ELSEVIER

Seminars in
Pediatric
Neurology

A 7-Year-Old Girl With Hypertrophic Cardiomyopathy and Progressive Scoliosis

Radhika Dhamija, MBBS, and Salman Kirmani, MBBS

We report a 7 year old girl who was evaluated for progressive thoracolumbar scoliosis and hypertrophic cardiomyopathy. Neurological examination was found to be abnormal and significant for absent reflexes and weakness distally in lower extremities and positive Romberg sign. Electromyogram showed length-dependent, axonal, sensorimotor polyneuropathy. Frataxin levels were low at 3ng/mL. Molecular testing for Friedreich ataxia showed significantly expanded GAA repeats at 799 (abnormal >67 GAA repeats) on one allele and a heterozygous disease causing mutation, c.317T>C (p.Leu106Ser) on the other allele, confirming the diagnosis. A review of Friedreich ataxia is provided in the case report.
Semin Pediatr Neurol 21:67-71

Case

Our patient first presented at the age of 7 years to the cardiology clinic for evaluation of a heart murmur. The murmur had been incidentally detected by her primary care provider at a well-child visit. The cardiac examination at this visit was significant for a nonpositional distinct grade 2/6 systolic ejection murmur heard loudest at the left upper sternal border. To further evaluate the heart murmur various cardiac investigations were done as listed later.

Electrocardiogram showed normal sinus rhythm with right axis deviation. Echocardiogram showed hypertrophic non-obstructive cardiomyopathy. Cardiac magnetic resonance imaging showed generalized increase in left ventricular wall thickness, most prominent in the septum (13 mm) consistent with hypertrophic cardiomyopathy.

There was no reported family history of early or sudden death or a known cardiomyopathy. First-degree relatives underwent echocardiography and they were normal. However, these imaging findings in a young child lead to a suspicion of a familial cardiomyopathy, and she underwent genetic testing for the same. A panel-based sequencing test through a commercial laboratory (*Familion*) was performed looking at the following genes: *ACTC*, *GLA*, *LAMP2*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *PRKAG2*, *TNNT2*, *TNNI3*, *TNNC1*, and *TPM1*. No mutations were detected.

She was then referred to medical genetics and neurology for further evaluation

The proband was born at term via spontaneous vaginal delivery and there were no unusual exposures during pregnancy. She was a product of a non-consanguineous union. There were no perinatal or neonatal complications, and her birth weight was 3.68 Kg. There was no family history of neurologic or neuromuscular disorders.

At this visit, it was learnt that she had not been able to keep up with her peers in terms of endurance. She was also noted to have difficulties with coordination. She denied history of prostration with illness or unusual body odors. There was no concern of regression of milestones. There were no concerns about her cognitive abilities.

She had been evaluated earlier locally, and some metabolic investigations were pursued including levels of plasma amino acids, level of plasma carnitine, acylcarnitine profile, and levels of urine organic acids, which were all within normal limits. Levels of creatine kinase, aldolase, and lactate were also within normal limits.

On examination at the age of 7.5 years, she was found to be nondysmorphic in appearance. The findings of general physical examination showed no neurocutaneous stigmata or organomegaly. The findings of cardiac examination were significant for a systolic murmur. The murmur was a distinct grade 2/6 systolic ejection murmur heard loudest at the left upper sternal border and was nonpositional in nature. Neurologic examination was significant for normal cranial nerve examination including normal bedside hearing and funduscopic examination. Extraocular movements were found to be intact in all directions with no nystagmus,

Author contributions: Both R.D. and S.K. were involved in the diagnosis and management of this patient. R.D. wrote the draft of the manuscript, and both R.D. and S.K. contributed to the editing and final version of the manuscript.

From the Department of Medical Genetics, Mayo Clinic, Rochester, MN.
Address reprint requests to Radhika Dhamija, MBBS, Department of Medical Genetics, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: Dhamija.radhika@mayo.edu

1071-9091/14/$-see front matter
http://dx.doi.org/10.1016/j.spen.2014.04.003

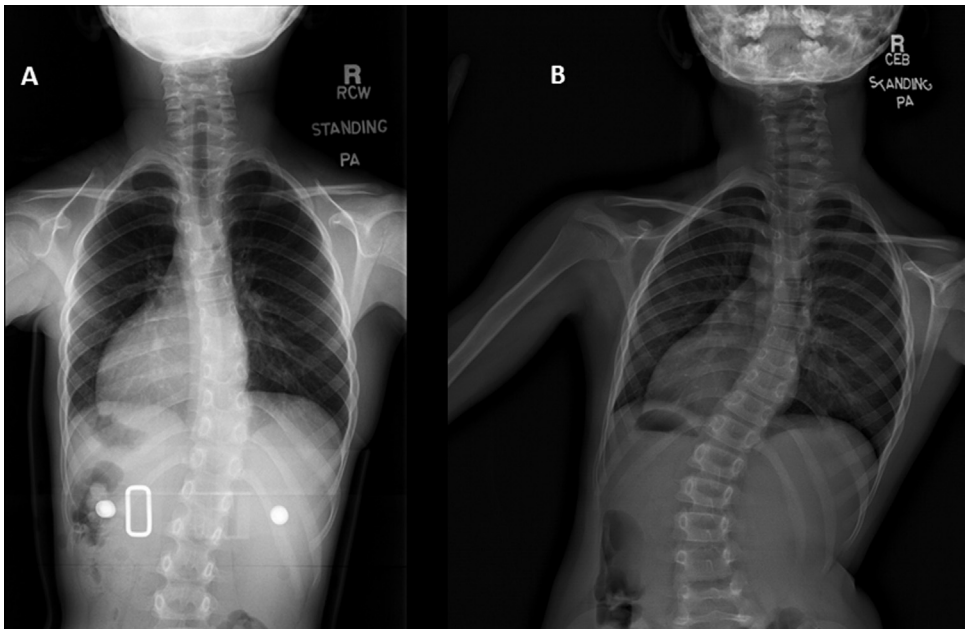

Figure (A) and (B) X-ray showing progressive scoliosis.

although her saccadic eye movements were mildly abnormal. No dysarthria was noted. She had normal tone, bulk, strength, and deep tendon reflexes in the upper extremities. She had normal tone and bulk in the lower extremities. There was mild weakness distally in the lower extremities, though no weakness was appreciated proximally. She had high arches and flexed toes at rest bilaterally. Deep tendon reflexes were absent at the knees and ankles even with reinforcement maneuvers. She was able to rise easily from the floor and had a negative Gower sign. No dysmetria was noted. Gait examination was noted for mild difficulties with tandem gait and walking on her heels, though she was able to walk on her toes. Romberg sign was positive. Sensory examination to pain and temperature was normal. Thoracolumbar scoliosis was also noted on spine examination.

In retrospect, it was noted that the scoliosis had been progressively worsening over the past 1 year. This was further evaluated with an x-ray of the spine that showed right thoracolumbar scoliosis measuring 30° from T5-L2 (Fig. showing progressive worsening). Magnetic resonance imaging of the entire spine was done to rule out an intraspinal structural cause for progressive scoliosis, and the findings of the image were normal.

To further define the abnormal neurologic findings in the lower extremities, an electromyography was performed. This showed a length-dependent, axonal, sensorimotor polyneuropathy.

The concern for a mitochondrial disorder was raised owing to multisystemic involvement, that is, cardiac and neurologic. She subsequently had genetic testing for mitochondrial DNA-based disorders by next-generation sequencing (BCM, Houston, TX), and this did not show any deleterious mutations or deletions.

The abnormal electromyography, in conjunction with hypertrophic cardiomyopathy and absent reflexes, pointed toward Friedreich ataxia. Frataxin levels were checked, and they were low at 3 ng/mL (normal: >19 ng/mL). Molecular testing was done for the number of GAA triplet repeats in intron 1 of *FXN*. One allele was found to be significantly expanded at 799 (abnormal >67 GAA repeats). The other allele was not expanded and had a repeat size of 5 (normal range <33). Sequencing of *FXN* showed a heterozygous disease causing mutation, c.317 T > C (p.Leu106Ser), confirming the diagnosis of Friedreich ataxia (FRDA) and showing that the patient was a compound heterozygote with repeat expansion on 1 copy and a point mutation on the other copy of *FXN*. Parental testing was done, and the father was found to carry the expanded allele and the mother carried the point mutation. The proband's 14-year-old brother was completely asymptomatic from a cardiac and neurologic standpoint, and given the lack of clinical findings, parents chose not pursue testing for him.

Discussion

FRDA, first described by Friedreich in 1863, is an autosomal recessive multisystemic neurodegenerative disease characterized by slowly progressive ataxia typically before 25 years of age.[1] It is a classic mitochondrial disease due to mutations in the nuclear gene *FXA*. It accounts for approximately 70% of all inherited ataxias with a prevalence of 0.5-3/100,000 in individuals of Western European lineage. It is associated with spasticity in the lower extremities, progressive scoliosis, absent reflexes in lower extremities, loss of position and vibration sensation, and dysarthria.[3] Approximately 70% of individuals with FRDA will have cardiomyopathy; most commonly hypertrophic and about 10%-15% will develop diabetes mellitus. Approximately 20%-25% will have an atypical presentation with either later onset of neurologic disease (>25 years) or retained deep tendon reflexes in the lower extremities.[4,5]