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Cardiac Transplantation in Friedreich Ataxia

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Abstract

In this paper, we describe a 14-year-old boy with a confirmed diagnosis of Friedreich ataxia who underwent cardiac transplantation for left ventricular failure secondary to dilated cardiomyopathy with restrictive physiology. His neurological status prior to transplantation reflected early signs of neurologic disease, with evidence of dysarthria, weakness, mild gait impairment, and limb ataxia. We review the ethical issues considered during the process leading to the decision to offer cardiac transplantation.

Keywords

cardiac transplantation; cardiomyopathy; Friedreich ataxia

Introduction

Cardiomyopathy is a well-recognized complication of Friedreich ataxia, first described several decades before the discovery of the condition's genetic basis.[1–3] The prevalence of cardiomyopathy in pediatric patients with Friedreich ataxia ranges from 57% to 81%,[4,5] with some evidence suggesting the length of the GAA repeat expansion in intron 1 of the *FXN* gene influences age of onset and severity of cardiomyopathy[6–9] A recent study of 61 deceased patients with genetically confirmed Friedreich ataxia revealed that cardiac dysfunction was the cause of death in 59% of the cohort.[10] Among these deaths, the most common cause (30%) was end-stage congestive heart failure, followed by cardiac failure complicated by arrhythmia (8%) and isolated arrhythmia (8%). Median age at death due to

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Conflict of Interest

The authors have no conflict of interest to disclose. The study was approved by the Research Ethics Board of the Hospital for Sick Children.

Author Roles

G.Y. wrote the first draft of the manuscript, and contributed neurological and quality of life data, T.S., W.L., and J.M. contributed detailed neurological assessments and data, and J.W., K.G., S.M., A.D., and P.K. contributed detailed pre- and posttransplant cardiac assessments and data.

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cardiac causes was 26 years. Although death in childhood due to complications of cardiomyopathy is rare in patients with Friedreich ataxia, there are cases where cardiac symptoms precede neurological symptoms both in age of onset and severity.[11–13] In this paper, we describe a patient whose symptoms were predominantly cardiac in nature who underwent successful cardiac transplantation for Friedreich ataxia-associated dilated cardiomyopathy.

Case Report

Our patient, a 14-year-old boy, presented to medical attention at the age of 5 years with failure to thrive, fatigue, and fine motor difficulties. He was born following a normal pregnancy and delivery, and early developmental milestones were achieved at the appropriate times. He subsequently developed mild balance and gait abnormalities, but never required aids for ambulation. Molecular genetic testing of the *FXN* gene at age 11 years revealed an expanded GAA repeat of 800 on one allele and 1250 on the other, confirming a diagnosis of Friedreich ataxia. Initial cardiac evaluation at age 12 years revealed normal sinus rhythm on electrocardiogram with no chamber hypertrophy by electrocardiographic criteria; however, an echocardiogram demonstrated a dilated left ventricle with a z-score of +3.3 and low normal systolic function with an ejection fraction of 55%. There were no regional wall motion abnormalities or outflow tract obstruction, and right ventricular end-diastolic and left atrial dimensions were normal.

His cardiac status worsened progressively over the following year and echocardiogram at 13 years revealed moderately reduced left ventricular systolic function with an ejection fraction of 46%, z-score of +3.5, and increased septal thickness. He was started on idebenone 300 mg three times daily and ramipril 2.5 mg daily. By age 14 years he had developed marked left ventricular dysfunction, left ventricular dilation, and mild mitral regurgitation. Echo revealed severe global left ventricular dysfunction with an ejection fraction of 23% and a z-score of +5.5. There was evidence of restrictive physiology with a dilated left atrium (*z* score +4).

Neurological examination at 14 years revealed a narrow-based gait with mild instability. He was unable to carry out a tandem gait, but was able to stand with his feet together. On cerebellar testing he had very mild dysmetria, and upper limb pronation and supination were slightly irregular and slow. Examination of speech revealed minimal dysarthria. He had mild gaze-evoked nystagmus and saccadic smooth pursuit. Deep tendon reflexes were absent and plantar response was extensor. Muscle bulk, tone, and strength were normal. His total score using the Friedreich Ataxia Rating Scale was 34 (a total score of 0 indicates a normal neurological exam).[14] Evaluation of quality of life using the PedsQL 4.0 Pediatric Quality of Life Inventory (where higher scores represent better quality of life)[15] revealed a total score of 49 of 100, physical functioning summary score of 23 of 100, and psychosocial summary score of 61 of 100. He had scoliosis, which required treatment with a back brace, and no evidence of optic atrophy, hearing loss, or diabetes. His main symptoms were judged to be related to heart failure, specifically fatigue and limitation of physical activity, with symptomatic dyspnea.

He was admitted to the Hospital for Sick Children at age 14 years 7 months with symptoms of lethargy, fatigue, and decreased cardiovascular perfusion. The echocardiogram on admission revealed a dilated left ventricle with severe systolic dysfunction, an ejection fraction of 23%, and right ventricular estimated systolic pressure of 30 mmHg. His electrocardiogram on admission showed prolonged PR and QRS intervals with intraventricular conduction delay and right-axis deviation. Given the acute clinical deterioration, he was initially discussed as a possible candidate for palliative care; however,

over the intervening period of multidisciplinary discussion and consultation, his possible candidacy for heart transplantation was explored. After multiple discussions with the patient, his parents, and the Genetics, Neuromuscular, Psychiatric, Adolescent Medicine, Rehabilitation Services, and Transplantation Teams, a group consensus was reached to list him for heart transplantation.

Because of continued deterioration and progressive congestive heart failure, he was placed on a Berlin Heart EXCOR® (Berlin Heart AG, Berlin, Germany) ventricular assist device 2 weeks prior to undergoing heart transplantation at age 14 years, 10 months. The transplant procedure was uneventful and he was extubated within 48 hours without difficulty, but required continuous positive airway pressure intermittently for several weeks posttransplantation. Two weeks after heart transplantation he became hypertensive and had a seizure, with brain changes on magnetic resonance imaging consistent with posterior reversible encephalopathy syndrome. He required a brief readmission to the Critical Care Unit during this time period and his symptoms resolved with blood pressure control. He had no further seizures after this event.

He had significant muscle weakness in the months after transplantation, including difficulty swallowing, and was managed in a rehabilitation facility during the 3 months posttransplantation. He required nasogastric tube feeding, and gastrostomy tube insertion was done 6 weeks after transplantation without complication. He had only mild acute cellular rejection on posttransplantation surveillance endomyocardial biopsy, and has been maintained on a steroid-free regimen of tacrolimus and mycophenolate mofetil.

Clinical evaluation at 20 months after transplantation (age 16 years, 6 months), revealed essentially normal cardiac function but evidence of neurological progression. He had full oral intake without any need for gastrostomy feeds but needed assistance with activities of daily living that required fine motor skills (dressing, bathing), and he was unable to walk unassisted. His Friedreich Ataxia Rating Scale total score was 131, with the main areas of deficit being upper limb coordination and upright stability/ambulation. Evaluation of quality of life using the PedsQL revealed overall improvement with a total score of 54/100, and a physical functioning summary score of 44/100, which was increased compared with the pre-transplantation physical functioning score of 23/100. His psychosocial summary score remained relatively stable at 60/100. His medication regimen included idebenone 150 mg three times daily, omeprazole 40 mg daily, amlodipine 25 mg daily, ramipril 3.75 mg daily, tacrolimus 5 mg daily, and mycophenolate mofetil 500 mg twice a day. He had no evidence of glucose intolerance or diabetes.

Discussion

This is the third reported case of heart transplantation in a patient with Friedreich ataxia. Leonard and Forsyth[16] described a 4-year-old boy who successfully underwent heart transplantation for dilated cardiomyopathy prior to development of neurological symptoms and genetic diagnosis of Friedreich ataxia. Sedlak and colleagues[17] described a 34-year-old man who received a heart transplant for end-stage congestive heart failure caused by dilated cardiomyopathy. Their rationale for offering heart transplantation to this patient focused on the fact that his predominant symptoms were due to the severity of the congestive heart failure; the transplant team, therefore, thought the patient would have a reasonable quality of life after transplantation.

The ethical issues surrounding the criteria for eligibility for heart transplantation, which stem from the need for appropriate allocation of a scarce resource, are well-recognized.[18–20] Listing practices and requirements vary considerably among institutions and from one organ

type to another, and there are many ethical principles that should be considered when determining access to the heart transplantation waiting list, and allocation of a donor organ. There appears to be general consensus that heart transplantation should be reserved for patients most likely to benefit both in terms of quality of life and survival; however, the specific ethical considerations unique to each situation must be considered on a case-by-case basis.[18]

For our patient, the main ethical principles that required discussion in a multidisciplinary forum were justice, as it was clear that our patient would not survive without a heart transplant, and utility, where the argument was made that offering heart transplantation may not be appropriate for a patient with progressive neuromuscular disease. It was emphasized that the patient's life expectancy from age 14 with a functioning transplanted heart would likely be limited by the longevity of the allograft, rather than the natural history of his neurologic deterioration. It was also determined that the patient and his family had the comprehension and ability to understand the complex procedures involved with transplantation surgery and posttransplantation care. Cognitive status was completely normal and quality-of-life assessments from the patient's perspective revealed that he had a strong desire for long-term survival and to improve his sense of physical well-being, which he felt could be achieved by receiving a heart transplant. Social evaluation of the supports available to our patient revealed the family was committed to supporting the patient through the transplant procedure. This combination of factors—together with evidence from several studies that suggest cardiac transplant may be the most effective therapy for dilated cardiomyopathy[21,22] and that patients with dilated cardiomyopathy have a lower incidence of death posttransplantation compared with other types of cardiomyopathy[23]—led to a group consensus to offer cardiac transplantation to our patient, despite his underlying diagnosis of Friedreich ataxia. Despite progression of his neurological symptoms, his physical functioning summary score on the PedsQL 4.0 Inventory was much higher posttransplant compared with his pre-transplant scores, likely due to the marked improvement in his cardiac status.

The long-term outcome, despite a technically successful transplant and normal cardiac function 20 months after heart transplantation, is unknown. The cause of our patient's neurologic progression posttransplant is likely due to a combination of prolonged hospitalization and subsequent deconditioning, medication use, and disease progression, which could still limit his lifespan and his quality of life in the coming years. The need to develop better predictors of disease progression in Friedreich ataxia to assist in long-term prognostication cannot be overemphasized.

Conclusion

The ethical considerations that must be considered in the decision process to offer heart transplantation to a patient with a progressive neurodegenerative disease are complex and are best discussed in a multidisciplinary forum. The presence of a diagnosis of neurodegenerative disease is not prima facie an absolute contraindication to cardiac transplantation.

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