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Tremor and Other Hyperkinetic Movements

Brief Reports

Tics and Shorter Stature: Should We Be Looking for an Association?

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Abstract

Background: Tic disorders have commonly occurring and well recognized comorbidities including obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD). Shorter stature is not generally appreciated as an associated feature.

Methods: Case reports and a literature review.

Results: We describe four recently encountered patients with tics and shorter stature. The literature suggests that in addition to OCD and ADHD, shorter stature may also commonly accompany tic disorders. A variety of neuroendocrine mechanisms have been proposed.

Discussion: The potential associations between shorter stature and tic disorders and the common comorbidities OCD and ADHD deserve more attention. More research is needed to establish the strength of these associations and the underlying neurobiological mechanisms.

Keywords: Tics, Tourette syndrome, short stature, height, neuroendocrinology

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Introduction

Tourette syndrome (TS) is a childhood-onset condition characterized by chronic motor and vocal tics. A number of comorbidities have been established to commonly accompany TS, including obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD).[1] Tics can also be seen in other neurodevelopmental conditions such as autism spectrum disorder (ASD).[2] Since January 2014, we have evaluated 48 children referred for tics, and we encountered 4 patients with tics and shorter stature, a condition not generally associated with tics. We now present these cases and discuss the literature regarding possible links between tics and shorter stature.

Case reports

Case 1. A 13-year-old female was born with the umbilical cord wrapped around her neck, requiring an emergency cesarean section. From birth, she had a small head circumference and an abnormal growth curve, remaining in the 3rd to 4th percentile for length/height and in the 5th to 9th percentile for weight. At the age of nine, she developed motor tics including eyeblinking, eye rolling, facial movements, platysma tightening, eyebrow raising, bruxism, and a throat-clearing vocal tic. She reported some mental fogginess in school with problems following directions and also some obsessiveness with certain thoughts and images staying in her consciousness. The tics did not respond to guanfacine, and although she experienced some relief with topiramate 25 mg/day, this drug caused mental slowness and it was stopped. The eyeblinking tics improved following local intramuscular injections of botulinum toxin. One of the patient's two older sisters has short stature (below the 1st percentile) but no tics. The other sister's height is in the 45th percentile, the mother is in the 40th percentile, and the father is in the 50th percentile. The patient has no other medical problems, is mildly delayed in sexual development (Tanner staging, treated with estrogen), has not been treated with any other medications, has no known cause of shorter stature, and has a normal nutrition and dietary history.

Case 2. This 14-year-old female experienced developmental delays in physical, academic, emotional, impulse control, attention, and social

areas. She was born with decreased muscle tone and had early difficulty with visual tracking. She was diagnosed with a sensory integration disorder (sensitivity to noises) in early childhood. She had delayed social and emotional milestones. Ultimately, she was diagnosed with ASD. Her growth curves were abnormal, with height in the 19th percentile at the age of eight and the 1st percentile at age 14. Her weight is currently in the 7th percentile. She had delayed dentition, breast development, and puberty onset. At age 12 she was found to have low thyroxine (3.6 mcg/dL) but has not received thyroid replacement therapy. The patient first developed tics at age 3, including fist clenching, foot tapping, and head shaking. Because the tics caused impaired functioning and impacted her self-esteem, she was treated with guanfacine 1 mg/day with limited improvement. Risperidone up to 1.5 mg/day was added but was not tolerated and offered no benefit. Aripiprazole 2.5 mg at bedtime has led to an improvement in the tics. The patient's mother and father are in the 36th and 45th percentiles for height, respectively. The patient has no other medical problems, has taken no other medications on a chronic basis, and has no known nutritional or dietary problems or other known causes of shorter stature.

Case 3. This 14-year-old male first manifested tics around the age of eight, including lip licking, eyeblinking, head jerking, and teeth clicking. His length/height has remained in the 10–15th percentile. At ages 11 and 14, his weight was in the 24th and 12th percentiles, respectively. He is scheduled to have an endocrinological evaluation for shorter stature. Both parents are in the 45th–55th percentiles for height. The patient has not taken any medication on a chronic basis, has no other health problems, no other known causes of shorter stature, and no known nutritional or dietary problems.

Case 4. This 14-year-old male was diagnosed with ADHD in the 3rd grade due to short attention span and distractibility. He has been treated with guanfacine, clonidine (currently 0.3 mg/day), and methylphenidate (currently 10 mg/9 hours transdermally). Around the age of seven, he developed mild motor (eyeblinking, neck, facial) and vocal (throat clearing) tics, as well as some mild obsessive-compulsive features (perfectionism, evening up). His height and weight were between the 10th and 25th percentiles for the first 10 years of life but are currently at the 4th and 6th percentiles, respectively. His bone age is estimated at age 12 years and 0 months, nearly two standard deviations below his chronological age. He has been referred to an endocrinologist for evaluation of short stature. The patient's older brother has TS, ADHD, and mild obsessive-compulsive symptoms, but his height is in the 63rd percentile. The parents are in the 50th–55th percentile for height. The patient has no other medical problems, has not taken any other medications on a chronic basis, has no other known causes of shorter stature, and no known nutritional or dietary problems.

Discussion

Short stature is defined as height that is more than two standard deviations below the mean for an individual's age and sex or in the bottom 3% of the population, and it affects approximately 2.3% of the US population.[3] Lesser degrees of low height are referred to as "shorter" stature. Short or shorter stature may be caused by growth hormone failure, other endocrine disorders such as hypothyroidism, a variety of chronic illnesses, or malnutrition.[3] Short stature is also commonly associated with certain genetic diseases, such as a homeobox *SHOX* gene mutation or Down syndrome.[4]

The four cases described here presented with tic disorders and shorter stature. They exhibited some heterogeneity in that tics occurred in the context of TS or ASD. In addition, potential confounding factors that might contribute to shorter stature, including perinatal problems, relatives with short or shorter stature, comorbidities such as OCD and ADHD, and medication use, make it difficult to establish a link between shorter stature and tics per se. There may be an association between shorter stature and brain neurodevelopmental disorders in general.

Few previous reports have linked tic disorders to shorter stature. A review of the neurological manifestations of celiac disease mentioned one case with chronic tics, ADHD, and short stature.[5] A study in Israel found that among 38 children with TS, 45% were in the lowest height quartile.[6] The authors speculated that brain neurotransmission disturbances in TS may adversely affect neuroendocrine function, resulting in reduced height. Indeed, the dopamine D2 receptors thought to underlie a dopamine neurotransmission abnormality in TS also play a role in growth hormone release.[3] Allelic variations in the D2 receptor gene have been identified in children with short stature.[7] Disturbances of the endogenous opioid system have also been suggested to occur in TS,[8] and this system is known to interact with the hypothalamic-pituitary axis and influence growth.[9] Thus, any association between tic disorders and reduced height may be related to neurotransmitter and/or neuroendocrine disturbances.

One potential mechanism is suggested by certain genetic syndromes characterized by a combination of tics and short stature. Deletions of chromosome 22q11.2 have been associated with developmental delay and ASD. Such deletions may result in reduced expression of the catechol-O-methyltransferase (*COMT*) gene, which is involved in metabolizing dopamine and other catecholamines.[10] Low COMT activity has been associated with tics and other hyperkinetic movement disorders.[11] Some patients with 22q11.2 deletions have exhibited cervical and thoracic vertebrae fusion (Klippel-Feil anomaly) that can contribute to short stature, but short stature has also been observed in individuals with this syndrome without vertebral fusion.[10]

OCD is clinically and genetically associated with TS and is considered along with ADHD to constitute the "TS triad."[1] Thus, it is notable that short stature has been reported to be common in adolescent males, but not females, with OCD.[12] Blunted nocturnal growth hormone secretion, decreased pituitary gland volume, and delayed onset of puberty have all been observed in OCD patients.[12] Abnormal serotonin neurotransmission in the brain has been suggested to occur in OCD, and some serotonin receptor subtypes (1D and 2C) play a role in the neuroendocrine regulation of growth hormone.[13] Because of the genetic link between OCD and TS, it is possible that

these mechanisms may contribute to shorter stature in individuals with tic disorders.

It is believed that long-term treatment of ADHD with stimulant medications is associated with a small but significant reduction in growth,[14] and it has been suggested that the mechanism involves drug-induced dopamine transporter blockade and resultant elevated dopamine levels in the hypothalamus.[15] Whether ADHD itself is linked to growth reduction or delay is more controversial.[14,16,17]

Thus, several sources of evidence, although preliminary, indicate a potential link between shorter stature and tics, as well as the associated conditions OCD and ADHD. Our case series raises the possibility of an association between tics and shorter stature but cannot provide more than suggestive evidence given that it is not case-controlled and there are potentially confounding clinical aspects for the four cases. Further research is needed to establish the strength of the associations and to clarify underlying neuroendocrine mechanisms.

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