Hepatic dysfunction in kidney transplant recipients: prevalence and impact on graft and patient survival

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Abstract

Background. Liver disease has emerged as an important cause of morbidity and mortality in renal transplant recipients. Liver insufficiency is the cause of death in up to 28% of long-term survivors after renal transplantation. The aim of this work was to evaluate the prevalence and causes of hepatic dysfunction in renal transplant recipients in Egypt, and its impact on both renal graft function and patient survival.

Methods. This study comprised 447 kidney transplant recipients who received their grafts between January 1999 and December 2003 at Mansoura Urology and Nephrology Center. Among these recipients, 104 patients showed persistent hepatic dysfunction, while the remaining 343 had normal liver function or transient hepatic dysfunction of less than 6 months' duration.

Results. We found that the prevalence of persistent hepatic dysfunction in our recipients was 23.3%. Infections such as hepatitis C virus (HCV), with longer dialysis duration and blood transfusion as risk factors), HBV, and cytomegalovirus (CMV), were the main causes of persistent hepatic dysfunction, while hepatitis E was associated with hepatic dysfunction. We did not find a significant impact of hepatic dysfunction on either patient or graft survival.

Conclusions. Viral infections—especially HCV and CMV—were more prevalent in the group of patients with persistent hepatic dysfunction, with duration of dialysis as an important risk factor for HCV infection. Dose-dependent cyclosporine-induced hepatic dysfunction was observed early post-transplant. Neither tacrolimus- nor sirolimus-associated hepatic dysfunction was dose-dependent. Hepatic dysfunction had no significant impact on either patient or graft survival; however, this finding may be due to the relatively short duration of follow up.

Key words Hepatic dysfunction · Renal allograft transplant

Introduction

Chronic liver disease is one of the leading causes of late morbidity and mortality among recipients of long-surviving allografts. There are many causes of liver dysfunction following renal transplantation. Drugs were responsible for approximately half of all cases of liver dysfunction in some series.

Viral infection is an important cause of hepatic complications post-transplantation. In developing countries, kidney transplant recipients are more prone to viral infections due to many risk factors such as malnutrition, poverty, and tropical climate. In Egypt, the most common virus that leads to hepatic complications is hepatitis C virus (HCV), which has the highest prevalence in developing countries. In chronic HCV infection, liver cirrhosis and hepatocellular carcinoma take place over the years.

Hepatic dysfunction after kidney transplantation is expected to be more prevalent among Egyptians due to the impact of schistosomiasis and HCV. However, no published data concerning this valuable subject are available.

So, the aim of this work was to evaluate the prevalence and causes of hepatic dysfunction in renal transplant recipients, and its impact on both renal graft function and patient survival.

Patients and methods

Between January 1999 and December 2003, 447 patients with chronic renal failure were transplanted at Mansoura Urology and Nephrology Center. We adopted a policy that all patients should have normal liver function before transplant.
plantation and any patient with elevated liver enzymes should be thoroughly evaluated. We found that most patients had HCV and they were followed up until normalization of liver enzymes for at least 6 months. All patients were classified irrespective of their pre-transplant virology--as either belonging to a non-hepatic group (patients who had normal liver functions throughout the study period or had transient elevation of transaminases for less than 6 months; \( n = 343 \)) or a hepatic group (those who had persistent elevation of transaminases for 6 months or more (\( n = 104 \)).

All patients received azathioprine and prednisolone (conventional protocol) or a triple protocol consisting of prednisolone, cyclosporine A (CsA), and azathioprine. Prednisolone was started on the transplantation day (8.5 mg/kg per day), and was reduced to a maintenance dose of 0.15 mg/kg per day by the ninth month. CsA was started orally 2 days before transplantation at a dose of 8.5 mg/kg per day, and then adjusted to maintain the whole blood level between 200 and 400 ng/ml during the first 2 months and between 100 and 150 ng/ml thereafter. Azathioprine was added on the third day post-transplantation at a dose of 1 mg/kg per day. Tacrolimus (FK 506) was used as the primary immunosuppressive drug in high-risk patients. Sirolimus-based immunosuppressive protocols were also used, utilizing tacrolimus or mycophenolate mofetil (MMF) and steroid.

All patients were evaluated by the end of first month and then at 3, 6, and 12 months after the transplantation date, and then annually until the last follow up, (5 years after transplantation). At each visit, each patient was evaluated clinically, with special emphasis on signs of hepatic dysfunction. The medical records of all patients were examined regarding the following details.

Clinical data

The following parameters were reviewed: recipient age and sex, cause of endstage renal disease, HLA-A-B-DR matching, pre-transplant viral status, and blood transfusion details, history of schistosomal infestation, pre-transplant dialysis (type and duration), type of primary immunosuppression, and donor age and sex.

Laboratory data

Each visit, the graft was assessed by carrying out examinations of serum creatinine, blood urea, and creatinine clearance, and urine analysis; in addition to a complete blood picture, drug levels and plasma cholesterol were examined and plasma sugar was measured in diabetics. Liver function tests--bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total plasma protein, albumin, prothrombin time, and INR--were performed every third visit. Viral profiles--hepatitis B surface antigen (HBs Ag), anti-HCV antibody, HCV polymerase chain reaction (PCR), anti-cytomegalovirus (CMV) IgM, and anti-HIV 1 and 2--were performed shortly before transplantation and at least once post-transplantation.

Radiological data

Abdominal ultrasonography was used to evaluate the graft, liver, and spleen as regards size, echogenicity, anatomical abnormalities, and presence or absence of ascites.

Histopathological data

Graft biopsies were performed in each patient for whom there was a clinical suspicion of rejection, and rejection was classified according to the Banff schema of 1997.

Statistics

Bivariate analysis techniques were used for the initial evaluation of differences. The \( \chi^2 \) and Fisher’s exact tests were used for comparisons of frequencies of qualitative variables and the unpaired \( t \)-test was used for comparisons of quantitative variables. A \( P \) value of less than 0.05 was considered significant. All analyses were carried out using the computer package SPPS for Windows (release 10, SPSS, Chicago, IL, USA).

Results

The two groups were comparable regarding the demographic data, except for a significantly longer duration of hemodialysis (\( P = 0.001 \)) and a higher prevalence of CMV infection (\( P = 0.01 \)) in the hepatic patients (Table 1). The most common original kidney diseases were chronic interstitial nephritis and chronic glomerulonephritis, and the rates were comparable in the two groups. Also, we found no significant differences between the groups regarding the number of HLA A, B, DR mismatches; number of blood transfusions; or Child Pugh score at the start and during the follow-up periods. All patients were Child class A when evaluated at the last follow up.

Hepatic dysfunction was significantly more prevalent among the sirolimus (\( P = 0.008 \))- and tacrolimus (\( P = 0.007 \))-based immunosuppression groups (Fig. 1). The percentage of HCV-positive patients was significantly higher in the hepatic group at different times of follow up (\( P = 0.001 \); Fig. 2). Liver enzymes (ALT, AST) were significantly higher in the hepatic group compared to the non-hepatic group at different follow-up intervals (\( P = 0.001 \)). We found no significant differences between the groups regarding mean prothrombin concentration, serum albumin, bilirubin, or creatinine. Also, we found no significant differences between the groups regarding hemoglobin levels or platelet counts.

In spite of a significant rise in the mean CsA level 1 month after transplantation in the hepatic group, we found no significant differences in its dosages between the two groups at different follow-up periods. Regarding the other immunosuppressive agents, we found no significant differ-