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Intermediate and long-term results after pediatric heart transplantation: incidence and role of pretransplant diagnosis

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Abstract From November 1985 to 31 July 1997, 65 pediatric patients underwent heart transplantation at Bambino Gesù Hospital in Rome. Two of them underwent retransplantation, both 6 years after the first transplant. The 67 transplant patients had a mean age of 59 months; 11 were under 1 year of age. Their indications for transplantation were cardiomyopathies (38), lymphocytic myocarditis (8), and congenital heart diseases (19). Two patients of the first group successfully received a combined heart and kidney transplant. The 1-, 5-, and 11-year actuarial survival rates for the 65 patients who underwent heart transplantation were 68%, 62%, and 42%, respectively. In the 1st postoperative year in patients who had had cardiomyopathy, a total of 50 episodes of acute rejection (AR), with one death, occurred (mean 1.7 AR/patient per year ± 1.5) and, in patients who had had congenital heart diseases, 19 ARs (one death) occurred with a mean of 1.58 AR/patient per year ± 1.4. The incidence of AR was significantly higher in patients who had had myocarditis with a total of 26 episodes (mean 3.7 AR/patient per year ± 2) and one death. Rehabilitation of heart transplanted children and infants was complete (NYHA class 1) in 52% of patients of this series. We conclude that heart transplantation may give a good intermediate and long-term survival in selected patients; the extension of indications to desperately ill patients, or patients with systemic diseases or complex congenital heart diseases may bring less encouraging results, but should not be definitely excluded. Scarcity of donors remains the main limit, being still the first cause of death for patients on our waiting list. Our limited experience seems to suggest that, as described in adults, the cellular amplification of the immune response might affect the post-heart transplant follow up of pediatric patients with myocarditis resulting in a poor outcome for this population.

Key words Pediatric heart transplantation · Long-term follow up · Pediatric myocarditis

Introduction

Heart transplantation is a therapeutic option for many infants suffering from severe forms of cardiomyopathies and congenital heart diseases [2, 4, 23, 24, 25]. According to the 1996 report of ISHLT Registry, 1- and 3-year survival rates are 73% and 66%, respectively [12]. In the literature, there are still few data about long-term follow-up. Our data, regarding short-term follow up, compare favorably with international ones. This paper reports our 11-year experience trying to assess a possible incidence of pretransplant diagnosis on long-term results.

Patients and methods

From November 1985 to 31 July 1997, 134 patients (66 males, 68 females), with ages ranging from 1 day to 18 years (mean age 4.3 years, median 3 years) have been listed for heart transplantation. The indications for transplantation were cardiomyopathies in 67 patients (50%), biopsy-proven myocarditis in 11 (8.2%), and congenital heart diseases in 56 (41.8%). It is worth noting that, in agreement with International Registry data, the indication to transplant for congenital heart diseases increased progressively to become, in the last 3 years, the main indication. Nine patients were removed from the list for various reasons, 6 are at present on the waiting list, 54 (45%) died after a mean wait of 3.1 months, and 65 underwent transplant after a mean wait of 4 months (Table 1). Two patients underwent retransplantation, both 6 years after the first transplant.

The 67 transplants (including the 2 retransplanted patients) had a mean age of 59 months; 11 were under 1 year of age. Their indications for transplantation were cardiomyopathies (38: group 1), lymphocytic myocarditis (8: group 2), and congenital heart diseases (19: group 3) (Table 2). Two patients of the first group successfully received a combined heart and kidney transplant: in both cases, the renal disease seemed to be unrelated to cardiomyopathy [15].

Grafts came from northern Italy (26), from central and southern Italy (24, of which 6 came from Bambino Gesù Hospital, where 2 were taken with a "domino" procedure), and from Europe (17, namely, 9 from Spain, 4 from France, and 1 each from Austria, Germany, Holland, and Great Britain). Total donor organ ischemic time ranged from 65 to 390 min with a mean of 210 min. Grafts were harvested by the standard technique for multiorgan harvesting. Particular care was taken for those recipients with a previously palliated congenital heart disease, as several authors described [3, 10, 11, 16, 17, 20]. Organ preservation was accomplished by infusion of cardioplegic solution (St. Thomas II) and storage was at 4°C in Euro-Collins solution. Two patients required prolonged mechanical circulatory support by ECMO (7 h and 4 days) and both patients survived this procedure.

Immunosuppression was achieved by three or four drugs: cyclosporine in such doses as to obtain blood levels of 250–300 ng/ml in the 1st year posttransplant, 1–3 mg/kg azathioprine, i.v. steroids in the first 2 or 3 days and then p.o. (stopped after 15–30 days), and antilymphocyte serum for 4–5 days, only in patients over 2 years of age. Maintenance immunosuppressive therapy was based on one drug (cyclosporine), two drugs (cyclosporine + azathioprine or methotrexate), or three drugs (cyclosporine + azathioprine or methotrexate + steroids), according to the patient's immune response and to the time since transplant.

Early in the series, postoperative surveillance was mainly based on endomyocardial biopsy. More recently it has mostly been accomplished by non-invasive methods, biopsy being carried out only when non-invasive clinical and instrumental findings gave dubious results [5, 13]. Non-invasive monitoring is based on clinical signs (malaise, irritability, hyperpyrexia, inappetence, alterations in the cardiac and/or respiratory rate, cardiac decompensation), instrumental signs (ECG: appearance of rhythm disorders, chest X-rays: cardiomegaly and/or pulmonary congestion, echocardiogram: pericardial effusion, intraventricular septum and/or left ventricular wall thickening, systolic and/or diastolic alterations), and laboratory signs (changes in lymphocytic subsets, T4/T8 ratio, and CPK values, lymphocytic blastic transformations). All patients annually underwent a cardiac catheterization with endomyocardial biopsy, selective coronary angiography, and study of the coronary reserve.

All patients received antiherpetic prophylaxis. Acyclovir was administered for about 3 months and non-specific immunoglobulins were given intravenously during the 1st postoperative week and whilst infusion routes were present. Rejection episodes were treated by oral steroids when clinical signs were not patent and by i.v. steroids in the presence of clear symptoms. Antilymphocyte serum was added when steroid treatment did not prove effective. In those patients who required chronic steroid therapy, the introduction of methotrexate enabled steroid discontinuation with the disappearance of steroid side effects (hirsutism, obesity, osteoporosis, alteration of lipid metabolism) [7, 22]. As well as survival rates, for each of the three groups, we considered the occurrence of acute rejection (AR) episodes during the 1st year after transplantation and in the following years, chronic rejection, and the need for immunotherapy. Data were analyzed using a *t*-test.

Table 1 One hundred and thirty-four pediatric heart transplant candidates: the risk of the waiting list

	Number	Mean wait (months)
Transplanted patients (2 heart and kidney; 2 retransplants)	65	4
Died waiting	54 (45%)	3.1
Out of list for various reasons	9	–
At present in waiting list	6	–
Total	134	–

Table 2 Indications for 67 pediatric heart transplants

Cardiomyopathies	Number	Congenital heart defects	Number
Dilative	26	Single ventricle variants	5
Restrictive	7	Transposition complex	3
Toxic (adriamycin)	3	HLHS	3
Metabolic	2	Unbalanced CAVC	1
Chronic rejection	2	Fontan failure	2
		Tumor	3
Total	40	Total	19
Myocarditis	8		

Results

Survival

The 1-, 5-, and 11-year actuarial survival rates for the 65 patients who underwent heart transplantation are 68%, 62%, and 42%, respectively (Fig. 1). The 5- and 11-year actuarial survival rates for the 44 patients who survived longer than 1 year are 93% and 63%, respectively, with a mean follow up of 63.5 months (Fig. 2). The follow up of the 65 patients ranges from 0 to 138 months.

Group 1

Thirty-eight patients were transplanted for cardiomyopathies of various origin (dilative, restrictive, hypertrophic, toxic, metabolic, chronic rejection) and of these

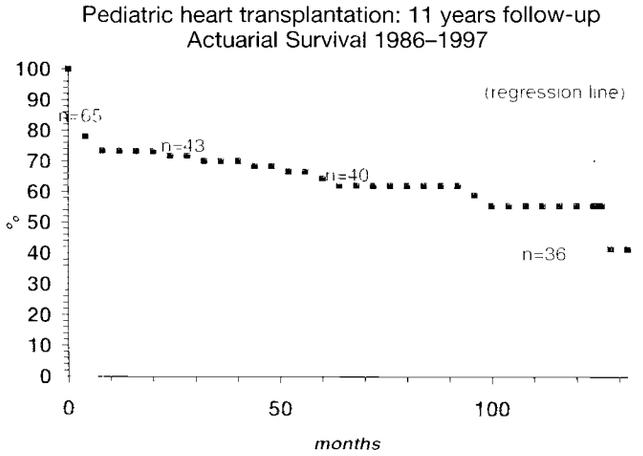

Fig. 1 Actuarial survival curve showing 1-, 5-, and 11-year survival at "Bambino Gesù" hospital in Rome (1986–1997)

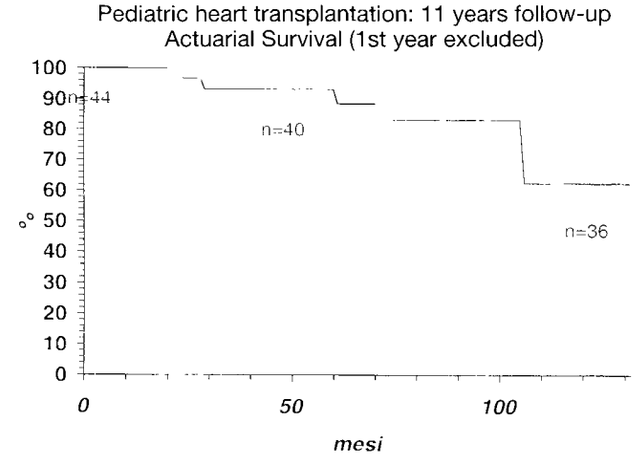

Fig. 2 Actuarial survival curve showing 5- and 11-year survival of the 44 patients who survived more than 1 year

8 died during the 1st postoperative month. The 30 who survived the operation had a mean follow up of 54 months. Five of them died in the 1st postoperative year and 5 later. At present, 20 are alive and well: 7 are on monotherapy (cyclosporine), 8 on double therapy (cyclosporine + azathioprine), and 5 on triple therapy (cyclosporine + azathioprine + steroids). One patient is receiving methotrexate. The causes of death are listed in Tables 3 and 4.

Group 2

Eight patients were transplanted for lymphocytic myocarditis and 1 died in the 1st postoperative month (Table 3). Among the 7 survivors (mean follow up

Table 3 First postoperative year: causes of death

Cause of death	Cardiomyopathies	Myocarditis	Congenital heart defects
First month			
Pulmonary hypertension/ graft failure	4	0	3
Preoperative terminal conditions	1	0	2
Bleeding	0	0	2
Neurological damage	1	0	0
Immune reaction	1	0	0
Acute rejection	0	1	0
Viral/bacterial infections	1	0	0
Second month – 1st year			
Acute rejection	2	0	0
Viral/bacterial infections	1	0	0
Mycotic infections	2	0	0

Table 4 Causes of late deaths (after 1st postoperative year)

Cause of death	Cardiomyopathies	Myocarditis	Congenital heart defects
Chronic rejection	2	1	0
Therapy discontinuation	1	0	2
PTLD	1	0	0
Respiratory failure[a]	1	0	0

[a] Patient with metabolic disease

57 months), 1 died of chronic rejection 6 years after transplantation. The other 6 are alive and well and all of them are on double therapy receiving methotrexate for recurrent episodes of AR.

Group 3

Nineteen patients were transplanted for congenital heart diseases, with 7 perioperative deaths. Twelve patients survived with a mean follow up of 51 months. Two of them died later from none compliance to therapy. At present, 10 are alive and well, 3 patients are on monotherapy, 2 on double, and 5 on triple, and 3 patients receive methotrexate. The causes of death are given in Tables 3 and 4.

Rejection

In the 1st postoperative year in group 1, a total of 50 episodes of AR, with one death, occurred with a mean of 1.7 AR/patient per year ± 1.5. In group 3, 19 ARs (one death) occurred with a mean of 1.58 AR/patient

Table 5 Acute rejection (AR)

Group	Number: AR/patient in first year	Number: late AR/patient per year
1	50: 1.7 ± 1.5*	13: 0.12
2	26: 3.7 ± 2	10: 0.37
3	19: 1.58 ± 1.4**	7: 0.18

* $P = 0.005$
** $P = 0.01$

per year ± 1.4. The incidence of AR was significantly higher in group 2, with a total of 26 episodes (mean 3.7 AR/patient per year ± 2) and one death (Table 5). In the following years, 13 ARs occurred in group 1 (mean 0.12 AR/patient per year), 7 in group 3 (mean 0.18 AR/patient per year), and 10 in group 2 (0.37 AR/patient per year). Chronic rejection was diagnosed in 5 patients: 2 in group 1 (both died), 2 in group 2 (1 death and 1 retransplant), and 1 in group 3 (retransplant).

Complications

Apart from rejection and infections, which caused six and four deaths, respectively, neurological problems represented the main complications. In 6 patients (3 deep coma, 2 seizures, and 1 memory and behavioral impairment), these were related to cyclosporine treatment in 1, to acute graft decompensation in 1, and, probably, to donor-recipient size mismatch in 4 [19, 21]. One of these patients died, 1 is alive with severe cerebral damage, and 4 are alive without chronic neurological sequelae.

In the immediate postoperative period, 12 patients required antihypertensive therapy, which was discontinued during the 1st year except in 3 patients on chronic treatment with Ca antagonists and ACE inhibitors. Two patients have persistently elevated creatinine levels (> 1.4 mg/dl) with a reduction of glomerular filtration: one is the 11-year-old boy with the longest follow up (138 months) and the other has a history of graft rejection. One patient, after EBV seroconversion, developed a serious lymphoproliferative syndrome resistant to high-dose α-interferon treatment and to laser therapy. Despite tracheotomy, this patient died 8 years after transplantation because of respiratory tract obstruction. Two patients underwent cholecystectomy, 4 patients showed a moderate grade of bone demineralization, and one had avascular necrosis of the right hip.

Rehabilitation

At present, 36 patients, including the two retransplanted ones, are alive. One patient, with familial deafness, who underwent retransplantation 6 years after the first transplant, has severe neurological damage. One patient, who received a transplant for failing Fontan with protein-losing enteropathy, has not yet shown complete regression of the intestinal symptoms and has well below normal growth curves. The remaining 34 patients have normal growth, development, and neurological outcome. All of them have returned to normal activities for their ages, including school and sports. Sixteen patients regularly practice non-competitive sport activities.

Discussion

Reported data show a remarkable incidence of early mortality on the survival curve. In cardiomyopathy patients, mortality seems to depend on a loose candidate selection (high pulmonary resistance, preterminal conditions) [8], especially in the early years of our experience. In congenital heart disease patients, mortality was markedly influenced by the problems deriving from previous palliations and by concomitant reconstructive interventions. The learning curve positively affected cardiomyopathy patient's survival: in the last 16 patients transplanted for cardiomyopathy, no deaths occurred during the 1st postoperative month.

The introduction of right ventricular endomyocardial biopsy has facilitated the diagnosis of myocarditis in patients presenting a left ventricular dilatation [9]. On the basis of histological data, most of these cases can be identified as "lymphocytic myocarditis" [14]. Enteroviruses and echoviruses have been reported as the most common causative organism in viral myocarditis. Medical treatment is supportive and the use of immunosuppressive therapy remains controversial. Outcome data suggest a good prognosis for the majority of patients, although 20–30 % of survivors will develop an irreversible dilative cardiomyopathy requiring heart transplantation. The supposed autoimmune cause of myocarditis may predispose the recipient to aggressive rejection. Published data suggest that, in adult patients, preoperative myocarditis is associated with a poor outcome after heart transplantation [18]. In our experience with the pediatric population, myocarditis patients present poor results if compared to the others. The main differences are in the incidence of AR and in the need for maintenance drug therapy. The number of ARs is significantly higher in myocarditis patients than in the other groups of patients. Furthermore, all myocarditis patients required treatment with methotrexate. We speculate that both a local and a systemic cellular amplification of the immune response affect the post-heart transplant follow up of these patients.

Of the 44 patients that survived for more than a year, 8 died, 3 from family non-compliance (interruption of immunosuppressive therapy), 1 after 8 years from the natural evolution of her metabolic disease [6], 3 from

chronic rejection (all of them were listed for retransplantation) and 1 from posttransplant lymphoproliferative disease. Non-compliance in families and teenagers is a special problem for all transplantation centers: an increased effort to educate and support the patients may avoid these preventable and unfortunate deaths in the future.

The tendency to use reduced immunosuppressive therapy in pediatric patients is generally accepted to reduce the complications arising from the chronic use of steroids: the majority of our patients receives only monotherapy or, at most, double therapy. Because of the wide age range of pediatric patients, responses to immunosuppressive therapy are highly varied, especially with respect to the induction of immunosuppression with cytolytic agents. The incidence of graft rejection in these patients may be due to the variation in age and to milder immunosuppressive regimens than those used in adults. This may result in a greater need for retransplantation in these children. Lymphoproliferative syndrome, posttransplant lymphoproliferative disease (PTLD), is related to EBV infection in the majority of cases. Primary infection by EBV is common in children and young adults: this may partially explain the increased incidence of PTLD observed by some authors in transplanted pediatric patients [1]. In our experience, the milder immunosuppressive therapy may account for the low incidence of this complication. These findings highlight the fact that a decreased occurrence of late complications does not always parallel a decreased incidence of organ rejection. Although the actuarial survival is still far from the ideal and early and late complications still affect our results, rehabilitation of heart transplanted children and infants is complete (NYHA class 1) in 52% of patients in our series.

Eleven years ago, pediatric heart transplantation was still in its pioneer phase. Today, many centers all over the world successfully accomplish heart transplantation in children. On the basis of our experience and of that of other centers collected in International Registry data, we conclude that heart transplantation may give a good intermediate and long-term survival in selected patients; the extension of indications to desperately ill patients, or patients with systemic diseases or complex congenital heart diseases may bring less encouraging results, but should not be definitely excluded. The scarcity of donors remains the main limit, being still the first cause of death for patients on our waiting list. Our limited experience seems to suggest that, as described in adults, the cellular amplification of the immune response might affect the post-heart transplant follow up of pediatric patients with myocarditis resulting in a poor outcome for this population.

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