ORIGINAL ARTICLE

Evaluation of Complications in Children after Liver Transplantation: A Single Centre Study

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ABSTRACT

Objective: To evaluate complications in children after liver transplantation so an early referral and appropriate management could be instituted to improve the late outcome.

Study Design: Retrospective observational study.

Place and Duration of Study: The study was carried out at the Department of Pediatric Gastroenterology, Hepatology & Nutrition, KFSH&RC, Jeddah, Kingdom of Saudi Arabia. The data between 1/10/2006 and 1/10/216 was included and analysed.

Materials and Methods:

Sample Size: 15 patients fulfilled the criteria of selection and were recruited in the study.

Sampling Technique: The data was collected from the hospital's electronic records: power chart system.

Data Collection Procedure: A spread sheet was designed to collect data regarding demographics, primary diagnosis, long-term morbidity such as drug related complications, viral and bacterial infections, recurrence of cholestasis and primary disease, lympho-proliferative disease and graft versus host disease.

Data presentation: The data was presented in percentages and frequencies in the form of charts and a table.

Results: Among 15 children 12 were males, male to female ratio was 4:1. The median age at liver transplant was 2.5 years. Eight patients (53%) had either one or more episodes of bacterial infections, in the form of UTI, Sepsis, and throat infection. Five children (34%) developed EBV infection and 3 (20%) had CMV infection. Hypomagnesaemia was found in 14 (93%) children, while hyperphosphataemia and hypophosphatemia were noted in 9 (60%) and 5(33%) children respectively. Three (20%) children developed renal failure. Two (13%) children had recurrence of cholestasis, 1 (7%) child developed biliary stricture and another (17%) had chronic rejection. Only one child expired and the overall survival rate was 93%.

Conclusion: Infections and drugs related electrolyte abnormalities were the most common complications noted in children, 6 months after liver transplantation. With early detection and appropriate management, majority of complications could be detected and managed, which would have an impact on the long term survival.

Key Words: Liver transplantation, Complications, Infections, Drugs, Electrolytes

INTRODUCTION

First human liver transplantation (LT) was performed by Starzl in 19631 . Since then, it has evolved through many experimental procedures. Early efforts at LT had a significant intra-operative and post-operative mortality. Despite advances in surgical techniques, one-year survival remained poor throughout the 1970s, being only 30% in 1978. The advent of Cyclosporine in 1981 made a significant increase in early survival and reduced the need for long-term use of high dose steroids. The introduction of newer immunosuppressive drugs helped further to improve the outcome. At present, liver transplantation has become a preferred choice of therapy for acute and chronic liver failure. Children now comprise up to 12.5% of all liver transplantation recepients.2 The current one-year survival of children after LT for chronic liver disease has improved to 80–90%, and the majority has been enjoying a good quality of life.3

Several years ago, the main issue for children with end-stage liver disease had been to find a liver transplant. But today the focus has shifted to long-term follow-up and prevention of immunosuppression-related complications, as early identification and treatment of complications have made a big impact on patients survival.4,5 This led us to look into the possible complications, six months after the liver transplantation and their outcome in our centre.

MATERIALS AND METHODS

Operational Definitions

Late Infections: Any infection after six months of liver transplantation

Long term complications: complications due to any cause after six months of liver transplantation

Recurrence of cholestasis: cholestasis manifested clinically as well as by laboratory results after liver transplantation

Hypothesis

Liver transplantation has been the standard care of therapy for life-threatening paediatric liver diseases. The immediate prognosis and long term survival after LT has improved over time. So, it has become more important to know about the long term post LT complications and their outcome. Hence that would raise an awareness amongst both paediatric hepatology team and general paediatricians for the purpose of timely management of possible complications.

Sample Selection:

Inclusion Criteria: All children below the age of 18 years, who had undergone liver transplantation more than six months earlier, were included in the study.

Exclusion Criteria: Children who had undergone liver transplantation less than six months earlier were excluded from the study.

Data Collection Procedure: A spread sheet was designed and used to record data including the demographics, primary diagnosis, long-term morbidity such as drug related complications, viral and bacterial infections, recurrence of cholestasis and primary disease, lympho-proliferative disease and graft versus host disease.

Data Analysis: The data was presented in percentages and frequencies in the form of charts and a table.

RESULTS

Among 15 children 12 were males, male to female ratio was 4:1. The median age of liver transplant was 2.5 years. Regarding primary pathology, 6 children (40%) had PFIC type II, 1 child (7%) was with idiopathic hepatitis, 2 children (13%) had Alagille syndrome, 1 child (7%) was with biliary atresia, 2 children (13.3%) with sclerosing cholangitis , 1 child (6.6%) with congenital hepatic fibrosis, 1 child (6.6%) with had Criggler Najjar Syndrome and 1 child (7%) had mitochondrial disease (Fig1). Eight patients (53%) developed one to three episodes of bacterial infections, in the form of UTI, Sepsis, and throat infection. The isolated organisms included, Haemophilus influenzae, Staphylococcal aureus, Salmonella, Micrococus, Streptococcal pneumoniae, Acinobacter, and Aeromonas hydrophilia. Organisms causing urinary tract infection included, E-coli and Enterococus Faecalis. Two children developed Streptococcal throat infection. Eight patients contacted viral infections: 5(33%) of these were infected with EBV and the other 3 had contacted CMV infection. It is worth noting that none of the our patients who contacted EBV infection developed EBV related post transplant lymphoproliferative disorder (PTLD). Among other viral infections, Rhinovirus, Influenza b, Adenovirus, Parainfluenza viruses were noted in 4(26%) children (Table 1). Most commonly noted electrolyte imbalance was hypomagnesaemia, which was found in 14 children (93%). Hyperphosphataemia and hypophosphataemia were noted in 9 (60%) and 5(33%) children respectively. No other electrolyte imbalance was noted after in our patients. Three children (20%) developed renal failure. Of these patients: one child had underlying polycystic kidney disease, second child had vesicoureteric reflux and the third child developed renal failure, possible as complication of Tacrolimus toxicity. Regarding hepatobiliary and vascular complications we found 2 (13%) children with recurrence of cholestasis, 1 (7%) child with biliary stricture and 1(7%) child had chronic rejection. Figure 2 can be referred for the spectrum of complications. Figure 1: Aetiology of liver transplanted patients

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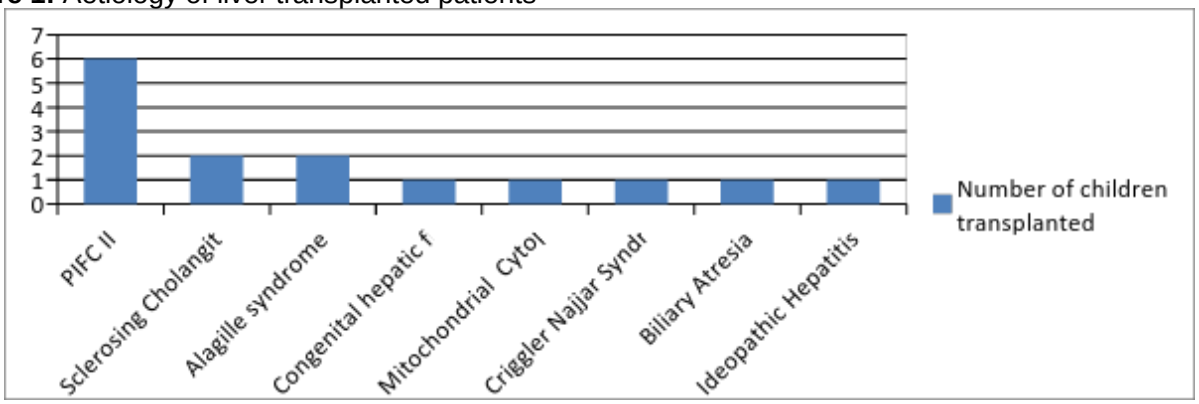

Figure 2: Spectrum of complications after liver transplantation

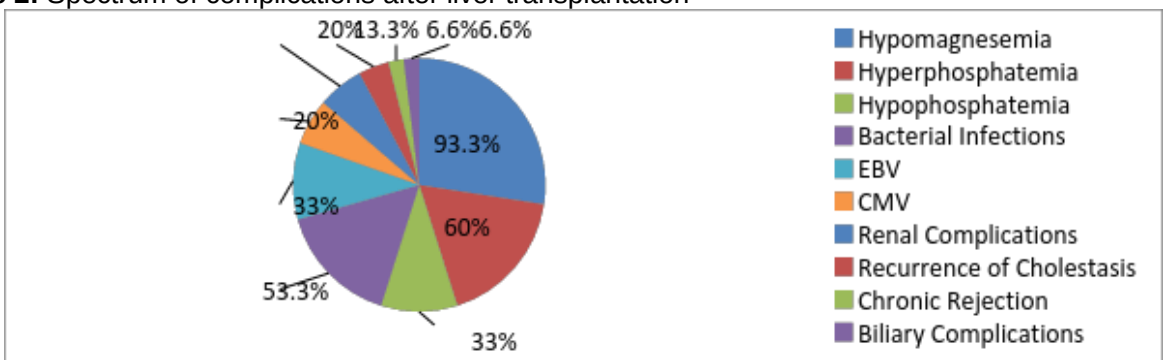

Table 1: Common Organisms causing bacterial and viral infections in affected patients Diagnosis Organisms Sepsis

Diagnosis	**Organisms**
Sepsis No. of children 4(27%)	Haemophilus influenzae, Staphylococcal aureus, Salmonella, Micrococcus, Streptococcal pneumonia, Acinobacter, Aeromonas hydrophilia
Urinary Tract Infection No. of children 2(13%)	E-coli, Enterococcus faecalis
Throat Infection No. of children 2(13%)	Group A Streptococci
Viral Infections No.of children 5(33%)	Epstein Barr virus
Viral Infections No. of children 3(20%)	Cytomegalovirus
Other Viral Infections No. of children 4(27%)	Rhino virus, Influenza b, Adenovirus, Parainfluenza

Overall survival was 93%.Only one child expired but that was due to chronic graft rejection.

DISCUSSION

Although liver transplantation has led to marked improvement in survival rate, many children still can have complications like recurrent bacterial and viral infections, graft versus host disease, drug toxicity, CMV or EBV related post- transplant infections, recurrence of cholestasis, post-transplant lympho-proliferative disorder and recurrence of the primary disease.6 Traditionally the infections have been categorized into three time zones, according to the time period after the LT. These are called as: early (0-30 days), intermediate (1-6 months), and late (>6months).7,8 We have reported the data regarding late infections only in our patient population who had LT at least 6 months earlier. Generally bacterial

infections are common during the first two weeks after liver transplantation due to use of Calcineurin inhibitors (tacrolimus and cyclosporine), steroids or anti-lymphocyte antibodies to prevent severe rejection.9,10 But in our study even after six months of LT a significant number of children had bacterial infections despite being on optimum immunosuppression therapy. Multiple studies have shown that viral infections induced by CMV, EBV, herpes simplex, herpes zoster, adenovirus and parvovirus B19 are common after liver transplantation and the most likely cause has been due to over immunosuppression.11,12,13,14,15 In our study CMV,EBV, Rhino virus, Influenza b, Adenovirus and Parainfluenza virus were found to be the main organisms causing infection. CMV and EBV infections were treated successfully by ganciclovir and by reducing the dose of immunosuppressive drugs respectively. Infections by other viruses were resolved spontaneously without any further treatment. The most likely cause of hypomagnesaemia was due to tacrolimus toxicity which was corrected by reducing the dose of tacrolimus and by adding magnesium oxide. Similarly hyperphosphataemia and hypophosphataemia were treated accordingly. One of the potential complications after LT has been the renal toxicity. It has been reported in about 9 % of patients after LT. The cause of long term nephrotoxicity is found to be secondary to drugs like Calcineurin Inhibitors.16,17 In our study 3(20%) children developed renal failure but it was only in one patient that was related to drug toxicity. In the other two patients renal failure was found to be secondary to underlying polycystic kidney disease and vesicoureteric reflux. The reported incidence of hepatobiliary complications is 5-30%.18 We found only 1(7%) child who developed biliary stricture which is comparable to international studies. Recent studies have also shown that the incidence of chronic rejection has decreased from 10% to 5%.19.20 In our study only 1(7%) child developed chronic rejection. The literature has also shown that portal vein or hepatic artery thrombosis are considered as immediate complications after liver transplantation.21 But we did not encounter any such complication in our group of patients. This may have been due to the fact that we collected the data six months after the liver transplantation. Although recurrence of primary disease has been reported but no recurrence of disease was found. 22 ,23,24 Overall survival was excellent in our study.

CONCLUSION

Infections and drugs related electrolyte abnormalities were the most common complications in children after 6 months of liver transplantation. Majority of complications after liver transplantation are treatable. With early detection and appropriate management the outcome and survival rate are good after liver transplantation in children.

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