Heart transplantation in X-linked dilated cardiomyopathy

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Key words:
Dilated cardiomyopathy; Heart transplantation.

Background. **X-linked dilated cardiomyopathy (DCM) is a clinical phenotype of dystrophinopathy characterized by preferential myocardial involvement without overt signs of skeletal muscle disease. X-linked DCM is a familiar myocardial disease characterized by ventricular dilation resulting in progressive heart failure and/or sudden death, and it may be differentiated from other DCMs. The aim of this retrospective study was to assess that patients with end-stage X-linked DCM can safely undergo heart transplantation.**

Methods. **Between August 1989 and January 2000, 7 patients presenting with X-linked DCM underwent heart transplantation for end-stage disease at our Institution. The patients' age ranged from 16 to 31 years (mean 24.4 years) and all were in NYHA functional class IV.**

Results. **The mean follow-up was 44 months (range 22-66 months). Only one sudden death occurred at 66 months of follow-up; all the other patients are doing well and are in NYHA functional class I.**

Conclusions. **Our data suggest that heart transplantation can be considered as the treatment of choice for refractory cardiac failure in X-linked DCM.**

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Introduction

X-linked dilated cardiomyopathy (DCM) is a clinical phenotype of a genetically inherited disease resulting from defects of the dystrophin gene[1,2]. Other mutations of the dystrophin gene are associated with typical muscular dystrophy: Duchenne's muscular dystrophy[3] and Becker's muscular dystrophy[4]. X-linked DCM is characterized by preferential myocardial involvement with only minimal signs and symptoms of skeletal muscle involvement: serum levels of the skeletal muscle isoform of creatine phosphokinase (CPK) can be increased and muscle biopsy can reveal dystrophic changes and decreased dystrophin immunostaining. In X-linked DCM the cardiac symptoms are the dominant problem, ranging from conduction defects to refractory cardiac insufficiency determining end-stage cardiac disease that can be considered as an indication for heart transplantation (HT).

X-linked DCM may be clinically indistinguishable from idiopathic DCM that constitutes the most common diagnosis indicating HT. The differential diagnosis is particularly difficult if peripheral muscle involvement is not evident and/or if serum CPK levels are normal or only slightly increased. Furthermore, at endomyocardial biopsy, dystrophin defects can be missed unless specifically investigated. DNA analysis on peripheral blood leukocytes allows the assessment of dystrophin defects and the identification of female carriers.

The objective of this study was to assess whether patients with end-stage X-linked DCM can safely undergo HT. Our results showed that HT is life-saving in these patients, since disability is mainly due to the cardiac disease and to complex rhythm disorders.

Methods

Between August 1989 and January 2000, 7 patients diagnosed with X-linked DCM underwent HT for end-stage disease at our Institution. An additional patient was enrolled in the transplant list but died 4 months after inclusion. The patients' age ranged from 16 to 31 years (mean 24.4 years). Muscular discomfort was not the limiting factor of their daily activities if compared to effort or rest dyspnea: all were in NYHA functional class IV. Right heart catheterization was performed before HT in all patients: in 5 cases (71.4%) the pulmonary vascular resistance values were high; after pharmacological testing with

sodium nitroprusside infusion, 2 patients still showed values > 2.5 Wood Units. The patients' characteristics are shown in tables I and II.

The standard protocol included endomyocardial biopsy which was performed in all patients at the time of right heart catheterization. Samples were processed for light microscopy and ultrastructural studies and routine immunohistochemical studies were performed in order to diagnose or exclude myocarditis: actually, this is our study protocol for all patients diagnosed as having DCM. Four monoclonal antibodies that recognize the N-terminal, rod, mid-rod (exons 49-51) and C-terminal domain epitopes of the dystrophin molecule (Novocastra Laboratories, Newcastle Upon Tyne, UK) were used for immunostaining of the frozen myocardial sections.

The DNA was isolated from peripheral blood leukocytes by standard methods. Analysis of the dystrophin gene was performed with different multiplex and single polymerase chain reaction assays and automated DNA sequencing. We monitored the CPK values before HT and found a mean value of 1227 mU/ml (range 699-1970 mU/ml, Table III).

Results

Biatrial HT was performed in 5 patients whereas in 2 the bicaval technique was employed. All patients survived the procedure; the mean weaning time from ventilatory support was 15 hours (range 4-56 hours); the mean hospital stay was 13 days (range 8-16 days). It is important to notice that the CPK values decreased to below 200 within 5 days (range 2-9 days). This decrease did not persist during the following months and in all cases but one serum CPK increased to levels similar to those observed prior to HT. We did not find late clinical evidence of progression of the skeletal muscle disease. All patients increased in weight postoperatively for an average weight increase of 27.5% with respect to preoperative values. The mean follow-up was 44 months (range 22-66 months). One sudden death occurred at 66 months of follow-up; all the other patients are doing well and are in NYHA functional class I (Table I).

Table II. Pre-transplant pulmonary vascular resistances.

Patient	Wood Units	Wood Units with sodium nitroprusside
1	1.2	–
2	7.2	1.9
3	3.3	2.9
4	5.2	3.3
5	3.9	1.9
6	3.9	1.5
7	1.6	0.8

Table III. Creatine phosphokinase (CPK) values immediately before and after heart transplantation (HT).

Patient	CPK pre-HT (mU/ml)	Days from HT to CPK < 200 mU/ml
1	–	–
2	1500	6
3	699	2
4	1293	5
5	1320	5
6	1970	9
7	921	4

Discussion

According to previous reports the incidence of dystrophin-related genetic abnormalities among patients with DCM is 6.5%; this is quite remarkable[5]. For this reason, it is our opinion that all male patients evaluated for DCM should undergo screening for a correct diagnosis. Once the correct diagnosis has been made, those who benefit most are the patient's relatives: brothers for potential preclinical diagnosis, sisters and maternal aunts as potential carriers of the genetic disease.

Since 1994, after discovering a dystrophin defect in patient no. 1, we have undertaken a combined immunohistochemical study of endomyocardial biopsies and molecular DNA screening for the most common dystrophin gene defects associated with DCM in men[5].

Table I. Patients' characteristics.

Patient	Date HT	Age at HT (years)	NYHA class at HT	Type of HT	Follow-up (months)	NYHA class at follow-up
1	08/31/89	31	IV	Biatrial	66	Deceased
2	06/02/97	16	IV	Bicaval	53	I
3	01/22/98	28	IV	Biatrial	46	I
4	04/12/98	18	IV	Biatrial	43	I
5	04/21/98	22	IV	Biatrial	43	I
6	12/18/98	26	IV	Biatrial	35	I
7	01/17/00	30	IV	Bicaval	22	I

HT = heart transplantation.

Routine and laboratory evaluation cannot identify X-linked cardiomyopathies and distinguish it from idiopathic cardiomyopathy: in fact, serum CPK levels can be normal or lower than those found in Becker's muscular disease. In a series of 201 patients presenting with DCM, 14 had raised levels of serum CPK with normal serum CPK-MB: 10 of them (71.4%) belonged to the group affected by dystrophin defects[5]. Therefore, in patients affected by DCM serum CPK elevations can be highly suspicious, but are not sufficient for X-linked DCM screening.

Cardiac manifestations of dystrophin mutations may be due to functional differences between the cardiac and skeletal muscle dystrophin proteins: Meng et al.[6] showed that dystrophin is associated with Z-discs in the myocardium, but not in the skeletal muscle. Franz et al.[7] showed that dystrophin interacts with actin and the sarcolemmal dystrophin-associated glycoprotein complex: conformational changes in the rod region can modify this interaction and determine membrane instability.

In view of the outcomes observed in the present series, we would like to stress that when X-linked DCM determines an end-stage cardiac disease refractory to maximal medical therapy, HT should be immediately considered. The procedure is safe and no operative death occurred in the present series. All the patients returned to a relatively normal life. Only one sudden death occurred at 66 months of follow-up. All the other 6 patients are alive and in NYHA functional class I. All the patients showed a fall in CPK values in the immediate postoperative period, but in the following routine visits these values returned to preoperative levels in all but one.

In conclusion, HT has been successfully performed in patients with Becker's disease[4,8,9] or with Duchenne's muscular dystrophy[10] who present with disabling skeletal muscle disease with cardiac involvement: the clinical conditions and the skeletal muscle symptoms of these patients are worse than those observed in patients with X-lined DCM. Our data suggest that HT must be considered as the treatment of choice for the management of severe heart failure in patients with dystrophin-related genetic abnormalities. HT is a life-saving procedure in these patients in whom myocardial end-stage disease and serious rhythm disturbances are severely disabling and life-threatening. Great attention should be given to the screening of relatives who may be carriers of the genetic disease.

References

1. Muntoni F, Di Lenarda A, Porcu M, et al. Dystrophin gene abnormalities in two patients with idiopathic dilated cardiomyopathy. Heart 1997; 78: 608-12.
2. Muntoni F, Wilson L, Marrosu G, et al. A mutation in the dystrophin gene selectively affecting dystrophin expression in the heart. J Clin Invest 1995; 96: 693-9.
3. Rees W, Schuler S, Hummel M, Hetzer R. Heart transplantation in patients with muscular dystrophy associated with end-stage cardiomyopathy. J Heart Lung Transplant 1993; 12: 804-7.
4. Orlov YS, Brodsky MA, Allen BJ, Ott RA, Orlov MV, Jay CA. Cardiac manifestations and their management in Becker's muscular dystrophy. Am Heart J 1994; 128: 193-6.
5. Arbustini E, Diegoli M, Morbini P, et al. Prevalence and characteristics of dystrophin defects in adult male patients with dilated cardiomyopathy. J Am Coll Cardiol 2000; 35: 1760-8.
6. Meng H, Leddy JJ, Frank J, Holland P, Tuana BS. The association of cardiac dystrophin with myofibrils/Z-disc regions in cardiac muscle suggests a novel role in the contractile apparatus. J Biol Chem 1996; 271: 12364-71.
7. Franz WM, Muller M, Muller OJ, et al. Association of nonsense mutation of dystrophin gene with disruption of sarcoglycan complex in X-linked dilated cardiomyopathy. Lancet 2000; 355: 1781-5.
8. Casazza F, Brambilla G, Salvato A, Morandi L, Gronda E, Bonacina E. Cardiac transplantation in Becker muscular dystrophy. J Neurol 1988; 235: 496-8.
9. Donofrio PD, Challa VR, Hackshaw BT, Mills SA, Cordell AR. Cardiac transplantation in a patient with muscular dystrophy and cardiomyopathy. Arch Neurol 1989; 46: 705-7.
10. Melacini P, Fanin M, Angelini A, et al. Cardiac transplantation in a Duchenne muscular dystrophy carrier. Neuromuscul Disord 1998; 8: 585-90.