old boy with ataxia and abnormal movements

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CLINICAL CASE

An 8-year-old boy presents with ataxia and chorea. The patient was born at term to a nonconsanguineous Caucasian couple following an unremarkable pregnancy. The neonatal period was complicated by respiratory distress, requiring intubation and treatment for presumed congenital pneumonia. He was hypotonic as an infant and presented with ataxia and gross motor delay at 18 months. While his ataxia remained static, he developed dystonia, choreoathetosis, and attention deficit hyperactivity disorder (ADHD). The patient's father had a clinical diagnosis of ataxic cerebral palsy (CP).

On physical exam, he had ataxia as well as choreoathetoid movements in his hands and dystonic posturing of his feet. Tone was intermittently increased, likely related to involuntary movements. No spasticity was noted. Deep tendon reflexes were normal. Plantar response was equivocal bilaterally. Rapid alternating movements and finger-to-nose testing were difficult due to involuntary movements. Limited stride length and hyperextension of the knees were noted in gait.

MRI of the head was normal. Laboratory investigations were normal, with the exception of mildly elevated thyroid-stimulating hormone. Chromosomal microarray was normal.

Clinically, the child was diagnosed with ataxic CP, however, further genetic investigation was done given the atypical presentation and a positive family history.

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DISCUSSION

Further investigation of our patient by whole exome sequencing revealed a pathogenic mutation in the *NKX2-1* gene, consistent with a diagnosis of benign hereditary chorea (BHC). This genetic mutation was also identified in the patient's father.

CP is the most common disorder of movement in childhood (1). It is a nonprogressive disorder of movement and posture caused by disturbance to the developing brain (1). Such disturbances interrupt or otherwise impair the normal pattern of brain development leading to permanent, nonprogressive brain impairment. Classically, this disturbance is attributed to perinatal insult, but genetic causes are also important considerations. CP is diagnosed by history and clinical presentation. MRI brain may be used to clarify diagnosis, however, epidemiological studies consistently report that 15% of children with a clinical diagnosis of CP have normal brain imaging (1). Red flags, which indicate more detailed investigations are needed in a patient with a clinical diagnosis of CP, include normal brain imaging, significant family history, lack of perinatal risk factors for CP, fluctuations in motor function, dysmorphic features or sensory signs, and should prompt further investigations. With the clinical use of genetic testing for diagnosis, genetic causes of CP as well as genetic mimickers of CP are more readily identified. As well as genetic causes, there are disorders that, in their earlier stages, also mimic CP including many leukodystrophies, hereditary spastic paraplegias, and neurotransmitter disorders (in particular dopa-responsive dystonia) (1).

BHC is an autosomal dominant movement disorder of childhood-onset, predominantly characterized by a nonprogressive chorea (2). While there is significant inter- and intrafamilial variation, BHC begins in infancy with low muscle tone and often comes to medical attention due to motor developmental delay. The onset of a generalized chorea is usually seen at 2.5 to 3 years of age. The chorea remains stable and has been seen to improve in late adolescence or early adulthood (2).

Other movement disorders have also been reported concurrently with BHC, including ataxia, dysarthria, intention tremor, dystonia, and motor and vocal tics (2). Patients with BHC are predominantly not affected by seizures or cognitive delay; however, psychiatric symptoms including psychosis, schizophrenia, obsessive-compulsive disorder, and ADHD have all been reported in patients with *NKX2-1* mutations (2). Among the psychiatric symptoms described in BHC, ADHD is the most commonly reported (2).

As is the case for our patient, there are multiple reports of thyroid and lung dysfunction in association with BHC including respiratory distress syndrome following delivery, asthma, recurrent pulmonary infections and chronic lung disease, as well as congenital hypothyroidism or subclinical hypothyroidism throughout childhood and adulthood (2). Neurological symptoms are reported to be present in 100% of cases of *NKX2-1* mutations, with lung involved in 78% of the cases and thyroid dysfunction in 75% of the cases (2). The combination of neurological, lung and thyroid dysfunction has been reported to occur concurrently in 30 to 36% of patients which is why BHC is also referred to as NKX2-1-associated disorders or brain-lung-thyroid disease, reflecting BHC's ever-expanding phenotype (2).

At this time, there are no guidelines for management or treatment for patients with BHC. There are, however, several reports of treatment of the associated hyperkinetic movement disorder with medications such as tetrabenazine, levodopa, sodium valproate, trihexyphenidyl, and sulpiride (2). It is recommended to involve respirology and endocrinology services should the patient shows symptoms of lung or thyroid dysfunction. Supportive services, such as educational aids, physiotherapy, and occupational therapy have been particular helpful to our patient.

The diagnosis of BHC should be considered in all cases of early-onset chorea preceded by hypotonia and motor developmental delay and associated thyroid or lung dysfunction would further support this diagnosis.

CLINICAL PEARLS

- Consider further investigation when a patient presents with features that are considered 'red flags' in the context of CP, in particular normal brain imaging, perinatal history not consistent with CP, progression of motor or sensory signs, neurodevelopment regression, or positive family history.
- The diagnosis of BHC should be considered in patients with early-onset chorea, especially when preceded by hypotonia and motor developmental delay.
- A clinical triad of early-onset nonprogressive chorea, thyroid dysfunction, and lung involvement strongly suggests an *NKX2-1* mutation (1). Screening for *NKX2-1* mutations has been strongly recommended in patients with symptoms corresponding to BHC (1,2).

Informed consent was obtained for this case.

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References

1. Lee RW, Poretti A, Cohen JS, et al. A diagnostic approach for cerebral palsy in the genomic era. Neuromolecular Med 2014;16(4):821–44.
2. Peall KJ, Lumsden D, Kneen R, et al. Benign hereditary chorea related to NKX2.1: Expansion of the genotypic and phenotypic spectrum. Dev Med Child Neurol 2014;56(7):642–8.