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Donor Gender Does Not Affect Liver Transplantation Outcome in Children

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Abstract

The liver is recognized as a sex hormone-responsive organ. Gender-specific differences in liver function are known to exist. Recently, a higher failure rate for organs transplanted in adults from female donors to male recipients has been reported. This increased failure rate of livers obtained from adult females and transplanted into adult males is thought to occur, at least in part, as a result of intrinsic gender-specific differences in hepatocyte cell surface expression and to alterations in the hormonal milieu of the donor liver in the recipient. To determine whether the same graft-recipient gender-determined failure rates pertain in the pediatric liver transplant population, the outcome of 335 primary liver transplants performed in children at the University of Pittsburgh Medical Center was examined. No difference in transplant outcome was demonstrated in children based on the gender pairings between the donor and recipient whether or not variables such as the age, etiology of the liver disease, and the blood group of the recipient were included in the data analysis. Thus, in contrast, to the situation in adults, the gender of the donor does not influence the outcome of liver transplantation in children and should not be used as a criterion for donor selection. This difference between adults and children may be due, at least in part, to gender differences in hepatocyte phenotypic expression induced as a consequence of puberty.

Keywords

transplantation; sex differences; pediatric transplants

Orthotopic liver transplantation (OL/Tx) is a well-established and effective method of surgically treating patients with advanced liver disease. With the increasing success and number of liver transplant procedures and centers throughout the world, the emphasis at these centers has been directed towards identifying factors that determine outcome. For several years now the liver has been recognized as a sex hormone-responsive organ (1–4). The observation that the levels of sex hormone receptors within the liver differ between the sexes after puberty has raised questions relative to donor liver function, phenotypic expression, and overall outcome (survival and/or graft failure) when an organ obtained from an individual of one gender is transplanted into an individual of a different gender (5).

The plasma level of sex hormones is low and the number of sex hormone receptors within the liver is small during the prepubertal period as compared to that seen in adults (6). Moreover the vast majority of the sexual dimorphic differences in liver cell phenotypic expression, function, and behavior are not manifest prior to puberty. Therefore the present study was

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undertaken to determine if the donor–recipient gender match has any influence upon the outcome of clinical CLTs performed in children, most of which (>99%) occur in children less than 12 years of age.

MATERIALS AND METHODS

Patients

All children who underwent OLTx at the University Health Center, Pittsburgh, Pennsylvania, between January 1981 and December 1988 were included in this study. For the purpose of this study, a child was defined as a recipient less than 12 years of age. Details of the evaluation and selection process and the technique of OLTx utilized at this center have been reported previously (7–9). The pre-, intra-, and postoperative care of all recipients during this period has been essentially identical, with minor variations occurring solely on the basis of unforeseen complications that might arise in individual cases. The immunosuppressive regimen used consisted of a combination of cyclosporine and steroids (10), to which OKT3 (Orthoclone, Ortho Pharmaceutical Corporation, Raritan, New Jersey) or ALG recently has been added in cases with steroid-resistant acute cellular rejection (11).

Variables Assessed

The following variables were recorded for all recipients: age, gender, primary liver disease necessitating orthotopic liver transplantation, graft and patient survival, and ABO blood group. The age and gender of the donor was obtained also. For the purpose of this study, a transplant failure was regarded as either graft failure or patient death occurring within 60 days of the original transplant procedure. To avoid confounding variables relating to prior surgery and immunosuppressive therapy, only the results of first organ transplants were studied.

Statistical Analysis

The odds ratio with its 95% confidence interval (CI) was used to approximate relative risk and the significance of association and differences in proportions were tested using chi square (14, 15). A *P* value less than 0.05 was considered to be significant.

RESULTS

A total of 457 primary liver grafts were performed at the Children's Hospital, Pittsburgh, Pennsylvania, between January 1, 1981, and December 31, 1988. For 122 grafts, the gender of the donor was unknown. Of the 213 male donors, 105 were transplanted into male recipients and 108 into female recipients. Of the 122 female donors, 57 were transplanted into male recipients and 65 into female recipients (Table 1).

The results of transplanting a liver from a male or female pediatric donor into either a recipient of the same or opposite gender is shown in Table 1. No statistically significant differences between these groups was evident either for graft or patient survival.

Because the age of the pediatric recipient has been shown to be an important factor that determines transplant outcome, the results with transplantation of a liver within and between the sexes for pediatric recipients ≤2 years old and >2 years old were analyzed separately and are shown in Table 2. Again no differences were seen between the two groups based on gender pairing of the donor and recipient. The same result occurred when the comparisons were made using 5 years of age as the arbitrary age-dependent variable.

The commonest indication for OLTx in the pediatric population is biliary atresia. One hundred seventeen of the 457 recipients in this series (27.8%) were transplanted for this indication, and

the outcome for each gender pair transplanted for this indication is shown in Table 3. An almost identical failure rate as recorded for the entire pediatric transplant population was seen.

When the ABO blood group compatibility between the donor and recipient was assessed and the pediatric cases were stratified according to this variable, again no gender effect was seen for graft survival placed between compatible donors and recipients (Table 4). In the case of incompatible donor–recipient pairings, an arithmatic higher failure rate for the female to male gender pairings was noted, although the numbers within each group were too small for adequate statistical analysis to be performed. The largest number of pediatric transplants was performed in children of either blood groups O or A who received ABO-matched organs. The failure rate for organs transplanted between donor and recipient gender groups for these two blood groups is shown in Table 5. Again no statistically significant difference between the groups was evident based upon gender matching. An analysis of the results obtained with transplantation across all blood groups and gender pairings was not possible because the numbers within each cell were too small for adequate statistical analysis.

DISCUSSION

The precise function of the androgenic and estrogenic receptors within liver cells is not known. Certainly, one of the responses of the liver to exogenously administered estrogen is to enhance its synthesis of various transport proteins including sex-steroid-binding globulin (2) and thyroxine-binding globulin (12). In addition, the presence of specific estrogen-binding proteins within the liver, which presumably protect male hepatocytes from the unwanted effects of estrogen, have been identified and characterized in the liver (4). The amount of these proteins in the hepatic cytosol after puberty differ markedly between males and females (6). In addition, the levels of these proteins within the hepatocyte are very low prior to puberty as compared to that seen after puberty (6). In a previous study, it was suggested that the higher failure rate observed when adult female livers were transplanted into adult male recipients might be related, at least in part, to hormonal differences between the livers of males and females (5). Since the expression of such differences between male and female livers only become apparent after puberty, the present study was undertaken to determine if these same differences in graft survival segregated as relative to the donor–recipient gender matching are seen also in a pediatric population.

In animal studies, transplantation of organs from adult donors of one sex (male or female) to a recipient of the opposite sex results in the finding of cytosolic estrogen and androgen receptor activity similar to those found in female liver (4). These changes in the sex hormone-receptor expression of the liver have been postulated to account for the unfavorable outcome associated with transplantation of organs harvested from females that are subsequently transplanted into adult males (5). In contrast to what was seen in an adult liver transplant program, in the present study, no difference in outcome was found when the organ of one gender was transplanted into an individual of a different gender unless an ABO blood incompatibility also existed. This suggests that either no gender effects exist in pediatric liver transplantation or that those that exist are small and clinically insignificant.

The present study analyzed the outcome of the transplant only in terms of graft failure or recipient death. Since the effects of sex hormones and their influence on hepatic function is maximal only after puberty, it was hypothesized that no difference in the outcome of OLTx in pediatric recipient would be seen if the liver of a donor of one sex were to be transplanted into an individual of the opposite sex prior to puberty. The findings of this study are consistent with such a hypothesis. The present study clearly demonstrates that other factors, such as blood group compatibility between the donor and recipient, are more important in determining the clinical outcome.

Based upon these findings, obtained in a pediatric liver transplant population, it is recommended that the sex of the donor not be used as a criterion in selecting an appropriate pediatric recipient.

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Table 1

Donor–Recipient Gender Pairs and Transplant Outcome in Children

		Failure	
Donor–recipient	**Number**	***N***	**(%)**
M–M	105	18	17
M–F	108	30	28
F–M	57	21	37
F–F	65	18	28
Total	335	87	26

Table 2

Donor–Recipient Gender Matching in Pediatric OLTx and Transplant Outcome in Patients Segregated on Basis of Age

Donor–recipient	≤2 years			>2 years		
	Number	Failure	Percentage	Number	Failure	Percentage
M–M	34	8	24	31	10	32
M–F	28	13	46	29	8	28
F–M	19	8	42	89	22	25
F–F	24	8	33	81	10	12
Total	105	37	35	230	50	22

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Table 3

Donor–Recipient Gender Pairing and Effect on Outcome of OLTx Performed for Biliary Atresia

		Failure	
Donor–recipient	**Number**	***N***	**%**
M–M	39	11	28
M–F	29	10	34
F–M	35	9	26
F–F	35	9	26
Total	138	39	28

Table 4

Donor–Recipient Gender Pairs and Transplant Outcome as a Function of Blood Group Compatibility

	Compatible blood groups			Incompatible/nonideal blood groups		
		Failure			Failure	
Donor–recipient	Total	*N*	%	Total	*N*	%
M–M	55	21	38	2	0	0
M–F	58	17	29	7	2	29
F–M	104	26	25	4	4	100
F–F	100	16	16	5	2	40
Total	317	80	25	18	8	42

Table 5

Donor–Recipient Gender Pairings and Transplant Outcome in Children for Two Most Frequent Blood Groups

	Blood group O → O			Blood group A → A		
		Failure			Failure	
Donor–recipient	No.	*N*	%	No.	*N*	%
M–M	21	9	42	24	7	29
M–F	27	10	37	21	7	33
F–M	49	10	20	36	9	25
F–F	42	4	10	35	7	20
Total	138	43	31	116	30	26

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