Chapter 15
Urologic Complications of Friedreich's Ataxia

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Introduction

Friedrich's ataxia (FRDA) is the most common hereditary ataxia, affecting between 1/20,000 and 1/250,000 individuals of European descent [1]. First described by Nicholaus Friedreich in 1863, FRDA is generally diagnosed in adolescence with a constellation of gait disturbance, dysarthria, pathognomic musculoskeletal findings, and cardiac abnormalities [2]. While urologic manifestations of FRDA are not well described, the existing literature indicates that they are common and bothersome to patients with this disease.

Pathophysiology

FRDA is an autosomal recessive disorder typically caused by a homozygous GAA triplet repeat-expansion in the intron of the FXN gene on chromosome 9 [3, 4]. In a minority of cases (~2%), a heterozygous expansion and point mutation are present [5]. This intron expansion is thought to silence the FXN gene via epigenetic aberrations [6]. FXN encodes frataxin, a protein which is widely expressed in the human body, with high levels found in the heart, spinal cord, liver, pancreas, and skeletal muscles. It is involved in the activity of iron–sulfur cluster-containing components in the mitochondrial respiratory chain. Decreased frataxin levels lead to increased mitochondrial iron deposits, oxidative stress, lipid peroxidation, and cell death [7].

The widespread expression of this gene is likely responsible for the diverse constellation of symptoms found in individuals affected by FRDA. Neurologic symptoms stem from a combination of peripheral sensory neuropathy, spinocerebellar

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J. T. Stoffel, E. V. Dray (eds.), *Urological Care for Patients with Progressive Neurological Conditions*, https://doi.org/10.1007/978-3-030-23277-1_15

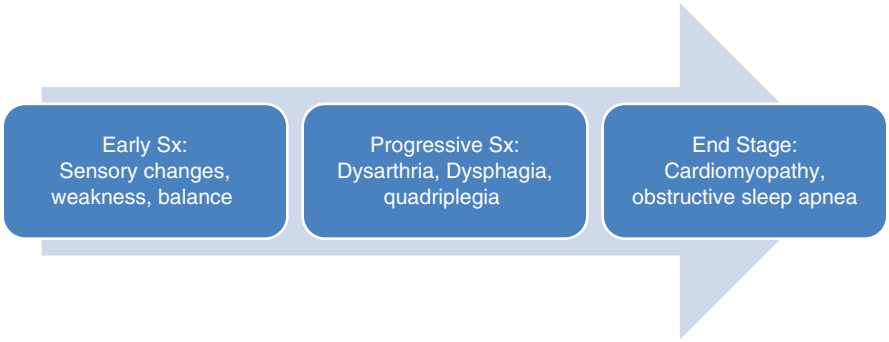

Fig. 15.1 Disease course

tract degeneration, cerebellar and supratentorial changes. Gait ataxia is an early symptom, which typically develops between 10 and 16 years of age and progresses to wheelchair reliance by the third decade. Dysarthria and dysphagia typically advance with disease duration. Optic neuropathy, nystagmus, and, in some cases, blindness may also occur, as well as sensorineural hearing loss. Musculoskeletal abnormalities include scoliosis, which often requires surgical correction, and foot deformities (pes cavus, talipes equinovarus). Pancreatic involvement leads to increased prevalence of diabetes mellitus compared to age-matched controls [8].

Cardiomyopathy is another hallmark of FRDA, and is responsible for >50% of disease-related deaths. Repolarization abnormalities (T wave inversion, ST depression or elevation) are frequently seen on electrocardiogram (ECG) even in early stages of the disease process. Echocardiogram may show concentric cardiac wall-thickening. Approximately 20% of individuals will have a reduced ejection fraction [9]. As the disease progresses, atrial fibrillation and heart failure may develop, ultimately leading to patient death.

Classically, FRDA presents between 10 and 16 years of age, with 36.5 being the average age of death [10]. Mortality is typically secondary to congestive heart failure and arrhythmias. Late onset and very late onset FRDA present at >25 years of age and > 40 years of age, respectively [11]. These atypical presentations are usually associated with a milder phenotype, less pronounced non-neurologic symptoms, and variable progression. Earlier onset and rapidity of neurologic decline is correlated with increased size of the GAA triplet expansion [4, 12]. Figure 15.1 summarizes the disease course.

Imaging

While there are no imaging criteria for the diagnosis of FRDA, MRI studies have shown cerebellar atrophy, as well as gray matter loss in the precentral gyri, corpus callosum, and pyramidal tracts. Diameter of the spinal cord is also reduced, especially at the cervical and thoracic level [13].

Diagnosis

Prior to the discovery of the genetic basis for FRDA in 1996, diagnosis of this disease was imprecise. Diagnosis is now based on identification of the characteristic homozygous GAA expansion on polymerase chain reaction. Clinical suspicion of the disorder is raised in children and adolescents with progressive ataxia and dysarthria. Exam findings include loss of lower limb deep tendon reflexes, distal vibratory sensation, and proprioception as evidenced by nose-finger ataxia and impaired heel-shin slide [11]. Babinski's sign is typically positive. Non-neurologic findings such as scoliosis, foot abnormalities, and ECG changes may also aid in diagnosis.

Treatment

Progression of FRDA is inevitable, and disease-modifying therapies have not yet been developed. Treatment is multidisciplinary and largely supportive, and should begin with referral to an ataxia specialist and genetic counseling. Recently published clinical management guidelines have supported the following baseline evaluations: neurological exam, ECG and echocardiogram, communication and swallow evaluation by speech therapy, physical therapy assessment for muscle strength and stability, auditory evaluation, vision screening, blood glucose testing, and Epworth sleepiness scale for identification of obstructive sleep apnea (OSA) [14]. Blood glucose testing, OSA evaluation, and auditory testing should be repeated annually. Patients should be referred to cardiology for palpitations or abnormal cardiac testing results. If blood glucose and glucose tolerance tests are abnormal, first-line intervention is diet and exercise. Initiation of an insulin regimen is necessary if behavioral modifications are not effective. Intensive inpatient rehabilitation programs may prolong mobility and aerobic exercise regimens may improve fatigue. Orthopedic surgery is indicated for scoliosis with >40% curvature. Prior to any surgical intervention, intensive cardiac clearance should be undertaken. Finally, it is advisable to work closely with palliative care as the disease progresses. Figure 15.2 summarizes the overall disease treatment goals.

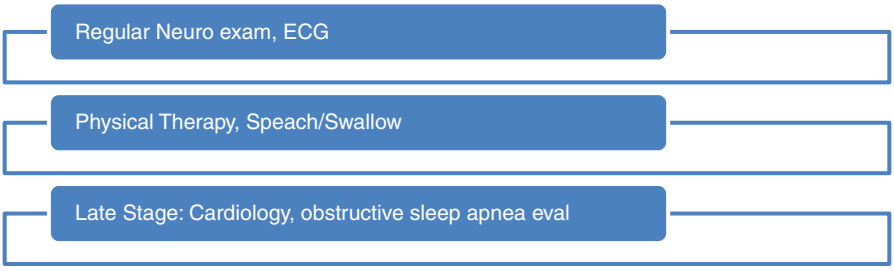

Fig. 15.2 Treatment goals

Urologic Manifestations of Friedreich's Ataxia

Urologic literature on FRDA is limited; however, urologic symptoms appear to be common and bothersome. An early study by Vezina et al. in a small cohort of FRDA patients showed that 53% of individuals reported urinary urgency and urge urinary incontinence [15]. On UDS, 41% of these patients had detrusor overactivity (DO) and 37.5% showed detrusor sphincter dyssynergia (DSD). In a study of mixed hereditary ataxias, Diez Rodríguez found that 85.5% of patients suffered from urinary urgency [16]. In this cohort, common UDS findings were detrusor overactivity (61.7%), DSD (37.5%), and impaired contractility (23.5%), with a high correlation between UDS findings and clinically reported symptoms. Normal UDS results were documented in 15% of patients. The impact of these early reports is somewhat lessened by the inaccuracy of FRDA diagnoses prior to genetic testing.

More recently, Musegante administered a series of validated questionnaires evaluating urinary symptoms to 258 patients with genetically confirmed FRDA [17]. Eighty-two percent of patients who responded to the questionnaires reported lower urinary tract symptoms (LUTS) and 22% of patients reported that these symptoms impacted their quality of life. The most common complaint was urinary frequency (63%), followed by nocturia in 46% of patients and urinary incontinence in 36%. Eighteen percent of respondents reported difficulty voiding. Subsequently, 22 of these patients agreed to undergo UDS (average age 32 years). Urinary urgency (75%) and urge incontinence (61%) were disproportionately present in this group when compared to the total cohort. Four patients had normal UDS results, 8 (28.5%) had DSD, 5 (17.9%) were found to have DO, and 9 patients (32.6%) had decreased detrusor contractility. Post-void residual (PVR) > 100 cc was common (39%). No patients were found to have impaired compliance. Interestingly, no association was found between reported urinary urgency and DO on UDS. While 4 of these patients had mild-to-moderate hydronephrosis on renal ultrasound, all serum creatinine values were normal.

Pelvic symptoms are not limited to urinary complaints. A questionnaire-based study by Lad et al. of genetically confirmed FRDA patients showed that urinary, bowel, and sexual symptoms frequently coexist in the population [18]. Of the 59 patients in this study (average age 35 years), 80% reported LUTs, 64% reported bowel complaints, and 83% ascribed to sexual symptoms. Frequency (75%) and urgency (59%) were the most common urinary complaints. Constipation was reported in 86% of individuals with bowel complaints. Seventy-three percent of patients with urinary complaints also had bowel dysfunction, and all patients with sexual dysfunction also had LUTs. Increased severity of LUTS was noted in patients with late-onset FRDA and those with longer duration of disease. Of note, despite the prevalence of urinary symptoms in this study, only 24% of patients had prior treatment for urinary complaints. Table 15.1 summarizes common urinary symptoms and urodynamic findings.

Table 15.1 Urologic symptoms/findings

Common symptoms
Urinary urgency/frequency
Nocturia
Urinary incontinence
Constipation
Urodynamics:
PVR > 100
DO
DSD
Bladder compliance normal

In summary, most FRDA patients experience LUTS, with urinary urgency and frequency being the most common complaints, and these symptoms appear to be undertreated. UDS abnormalities are varied, and may include DO, DSD, and decreased detrusor contractility. Bowel and sexual symptoms are common in the setting of urinary complaints and bothersome considering the young age of the patient population.

Urologic Treatment in Friedreich's Ataxia

Consensus guidelines for care of patients with FRDA recommend PVR assessment and urinalysis in all patients with urologic symptoms [14]. Initiation of clean intermittent catheterization (CIC) is recommended with PVR > 100 cc; however, extrapolating from data for neurologic and non-neurologic incomplete bladder emptying, this may be overly conservative [19, 20]. Based on the high prevalence of DSD on UDS and poor correlation between urologic symptoms and UDS findings in the existing literature, a low threshold for performing UDS in this patient population is advisable [15–17]. It is reasonable to consider a renal ultrasound in the setting of decreased compliance or DSD; however, there is no data regarding upper tract deterioration in this disease. As with other neurogenic bladder conditions, repeat UDS should be performed in the setting of changing symptoms or worrisome baseline UDS findings.

No trials regarding treatment of urologic symptoms in FRDA exist, and therefore no evidence-based recommendations on pharmacotherapy can be made. Extrapolating from the neurogenic bladder population, a urinary antispasmodic is the appropriate first-line therapy for storage symptoms, followed by Intravesical Botox® if refractory. In patients with incomplete bladder emptying who cannot perform CIC due to functional limitations, suprapubic tube placement should be considered. Patients with bowel symptoms should be encouraged to make dietary modifications and referred to gastroenterology as constipation may impact urinary complaints. Patients should also be evaluated for sexual dysfunction. While

Table 15.2 Key urologic interventions

CIC for urinary retention
Anticholinergics for OAB
Onabotulinum for OAB
Surgical Risk: High due to respiratory weakness, potential cardiac pathology

phosphodiesterase inhibitors may be considered for erectile dysfunction, cardiology should be consulted prior to initiating therapy to avoid cardiac complications. Finally, prior to any urologic surgery, thorough cardiac clearance is obligatory. Table 15.2 summarizes the urologic treatment goals.

Conclusion

FRDA is an early onset, progressive neurologic condition with potentially significant bothersome urinary symptoms. Urologic care is mostly supportive and focused on reducing the quality of life impact from urinary incontinence and/or retention. Since FRDA patients carry significant surgical risk due to underlying respiratory weakness and cardiac pathology, any operative procedure needs considerable preoperative evaluation and clear treatment goals need to be discussed.

References

1. Vankan P. Prevalence gradients of Friedreich's ataxia and R1b haplotype in Europe colocalize, suggesting a common Palaeolithic origin in the Franco-Cantabrian ice age refuge. J Neurochem. 2013;126(Suppl):11–20.
2. Parkinson MH, Boesch S, Nachbauer W, Mariotti C, Giunti P. Clinical features of Friedreich's ataxia: classical and atypical phenotypes. J Neurochem. 2013;126:103–17.
3. Campuzano V, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science. 1996;271:1423–7.
4. Dürr A, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med. 1996;335:1169–75.
5. Cossée M, et al. Friedreich's ataxia: point mutations and clinical presentation of compound heterozygotes. Ann Neurol. 1999;45:200–6.
6. Evans-Galea MV, et al. FXN methylation predicts expression and clinical outcome in Friedreich ataxia. Ann Neurol. 2012;71:487–97.
7. Branda SS, Yang ZY, Chew A, Isaya G. Mitochondrial intermediate peptidase and the yeast frataxin homolog together maintain mitochondrial iron homeostasis in *Saccharomyces cerevisiae*. Hum Mol Genet. 1999;8:1099–110.
8. Cnop M, Mulder H, Igoillo-Esteve M. Diabetes in Friedreich ataxia. J Neurochem. 2013;126(Suppl):94–102.
9. Regner SR, et al. Analysis of echocardiograms in a large heterogeneous cohort of patients with friedreich ataxia. Am J Cardiol. 2012;109:401–5.
10. Tsou AY, et al. Mortality in Friedreich ataxia. J Neurol Sci. 2011;307:46–9.

11. Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. Br Med Bull. 2017;124:19–30.
12. Reetz K, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 2015;14:174–82.
13. Dogan I, et al. Structural characteristics of the central nervous system in Friedreich ataxia: an in vivo spinal cord and brain MRI study. J Neurol Neurosurg Psychiatry. 2018;1(3) https://doi.org/10.1136/jnnp-2018-318422.
14. Corben LA, Lynch D, Pandolfo M, Schulz JB, Delatycki MB. Consensus clinical management guidelines for Friedreich ataxia. Orphanet J Rare Dis. 2014;9:1–12.
15. Vezina JG, Bouchard JP, Bouchard R. Urodynamic evaluation of patients with hereditary ataxias. Can J Neurol Sci. 1982;9:127–9.
16. Diez Rodríguez JM, et al. Clinico-urodynamic correlation in the hereditary ataxias. Arch Esp Urol. 2003;56:915–25.
17. Musegante AFA, Almeida PNS, Monteiro RTM, Barroso U. Urinary symptoms and urodynamics findings in patients with Friedreich's Ataxia. Int Braz J Urol. 2013;39:867–74.
18. Lad M, et al. Urinary, bowel and sexual symptoms in a cohort of patients with Friedreich's ataxia. Orphanet J Rare Dis. 2017;12:1–6.
19. Stoffel JT, et al. AUA white paper on nonneurogenic chronic urinary retention: consensus definition, treatment algorithm, and outcome end points. J Urol. 2017;198:153–60.
20. Dray E, et al. Does post-void residual volume predict worsening urological symptoms in patients with multiple sclerosis? J Urol. 2018;200:868–74.