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Clinical Short Communication

Cardiac transplantation in Friedreich Ataxia: Extended follow-up

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ABSTRACT

Friedreich Ataxia (FRDA) is an autosomal recessive neurodegenerative disorder most commonly caused by guanine-adenine-adenine (GAA) trinucleotide repeat expansions in both alleles of the FXN gene. Although progressive ataxia remains the hallmark clinical feature, patients with FRDA are at high risk of developing cardiomyopathy, often resulting in premature death. There is no specific treatment for FRDA-associated cardiomyopathy; even in advanced cardiac failure cardiac transplantation is not commonly pursued. This case series describes extended follow-up of three FRDA cases with end-stage heart failure but mild neurologic disease who underwent successful heart transplantation. We also review and examine the ethical considerations for heart transplantation in the setting of neurodegenerative disease.

1. Introduction

Friedreich Ataxia (FRDA) is a progressive disorder affecting approximately 1 in 50,000 individuals in the United States, making it the most common form of inherited ataxia [1]. The disease is autosomal recessive, and an expanded guanine-adenine-adenine (GAA) triplet repeat on the *FXN* gene is the cause of the disease in 96% of patients. Clinically, FRDA is primarily characterized by ataxia, gait abnormalities, loss of proprioception, and are flexia with a mean age of onset between 10 and 15 years [1,2]. Individuals diagnosed with FRDA later in life usually carry shorter GAA repeat expansions, and as a result, typically have a slower disease progression [3–5]. Those with an earlier age of onset usually progress more rapidly, often presenting with more severe neurologic phenotypes. Patients with FRDA can develop a panoply of non-neurological features such as scoliosis, diabetes mellitus, pes cavus, and loss of visual acuity [6].

Patients are also at risk of developing various components of heart disease, including cardiac hypertrophy, myocardial fibrosis, arrhythmias, and end-stage heart failure. Such difficulties make heart disease the leading cause of death in FRDA, accounting for approximately 60% of deaths from the disease [7]. The typical course of heart disease in FRDA has been conceptualized as a gradual progression from left ventricular (LV) hypertrophy to later fibrosis and ventricular thinning by ages 20–50 [8–10]. Such patients experience arrhythmias and loss of systolic function, particularly as they age, often leading to premature death [9]. Thirty percent of these deaths are caused by end-stage congestive heart failure, with a median age of death of 26 years [7].

Currently, there is no known cure for FRDA cardiomyopathy and much controversy surrounds the design and implementation of appropriate therapeutic intervention, with little standardization in this population [11]. Four previous case reports demonstrate the short-term success of cardiac transplantation in abating life-threatening cardiomyopathy [11–14]. In this paper, we describe three additional patients with mild-to-moderate neurologic disease but severe cardiac dysfunction who subsequently underwent successful cardiac transplantation.

2. Materials and methods

This study is part of a larger natural history study in FRDA that was approved by the Institutional Review Board (IRB) at the Children's Hospital of Philadelphia, and informed consent from adult participants or the parent/guardian of participants under 18 years old was obtained prior to participation. Three patients with a history of precipitous heart failure who underwent heart transplantation and who have not

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been previously reported in the literature were identified as part of a retrospective review of FRDA patients' medical records for inclusion in this case series. Patients with genetically confirmed FRDA were recruited during their clinical visits. All subjects were identified through the clinical practice of the principal investigator or other collaborators, including referrals from other practices. Over the past 20 years, this practice has evaluated 379 individuals with FRDA.

3. Results

3.1. Patient 1

(GAA repeat lengths of 690 and 940) was diagnosed with FRDA at age 12, 7 years after cardiac failure and heart transplantation. At age 5, the patient presented with severe myocarditis confirmed by cardiac biopsy. Neurological assessment was grossly normal at this time. While the patient was awaiting transplantation, he experienced cardiac arrest requiring resuscitation. He was subsequently underwent a biventricular assist device placement and a heart transplant 2 days later. After transplant, the patient was started on a maintenance immunosuppressive regimen of cyclosporine, azathioprine, and prednisone. He suffered a perioperative stroke, as manifest by difficulties with speech, gait, and vision. Given the constellation of symptoms and the diagnosis of a sibling with FRDA, concern was raised for underlying FRDA. Genetic testing confirmed the diagnosis of FRDA. Spontaneous stroke recovery allowed this patient to initially regain speech, gait and vision skills. The patient underwent scoliosis surgery 5 years post-transplant. His neurological dysfunction progressed, in that he now uses a wheelchair and requires assistance for many activities of daily living. The patient's cardiac function has remained stable 19 years post-transplant. Allograft function has been preserved since transplant without evidence of rejection.

3.2. Patient 2

(GAA repeat lengths of 158 and 1133) is a 42-year-old male diagnosed with FRDA at age 24 after presenting with balance difficulties and increased dizziness in the context of a family history of FRDA. He developed shortness of breath during his late teens, presumptively related to cardiomyopathy, though he was not diagnosed with heart failure until the age of 27, upon presentation to the emergency department with an EF (ejection fraction) of 15%. A prophylactic automated implantable cardioverter-defibrillator (AICD) was placed at age 33. After that time, the patient experienced multiple episodes of ventricular fibrillation triggering cardioversion from the device. By age 35, his cardiac function declined further, requiring placement of a left ventricular assist device (LVAD). At age 37 the patient received a heart transplant due to severe congestive heart failure. Following transplant, the patient received standard immunosuppressive therapy, consisting of tacrolimus, mycophenolate mofetil, and prednisone. Two weeks later, his post-operative course was complicated by junctional rhythm requiring a permanent pacemaker. Approximately three weeks post-transplant, the patient had an episode of grade 1B rejection treated with pulse steroids over a three day course. A week later, he was noted to have a positive retrospective crossmatch, which was successfully treated with intravenous immunoglobulin. Neurologically, the patient remains ambulatory and uses a walker when in the community. The patient's cardiac status has remained stable 5 years post-transplant, without any further episodes of allograft rejection.

3.3. Patient 3

(GAA repeats of 400 and1167) presented with neurological symptoms of FRDA at age 26, reporting dizziness and intermittent head tremors followed by a loss of balance. The patient had multiple brain MRIs (magnetic resonance imagining), all of which were normal. As symptoms worsened, she underwent genetic testing for spinocerebellar ataxias (SCA) and results were negative for any mutations associated with known SCA types. Other extensive lab work was negative alongside EMG (electromyography)/nerve conduction tests. At age 31, the patient was diagnosed with dilated cardiomyopathy when she presented to the emergency department with shortness of breath, tachycardia but no chest pain. The patient was started on cardiac treatment for dilated cardiomyopathy. Around this time, her gait worsened. At age 34, the patient was diagnosed with FRDA and required use of a walker, at which time she was started on idebenone therapy. Between the ages of 34 and 37, the patient's cardiac function worsened and her EF decreased, attributed to a late decline following post-partum cardiomyopathy, confounded by an 80-pound weight loss. At age 37, the patient required AICD placement and within months, heart transplantation. Post-transplant, she was started on maintenance immunosuppression therapy with cyclosporine. Since that time, the patient has had one episode of Grade 2R/3A cellular rejection. This was successfully treated with intravenous methylprednisolone and a prednisone taper, and a subsequent change in medication was made from cyclosporine to tacrolimus and mycophenolate mofetil. Since transplantation, the patient's ataxia has progressed with increase in stiffness, non-volitional leg jerks, and dysphagia; she walks occasionally, but has become largely wheelchair dependent. Cardiac status has been stable since transplantation 8 years ago, and she has had no further episodes of allograft rejection on the same maintenance immunosuppressive regimen.

4. Discussion

This case series presents a group of individuals with FRDA with differing courses to cardiac transplantation. Onset of cardiac disease occurred over a broad age range (5–27) and was discovered in individuals with both relatively short and long GAA repeat on the shorter allele of the *FXN* gene. In one individual, cardiac dysfunction appeared before neurological dysfunction (patient 1). In addition, progression to cardiac failure was slow in one individual, abrupt in another, and in the third contained chronic and subacute progression. Each of the three patients progressed neurologically over time without an overt effect on native cardiac function and without apparent post-transplant graft decline. These features emphasize the differences in presentation and progression of heart disease in FRDA and its independence from neurological dysfunction, consistent with cardiac disease in FRDA being a cell autonomous phenomenon.

In this series, two patients presented with acute decompensated heart failure prior to their diagnosis of FRDA. This phenomenon has been reported in other case reports as well. Overall, these observations emphasize that the rate and nature of progression to end stage heart failure in individuals with FRDA is highly variable and, at least in these unusual individuals, not easily predicted by their neurologic status or GAA triplet repeat length.

Such variability may be partially explained by factors beyond of the primary diagnosis of FRDA, such as genetic heterogeneity outside the FXN locus, environmental factors or secondary insults. Patient 1 initially carried the diagnosis of viral-induced dilated cardiomyopathy, characterized by inflammation of the heart muscle. The subsequent identification of FRDA forces one to reassess that diagnosis, or consider the possibility that the combination of FRDA and a viral infection led to severe dysfunction. One could argue that patient 3 may have also had two diagnoses contributing to her cardiac decline, namely post-partum cardiomyopathy in addition to FRDA cardiomyopathy. Likewise for patient 2, it is unclear whether he had one unifying diagnosis (FRDA) with unusually severe cardiac manifestations, or a second predisposing risk factor (such as a familial or primary idiopathic cardiomyopathy) that has not yet been identified.

The three patients in this series add to the literature of four previously reported heart transplants in patients with heart failure and FRDA [11–14]. Here, though, the individuals have been followed since their transplant for extended periods of time. The first study to track cardiac

outcomes in FRDA longitudinally was by Pousset et al. [15]. This 22-year follow-up revealed that survival in FRDA is directly determined by the degree of cardiac involvement, and that patients with progressive decline of LV ejection fraction had a worse prognosis [15]. Routine cardiac follow-up was cited as critical, but that more studies needed to be done to explore cardiac intervention to slow progression of FRDA [15]. Their study was limited by excluding early onset individuals with potentially fatal cardiac dysfunction [15]. Our case series demonstrates the safety and efficacy of heart transplantations as a possible treatment option for end-stage heart failure in the setting of neurologic disease in both early- and late-onset individuals.

All three patients described in this series progressed neurologically following transplant, although with no discernable negative impact on cardiac graft function. Immunosuppressive therapy did not improve or stabilize neurologic function. Taken with the previously reported cases of cardiac transplantation, these cases suggest that heart transplantation is a viable option for FRDA patients who present with end stage heart failure. This is particularly important for individuals with a severe cardiac phenotype and short GAA repeat lengths, as these individuals are less likely to die prematurely due to other symptoms of FRDA [7]. It is also important in the context of developing genetic approaches to therapy of FRDA. Such approaches may be tissue-specific, leading to the possibility that cardiac transplantation might be feasible even for individuals with severe neurologic involvement if their neurological degeneration can be treated successfully with gene therapy [16].

Ethical considerations must be taken into account for patients who are potential candidates for heart transplantation but present with progressive neurologic disease. Multidisciplinary forums must address an array of complex issues, including utility, quality of life, justice, life expectancy, and contraindications when considering heart transplant allocation within in the setting of FRDA [11,14,17]. We previously reported that the mean age of death in FRDA is 36.5 years, with 59% of deaths caused by cardiac dysfunction [18]. Patients with cardiac dysfunction died at significantly younger ages (median 26 vs. 41 years), and had shorter disease duration by 10 years compared to patients without cardiac dysfunction [18]. Overall, our case series demonstrates that by eliminating the leading cause of death in FRDA, cardiac transplantation should improve survival and quality of life of patients with FRDA. As such, a patient who undergoes transplantation is predicted to live as long – if not longer – than the median survival for heart transplant recipients (11 years), thereby eliminating the issue of life expectancy when considering a patient's eligibility for heart transplant [19]. In the case that the graft fails unexpectedly, repeat cardiac transplantation would be a viable option, after reviewing risk factors and other medical considerations relevant to the individual patient. However, diagnosis of FRDA should not be viewed as an absolute contraindication that would negatively impact a patient's candidacy for heart transplantation or re-transplantation.

5. Conclusions

The present series illustrates the long-term viability of cardiac transplantation in three FRDA patients who remain alive, cognitively intact, and socially engaged at 19, 5, and 8 years after heart transplantation, respectively.

Conflicts of interest

None.

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References

[1] D.R. Lynch, et al., Friedreich ataxia: effects of genetic understanding on clinical evaluation and therapy, Arch. Neurol. 59 (5) (2002) 743–747, http://dx.doi.org/10.1001/archneur.59.5.743.
[2] M. Pandolfo, Friedreich ataxia: the clinical picture, J. Neurol. 256 (1) (2009) 3–8, http://dx.doi.org/10.1007/s00415-009-1002-3.
[3] L.S. Friedman, et al., Measuring the rate of progression in Friedreich ataxia: implications for clinical trial design, Mov. Disord. 25 (4) (2010) 426–432, http://dx.doi.org/10.1002/mds.22912.
[4] M. Patel, et al., Progression of Friedreich ataxia: quantitative characterization over 5 years, Ann. Clin. Transl. Neurol. 3 (9) (2016) 684–694, http://dx.doi.org/10.1002/acn3.332.
[5] Reetz, Kathrin, et al. "Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): analysis of two-year longitudinal cohort data." Lancet Neurol. (In press).
[6] M.H. Parkinson, et al., Clinical features of Friedreich's ataxia: classical and atypical phenotypes, J. Neurochem. 126 (s1) (2013) 103–117, http://dx.doi.org/10.1111/jnc.12317.
[7] A.Y. Tsou, E.K. Paulsen, S.J. Lagedrost, S.L. Perlman, K.D. Mathews, G.R. Wilmot, B. Ravina, A.H. Koeppen, D.R. Lynch, Mortality in Friedreich ataxia, J. Neurol. Sci. 307 (1–2) (2011) 46–49, http://dx.doi.org/10.1016/j.jns.2011.05.023.
[8] R.L. Hewer, The heart in Friedreich's ataxia, Br. Heart J. 31 (1) (1969) 5, http://dx.doi.org/10.1136/hrt.31.1.5.
[9] D.R. Lynch, S.R. Regner, K.A. Schadt, L.S. Friedman, K.Y. Lin, M.G. St. John Sutton, Management and therapy for cardiomyopathy in Freidreich's ataxia, Expert. Rev. Cardiovasc. Ther. 10 (6) (2012) 767–777, http://dx.doi.org/10.1586/erc.12.57.
[10] R.M. Payne, G.R. Wagner, Cardiomyopathy in Friedreich ataxia: clinical findings and research, J. Child Neurol. 27 (9) (2012) 1179–1186, http://dx.doi.org/10.1177/0883073812448535.
[11] P. Ivak, A. Zumrová, I. Netuka, Friedreich's ataxia and advanced heart failure: An ethical conundrum in decision-making, J. Heart Lung Transplant. (2016), http://dx.doi.org/10.1016/j.healun.2016.06.021.
[12] H. Leonard, R. Forsyth, Friedreich's Ataxia Presenting after Cardiac Transplantation, 84(2), 2001 167–168, http://dx.doi.org/10.1136/adc.84.2.167.
[13] T.L. Sedlak, M. Chandavimol, L. Straatman, Cardiac Transplantation: a Temporary Solution for Friedreich's Ataxia-Induced Dilated Cardiomyopathy, 23(11), 2004 1304–1306, http://dx.doi.org/10.1016/j.healun.2003.09.015.
[14] Yoon G, Soman T, Wilson J, George K, Mital S, Dipchand AI, McCabe J, Logan W, Kantor P. Cardiac transplantation in Friedreich ataxia. J. Child Neurol. 27(9): 1193–6. http://dx.doi.org/10.1177/0883073812448229.
[15] F. Pousset, et al., A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia, JAMA Neurol. 72 (11) (2015) 1334–1341.
[16] B. Belbellaa, H. Puccio, Toward gene therapy for Friedreich ataxia-associated cardiomyopathy, Med. Sci. 30 (10) (2014) 842, http://dx.doi.org/10.1051/medsci/20143010008.
[17] K.C. Sokol, et al., Ethical issues in children with cardiomyopathy: making sense of ethical challenges in the clinical setting, Prog. Pediatr. Cardiol. 23 (1) (2007) 81–87, http://dx.doi.org/10.1016/j.ppedcard.2007.05.010.
[18] A.Y. Tsou, et al., Mortality in Friedreich ataxia, J. Neurol. Sci. 307 (1) (2011) 46–49.
[19] L.H. Lund, et al., The registry of the International Society for Heart and Lung Transplantation: thirty-third adult heart transplantation report—2016; focus theme: primary diagnostic indications for transplant, J. Heart Lung Transplant. 35 (10) (2016) 1158–1169.