

New Observations Letters

The Movement Disorder of Brain-Lung-Thyroid Syndrome Can be Responsive to Methylphenidate

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Ethics Statement: All patients that appear on video have provided written informed consent; authorization for the videotaping and for publication of the videotape was provided.

Introduction

Benign hereditary chorea is a rare disorder characterized by childhood-onset, non-progressive chorea, with or without associated respiratory and thyroid dysfunction.¹ It is referred to as “brain-lung-thyroid” syndrome when all three systems are involved.² It is caused by autosomal dominant mutations in the *NKX2-1* gene (previously *TITF-1*), on chromosome 14.³ It is a genetically heterogeneous condition, with over 30 different causative mutations identified.⁴

Other neurological manifestations of benign hereditary chorea and *NKX2-1*-related disorders include dystonia, myoclonus, tics, tremor, dysarthria, ataxia, hypotonia, and motor developmental delay. Neuropsychiatric symptoms such as attention deficit hyperactivity disorder (ADHD), have also been reported.^{1,5}

Pharmacologic treatment of chorea and other abnormal movements in *NKX2-1*-related disorders has been disappointing. It typically involves levodopa or tetrabenazine; however, side effects are often limiting.⁵ We report and illustrate the case of a young female patient with brain-lung-thyroid syndrome and an immediate improvement of her involuntary movements with methylphenidate (Video 1).

Methods

We obtained written informed consent from the subject and legal representative under a study approved by the ethics committee of the Montreal Children's Hospital. We performed a retrospective chart review and assessed the patient before and after methylphenidate hydrochloride ingestion.

Results

The patient was born at term following an uncomplicated pregnancy. She suffered from transient respiratory distress. She was first referred to the neurology department at 2 years of age for hypotonia and motor delay. Thyroid function tests were performed at age 2 as part of the investigations for hypotonia and revealed hypothyroidism. The patient also had asthma. Chorea was noted on examination, predominantly in the limbs, with superimposed generalized dystonia and occasional myoclonic jerks. The cranial muscles were relatively spared. The patient was found to carry a *de novo* heterozygous missense mutation in *NKX2-1* (NM_001079668, hg19). This variant (c.626G>C, p.Arg209Pro) has not been reported in any online database



Video 1. Immediate Improvement of the Involuntary Movements with Methylphenidate. The patient executed the following tasks prior to and 30 minutes after methylphenidate hydrochloride administration: running, performing rapid alternating movements, pouring water into a cup, and writing a series of loops with her dominant hand. There was a significant reduction in her choreic movements and dystonic postures, especially in the limbs. All tasks were carried out faster and with more precision after receiving her medication.

(ESP, 1000g, ExAC, gnomAD). It affects a highly conserved amino acid and is located in a highly conserved region involved in DNA binding.⁶ dbNSFP databases provided by Annovar predict the variant to be pathogenic. It has been published as pathogenic in three individuals from one family with childhood-onset hypothyroidism and movement disorders.⁶

Psychostimulant medication was initiated at the age of 5 for a comorbid diagnosis of ADHD. The patient experienced a sudden and dramatic improvement of her gait and stopped using her walker. She is now 10 years old and was initially treated with methylphenidate (up to 20 mg daily), and later with controlled-release methylphenidate hydrochloride (up to 30 mg daily). The medication adjustments were made based on her ADHD symptoms and treatment impact on her appetite. She has been on the same regimen since age 8 and has not required any additional treatment for her abnormal movements. She exhibits significant reduction of her choreic movements and dystonic postures within 30 minutes after receiving her daily dose, with consequent improvement in her gait, speech, and fine motor skills. These benefits consistently last throughout the day. The patient and her parents report that the involuntary movements only become more bothersome in the evening and peak in the morning prior to methylphenidate ingestion. This is consistent with the reported duration

of action (8 to 12 hours) of extended-release forms of stimulant medications.⁷

Discussion

The central nervous system stimulant methylphenidate is typically not considered as a treatment option for chorea or other movement disorders. However, it was previously associated with incidental improvement in two patients with benign hereditary chorea.^{8,9} In 1996, Friederich first reported subjective improvements of handwriting and gait in a young male patient treated with methylphenidate.⁸ He hypothesized that this response was the result of a reduction in stress exacerbating the chorea rather than a direct effect. The dramatic, immediate response in our patient argues against this hypothesis.

Questions remain about the role of dopamine in benign hereditary chorea. *NKX2-1* is believed to be involved in the embryologic striatum development.^{10,11} Immunohistochemical studies on an affected post-mortem brain revealed loss of striatal interneurons and efferent fibers.¹¹ In addition, a recent dopaminergic neuronal imaging study found decreased dopamine receptor binding.¹²

Tetrabenazine is a dopamine-depleting agent that inhibits the vesicular monoamine transporter 2, whereas levodopa is a dopamine precursor converted to dopamine by striatal enzymes. Both have shown suboptimal results in the treatment of movement disorders in patients with benign hereditary chorea and *NKX2-1*-related disorders.⁵ Methylphenidate is a dopamine reuptake blocker that facilitates dopaminergic transmission. Although dopamine appears to be involved in the pathogenesis of *NKX2-1*-related disorders, the benefit of methylphenidate over levodopa and other dopaminergic medications remains unexplained.

This case illustrates for the first time an immediate and objective response to methylphenidate in a patient with brain-lung-thyroid syndrome. Further research is warranted to better document and explain this response. Our report supports a trial of methylphenidate to improve functional abilities in patients affected by *NKX2-1*-related disorders, especially given its more favorable side effect profile compared to other pharmacologic agents.

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