DOI: 10.15825/1995-1191-2021-4-26-31

THE INCIDENCE AND RISK FACTORS OF CHRONIC REJECTION IN ACUTELY REJECTED PEDIATRIC LIVER TRANSPLANTATION

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Background. Chronic graft rejection (CR) represents an increasing concern in pediatric liver transplantation (LT). Risk factors of CR in this population are uncertain. In present study, we aimed to ascertain if clinical parameters could predict the occurrence of CR in LT children. **Methods.** We retrospectively analyzed the results from 47 children who had experienced acute hepatic rejection in Namazee hospital, Shiraz, Iran during 2007–2017. **Results.** Out of 47 children, 22 (46.8%) and 25 (53.2%) were boys and girls respectively. Ascites, gastrointestinal bleeding, and spontaneous bacterial peritonitis were observed in 20 (44.4%), 14 (31.1%), and 4 (9.1%) respectively. Post-transplant vascular and biliary complications were observed in 3 (7%) and 4 (9.3%) cases respectively. The mean time from LT to normalization of liver enzymes was 14.2 ± 7.5 days. The mean of acute rejection episodes was 1.4 ± 0.6 (median = 1 (22, 46.8%), range of 1–3). Six (12.7%) patients experienced CR. The mean time from LT to CR was 75 ± 28.4 days. A significant association was found between CR and patients' condition (being inpatient or outpatient) before surgery (P = 0.03). No significant relationship was found between CR and post-transplant parameters except for biliary complications (P = 0.01). Both biliary complication (RR = 33.7, 95% CI: 2.2–511, P = 0.01) and inpatient status (RR = 10.9, 95% CI: 1.1–102.5, P = 0.03) significantly increased the risk of CR. **Conclusion.** Being hospitalized at the time of LT, and development of biliary complications might predict risk factors for development of CR in LT children.

Keyword: Liver transplantation, Graft rejection, Host vs Graft Reaction.

ЧАСТОТА ВОЗНИКНОВЕНИЯ И ФАКТОРЫ РИСКА РАЗВИТИЯ ХРОНИЧЕСКОГО ОТТОРЖЕНИЯ ПРИ ОСТРОМ ОТТОРЖЕНИИ ТРАНСПЛАНТИРОВАННОЙ ПЕЧЕНИ У ДЕТЕЙ

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Актуальность. Хроническое отторжение (ХО) трансплантата становится все более серьезной проблемой при трансплантации печени (ТП) у детей. Факторы риска ХО в этой популяции остаются неопределенными. В настоящем исследовании мы стремились выяснить, можно ли спрогнозировать возникновение ХО у детей с ТП по клиническим параметрам. **Методы.** Мы провели ретроспективный анализ 47 случаев острого отторжения трансплантата печени у детей, прооперированных в больнице Намази (г. Шираз, Иран) в период с 2007-го по 2017 год. **Результаты.** В исследование включили 47 детей: 22 (46,8%) мальчика и 25 (53,2%) девочек. Асцит, желудочно-кишечное кровотечение и спонтанный бактериальный перитонит

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наблюдались в 20 (44,4%), 14 (31,1%) и 4 (9,1%) случаях соответственно. Посттрансплантационные сосудистые и билиарные осложнения отмечались в 3 (7%) и 4 (9,3%) случаях соответственно. Показатели печеночных ферментов нормализовались в среднем через 14,2 ± 7,5 дня после ТП. Среднее количество эпизодов острого отторжения составило 1,4 ± 0,6 (медиана = 1 (22; 46,8%), диапазон 1–3). У 6 (12,7%) пациентов наблюдалось ХО. Среднее время от ТП до ХО составило 75 ± 28,4 дня. Мы выявили статистически значимую корреляцию между ХО и предоперационным периодом (нахождение в стационаре или амбулаторная подготовка, p = 0,03). ХО статистически значимо коррелировало с наличием билиарных осложнений (p = 0,01), другие послеоперационные факторы статистически значимо на него не влияли. Билиарные осложнения (ОР = 33,7, 95% ДИ 2,2–511, p = 0,01) и предоперационный статус пациента (ОР = 10,9, 95% ДИ 1,1–102,5, p = 0,03) значительно повышали риск ХО. **Заключение.** Госпитализация при подготовке к трансплантации и раннее выявление билиарных осложнений могут предотвратить развитие ХО трансплантата у детей после ТП.

Ключевые слова: трансплантация печени, отторжение трансплантата, реакция ТПХ.

INTRODUCTION

In the courtesy of substantial improvements in pre- and post-transplant care, patients who are organ transplanted now encounter lower rate of early complications after surgery. However, patients are still at risk of long-term complications and in particular, chronic graft rejection (CR). Accordingly, CR is the most debating and concerning survival-limiting complication in liver transplanted patients and is encountered in 2–20% of the patients [1, 2]. CR is generally defined by foamy changes in sinusoidal and vascular beds as well as the loss of >50% of portal bile ducts [3, 4]. The most identifiable feature in biopsy specimens, however, is the loss of bile ducts as foamy changes which are usually restricted to large arteries. Nevertheless, the loss of bile ducts is considered as a late feature of CR [3]. Immunosuppressive therapies have had the least impacts in progression of tissue degeneration in advanced CR. The majority of patients affected with advanced CR are required to be re-transplanted [5]. In accordance, CR is the main reason for graft failure in pediatric population [6]. After nearly five decades experience on pediatric LT, survival rate for patients hits 90% in 1-year post transplant [7]. This survival rate could particularly be attributed to improvements in preoperative managements, optimizing donor selection strategies, and developing proficient surgical methods. The majority of these advancements, however, contribute to lower acute and short-term complications while long-term complications, and in particular, CR, is still relatively common encountered feature. Compared to adult LT (2–5%), CR is encountered in higher ratios (8–12%) in pediatric patients [6]. Parameters associated CR are not well known in pediatric LT. Based on this, studying risk factors related to incidence of CR is of crucial importance to early identify CR in pediatric LT.

METHODS

This was a retrospective study performed in Organ transplant center of Nemazi Hospital, Shiraz, Iran. Data on CR was gathered from 47 pediatric patients who had experienced acute rejections. A comprehensive view on these patients has been reported earlier by ours. These patients had biopsy diagnosed acute rejection. Chronic rejection was diagnosed in these patients based on the loss of >50% of portal bile ducts. Statistical analysis was performed in SPSS 19 software using appropriate descriptive and analytical tests.

RESULTS

From 47 children, 22 (46.8%) and 25 (53.2) were boys and girls respectively. Family history of liver disease was noted in 9 (19.1%) of the patients. None of the patients had renal insufficiency, cyanosis or hepatopulmonary syndromes pre-transplant. However, ascites, gastrointestinal bleeding, and spontaneous bacterial periodontitis (SBP) were observed in 20 (44.4%), 14 (31.1%), and 4 (9.1%) of patients respectively.

Only 6 (13%) of the patients had been hospitalized at the time of transplantation. Cadaveric transplants were done in 33 (71.7%), while the grafts came from either fathers or mothers in 4 (6.5%) and 10 (21.7%) cases respectively. The means for the numbers of transfused FFP, whole blood, and packed cell units before LT were 1 ± 1.7, 0.4 ± 1.4, 0.6 ± 1.5 respectively. basic clinical features of the patients have been noted in table 1.

One (2.2%) patient developed diabetes, and 1 (2.2%) developed renal insufficiency after transplantation. Serological tests for cytomegalovirus (CMV) was positive for 1 (2.2%) case after transplantation. Bayloma was noted in 6 (14%) of the patients after the surgery. Post-transplant vascular and biliary complications were observed in 3 (7%) and 4 (9.3%) of the cases respectively. No cases developed post-transplant lymphoproliferative disorder (PTLD) following LT.

The mean time from LT to normalization of liver enzymes was 14.2 ± 7.5 days. The mean of acute rejection episodes was 1.4 ± 0.6 (median = 1 (22, 46.8%), range of 1–3). Six (12.7%) patients experienced chronic rejections. The mean time from transplantation to CR was 75 ± 28.4 days. Table 2 represents features of the six patients who developed CR.

No association was identified between CR and sex, blood group, child class, pre-transplant complications

(SBP, GI bleeding, ascites, hepatopulmonary syndrome, cyanosis, renal insufficiency), and graft origin (cadaveric, parental). However, fisher exact test revealed a significant association between CR condition (being inpatient of outpatient) of the patients before surgery (P = 0.03). Beside biliary complications (P = 0.01, table 3), no significant relationship was found between CR and post-transplant parameters (diabetes, renal insufficiency, CMV infection, and vascular complications). In regression analysis, both biliary complication and inpatient status increased the risk of CR significantly (table 4).

DISCUSSION

Graft failure due to CR is a growing concern in pediatric LT. Mechanisms behind CR are of great interest for researchers in order to make progress on patient and graft outcome. In respective to the adults, LT in children offers a superior prognosis. This is governed by a variety of factors such as graft quality and viability (source, harvesting, preserving and transporting) as well as efficiency of surgical techniques and inter-individual patients' related factors.

In our study, 6 (12.7%) patients encountered CR. The mean time from LT to CR was 75 ± 28.4 ranging from 35–102 days. It has been noted that graft failure is mostly encountered within three months after LT, while 85% of rejections occurred within six months [8]. In a study in Brazil on 537 LT children, 29 (5.4%) developed CR [6]. In another report in 22 pediatric LT, 2 (9%) encountered CR [9]. In a study by Dattani et al., 2% of 46 LT children developed CR [10]. CR development is a multifactorial phenomenon. This could be provoked in grafts from unrelated donors as CR was reported in 14.7% of patients transplanted with unrelated while in 7% of related allografts [11]. Overall, CR is a relatively common feature in pediatric LT, however, its risk factors and underlying pathological and immunological mechanisms need to be more elucidated.

In our patients, neither of recipients' age, weight, PELD/PELD or child scores, and nor acute rejection episodes, hospitalization period, time laps for normalization of liver enzymes, and receiving blood components or bleeding during surgery were associated with occurrence of CR. Nevertheless, status of the patients at the time of LT (i.e. inpatient or outpatient), the ICU stay duration, and post-transplant biliary compilations were significantly associated with CR. Among risk factors of CR in LT are recurrent acute rejections [3, 6, 12], viral infections [13–16], low-dose immunosuppression therapy, anti-viral therapy [2], underlying liver disease [17, 18], human leukocyte antigen (HLA) mismatch [18–20], ABO-incompatible graft [21, 22], donor-specific antibodies (DSA) against HLA or other immune determinants (i.e. complement system) [23–25], and post-transplant complications (i.e. vasculopathies and sinusoidal fibrosis [16]. In another study, however, none of 36 patients who

Table 1

Basic clinical features in 47 liver transplanted children

Parameter		Amount
Blood groups	A+	17 (36.2)
	B+	8 (17)
	B–	2 (4.3)
	O+	17 (36.2)
	O–	2 (4.3)
	AB+	1 (2.1)
Child class	A	12 (22.2)
	B	24 (58.3)
	C	11 (19.4)
Age at transplant (years)		9.6 ± 9.5
Weight at transplant (Kg)		23.7 ± 13.4
PELD/MELD score		18.7 ± 10.5
Child Score		7.6 ± 2.3
Hospitalization episodes		2.5 ± 2
Bleeding volume (ml)		327.6 ± 420.3
Surgery time (hours)		192.8 ± 109.6
ICU stay after transplantation (days)		10.7 ± 5.1
Hospital stay after transplantation (days)		14.2 ± 5.9

Table 2

Features of six children who developed chronic graft rejection after liver transplantation

Features	P 1	P 2	P 3	P 4	P 5	P 6
Gender	M	F	M	M	M	F
Age at transplant (years)	6	3	2.5	10	11	2
PELD/MELD score	24	16	28	40	14	18
Child Score	6	11	8	12	6	7
Time to liver enzyme normalization (days)	17	8	28	17	10	12
Acute rejection episodes	1	1	1	2	2	2
Time to chronic rejection (days)	102	94	89	43	87	35
Status before transplant	inpatient	inpatient	outpatient	inpatient	outpatient	outpatient
Type of transplant	Mother	Mother	Cadaver	Cadaver	Cadaver	Cadaver
Biliary complications	Yes	No	No	No	No	Yes

Note. P – patient; M – male; F – female.

received long-term low dose immunosuppressive therapy developed CR [26]. In fact, tacrolimus based immunosuppressive treatment has been reported as an effective factor for preventing CR [4, 27], however, other studies suggested that immunosuppression regimes could not be definitive determinants in prevention of CR [6, 26]. DSAs which have been mainly against HLA II and C3d component of complement system are seen in increasing frequencies with the time after transplantation (8% within 5 years while 50% in >15 years of LT) [23]. Nevertheless, DSAs may not be specific for detection of CR as they have also been described in as high as 56% of patients without any evidences of CR [25]. Allografts In patients positive for CMV infection have shown more pronounced fibrotic and vasculopathy, as well as necrotic changes [13]. This has been attributed to higher expression of vascular growth factors (such as platelet derived growth factor and fibroblast growth factor; i.e. PDGF and FGF) [13]. On the other hand, chronic stimulation of inflammatory cytokines has been suggested as a possible contributor to the aggravation of hepatic inflammation and CR [13]. Some other risk factors have also been described for CR. Of these are recipient general health and absence of autoimmune disorders, as well as recipient age and gender [12, 22]. These implications are mainly acknowledged from adult studies, and on the other hand, these risk factors have been inconsistent among different populations.

In the study of Tannuri et al., CR was not asscoiated with neither of the age or gender of recipients, nor with graft origin, unerlying liver disease, acute rejection episodes, viral infections (CMV and EBV), immunosuppressive treatement, and post transplant complications (i.e. PTLD, vascular, and biliary complications) [6]. Instead, ductopenia was noted as the sole predictor of CR in the recent reprot [6]. Here we found that billiary complications afetr LT signfiicantly increased the risk of CR (Adjusted relative risk = 33.7, 95% CI: 2.2–511). Biliary complication is a respectively common sequala after LT [28, 29]. Some factors that may contribute to the development of biliary defects have been noted as high serum bilirubin, advanced donor age, MELD score, acute

Table 3

Univariate analysis for association of clinical characteristics pre and post liver transplantation with occurrence of chronic graft rejection

Parameters		Chronic rejection		p
		Yes (n = 6)	No (n = 41)	
Biliary	Yes	2	3	0.01*
	No	4	38	
Status	Inpatient	2	3	0.03*
	Outpatient	4	37	
Age at trans		15.5 ± 2.7	8.7 ± 4.3	0.11
Weight at trans		27 ± 18.1	23.1 ± 12.6	0.74
PELD/MELD score		22.7 ± 11.7	18.1 ± 10.5	0.40
Child score		8 ± 2.7	7.5 ± 2.3	0.61
FFP units		1.2 ± 1.4	1 ± 1.8	0.38
Whole blood units		0.25 ± 0.5	0.52 ± 1.5	0.89
Hospitalization before		1.5 ± 0.5	2.7 ± 2.1	0.16
Bleeding volume at surgery		568 ± 567.5	296 ± 396.1	0.18
ICU stays after transplant		5.5 ± 3.9	11.5 ± 4.8	0.007**
Surgery time		230 ± 62.4	189.7 ± 112.8	0.84
Hospital stay after transplant		13 ± 6	14.5 ± 5.9	0.93
Days to normalization of liver enzymes		14.8 ± 6.6	14.1 ± 7.8	0.56
Acute rejection episodes		1.4 ± 0.5	1.4 ± 0.6	0.84

Note. * – Fisher exact test; ** – Mann Whitney U test.

Table 4

Logistic regression analysis for selected variables and risk of chronic rejection in pediatric liver transplantation

Parameters		RR	95%CI	p	Adjusted RR	95%CI	p
Status	Outpatient	Ref			Ref		
	Inpatient	9	1.3–60.4	0.02	10.9	1.1–102.5	0.03
Biliary complications	No	Ref					
	Yes	26.2	2.1–316	0.01	33.7	2.2–511	0.01

rejections and biliary structural defects following LT [29]. Furthermore, patients with primary biliary cirrhosis had higher risk for occurrence of biliary complications after LT [29]. Recently by proposing a chronic antibody-mediated rejection (cAMR) score based on a variety of serological, histological and clinical parameters, it was possible to predict a risk-stratification for graft failure following 10 years of LT [16]. Overall, many inter and intra individual, as well as procedural factors are important in development of CR in LT.

In addition to clinical parameters, lights have also been shed on the molecular and cellular mechanisms involved in hepatic CR. In study of Wei et al. in animal model of CR, it was found that the expression of at least sixty two proteins were modulated in the face of CR development [30]. Among these, CLU (clusterin), a widely expressed secretory glycoprotein with proposed roles in protein hemostasis, graft survival, apoptosis, immune tolerance and tumorigenesis was suggested as a reliable early indicator of CR [30–32]. Two other possible early indicators of CR proposed by Wei et al. included keratin type I cytoskeletal 19 (Krt19) and lipocalin 2, a neutrophilic gelatinase with respective roles in regulating bile duct biogenesis and immune system [30]. In addition, Th2 lymphocytes seems to contribute in hepatic CR by production of IL-10 and promoting humoral and inflammatory responses [33]. Through balancing Th1/Th2 responses, invariant natural killer T cells (iNKT) may execute a substantial role in inducing immune tolerance toward liver allografts [34]. New evidences have suggested a role for hepatic mast cells in augmenting immune tolerance and graft preservation [35]. From other early molecular indicators of CR has been proposed increased expression of apoptotic receptor (i.e. FasL) on Kupfer cells and antigen presenting cells (APCs) within hepatic allografts [36]. Decreased expression of serine/threonine kinase; STK17A, with suggested roles in biliary biogenesis in liver allograft may also be an early predictor of hepatic CR [37]. More studies are necessary to unravel molecular adaptors responsible for CR in LT.

CONCLUSION

The only rescuing option in patients afflicted with CR may be re-transplantation. Considering this, and also potential reversibility of CR in early phases, accurate and timely diagnosis of CR in initial stages is of paramount importance. This necessitates identifying and monitoring at risk patients for CR. Our findings suggest that being hospitalized at the time of LT, and development of biliary complications might predict such high risk conditions.

Авторы заявляют об отсутствии конфликта интересов.
The authors declare no conflict of interest.

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Статья поступила в редакцию 13.02.2021 г.
The article was submitted to the journal on 13.02.2020