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

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1. Abstract

WereportacaseofslowlyprogressiveBecker'smusculardystrophyina52-year-oldmanwhorequiredcardiactransplantationfor intractablecongestiveheartfailure.Areferralwasmadeconcern- ing 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 thosewithBecker'smusculardystrophy.Formalassessmentsand neuromuscularfollow-uphavenotbeenclearlydocumentedinpatients having cardiac transplantation, and robust clinical evidence or guidance in this area is lacking.

2. Introduction

Musculardystrophiesareaheterogeneousgroupofgeneticmusculardisorderspresentingwithprogressivemuscularweaknesswhich havecharacteristicpathologicalfeaturesinthemusclebiopsyand areoftenassociatedwithotherorganinvolvementsuchascardiac, respiratory,orcentralnervoussystem[1,2].Cardiacinvolvement caninvolveprimarilythemyocardiumorconductivesystemorbe secondary to respiratory muscle involvement by causing cor pulmonale [3, 4]. Improved management of respiratory, cardiac, and othercomplicationsindifferenttypesofmusculardystrophy(MD) has led to increased survival of with many patients surviving into adulthood [2, 3, 5, 6]. With increased life expectancy of MD patients,neuromuscularphysiciansmaybeaskedtoprovideadvice 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

A52-year-old man was first evaluated in the Prosserman Family NeuromuscularClinicatage41forproximallowerlimbweakness manifestasdifficultyinclimbingstairs.Hereportedthathehada normalchildhoodanddevelopmentbutthathewasneverathletic. 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 weaknessprogressedslowlyandbyage37,hehaddifficultygettingup fromachairandrequiredsupporttoclimbstairs.Hehadnoother weakness, bulbar or respiratory symptoms. Physical examination revealedanormalcranialnerveexaminationandupperlimbpow- er. In the lower limbs, he had proximal weakness at 4/5 in hip flexors,quadriceps,andhamstrings,normaldistalstrengthandbilateralcalfhypertrophy.Deeptendonreflexesweredecreasedinthe 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 conductionstudies and chronic myopathicchanges 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 age52, he was treated with cardiac resynchronization therapy plus a defibillator (CRT-D). Shortly thereafter, he developed intractable end-stageheartfailurepresentingwithshortnessofbreath,cough, orthopnea, and paroxysmal nocturnal dyspnea necessitating admissionforcontinuousfurosemideinfusion.Inlightoftherefrac- tory cardiomyopathy, advanced heart failure therapies includinga left ventricular assist device (LVAD) or cardiac transplantation were considered. As part of the eligibility evaluation for cardiac transplantation,hewasreferredtoourclinicforanopiniononhis neuromuscularcourseandprognosis.Examinationshowednormal 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 musclesand4/5powerindistallowerlimbmuscles.Deeptendon reflexeswerereducedglobally.Gaitwasimpossibletoassessashe was bedridden due to severe heart failure.

We recommended that this BMD patient be eligible for cardiac transplantationgiventhathehadremainedambulatorywithslowly progressiveweaknessuntilage52whensevereheartfailurepre- cludedambulation. He hasnotyet had the procedure.

4. LiteratureReview

DuchenneAndBecker'sMuscularDystrophy

Since1988,cardiactransplantationhasbeenreportedbothincase reportsandcaseseriesinpatientswithDuchennemusculardystrophy(DMD)andBMDwithend-stageheartfailureasafinaltreat- ment 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 Table1.Someofthedystrophinopathypatientswhohadsuccess- ful cardiac transplantation were neurologically asymptomatic at the time of transplantation despite the severe dilated cardiomyopathy necessitating cardiac transplantation [10, 11, 14, 21, 22, 27]. Otherstudiesreportedpatientswithdystrophinopathy-relatedcardiomyopathywithmildtomoderatemuscularweaknesswhotolerated the transplantation procedure well; most of these were BMD patientsratherthanDMD[7,8,12,14,15,18,21,23].Intwocase reportspublishedrecently[24,26],theauthorsreportedtwoDMD 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 dystrophywhounderwentcardiactransplantation[9,16,17,19,25,28]. Unfortunately, the degree of muscular and respiratory weakness wasnotdocumentedinthesestudies,butmostwereBMDpatients who have less severe muscular and respiratory weakness than DMD patients or those with other muscular dystrophies.

Table1:Summaryofstudiesreportingcardiactransplantationindifferenttypesofmuscular dystrophies.

Author	Yearandtypeof the study	Number and type of neuromuscular patients who underwentcardiac transplantation	Degreeofmuscularweakness before transplantation	Summaryof outcome	Durationofpost-transplantation follow-up
Cripeet al[18]	2011-casereport	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 ofambulationwithrespiratorymuscle weakness requiring nightly CPAP	Successful transplantation	53 months
Piperataet al[26]	2020 - case report	1 DMD	Severe muscular weakness led to wheelchair-bonded state and mild respiratorymuscleweakness(FVC=2.4 liter; 60% of the predicted value)	Successful transplantation	3 months
Melacini et al[12]	2001- case series	1BMDand1 DMD carrier	ModeratemuscularweaknessinBMD and mild muscular weakness in DMD carrier	Successful transplantation	followed up for4 months and 42 months in BMD andDMDcarrier, respectively
Papaet al[21]	2017 - case series	3BMDandone x-linkeddilated cardiomyopathy	Two of BMD patients had mild muscular weaknesswithnorespiratoryinvolvement at the time of transplantation, the thirdBMDpatientand X-linked dilatedcardiomyopathypatientwere neurologically asymptomatic	Uneventful transplantationand post-operative course	Meanfollowupof 144.4 months

Casazza et al[7]	1988 -case report	1 BMD	Mildmuscularweaknesswith	Successful transplantation	NA
Donofrio et al[8]	1989 - case report	1 BMD	Shoulder and pelvic girdle weakness, difficultyinarisingfromachairorsquat position	Successful transplantation, Good cardiac and functional outcome after transplantation	2 years
Piccoloet al[10]	1994- case report	1 BMD	Normal neurological examination except for slight bilateral calf hypertrophy	Successful transplantation	4 years
Finstereret al[11]	1999- case report	1BMD	Normal neurological examination	Successful transplantation	6 years
Leprince et al[13]	2002- case report	1 BMD	Severe muscular weakness	Successful transplantationwith improved muscular weakness after transplantation	18 months
Pataneet al[15]	2006- case report	1 BMD	Heartfailuresymptomsweremore disabling than neuromuscular symptoms	Successful transplantation	1 year
Katzbergetal[27]	2010 – case report	1 BMD	Normal neurological examination	Successful transplantation	NA
Madeiraet al[22]	2018- case report	1 BMD	Normal neurological examination	Successful transplantation	15 years
Merchut et al[29]	1990- case report	1 EDMD	Mildproximalupperandlowerlimb weakness andminimal 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	cardiactransplantation in seven patients of a single family with LGMD type 1 B linkedtoamutationin LMNAgene	Mildmuscularweaknessinallpatients except one with end-stage dilated cardiomyopathy in all of them	Successful transplantation with no higher rates of early or latepost-operative complicationsthan other transplantation recipient	meanfollow-up of 8 years
Conraadsetal[33]	2002- case report	1 myotonic dystrophy type 1	Bulbar,respiratoryandlimb weakness	Successful transplantationwith prolonged mechanical ventilation andneed for intensive respiratory and peripheralmuscular trainingpre-and post-operatively	5 years
Papaet al [34]	2018- case report	1 myotonic dystrophy type 1	Mildmuscularweaknesswithno respiratory symptoms	Successful transplantation with a prolonged postoperative course due to transient severe respiratoryfailure requiring antibiotictherapy and mechanical ventilation	3 months
Picket al[35]	2017- case report	1 Fukoyama congenitalmuscular dystrophy	Mild muscular weakness	Uneventful transplantationbut post-operative course complicated byconvulsionsand acute renal failure	NA

Reesetal[9]	1993- case series	3 DMD, 1 BMD, 1 EDMD, and 1 unspecified muscular dystrophy out of 582 cardiactransplantation patients	NA	Uneventful transplantation, good toleration of immunosuppressant without difference on postoperative complications orrehabilitation process	meanfollowupof 40 months
Ruiz-CanoMJet al [14]	2003- case series	3BMD-1limb-girdle muscular dystrophy, and 1 desminopathy	2 of BMD patients had mild muscular weakness with no respiratoryinvolvement and the third BMD patient was asymptomatic, the LGMD patienthad mild muscular weakness, and desminopathy patient had mild muscular weaknesswithatrophyofdistalupperand lower limb muscles	All had uneventful transplantation except for desminopathy patient who hadprolonged postoperative course due to severerespiratory failure requiring mechanical ventilation	meanfollowupof 40 months
Connuck et al[16]	2008- case series	6/15BMDbut0/128 DMD had cardiac transplantation	NA	Successful transplantation	NA
Wuetal[17]	2010- case series	15 BMD, 3 DMD, 4 myotonicdystrophy, 3 limb-girdle MD, 1 EDMD, 1 mitochondrial,and2 undetermined	NA	Similar one-year and five-year survival between musculardystrophy andnon-dystrophic patient,The rates of post-transplantinfection, transplantrejection, and allograft vasculopathy also were similar betweentwo groups.	medianfollowup of 5.4 years
Fuchsetal[19]	2012- case series	5EDMDand4 BMD	NA	Successful transplantationand improvement in mobilization status	5 years
Stegeret al[20]	2013- case series	3BMDand1limb-girdle muscular dystrophy	Allpatientshadmuscularweakness before starting cardiac symptoms	Successful transplantationand uncomplicated post-operative course	Meanfollowupof 12.5 years
Kamdaret al[28]	2017- case series	47 neuromuscular cardiomyopathy patientscomparedtoa matchedcohortof235 patients which 46.8% of the neuromuscular group wereBMDasthemost common group	NA	Successful transplantationwith similarsurvivaland outcome compared with the matched non-neuromuscular cohort	5 years
Seguchiet al[23]	2019- case series	6 BMD, 2 dystrophinopathy related cardiomyopathy, and 1 alpha-dystroglycanopathy	All of them were ambulatory except for threeBMDpatientswhowerewheelchair bond	Successful transplantationwith improvementinthe ambulation status aftertransplantation	Meanfollowupof 4.3 years

Wellsetal[25]	2020- case series	81 patients had musculardystrophy, BMD was the most commongroupwith 42patientsfollowed by 11 EDMD, 4 LGMD, 3 DMD, and 2myotonicdystrophy patients	NA	With the similar course of transplantation,rate of complication, and survival comparing with non-dystrophic matched group, Amongthetypesof MD,nostatistically significant difference was observed in the post-transplant survival of patients with BMD versus patients with non-BMD	10 years

Emery-DreifussMD

There are three case reports of cardiac transplantation in Em-ery-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,theclinicalneuromuscularstatuswasnot reportedintwocaseseriesofEDMDpatientswhohadsuccessful 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].

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],butintheothercaseseriesreportingsevenmembersof a family with LGMD type 1B, the muscular weakness was noted asmildexceptinonepatient[32].Muscleweaknessinoneofthe case reports was reported as mild [14] , but not specified in the other [20] .

Myotonic Dystrophy

Cardiactransplantationwithacceptableoutcomesinmyotonicdystrophy have been reported in two case reports of patients having congestive heart failure [33, 34]and two case series [17, 25]of patientswithoutaspecifiedetiologyforheartfailure.Inonecase 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 beforetransplantation[33].Theothercasereportedaprolonged postoperative course due to transient severe respiratory insufficiency necessitating antibiotics and prolonged mechanical ventilationdespitethepresenceofonlymildmuscleweaknesswithout 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].

OtherMuscularDystrophies

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

TheAmericanHeartAssociationhassuggestedthatcardiactransplantationisnotanoptionforpatientswithsevereneuromuscular diseases given the increased risk of complications due to respiratory and pharyngeal muscle weakness. They suggest that cardiac transplantationcanbeconsideredforthosewithmilderrespiratory 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 failuregiventhepaucityofdonors.Theysuggestedacase-by-case approach without any specific characterization of severity of MD or other criteria for cardiac transplantation [37].

6. Discussion

Inthepast,neuromusculardisorderswereconsideredascontraindications for cardiac transplantation [38], but these conditions includepatientswithawidespectrumofdiseasesmanifestingindiversecombinationsofmusclegroupweaknessandinvolvementof otherorganssuchasheartandnervoussystem[1].Despitethediversityinmusculardystrophies,themostcommonlimitingfactors for transplant are severe respiratory and bulbar muscle weakness, which predispose these patients to prolonged ventilation support andhighercomplicationrates[14,25,33].Informationconcerning the severity and distribution of neuromuscular weakness is miss- ing in the largest case series of neuromuscular patients who had successfulcardiactransplantation[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,andsurvival[9,17,25,28].Mostofthesereportsarebased onpatientswithBMDwhohavemildermuscleweaknessorthose with dystrophinopathy who were asymptomatic or had mild to moderate muscle weakness before surgery [7, 8, 10-12, 14, 15,18,21-23].AseverephenotypeinDMDmaynotprecludecardiac transplantationalthoughtheevidenceislimitedtotwocasereports only [24, 26].

An exception to the hypothesis that patients with milder forms of dystrophycantoleratecardiactransplantationmaybeinmyotonic dystrophy type 1 patients, who experienced difficult post-operative coursesregardlessofthedegreeofmuscleorrespiratoryweakness 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 attainthe 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 ofknowledge.Theselectionprocessforcardiactransplantationin 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 neuromuscularexaminationinMDpatientswhoarecandidatesforcar- diac transplantation along with suitable follow-up durations and assessmentsaftersurgeryrecordedinamulticentredatabasemight help provide a more informed analysis of the effects of the cardiac transplantation on the neuromuscular disorder and prognosisin these patients. Information from such a database would allow developmentofanevidence-basedconsensusstatementregarding cardiac transplantation in different types of MD.

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