CHAPTER **27**

Friedreich's Ataxia: Literature Review and Case Presentation

Thomas Merrill, DPM
Gabriel Santamarina, DPM, MS
Mozhgan Alijani, DPM

INTRODUCTION

Friedreich's ataxia (FRDA) is a form of neuropathy that was first described by Nikolaus Friedreich in a series of 5 papers published from 1863-1877 (1). Freidreich was a third generation physician from Heidelberg, Germany. His grandfather was the first to describe idiopathic facial paralysis, also known as Bell's palsy. Friedreich trained to be a pathologist under Rudolf Virchow, who proposed the 3 contributions to thrombosis: endothelial injury, stasis of blood flow, and hypercoagulability. In addition, Friedreich was also credited with Friedreich's foot, a term used to describe a form of cavus foot.

Nikolaus Friedreich recognized the main pathology of this motor and sensory ataxia as sclerosis of the spinal cord and peripheral nerves. He also discovered that the illness was hereditary and had good insight into its pathogenesis. He discovered that the onset of this disorder most often occurrs in adolescence. The presentation includes ataxia, sensory neuropathy, scoliosis, foot deformity, and cardiomyopathy (1). It is reported that FRDA affects the central and peripheral nervous systems, the heart, skeleton, and the pancreas of endocrine. While cardiomyopathy is the most common cause of death in FRDA, it is best known for its disabling neurological phenotype (1). Genetic research found the causative gene, FXN in 1996. This revelation now allows for precise diagnosis of FRDA (1).

EPIDEMIOLOGY

FRDA is the most common autosomal recessive ataxia. Typically, FRDA is a disease of young people that affects male and females equally (2). The mean onset is between age 10 and 15 years and usually before 25 years (1). Most patients are wheelchair-bound by the age of 19 and the average life expectancy is only 40 years (3). The point prevalence can be as high as 3/100,000, and the carrier frequency estimated to be 1:50 to 1:100 among European, North African, Middle Eastern, and Indian origin (2). There is a 25% chance that children will develop FRDA when parents are both carriers (3). The number of persons with FRDA in the US at any given time can be estimated at 6,000, although, about 15,000 individuals worldwide have the disease (3).

GENETICS AND PATHOLOGY

Most patients with FRDA (98%) have a homozygous trinucleotide (GAA) expansion in intron-1 of chromosome 9 (4). Patients with short expansions have a later onset and a more benign disease course, with some not even being diagnosed during life (2). Long GAA repeat expansions lead to early onset, severe clinical illness, and death in young adults. There is also a correlation between the sizes of the GAA repeat expansion and the amount of frataxin produced. Most patients with FRDA have less than 20% of normal frataxin levels (3). To date, researchers are unclear as to the exact purpose of frataxin, but most agree insufficient frataxin is involved in the pathophysiology of this condition.

Drinkard et al suggested that there is a deficit in the respiratory chain enzyme complexes I, II, and III in this disease. In addition, there is a deficiency in the Krebs cycle enzyme aconitase in cells of patients with FRDA (5). Aconitase deficiency limits ATP repletion and decreases iron binding in the mitochondria (5). Iron overload may lead to the formation of reactive oxygen species and oxidative damage that could contribute to metabolic insufficiency in FRDA (5).

Multiple areas of degeneration of the central nervous system are seen in FRDA. Degeneration of the dorsal root ganglia and posterior columns of the spinal cord, spinocerebellar tracts, corticospinal tracts, and dentate nuclei of the cerebellum are pathology related to FRDA (6). Dorsal root ganglia in FRDA are small and may even be difficult to recognize during dissection. Diameter of the spinal cord is reduced at all levels, especially in the thoracic region (6).

CLINICAL MANIFESTATION

The first clinical manifestation, and the hallmark of FRDA, is often progressive limb ataxia. Parents of patients typically report to the physician that their child is becoming increasingly clumsy with physical activity. Ataxia can be defined as a loss of balance and coordination that does not result from direct muscle weakness. It is most likely a malfunction in one or more of sensory pathways, such as those for proprioception, those from vestibular system, and those from the cerebellum. Symptoms of ataxia all reflect

dysarthria, dysphagia, and dysmetria (3). Scoliosis is very common in FRDA (60-79%) and is remarkably progressive (2). Gradual deformity of the chest causes the patient to experience great problems with sitting comfortably. Pes cavus is roughly as common as scoliosis in FRDA patients (75% of this patient population) (2).

On physical examination, decreased vibration and proprioception and absence of lower limb deep tendon reflexes are noticeable. Furthermore, patients may have prominent Babinski sign, scoliosis, foot deformities, diabetes mellitus, visual disturbance, dysarthria and dysphasia, eye movement abnormalities, hearing and cognitive deficits, sleep apnea, urological disturbances, sexual problems, psychological issues, and cardiomyopathy.

Patients with FRDA predominantly have absent lower limb reflexes, but some have retained reflexes and may have spasticity (6). Systemic features of FRDA also include hypertrophic cardiomyopathy, and to a lesser extent diabetes mellitus, optic atrophy, and hearing loss (5). Balance impairment is another chief symptom in FRDA patients with cerebellar ataxia. Patients with spinocerebellar ataxia exhibit significantly impaired static and dynamic postural sway (e.g., increased postural sway during quiet standing and decreased limits of stability) compared to healthy controls (7).

In patients with FRDA, due to mitochondrial respiratory chain defects and mutations of mitochondrial or nuclear DNA, exercise capacity was 40-50% lower than controls and directly related to the degree of the mutation (7). Patients with FRDA may experience shorter step and stride lengths, unsteadiness, decreased gait velocity and increased gait variability compared to the healthy individuals (7). FRDA patients with cerebellar degeneration have increased stance and double limb support duration as a compensatory mechanism to increase stability during walking and avoid loss of balance, falls, and subsequent injury (7).

DIAGNOSIS/TESTING

The diagnosis of FRDA should include a detailed history and examination with emphasis on the age at onset, exacerbating or relieving factors, progression, family history, and associated other neurologic symptoms such as ataxia, visual symptoms, epilepsy, and cognitive decline. Clinical electrodiagnostic tests (surface electromyography, electroencephalography, combined EEG–EMG studies, somatosensory evoked potentials) are important for physiological classification of myoclonus (spinal, subcortical, or cortical myoclonus) in FRDA (8).

Diagnosis of FRDA is suspected when a series of findings are noticed, especially before the age of 25. These include: progressive ataxia of gait and limbs, decrease or loss of position sense and/or vibration sense in the lower extremities accompanied by muscle weakness, loss of stretch reflexes in the legs, or a family history consistent with autosomal recessive inheritance. More importantly pyramidal weakness of the legs, extensor plantar responses, scoliosis, pes cavus, hypertrophic cardiomyopathy, diabetes mellitus, optic atrophy, and deafness should warrant establishing the diagnosis of FRDA via FXN genetic testing.

Ancillary studies, neuro-physiology and magnetic resonance images (MRI) of the brain are helpful devices that support the diagnosis. However, genetic analysis confirms the diagnosis of FRDA (8). FRDA is established in a proband by detection of biallelic pathogenic variants in FXN that has 4 classes of alleles with GAA repeat sequences in intron 1 of FXN. Testing is targeted for abnormally expanded GAA repeat in intron 1 of FXN that eventually classifies the patient as one of the following: mutable normal alleles; full penetrance alleles; borderline alleles; or rare alleles of variant structure (4).

MRI in the diagnosis of FRDA was used before gene testing was available, and thinning of the cervical spinal cord was a consistent observation (2). MRI has demonstrated brain damage in FRDA in the form of regional atrophy of the medulla, peridentate cerebellar white matter, and superior cerebellar peduncles in T1-weighted imaging (4). The T2 and T2* relaxation time imaging techniques also have been used for the routine diagnosis of excess iron load in the liver, the heart, and other organs (9). Appropriate clinical evaluation and laboratory investigations can rule out other differential diagnosis of FRDA such as ataxia telangiectasia, spinocerebellar ataxias, hereditary motor and sensory polyneuropathy, or alcohol abuse (8).

MANAGEMENT

FRDA is a progressive neurodegenerative disease with no effective treatment. Major effort has been undertaken worldwide for the control and reduction of births of FRDA patients. Prenatal and antenatal diagnoses are increasingly used in certain endemic areas for the prevention of the disease (9). The introduction of primarily iron chelation therapy using the iron chelating drug deferiprone (L1) increases the prospect of reducing the morbidity and mortality rates observed in FRDA (9). Management and treatment are strongly dependent on the clinical manifestations and the extent of the FRDA. Mobility issues can be addressed with walking aids and wheelchairs. Medications are given for muscle spasticity. Surgical intervention for bony deformities such as scoliosis and foot deformities are sometimes necessary. Diet modification and hypoglycemic agents are implemented for diabetes complications, antispasmodics are used for bladder malfunction, and cardiac agents such as antiarrhythmic or anticoagulant medications are used versus pacemaker insertion. Scoliosis surgery is a major procedure involving fusion over multiple levels with high risk of

anesthetics and only temporary benefits to FDRA patients (2). Severe pes cavus deformity that impairs standing and walking can be managed with botulinum toxin injections of the gastrocnemius muscles or Achilles tendon lengthening (2). Since the main cause of death in FRDA patients is iron overload toxicity, a better understanding of the normal iron metabolic pathways, and the detection and categorization of the iron abnormalities and iron overload can lead to effective treatments and reduction of the morbidity and mortality in FRDA (9).

CASE PRESENTATION

A 40-year-old woman came to our clinic because of 2 concerns resulting from FRDA. First, she was unable to maintain her right foot in a rectus position. Her right foot at rest and during weight bearing maintained an equino varus position. The improper position of the ankle and rearfoot meant she could not maintain her bodyweight while ambulating, even with an assistive device such as a walker. She could not put weight on her foot to transfer into and out of the wheelchair. Secondly, her muscle weakness from FRDA kept her right knee and and right thigh in an abducted position that made her prone to injury when she used her scooter. She described the failure of multiple conservative measures such as bracing and shoe gear modification to the right lower extremity to improve her right foot position. The patient stated she often injured her right knee while using her motorized scooter and that this was the chief limiting factor to her activities of daily living (Figure 1).

Upon physical examination, the first thing noted was the accommodations the patient required to use her scooter. Using an elastic band at the knee, her mother tied the right lower extremity to the steering column in order to prevent injury. Despite this adjustment, her right foot could still not properly lay flat upon the foot pedals in the motorized scooter. The right thigh was in an externally rotated position while the foot was in varus in her motorized scooter (Figure 2). This necessary seated position kept the right knee exposed outside the protective frame of the scooter. Her positioning made it easy for her to injure the knee against walls, doorframes, and furniture.

The left ankle demonstrated flexible range of motion in dorsiflexion and eversion. The deep posterior muscle group to the right leg extremity demonstrated rigid spasticity against resistance. By comparison, the left leg muscle groups had appropriate muscle strength and flexibility against resistance. Muscle evaluation of the left and right thigh muscle showed significant weakness against resistance. Radiographic examination revealed there was no limiting bony deformity to the patient's range of motion to the right ankle and subtalar joint.

The surgical decision was an initial tendoAchilles lengthening. The surgical decision was discussed with both her primary care physician and the neurologist who was managing her FRDA. The surgical risk mainly involved myocardial infarction from cardiac arrhythmias. Both her neurologist and internist gave their clearance to proceed to surgery. The patient and her mother thought the decision to improve quality of life with surgical intervention was appropriate and worth the risk.

Minimal intravenous sedation was used and with a local anesthetic block, a right percutaneous Achilles tendon lengthening was performed. Greater than 10 degrees of dorsiflexion was observed after the lengthening procedure. The patient tolerated the procedure and anesthesia very well. A posterior splint was applied and the patient returned to our clinic 1 week later for postoperative care. A long leg walking boot was applied and she was allowed to balance and ambulate. She stated her pain level was minimal with only mild soreness to the right leg over the operative site,

Figure 1. Equinovarus right foot position and knee abduction affects the patient's ability to use her wheelchair.

Figure 2. The right foot would fall off the wheelchair unless a large rubber band was used to tie the knee to the steering mechanism.

Figure 3. Postoperative correction shows a plantar grade position with subtalar joint eversion and ankle dorsiflexion.

Figure 4. The weight-bearing position of the foot now realigns the knee and hip and eliminates the the need for the large rubber band.

and that that she felt like she was getting better and was excited that the foot appeared straight. The patient also reported that her right lower extremity spastic episodes had decreased. Her right foot was now able to purchase the ground fully without additional procedures. By the end of the patient's postoperative course, she could touch the foot pedals of her scooter without evidence to suggest further operative treatment would be necessary to the right leg (Figures 3, 4).

CONCLUSION

FRDA is complex inherited neurological disorder requiring multiple forms of management. In our case, surgery specifically addressed the patient needs and expectations. There is a significant risk of cardiac complications and postoperative mobility challenges with FRDA, therefore the most conservative surgery should be considered. Staging the procedures because of unpredictable disease progression is our preferred form of disease management. In this case, a simple percutaneous tendoAchilles lengthening had a dramatic positive effect on our patient. She can now balance on a weightbearing right foot to transfer to her chair, bed, and bath. Her right foot now stays on the wheelchair, her right hip is straight and she does not need the rubber band tied to her right knee. It is our hope that this management style will improve outcomes in the future for this patient population.

REFERENCES

1. Delatycki MB, Corben LA. Clinical features of Friedreich Ataxia. J Child Neurol 2012;27:1133-7.
2. Koeppen AH. Friedreich's Ataxia: pathology, pathogenesis, and molecular genetics. J Neurol Sci 2011; 303:1-12.
3. Ashley CN, Hoang KD, Lynch DR, Perlman SL, Maria BL. Childhood ataxia: clinical features, pathogenesis, key unanswered questions, and future directions. J Child Neurol 2012;27:1095-20.
4. Bidichandani SI, Delatycki MB. Friedreich Ataxia. In: Pagon RA, Adam MP, Ardinger HH, et al, (editors). GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
5. Drinkard BE.Keyser RE, Paul SM, Arena R, Plehn JF, Yanovski JA, et al. Exercise capacity and idebenone intervention in children and adolescents with Friedreich's Ataxia. Arch Phys Med Rehabil 2010;91:1044-50.
6. Corben LA, Lynch D, Pandolfo M, Schulz JB, Delatycki MB. Consensus clinical management guidelines for Friedreich Ataxia. Orphanet J Rare Dis 2014;30:184.
7. Stephenson J, Zesiewicz T, Gooch C, Wecker L, Sullivan K, Jahan I, et al. Gait and balance in adults with Friedreich's Ataxia. Gait Posture 2015;41:603-7.
8. Jain RS, Kumar S, Tejwani S. Familial segmental spinal myoclonus: a rare clinical feature of Friedreich's Ataxia. Springerplus 2015:Jul 8;4:330.
9. Kolnagou A, Kontoghiorghe CN, Kontoghiorghes GJ. Transition of thalassaemia and Friedreich Ataxia from fatal to chronic diseases. World J Methodol 2014;4:197-218.