Japanese Journal of Gastroenterology Research

www.jjgastro.com

Research Article

Open Access, Volume 1

Graft rejection after pediatric living related liver transplantation

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Received: Aug 27, 2021
Accepted: Sep 21, 2021
Published: Sep 24, 2021
Archived: www.jjgastro.com

Abstract

Background: Rejection is an important adverse event after pediatric liver transplantation (LT).

Aim: We aimed to study the incidence and risk factors for post-transplant rejection in pediatrics.

Methods: The study included 40 pediatric patients underwent LT. All patients' records were reviewed. A wide range of potential risk factors for rejection, were recorded.

Results: Rejection occurred in 13/40 (32.5%) of recipients. For the 13 rejecters, a total of 24 rejection attacks have occurred. 25% of which occurred during the 1st month post-LT. Acute rejection accounted for 54% of total rejection attacks, while chronic rejection occurred in 46%. LT for biliary atrasia (BA) was a significant risk factor for rejection. The means of transaminases levels were 268 ± 141 (IU/L) AST and 221 ± 119 (IU/L) ALT, biliary enzymes were 962 ± 687 (IU/L) for the ALKP and 485 ± 347 (IU/L) for the GGT, total BIL was 6.5 ± 7.1 (mg/dl), and FKL levels were 10.4 ± 5.6 (ng/ml) during the rejection attacks. Chronic rejection contributed to death of only one of the cases.

Conclusion: BA was a significant risk for rejection. Elevated transaminases and biliary enzymes but not FK trough level is alarming signs for presence of rejection.

Keywords: liver transplantation; pediatrics; rejection.

Abbreviations: ACR: Acute Cellular Rejection; BMI: Body Mass Index; ALKP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Transaminase; BA: Biliary Atresia; CR: Chronic Rejection; GGT: Gamma Glutamyl Transpeptidase; LDLT: Living Donor Liver Transplantation; LT: Liver Transplantation; TLC: Total Leucocyte Count.

Introduction

During the past years Liver Transplantation (LT) has become the standard therapy for acute and chronic liver failure. Nowadays, with a five-year patient survival rate of 73%, long-term outcome of patients is becoming a main concern for clinicians [1].

Graft rejection is a common catastrophic complication after LT. Three types of graft rejection were recorded; hyperacute, acute, and Chronic Rejection (CR). The hyperacute antibody mediated (due to preformed antibodies in recipients against the donor's major histocompatibility complex) rejection although described, is quite rare in LT and mainly acute and chronic rejection are of clinical significance [2].

The Acute Cellular Rejection (ACR) occurs due to recipient's T cells that recognize donor alloantigens. ACR represents sudden deterioration of graft function and liver biopsy shows infiltration with T cells and other leukocytes besides features of ductular injury and endothelitis. In CR, different mechanisms lead to ductopenia which include ischemia by obliterative arteriopathy and immune destruction of bile ductular cells [3].

The incidence of acute and chronic rejection had decreased with the improvement of immunosuppressive regimens. ACR mostly improves with steroids and generally, did not affect long term graft and patient survival [4]. Despite that ACR usually responds well to treatment, CR presents a more difficult situation and a high percentage of patients did not respond to increase in immunosuppressive doses. CR often leads to retransplantation and death [5].

We aimed to assess the incidence and risk factors for rejection after pediatric living donor liver transplantation (LDLT).

Patients and methods

This retrospective study revised the entire medical Patients' records of 40 pediatric patients underwent LDLT at the National Liver Institute, Menoufia University. The recipient pre-operative, operative, and post-operative data were collected in addition to the donor data on trying to suspect the probable risk factors for occurrence of rejection.

Pre-operative data included the recipients' age, gender, diagnosis, blood group, pre-LT infectious state, pre-LT steroid therapy, co-morbedity, immunization status. Post-operative data included the type, dose and duration of immunosuppressant. Reports of the ultrasound and laboratory investigations as complete blood count, liver function tests, and viral markers pre-LT, and during every rejection attack were revised.

Donor data included the relation to the recipient, age, gender, blood grouping, and body mass index (BMI). Operative data included cold ischemia time, warm ischemia time, anhepatic phase, and the duration of the operation.

The LT recipient has been suspected to have a rejection attack if presented with fever, malaise, right upper quadrant and right flank pain, jaundice, clay-colored stools, hepatomegaly and increased ascites accumulation after exclusion of other causes as infection, associated with elevated serum transaminases, biliary enzymes and bilirubin levels. Diagnosis was confirmed by liver biopsy.

Lines of treatment of rejection attacks, patients' response to treatment and patients' outcome were collected.

Statistical methods

Data were analyzed through the SPSS (statistical package for the social sciences), version 18.0, (SPSS Inc., Chicago, Illinois, USA). Qualitative data were expressed as frequency and percentage. Quantitative data were shown as mean ± stander deviation (SD). Significance was tested by Fisher exact test for qualitative variables. Mann Whitney U test were used to compare means and SD of quantitative variables between 2 groups. *P* (probability) value were considered significant if it was < 0.05.

Results

The study included 40 children underwent LDLT. They were 18 (45%) males and 22 (55%) females. Their age ranged from 1 to 17 years (mean 5.8 ± 5.5). The commonest indication for LT was biliary atresia (BA); 15 (37.5%) followed by familial progressive intrahepatic cholestasis (PFIC) 6 (15%).

Rejection occurred in 13/40 of recipients (32.5%) during the whole follow up period. For the 13 rejecters, a total of 24 rejection attacks have occurred. Twenty-five percent of which occurred during the 1st month post-LT. Acute rejection accounted for 54% of total rejection attacks, while chronic rejection occurred in 46% and none suffered hyper-acute rejection. All patients were on tacrolimus based immunosuppression.

The means of transaminases levels during the rejection attacks were 268 ± 141 (IU/L) for the AST and 221 ± 119 (IU/L) for the ALT, biliary enzymes were 962 ± 687 (IU/L) for the ALKP and 485 ± 347 (IU/L) for the GGT, Total BIL 6.5 ± 7.1 (mg/dl), and FKL levels were 10.4 ± 5.6 (ng/ml).

Transplantation for BA, was significantly higher in rejecters group than non-rejecters (P<0.05). Factors found not to be significant included age and sex of the recipient, pre-LTx steroid therapy, immunization, compatibility of donor/recipient blood groups, pre-operative viral and fungal infection and the donor's age, gender, BMI, and degree of relativity to the recipients (P>0.05). Surgical and donor data were comparable in both groups (Table 1).

The lowest incidence of rejection was in the patients who began their immunsupressives the day after LTx. Concerning the FK trough level (FKL), we found that 66.7% of rejection attacks were associated with high FKL and 12.5% were associated with normal FKL and only 20.8% were associated with low FKL levels. Most of acute rejection episodes improved with steroid boluses while, CR responded to increased immunosuppression in most of cases or with addition of Mycophenolate Mofetil.

Of the 40 transplanted patients 26 (65%) children were alive and 14 (35%) children died. Chronic rejection was responsible for death of only one patient.

Table 1: Pre-operative, operative and donor data of rejecters and non-rejecters.

	Rejectors N=13	Non-rejectors N=27	P-value
Recipient pre-operative data			
Gender Female Male	 7 (53.8%) 6 (46.2%)	 15 (55.5%) 12 (44.5%)	0.899
Age at LT (years)	3.05 ± 4.17	6.76 ± 5.86	0.076
Diagnosis BA Non-BA	 11 (84.6%) 2(15.4%)	 4 (14.8%) 23 (85.2%)	0.009
TLC × 10^3 (cells/cmm)	11 ± 6.31	7.4 ± 3.26	0.140
AST (IU/L)	255 ± 198	132 ± 89	0.110
ALT (IU/L)	88.3 ± 59.9	80.5 ± 105.2	0.812
Albumin (g/dL)	3.2 ± 1.02	3.4 ± 0.93	0.724
Total bilirubin (mg/dl)	15.2 ± 9.67	12.7 ± 13.5	0.592
Direct bilirubin (mg/dl)	13.04 ± 8.42	8.9 ± 9.36	0.269
Prothrombin concentration (%)	75.9 ± 19.72	65.36 ± 24.3	0.285
International normalized ratio	1.3 ± 0.29	1.42 ± 0.5	0.463
Creatinine (mg/dl)	0.42 ± 0.2	0.35 ± 0.26	0.459
Pre-LT steroid therapy not taken taken	 11 (84.6%) 2 (15.4%)	 27(100.0%) 0(0.0%)	0.346
Comorbidity absent present	 11 (84.6%) 2 (15.4%)	 23 (85.2%) 4 (14.8%)	1
Surgical data			
Cold ischemia time (min)	65.56 ± 27.4	53.5 ± 26.44	0.312
Warm ischemia time (min)	40 ± 12.2	38.93 ± 11.54	0.837
Anhepatic phase (min)	75 ± 64.03	44.6 ± 24.04	0.423
Period of operation (hours)	10.32 ± 1.84	10 ± 1.91	0.692
Donor data			
Age at LT (years)	32.33 ± 4.38	31.71 ± 5.62	0.757
Body mass index (kg/m^2)	27.35 ± 4.58	24.8 ± 3.59	0.172
Gender Male Female	 6 (46.2%) 7 (53.8%)	 9 (33.3%) 18 (66.7%)	0.419
ABO.compatibility Identical compatible	 8 (61.5%) 5 (38.5%)	 19 (70.3%) 8 (29.7%)	0.692

AST: Aspartate Transaminase; ALT; Alanine Transaminase; TLC: Total Leucocyte count.

Discussion

Pediatric LT is the treatment of choice for children suffering from end-stage liver disease. In the last two decades, a growing body of research has provided insight into the donor and recipient factors affecting graft and patient survival, and incorporation of these findings into clinical practice has improved graft and patient survival following pediatric LT [6].

In the current study, rejection occurred in nearly third of recipients. Acute rejection was the predominant type of rejection, occurred in more than half of the rejecters. *Rodríguez-Perálvarez et al.,* recorded that acute cellular rejection (ACR) occurs in 15–25% of LT recipients on Tacrolimus based immunosuppression regimens and generally improves with steroids in majority [4].

The alarming signs that alarmed our minds for occurrence of rejection in our patients were observation of deepening jaundice, decreased patients activity, abdominal pain besides elevation of hepatic and biliary enzymes and bilirubin levels. Low FK level wasn't a constant finding in our patients, in contrast it was high in 66.7% of rejection attacks. In agreement with our results *Staatz et al***.,** found that there was no significant correlation between FKL and the incidence of rejection [7]. This finding points out that one should not rely on FKL for the diagnosis or exclusion of rejection.

Most of acute rejection episodes improved with steroid boluses and didn't have adverse effect on graft or patient survival. CR patients responded to increased immunosuppression and addition of Mycophenolate mofetil except for one patient.

Identification of risk factors for rejection in pediatric transplant recipients is vital for understanding the pathogenesis of rejection and may help to prevent further graft loss. So we analyzed the pre-operative, operative, post-operative and donor data on trying to predict the suspected risk factors for occurrence of rejection.

In agreement with *Gupta et al***.,** [8] we found that the recipient age and gender were not associated with the occurrence of rejection. Contrary to our results *Murphy et al.,* [9] observed that children under the age of 1 year had a lower incidence of both ACR and CR than older recipients, as cell mediated immunity is still immature in very young babies.

In the present study, transplantation for BA was the only incriminated risk for occurrence of rejection ($P<0.05$), this may be due to the proposed immune mediated mechanisms of BA [10]. Moreover there was no statistical significant difference between identical and compatible donor/recipient blood groups and the occurrence of rejection. Similar to our results, *Gomez-Manero et al***.,** [11] found that there was no influence of the blood group on the occurrence of rejection.

Our results revealed that the lowest incidence of rejection was in patients who began their immunosuppressive the day after LT. Therefore, it would be better to start immunosuppressant after LT. Concerning the FKL, unexpectedly most of rejection attacks were associated with high FKL levels. None of the operative or donor parameters were statistically significant risk factors for rejection although cold ischemia time, warm ischemia time, anhepatic phase and duration of the operation were longer in rejecters than non-rejecters, also the BMI was higher in the former. So proper donor selection and using rapid surgical techniques to reduce ischemic phases may help further decrease of the incidence of rejection.

Conclusion

BA was a significant risk for rejection. Elevated transaminases and biliary enzymes but not FK trough level is alarming signs for presence of rejection. Early diagnosis and adequate treatment is vital for graft and patient survival.

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