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Clinical Observations

Benign Hereditary Chorea: A Case Report and Brief Review of Inherited Choreas

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ABSTRACT

BACKGROUND: Chorea as a nonprogressive abnormality is often associated with Sydenham chorea in the pediatric population. Benign hereditary chorea is a condition where chorea presents before age 5 years and runs a very slowly progressive course. **PATIENTS:** We present a family that was thought to have a variant of Huntington disease but on genetic testing was confirmed to have benign hereditary chorea. We describe a 7-year-old girl in this family who presented with involuntary movements and hyperactivity. **RESULTS:** Our family was determined to have benign hereditary chorea after extensive genetic testing and follow-up. **CONCLUSIONS:** When chorea presents as a familial entity, the differential diagnosis is limited and is often misdiagnosed as Huntington disease. In this family benign hereditary chorea was found to be the cause.

Keywords: benign hereditary chorea, inherited choreas, Huntington's disease, Wilson disease

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Introduction

Chorea as a nonprogressive abnormality is often associated with Sydenham chorea in the pediatric population. When it presents as a familial entity, the differential diagnosis is very limited. Benign hereditary chorea is a condition in which chorea presents before age 5 years and runs a slowly progressive course.

Patient Descriptions

We present a family that was initially suspected to have a variant of Huntington disease but on genetic testing was confirmed to have benign hereditary chorea.

This girl presented at age 7 years because of involuntary movements and hyperactivity. The movements were constantly present during awakefulness and involved the upper extremities and shoulder muscles. Her mother also reported that she had nocturnal enuresis which had not responded to imipramine. She had global developmental delay. She began crawling at 9 months of age but did not walk until age 2.5 years. She had speech delay and did not combine words until aged 4 years. She was toilet trained at age 4 years. Birth history was uneventful. She was born term, normal spontaneous vaginal delivery with a birth weight of 5 pounds 8 ounces. The neonatal period was uneventful and without jaundice. At the time of presentation she was able to read simple words and was able to add and subtract. She was in first grade with an individualized education plan and had been diagnosed with a learning disability. There were no other known illnesses. The family history was significant for the father having a similar disorder. He died at age 27 years. Her half brother, who was 8 years older, had a similar disorder.

There was no history of learning disability or developmental delay on the maternal side of the family.

On examination her weight was 20 kg (25th percentile, height was 113 cm (near the 10th percentile), and head circumference was 47 cm (3rd percentile)). She had continuous choreiform movements involving her truncal muscles, mainly the neck, shoulders, and proximal arm muscles. There was no ataxia, dystonia, or dysmetria. Strength, tone, and deep tendon reflexes were normal. She could not perform tandem walk and could not hop on either foot. There were no skin rashes or telangiectasias, no hepatosplenomegaly, and no cardiac murmurs.

Investigations including complete blood count, basic metabolic panel, copper, ceruloplasmin levels, serum lactate, vitamin E levels, serum amino acids, urine organic acids, and Huntington gene mutation were negative. Thyroid function tests revealed high thyroid stimulating hormone, which was repeated by endocrinology and found to be normal. Celiac disease panel and thyroid antibody panel were also negative.

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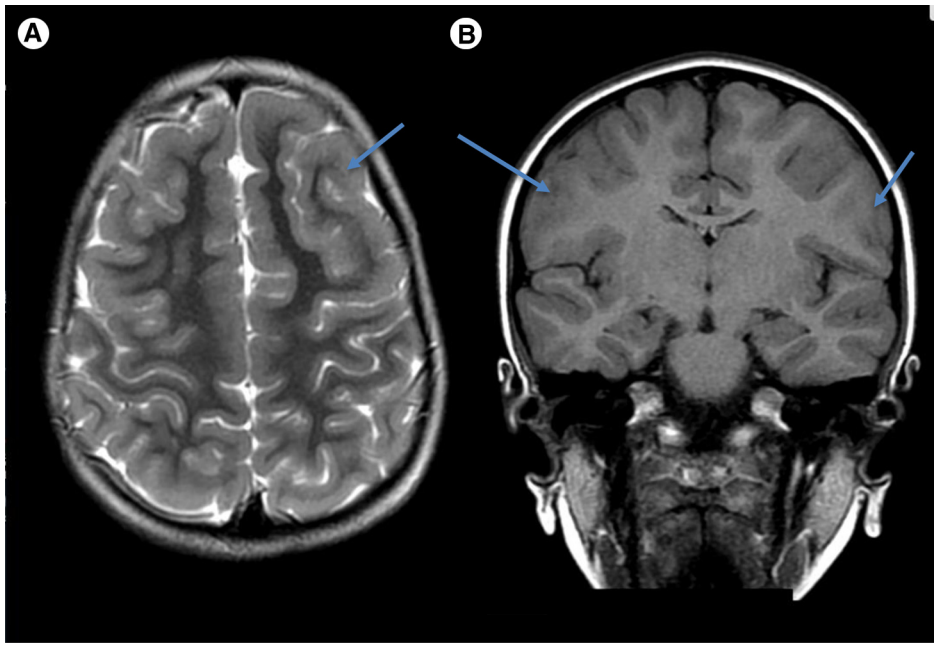

FIGURE.
Magnetic resonance imaging reveals subtle cortical dysplasia (arrows) in the frontal regions bilaterally with mild blurring of the gray-white interface (arrows). (A) Axial T_2-weighted image. (B) Coronal T_1-weighted image. (Color version of figure is available in the online edition.)

Magnetic resonance imaging (MRI) of the brain revealed subtle areas of cortical dysplasia in frontal regions bilaterally with mild blurring of the gray-white interface (Figure).

The sequencing of the gene for benign hereditary chorea (*TITF1* now referred to as *NKX2.1*) characterized a missense mutation in exon 3-C.701A>T (Gln234Leu) located on chromosome 14q13.2-13.3, which is considered a pathogenic mutation. She was treated for chorea with risperidone 0.5 mg twice daily and for her hyperactivity with atomoxetine at a dose of 25 mg daily with some improvement. Tetrabenazine was not tried because it was not then available.

Her paternal half brother, who is aged 7 years, was also being monitored in our clinic for global developmental delay, headaches, chorea mainly involving the upper extremities, truncal ataxia, and intermittent dystonic posturing. He had severe behavioral problems including aggression, violent behavior, and hyperactivity. He was in special education classes with an individualized education plan and had been diagnosed with learning disability. He was also diagnosed with symptomatic epilepsy at the age of 18 months and had been treated with valproic acid. Electroencephalography revealed focal spikes from the right parasagittal region and background slowing. He was being treated with topiramate for epilepsy and headaches. During the course of his evaluation, which included copper, ceruloplasmin levels, lactate, pyruvate levels, ataxia panel, thyroid function tests, and MRI of the brain, he was found to have hypothyroidism and was placed on thyroxine. Mutational analysis for benign hereditary chorea characterized a missense mutation in exon 3-C.701A>T (Gln234Leu) in *TITF1* (*NKX2.1*) located on chromosome 14q13.2-13.3, the same mutation that was present in his half sister.

Their father was diagnosed with muscular dystrophy at age 2 years because he had motor delay. He began walking at age 3 years. He was also observed to have involuntary movements at age 3 years. These were described as choreiform movements, which worsened with anxiety. His intelligence was thought to be subnormal, and he was diagnosed with learning disability.

Investigations included antistreptolysin O titers, thyroid function tests, ceruloplasmin, antinuclear antibody, phytanic acid, uric acid levels, lactic acid, electromyography, and nerve conduction studies. He was found to have hypothyroidism and was treated with thyroxine. He was also treated with sodium valproate as symptomatic therapy for choreiform movements. MRI of brain was reported to be normal with no evidence of caudate atrophy. He was lost to follow-up and died at age 27 years with pulmonary problems after experiencing a cardiac arrest at home. He had been admitted and treated for pneumonia before his death and had just returned from the hospital.

His postmortem examination revealed a small thyroid with no abnormality in the microscopic examination. There was evidence of acute bronchopneumonia bilaterally and chronic bronchitis. The brain was of normal weight with no evidence of atrophy of the basal ganglia, nor of the cerebral or cerebellar cortex. Ventricles were not dilated. Microscopy of the brain revealed no abnormalities except for the presence of focal astrocytosis in the body and tail of the caudate nucleus with an increase of corpora amylacea in the paraventricular region.

The heart revealed moderate atherosclerosis of the left anterior descending artery and right coronary artery.

Discussion

Chorea is a relatively uncommon movement disorder presenting in childhood. The most common etiology of chorea in children is Sydenham chorea in the developing countries, whereas cerebral palsy related chorea, drug induced chorea, and genetic choreas are more common in developed countries. Genetic choreas, although rare, can present in childhood and should be suspected if there is a family history of chorea or other movement disorder.

Benign hereditary chorea is an autosomal dominant disorder with a slowly progressive course. It was first described in 1966.[1] Since then, multiple families with this condition have been described.[2-4]

The patients usually present with chorea, gait disturbance, tremor, myoclonus, and developmental and cognitive delays. The phenotype has been expanded to include a combination of chorea, hypothyroidism, and lung disease termed *brain-lung-thyroid disease*.[5-7]