Acute Hepatic Allograft Rejection in Pediatric Recipients: Effective Factors

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ABSTRACT

Background: Acute cellular rejection (ACR), a reversible process, can affect the graft survival.

Objective: To evaluate the relation between ACR and clinical factors in recipients of allograft liver transplantation.

Methods: 47 recipients of liver were consecutively enrolled in a retrospective study. Their information were retrieved from their medical records and analyzed.

Results: Of the 47 recipients, 38 (81%) experienced acute rejection during 24 months of the transplantation. None of the studied factors for occurring transplant rejection, *i.e.*, blood groups, sex, age, familial history of disease, receiving drugs and blood products, type of donor, Child score, and Child class, was not found to be significant.

Conclusion: During a limited follow-up period, we did not find any association between ACR and suspected risk factors.

KEYWORDS: Acute cellular rejection; Liver transplantation; Pediatric; Graft survival; Transplant recipients; Graft rejection

INTRODUCTION

Nowadays, liver transplantation is a well-accepted treatment for end-stage liver diseases in pediatric patients [1]. The first attempt for liver transplantation was done by Dr. Starzel in 1963 on a 3-year-old boy with biliary atresia [2]. Despite of the technological, medical and surgical improvements, liver transplantation is still associated with mortality and morbidity. Acute cellular rejection (ACR) is one of the main post-transplantation complications affecting the graft function [3-5].

The incidence of ACR in children following liver transplantation has been reported between <20% and 50% based on the recipient age; in older children it is more frequent. ACR can occur at any time after liver transplantation [6]. Suspicion for ACR is made by chemical and biochemical evidence; the liver biopsy is mandatory for confirming the diagnosis. Histologic criteria for ACR is based on Sensor's triad of portal hepatitis, endotheliitis, and lymphocytic cholangitis [7].

Because of the reversibility and impact of ACR on long-term graft function, as well as the graft loss, we conducted this study to evaluate the impact of pre-, concomitant, and post-transplantation factors on ACR in recipients of allograft liver.

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Table 1: Characteristics of patients with acute liver transplant rejection

Factors	n (%)
Sex	
Male	22 (46)
Female	25 (52)
Blood group	
A	17 (35)
B	10 (21)
O	19 (40)
AB	1 (2)
Familial history	
No	35 (75)
Yes	12 (26)
Spironolactone before transplantation	
No	25 (53)
Yes	22 (47)
Furosemide before transplantation	
No	40 (85)
Yes	7 (15)
Donor type	
Dead	34 (72)
Father	3 (6)
Mother	10 (21)
Eradiated packed cell before transplantation	
No	34 (72)
Yes	13 (28)
Whole blood before transplantation	
No	32 (68)
Yes	15 (32)
FFP before transplantation	
≤4 units	44 (94)
>4 units	3 (6)

PATIENTS AND METHODS

Between 2012 and 2015, 318 pediatric patients with congenital hepatic disease received liver transplantation in Nemazi Hospital, affiliated to Shiraz University of Medical Sciences. Complete records of 47 consecutive pediatric patients with acute rejection were collected. Sex, age, weight, age at ACR, age at liver transplantation, Child score, blood group, family history of transplant, operation data and its complications, as well as post-transplantation treatments and their circumstances were retrieved from each record. The inclusion criteria were age between 1 and 18 years, presence of biopsy-proven ACR, and absence of other complications. The exclusion criteria were existence of other explanations for the observed signs and presence of secondary liver malignancy. Histological characteristics for ACR were lymphocytic portal inflammation, bile duct inflammation, and endotheliitis.

Table 2: Characteristics of patients with acute liver transplant rejection

Factors	Mean±SD
Age	8.3±4.4
Weight	23.73±13.41
Child score	7.65±2.34
Child class	1.97±0.65
Cold ischemia	14.73±18.29
Warm ischemia	44.75±12.99
PC* during	0.64±1.54
FFP	1.07±1.75
Follow-up period	2.23±1.89
Treatment delay	3.98±3.37

*Eradiated pack cell

The crude and adjusted associations between potential risk factors and acute rejection were estimated using univariate and multivariate Poisson regression models controlling for treatment delay, Child class, use of spironolactone, and whole blood transfusion before the transplantation,. All statistical analyses were performed using Stata SE *ver* 11 software. A p value <0.05 was considered statistically significant.

RESULTS

Totally, 47 patients underwent liver transplantation. They were followed for a mean±SD of 1.8±1.9 years. The mean±SD age of participants was 9.6±9.6 years; 25 (53%) recipients were female; 33 (72%) received the transplant from deceased donors, others from their live parents.

The characteristics of patients with acute

Table 3: Crude and adjusted relative risks (RRs) for the studied factors and acute rejection

Factors	Crude RR (95% CI)	p value	Adj RR (95% CI)	p value
PC* before transplantation	1.28 (0.58–2.82)	0.5	3.84 (0.89–16.62)	0.07
PC during surgery	1.00 (1–1.00)	0.5	1.001 (0.99–1.01)	0.7
Whole blood before transplantation	2.79 (1.04–7.52–	0.04	3.19 (0.48–21.07)	0.2
FFP before surgery	0.72 (0.22–2.34)	0.6	1.72 (0.40–7.36)	0.5
FFP during surgery	1.03 (0.96–1.10)	0.4	1.29 (0.77–2.17)	0.3
Blood group (compared with A)				
B	0.72 (0.31–1.68)	0.4	0.36 (0.08–1.59)	0.2
O	0.61 (0.29–1.29)	0.2	0.38 (0.10–1.36)	0.1
AB	0.59 (0.08–4.52)	0.6	0.60 (0.06–5.92)	0.7
Sex	1.40 (0.74–2.64)	0.3	1.33 (0.39–4.53)	0.6
Age	1.01 (0.95–1.06)	0.8	0.93 (0.70–1.24)	0.6
Weight	0.99 (0.96–1.02)	0.6	1.00 (0.93–1.08)	0.9
Familial history	0.86 (0.35–2.12)	0.7	1.005 (0.21–4.85)	0.9
MELD/PELD	0.98 (0.94–1.03)	0.5	1.01 (0.90–1.15)	0.8
Child score	0.95 (0.81–1.11)	0.5	0.66 (0.28–1.52)	0.3
Child class	0.57 (0.29–1.10)	0.09	0.78 (0.22–2.73)	0.7
Furosemide before surgery	0.916 (0.38–2.20)	0.8	1.97 (0.30–13.01)	0.5
Spironolactone before surgery	0.56 (0.29–1.07)	0.08	0.85 (0.20–3.54)	0.8
Albumin before surgery	0.90 (0.71–1.14)	0.4	1.24 (0.68–2.27)	0.5
Donor type (compared with deceased)				
Father	1.11 (0.34–3.68)	0.8	1.25 (0.13–11.50)	0.8
Mother	0.62 (0.28–1.36)	0.2	0.50 (0.09–2.61)	0.4
Cold ischemia	1 (0.98–1.01)	0.8	0.99 (0.96–1.02)	0.5
Warm ischemia	1 (0.97–1.02)	0.9	0.99 (0.94–1.04)	0.7
Infection	1.02 (0.139–7.46)	>0.99	1.28 (0.17–9.68)	0.8
Drug allergy	2.96 (0.40–21.58)	0.3	2.96 (0.40–21.58)	0.3
Treatment delay	1.03 (0.99–1.07)	0.09	1.01 (0.83–1.22)	0.9

*PC: Eradiated packed cell

liver transplant rejection are presented in Tables 1 and 2. Univariate analysis showed that blood transfusion before transplantation significantly increased the risk of acute rejection (RR=2.79, p=0.04). However, the effect abolished in multivariate analysis (RR=3.19, p=0.2) (Table 3).

DISCUSSION

Of 318 recipients of liver allografts, 47 developed acute rejection. The rejection was not associated with any of the factors investigated before and after the surgery. In univariate analysis, only receiving whole blood before the transplantation was found to be significantly associated with acute rejection. However, after controlling for potential confounders such as the treatment delay, Child class, and receiving spironolactone before the surgery, the association vanished. Multivariate analysis, showed that only receiving PC before surgery had a borderline significant association with acute transplant rejection. Receiving eradiated packed cell caused approximately a four-fold increase in the risk of rejection. No significant association was observed between other factors and the acute rejection. Wang, *et al*, conducted a retrospective study for evaluation of ACR

risk factors on 110 consecutive liver recipients and found a significant relation between recipients age and the occurrence of ACR. Their believed that a higher CD8 lymphocyte count in younger patients was the reason [8].

Shindoh, *et al*, performed a prospective study on 413 patients who received graft from living donors. They concluded that autoimmune liver diseases are associated with a higher risk of ACR and its relapse [9].

Fan, *et al*, compared the incidence and severity of ACR between living donor transplantation and cadaveric liver transplantation. They showed no significant difference between the studied groups; HLA mismatching and cold ischemic time had no impact on the incidence and severity of ACR too [10]. These findings are in keeping with those observed in our study. Toyoki, *et al*, evaluated the immunological advantage of living related liver transplantation compared with cadaveric transplants in 100 pediatric liver recipients. They confirmed a comparable incidence of ACR between groups in the first 24 months of transplantation. However, ACR episodes after one year were significantly lower in the living related liver recipients [11]. Similar to our results, in a systemic review and meta-analysis carried out by Hu, *et al*, the rate of ACR and graft survival was not related to donor types—alive or cadaveric [12].

Sandra, *et al*, designed a survey to evaluate the relation between donor and recipient sex mismatch on graft survival after liver transplantation. The study was done on 114 pediatric patients. The authors found a higher incidence of ACR in maternal grafts with sex mismatch [13], which was in contrast to the results of the current study.

Kinpan and his colleagues retrospectively investigated the information of 778 liver recipients to assess the impact of clinical factors on the ACR incidence. They concluded that old age, chronic hepatitis B, living donor, and use of interleukin-2 receptor agonists were associated with lower incidence of ACR [14]. Unfortunately, we could not record the exact dates of many events. Therefore, survival analysis was not performed for our data and only the associations were investigated during a limited follow-up period from each participant's entry to March 2016. Moreover, because our data collected and analyzed retrospectively, some necessary data might be ignored during the study.

In conclusion, our study did not find any risk factors for liver transplant rejection. Further multicenter prospective cohorts with larger sample sizes and longer follow-up periods are required to identify the independent risk factors of transplant rejection after liver transplantation.

CONFLICTS OF INTEREST: None declared.

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