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Cardiac Transplantation in Patients with Muscular Dystrophy: A Case Report and Review of Literature

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1. Abstract

We report a case of slowly progressive Becker's muscular dystrophy in a 52-year-old man who required cardiac transplantation for intractable congestive heart failure. A referral was made concerning prognosis of his muscular dystrophy in the multidisciplinary approach to transplant. A review of the literature provides limited guidance on cardiac transplantation in patients with muscular dystrophy although this procedure appears to be well-tolerated in those with Becker's muscular dystrophy. Formal assessments and neuromuscular follow-up have not been clearly documented in patients having cardiac transplantation, and robust clinical evidence or guidance in this area is lacking.

2. Introduction

Muscular dystrophies are a heterogeneous group of genetic muscular disorders presenting with progressive muscular weakness which have characteristic pathological features in the muscle biopsy and are often associated with other organ involvement such as cardiac, respiratory, or central nervous system [1, 2]. Cardiac involvement can involve primarily the myocardium or conductive system or be secondary to respiratory muscle involvement by causing cor pulmonale [3, 4]. Improved management of respiratory, cardiac, and other complications in different types of muscular dystrophy (MD) has led to increased survival of with many patients surviving into adulthood [2, 3, 5, 6]. With increased life expectancy of MD patients, neuromuscular physicians may be asked to provide advice in novel areas that lack a solid evidence base or guideline. Here, we report the case of a 52-year-old Becker muscular dystrophy (BMD) patient evaluated at the request of the cardiology service regarding eligibility for cardiac transplantation. We also present the results of a literature review regarding cardiac transplantation in MD, including any consensus recommendations.

3. Case Report

A 52-year-old man was first evaluated in the Prosserman Family Neuromuscular Clinic at age 41 for proximal lower limb weakness manifest as difficulty in climbing stairs. He reported that he had a normal childhood and development but that he was never athletic. His 74-year-old mother had difficulty climbing stairs starting at age 72 and examination showed that she had bilateral calf hypertrophy. Three of his sisters are healthy. He developed symptoms at age 28 with minimal difficulty in climbing stairs. The weakness progressed slowly and by age 37, he had difficulty getting up from a chair and required support to climb stairs. He had no other weakness, bulbar or respiratory symptoms. Physical examination revealed a normal cranial nerve examination and upper limb power. In the lower limbs, he had proximal weakness at 4/5 in hip flexors, quadriceps, and hamstrings, normal distal strength and bilateral calf hypertrophy. Deep tendon reflexes were reduced in the upper limbs, absent at the knees and normal at the ankles. Plantar reflexes were flexor. Sensory examination was normal. He had a waddling gait and positive Gower's sign.

His serum creatine kinase (CK) level was elevated at 1100 (normal < 240 U/L). Electrodiagnostic studies revealed normal nerve conduction studies and chronic myopathic changes on electromyography. Genetic testing showed deletion at exons 45-47 in the dystrophin gene establishing the diagnosis of BMD. At age 43, he was diagnosed with non-ischemic cardiomyopathy. Due to episodes of ventricular tachycardia, an implantable cardioverter-defibrillator (ICD) was placed at age 51, and subsequently at age 52, he was treated with cardiac resynchronization therapy plus a defibillator (CRT-D). Shortly thereafter, he developed intractable end-stage heart failure presenting with shortness of breath, cough, orthopnea, and paroxysmal nocturnal dyspnea necessitating admission for continuous furosemide infusion. In light of the refractory cardiomyopathy, advanced heart failure therapies including a left ventricular assist device (LVAD) or cardiac transplantation were considered. As part of the eligibility evaluation for cardiac transplantation, he was referred to our clinic for an opinion on his neuromuscular course and prognosis. Examination showed normal cranial nerves, diffuse muscular atrophy, most pronounced in the proximal lower limb muscles, 4/5 power in proximal upper limb muscles with normal distal power, 3/5 power in proximal lower muscles and 4/5 power in distal lower limb muscles. Deep tendon reflexes were reduced globally. Gait was impossible to assess as he was bedridden due to severe heart failure.

We recommended that this BMD patient be eligible for cardiac transplantation given that he had remained ambulatory with slowly progressive weakness until age 52 when severe heart failure precluded ambulation. He has not yet had the procedure.

4. Literature Review

4.1. Duchenne And Becker's Muscular Dystrophy

Since 1988, cardiac transplantation has been reported both in case reports and case series in patients with Duchenne muscular dystrophy (DMD) and BMD with end-stage heart failure as a final treatment option with successful outcomes [7–26]. The clinical neuromuscular status including the degree of muscular or respiratory weakness and outcome of the transplantation are summarized in Table 1. Some of the dystrophinopathy patients who had successful cardiac transplantation were neurologically asymptomatic at the time of transplantation despite the severe dilated cardiomyopathy necessitating cardiac transplantation [10, 11, 14, 21, 22, 27]. Other studies reported patients with dystrophinopathy-related cardiomyopathy with mild to moderate muscular weakness who tolerated the transplantation procedure well; most of these were BMD patients rather than DMD [7, 8, 12, 14, 15, 18, 21, 23]. In two case reports published recently [24, 26], the authors reported two DMD patients with severe muscular weakness in addition to respiratory involvement who also completed the cardiac transplantation uneventfully and one had a 53 month follow up after surgery [24]. There are six case series reporting patients with muscular dystrophy who underwent cardiac transplantation [9, 16, 17, 19, 25, 28]. Unfortunately, the degree of muscular and respiratory weakness was not documented in these studies, but most were BMD patients who have less severe muscular and respiratory weakness than DMD patients or those with other muscular dystrophies.

Table 1: Summary of studies reporting cardiac transplantation in different types of muscular dystrophies.

Author	Year and type of the study	Number and type of neuromuscular patients who underwent cardiac transplantation	Degree of muscular weakness before transplantation	Summary of outcome	Duration of post-transplantation follow-up
Cripe et al [18]	2011- case report	1 intermediate DMD	Mild muscular and respiratory weakness	Successful transplantation	4 years
Wittlieb-Webera et al [24]	2019 - case report	1 DMD	Severe muscular weakness led to loss of ambulation with respiratory muscle weakness requiring nightly CPAP	Successful transplantation	53 months
Piperata et al [26]	2020 - case report	1 DMD	Severe muscular weakness led to wheelchair-bonded state and mild respiratory muscle weakness (FVC= 2.4 liter; 60% of the predicted value)	Successful transplantation	3 months
Melacini et al [12]	2001- case series	1 BMD and 1 DMD carrier	Moderate muscular weakness in BMD and mild muscular weakness in DMD carrier	Successful transplantation	followed up for 4 months and 42 months in BMD and DMD carrier, respectively
Papa et al [21]	2017 - case series	3 BMD and one x-linked dilated cardiomyopathy	Two of BMD patients had mild muscular weakness with no respiratory involvement at the time of transplantation, the third BMD patient and X-linked dilated cardiomyopathy patient were neurologically asymptomatic	Uneventful transplantation and post-operative course	Mean follow up of 144.4 months

Casazza et al [7]	1988 - case report	1 BMD	Mild muscular weakness with	Successful transplantation	NA
Donofrio et al [8]	1989 - case report	1 BMD	Shoulder and pelvic girdle weakness, difficulty in arising from a chair or squat position	Successful transplantation, Good cardiac and functional outcome after transplantation	2 years
Piccolo et al [10]	1994- case report	1 BMD	Normal neurological examination except for slight bilateral calf hypertrophy	Successful transplantation	4 years
Finsterer et al [11]	1999- case report	1 BMD	Normal neurological examination	Successful transplantation	6 years
Leprince et al [13]	2002- case report	1 BMD	Severe muscular weakness	Successful transplantation with improved muscular weakness after transplantation	18 months
Patane et al [15]	2006- case report	1 BMD	Heart failure symptoms were more disabling than neuromuscular symptoms	Successful transplantation	1 year
Katzberg et al [27]	2010 – case report	1 BMD	Normal neurological examination	Successful transplantation	NA
Madeira et al [22]	2018- case report	1 BMD	Normal neurological examination	Successful transplantation	15 years
Merchut et al [29]	1990- case report	1 EDMD	Mild proximal upper and lower limb weakness and minimal distal leg weakness	Uneventful transplantation	18 months
Kichuk Chrisant et al [30]	2004- case series	2 EDMD	Mild proximal muscle weakness	Successful transplantation	21 months
Dell'Amore et al [31]	2007- case series	2 EDMD	Mild proximal muscle weakness	Successful transplantation	40-66 months
Ambrosi et al a [32]	2009- case series	cardiac transplantation in seven patients of a single family with LGMD type 1 B linked to a mutation in LMNA gene	Mild muscular weakness in all patients except one with end-stage dilated cardiomyopathy in all of them	Successful transplantation with no higher rates of early or late post-operative complications than other transplantation recipient	mean follow-up of 8 years
Conraads et al [33]	2002- case report	1 myotonic dystrophy type 1	Bulbar, respiratory and limb weakness	Successful transplantation with prolonged mechanical ventilation and need for intensive respiratory and peripheral muscular training pre- and post-operatively	5 years
Papa et al [34]	2018- case report	1 myotonic dystrophy type 1	Mild muscular weakness with no respiratory symptoms	Successful transplantation with a prolonged postoperative course due to transient severe respiratory failure requiring antibiotic therapy and mechanical ventilation	3 months
Pick et al [35]	2017- case report	1 Fukoyama congenital muscular dystrophy	Mild muscular weakness	Uneventful transplantation but post-operative course complicated by convulsions and acute renal failure	NA

Rees et al [9]	1993- case series	3 DMD, 1 BMD, 1 EDMD, and 1 unspecified muscular dystrophy out of 582 cardiac transplantation patients	NA	Uneventful transplantation, good toleration of immunosuppressant without difference on postoperative complications or rehabilitation process	mean follow up of 40 months
Ruiz-Cano MJ et al [14]	2003- case series	3 BMD- 1 limb-girdle muscular dystrophy, and 1 desminopathy	2 of BMD patients had mild muscular weakness with no respiratory involvement and the third BMD patient was asymptomatic, the LGMD patient had mild muscular weakness, and desminopathy patient had mild muscular weakness with atrophy of distal upper and lower limb muscles	All had uneventful transplantation except for desminopathy patient who had prolonged postoperative course due to severe respiratory failure requiring mechanical ventilation	mean follow up of 40 months
Connuck et al [16]	2008- case series	6/15 BMD but 0/128 DMD had cardiac transplantation	NA	Successful transplantation	NA
Wu et al [17]	2010- case series	15 BMD, 3 DMD, 4 myotonic dystrophy, 3 limb-girdle MD, 1 EDMD, 1 mitochondrial, and 2 undetermined	NA	Similar one-year and five-year survival between muscular dystrophy and non-dystrophic patient, The rates of post-transplant infection, transplant rejection, and allograft vasculopathy also were similar between two groups.	median follow up of 5.4 years
Fuchs et al [19]	2012- case series	5 EDMD and 4 BMD	NA	Successful transplantation and improvement in mobilization status	5 years
Steger et al [20]	2013- case series	3 BMD and 1 limb-girdle muscular dystrophy	All patients had muscular weakness before starting cardiac symptoms	Successful transplantation and uncomplicated post-operative course	Mean follow up of 12.5 years
Kamdar et al [28]	2017- case series	47 neuromuscular cardiomyopathy patients compared to a matched cohort of 235 patients which 46.8% of the neuromuscular group were BMD as the most common group	NA	Successful transplantation with similar survival and outcome compared with the matched non-neuromuscular cohort	5 years
Seguchi et al [23]	2019- case series	6 BMD, 2 dystrophinopathy related cardiomyopathy, and 1 alpha-dystroglycanopathy	All of them were ambulatory except for three BMD patients who were wheelchair bond	Successful transplantation with improvement in the ambulation status after transplantation	Mean follow up of 4.3 years

Wells et al [25]	2020- case series	81 patients had muscular dystrophy, BMD was the most common group with 42 patients followed by 11 EDMD, 4 LGMD, 3 DMD, and 2 myotonic dystrophy patients	NA	With the similar course of transplantation, rate of complication, and survival comparing with non-dystrophic matched group, Among the types of MD, no statistically significant difference was observed in the post-transplant survival of patients with BMD versus patients with non-BMD	10 years

4.2. Emery-Dreifuss MD

There are three case reports of cardiac transplantation in Emery-Dreifuss muscular dystrophy (EDMD) patients. One patient had mild proximal upper and lower limb weakness and minimal distal leg weakness and tolerated the transplantation uneventfully [29], but the clinical status was not recorded in the other 2 case reports [9, 17]. Similarly, the clinical neuromuscular status was not reported in two case series of EDMD patients who had successful cardiac transplantation [19, 25]. In two additional case of cardiac transplantation in EDMD patients, mild proximal weakness was evident at the time of cardiac transplantation and the surgery was reported as successful [30, 31].

4.3. Limb-girdle MD

Successful cardiac transplantation has been reported in two case reports [14,20] and two case series [17,32] of limb-girdle muscular dystrophy (LGMD) patients. The severity of neuromuscular weakness and also the type of LGMD was omitted in one case series [17] , but in the other case series reporting seven members of a family with LGMD type 1B, the muscular weakness was noted as mild except in one patient [32] . Muscle weakness in one of the case reports was reported as mild [14] , but not specified in the other [20] .

4.4. Myotonic Dystrophy

Cardiac transplantation with acceptable outcomes in myotonic dystrophy have been reported in two case reports of patients having congestive heart failure [33, 34] and two case series [17, 25] of patients without a specified etiology for heart failure. In one case report, the post-operative course was complicated by prolonged mechanical ventilation and the need for intensive respiratory and peripheral muscular training pre- and post-operatively due to the presence of bulbar, respiratory and limb musculature weakness before transplantation [33]. The other case reported a prolonged postoperative course due to transient severe respiratory insufficiency necessitating antibiotics and prolonged mechanical ventilation despite the presence of only mild muscle weakness without respiratory involvement before cardiac transplantation [34]. The case series reporting myotonic dystrophy patients did not detail the type of myotonic dystrophy or neuromuscular status in terms of skeletal or respiratory muscle weakness [17, 25].

4.5. Other Muscular Dystrophies

Single case reports of patients with congenital muscular dystrophies (one Fukuyama congenital muscular dystrophy and one alpha-dystroglycanopathy) have been reported in the literature [23, 35] . The alpha-dystroglycanopathy patient was ambulatory before cardiac transplantation and showed improvement in ambulation status after transplantation [23]. The patient with Fukuyama congenital muscular dystrophy had mild lower limb weakness in terms of a positive Gower's sign, gait impairment and difficulty running prior to cardiac transplantation, and although he tolerated the procedure well, his post-operative course was complicated by convulsions and acute renal failure preventing recovery to the pre-procedural motor function [35].

5. Recommendations for Cardiac Transplant in Muscular Dystrophy

The American Heart Association has suggested that cardiac transplantation is not an option for patients with severe neuromuscular diseases given the increased risk of complications due to respiratory and pharyngeal muscle weakness. They suggest that cardiac transplantation can be considered for those with milder respiratory and skeletal muscle weakness such as BMD [36]. In a 2018 publication on DMD care, Birnkrant et. al. suggested cardiac transplantation as only a theoretical option for those with severe heart failure given the paucity of donors. They suggested a case-by-case approach without any specific characterization of severity of MD or other criteria for cardiac transplantation [37].

6. Discussion

In the past, neuromuscular disorders were considered as contraindications for cardiac transplantation [38], but these conditions include patients with a wide spectrum of diseases manifesting in diverse combinations of muscle group weakness and involvement of other organs such as heart and nervous system [1]. Despite the diversity in muscular dystrophies, the most common limiting factors for transplant are severe respiratory and bulbar muscle weakness, which predispose these patients to prolonged ventilation support and higher complication rates [14, 25, 33]. Information concerning the severity and distribution of neuromuscular weakness is missing in the largest case series of neuromuscular patients who had successful cardiac transplantation [9, 16, 17, 19, 25, 28], although some reports indicate that outcome of cardiac transplantation in patients with MD is similar to the non-MD patients in terms of ability to tolerate the surgery, post-operative course, complications, and survival [9, 17, 25, 28]. Most of these reports are based on patients with BMD who have milder muscle weakness or those with dystrophinopathy who were asymptomatic or had mild to moderate muscle weakness before surgery [7, 8, 10-12, 14, 15, 18, 21-23]. A severe phenotype in DMD may not preclude cardiac transplantation although the evidence is limited to two case reports only [24, 26].

An exception to the hypothesis that patients with milder forms of dystrophy can tolerate cardiac transplantation may be in myotonic dystrophy type 1 patients, who experienced difficult post-operative courses regardless of the degree of muscle or respiratory weakness before transplantation which could be explained by the systemic nature of the myotonic dystrophy pathology making them more prone to the post-operative complications [33, 34]. Experience is limited also in congenital MD with one patient unable to attain the pre-transplantation level of motor status due to post-surgical complications [35].

A single inclusive recommendation regarding cardiac transplantation in MD does not appear to be feasible with our current state of knowledge. The selection process for cardiac transplantation in patients with MD requires a multidisciplinary team with a cardiologist, neuromuscular neurologist, respirologist, and physiatrist collaborating to stratify the risks before and after transplantation [25]. Going forward, information from a comprehensive neuromuscular examination in MD patients who are candidates for cardiac transplantation along with suitable follow-up durations and assessments after surgery recorded in a multicentre database might help provide a more informed analysis of the effects of the cardiac transplantation on the neuromuscular disorder and prognosis in these patients. Information from such a database would allow development of an evidence-based consensus statement regarding cardiac transplantation in different types of MD.

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