Child Neurology: Friedreich ataxia with upper motor neuron findings

A case study

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Abstract

A 16-year-old boy with hypertrophic cardiomyopathy, gait abnormalities, and balance problems was found to have Friedreich ataxia. Though Friedreich ataxia typically renders patients areflexic, this child had upper motor neuron findings of spasticity in both lower extremities, with crossed adductors, and 4+ deep tendon reflexes at the patella and Achilles bilaterally. This unusual presentation of an uncommon genetic disorder led to uncertainty of the patient’s true diagnosis until genetic testing confirmed that he had 2 alleles with the Friedreich ataxia mutation.

Introduction

Friedreich ataxia is an autosomal recessive genetic disease that occurs due to a trinucleotide expansion in the frataxin gene on chromosome 9. This homozygous trinucleotide expansion in the \(FXN\) gene leads to decreased production of frataxin. This impairs mitochondrial electron transport and interferes with cellular metabolism. Eventually this leads to atrophy of the dorsal root ganglia, further degeneration of the dorsal columns, and the gracile and cuneate nuclei proceed from there.\(^1\) The \(FXN\) expansion is unstable and can lengthen when passed from parent to child, worsening the child’s phenotype in a process called anticipation.

Friedreich ataxia is characterized by progressive ataxia of gait as well as hypertrophic cardiomyopathy. A common physical examination finding in such cases is the absence of deep tendon reflexes.\(^2\) This case report describes the diagnosis of a patient with Friedreich ataxia who had retained deep tendon reflexes, while also showing evidence of upper motor neuron findings of spasticity in both lower extremities, with crossed adductors, and 4+ deep tendon reflexes at the patella and Achilles bilaterally.

Case report

A 16-year-old Caucasian boy presented after a fall in his home. Though it was initially thought to be a syncopal episode, it became clear that he had lost his balance in the bathroom and fallen, but had never lost consciousness. On arrival, his troponin was elevated (0.0530 ng/mL), and his ECG showed t-wave inversion in inferolateral leads, with occasional premature ventricular contractions and premature atrial contractions. His echocardiogram showed hypertrophic cardiomyopathy with preserved ejection fraction and no left ventricular outflow tract obstruction. He was then transferred to the pediatric intensive care unit for monitoring on telemetry.

Upon further discussion, the patient revealed a 2-year history of balance problems and dizziness that had worsened over time. He reported that his problems with balance were most noticeable when he would try to stand up after sitting in a chair, and he had coordination problems while running, feeling like his limbs were difficult to control. He described instances when his legs
would feel wobbly after standing for prolonged periods. He also described having pain in his feet while standing or walking, which caused him to develop the habit of walking on his toes. There was a significant family history of cardiac disease on his father’s side, including a paternal uncle who died at age 39, but no history of gait or balance abnormalities.

The patient’s neurologic examination showed a mild bilateral nystagmus with mild ocular ataxia, an intact sensory examination including normal position and vibratory sense, 2+ bilateral upper extremity reflexes, 4+ bilateral patellar and Achilles reflexes, with sustained clonus, and upgoing plantar reflexes. He was found to have mild to moderate ataxia with dysmetria on both finger-to-nose and heel-to-shin testing bilaterally. His gait was wide-based, with a positive Romberg test, and an inability to stand with his feet together without swaying.

Genetic testing confirmed the diagnosis of Friedreich ataxia, as the patient had a GAA repeat expansion on both of his frataxin alleles. One had 1,070 repeats and the other had 830 repeats; the normal range is 12–33 repeats. MRI of the brain and spine showed no significant abnormalities.

Differential diagnosis

Neurology was consulted because of the patient’s progressive ataxia, which has a broad differential. Friedreich ataxia was considered, but on examination the patient retained reflexes in his extremities, which is atypical of the classic description of Friedreich ataxia, in which the reflexes are absent. Due to the upper motor neuron findings, as well as preserved reflexes, the differential diagnosis remained broad, and included mitochondrial disorders. Spinocerebellar ataxia and Charcot-Marie-Tooth polyneuropathy were also considered. Autosomal recessive ataxia with oculomotor apraxia type 2 was also on the differential; however, the patient did not have any visual symptoms, and his MRI did not show atrophy of the cerebellar vermis. After it was found that the patient had hypertrophic cardiomyopathy, the likelihood of his having Friedreich ataxia increased significantly. Given the high suspicion of Friedreich ataxia, we opted to send the Friedreich ataxia genetic test and wait for the results before performing a muscle biopsy.

Management

The patient underwent cardiac catheterization and loop recorder placement. He was recommended for outpatient physical therapy, and for follow-up with Genetics, Neurology, and Cardiology.

Discussion

In our patient, the retained reflexes and upper motor neuron findings on examination complicated the diagnosis of Friedreich ataxia. Given these atypical findings, we needed to review the available literature on the subject. This is an unusual presentation of Friedreich ataxia. There are reports of other cases in which the patients had retained reflexes, which have engendered the use of the title Friedreich ataxia with retained reflexes (FARR) to describe such findings. One study examining FARR mutations showed that the average expansion was slightly smaller (408 ± 252 vs 719 ± 184 GAA triplets) in patients with FARR when compared to patients with Friedreich ataxia. However, our patient’s expansion sizes were greater comparable to the average Friedreich ataxia expansion, despite his having retained reflexes. One study investigated 2 patients with Friedreich ataxia who had delayed onset of symptoms and also had retained reflexes. They had relatively short trinucleotide repeat sequences, and the somatic instability had led to a mixture of GAA-44 and GAA-66 repeats. It is speculated that the instability of these borderline genes can cause a milder Friedreich ataxia phenotype. However, in another study that included patients with Friedreich ataxia who had retained reflexes or hyperreflexia, a commonality in repeat length or age at onset was not found.

Another mutation associated with FARR is a point mutation at base 493 in the FXN gene that was seen in a patient with Friedreich ataxia who had retained reflexes. A different case report mentioned a missense mutation at G130V in the FXN gene that caused a child with Friedreich ataxia to have retained reflexes. Studies have shown that up to 4% of those with Friedreich ataxia have a trinucleotide expansion on one gene and a point mutation on the other, making it necessary to perform genetic sequencing whenever Friedreich ataxia is suspected.

The reason reflexes are retained, or even increased, is not clearly understood. The reflex arc is still intact, allowing for expression of corticospinal signs. Coppola et al. proposed that this depends on persistence of a number of Ia sensory fibers. Vibratory sense is also preserved or mildly impaired in patients with FARR, possibly because of relative preservation of more axons in the central tracts of the dorsal columns compared to typical Friedreich ataxia. However, these examination findings do not extinguish as the disease progresses, indicating that there are other factors involved.

Due to Friedreich ataxia’s rare occurrence, and the further irregularity of having retained reflexes, it was difficult to make the Friedreich ataxia diagnosis in this patient clinically. The genetic test takes weeks to come back, and the decision to wait for these
results before beginning an expensive and invasive workup of other mitochondrial diseases was wise. Increased awareness of this unusual presentation of Friedreich ataxia might lead other clinicians to the correct conclusion in their practice.

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**Disclosure**
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**References**
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