Characterizes of Liver Enzymes on Living Related Liver Transplantation Patients with Acute Rejection

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ABSTRACT
Background/Aims: To determine the biochemical data that reliably predict allograft injury from acute rejection (AR) in patients with living related liver transplantation (LRLT), liver function test and histopathological characteristics of AR were compared and analyzed retrospectively.

Methodology: From Aug. 1994 to Nov. 2000, 101 cases received orthotopic liver transplantation (OLT), which included 53 patients with LRLT in our series. Completed liver functions including aspartate transferase (AST), alanine transferase (ALT), bilirubin total/direct (Bil.T/D), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) were collected with peak level when AR was diagnosed by liver biopsy. The best data of the same patients when disease free, were compared and analyzed with non-parametric Wilcoxon signed ranks test and Mann-Whitney test. All of the ARs were reversed with steroid pulse therapy, and two cases converted to FK506. No steroid-resistant rejection or chronic disease free, were compared and analyzed with non-parametric Wilcoxon signed ranks test and Mann-Whitney test. All of the ARs were reversed with steroid pulse therapy, and two cases converted to FK506. No steroid-resistant rejection or chronic rejection was found in our series.

Results: In the patients with LRLT, 17 episodes in 13 patients with AR were found. The incidence of histological analysis proved AR was 12.9% (13/101) in OLT and 24.5% (13/53) in LRLT respectively. Among the liver function tests, AST (p<0.0001), ALT (p<0.0001), Bil.T (p=0.001), Bil.D (p=0.001), GGT (p>0.0001), and INR (p=0.034) were the significant predictors respectively in the patients with AR episode. Once liver enzymes had elevated, the AST/ALT ratio <1.0 showed a more significant difference in AR than in those of the no rejection group (p<0.0001). ALP showed significant difference in our series. The severity of histological change was not correlated to the degree of liver enzymes elevation.

Conclusions: Complete liver function tests especially AST, ALT, Bil.T/D, GGT and the ratio of AST/ALT are very sensitive tests in a group of patients receiving LRLT with AR. The severity of AR is based on the histopathologic change but is not related to the degree of liver enzymes elevation. Meanwhile, the outcome of acute rejection in living related liver transplantation is quite good.

INTRODUCTION
Although more effective and potent immunosuppressants to prevent rejection are available, acute graft (cellular) rejection is still a major problem following orthotopic liver transplantation especially in patients with living related liver transplantation (LRLT) (1). Acute rejection is characterized histologically by portal hepatitis, endothelialitis and lymphocytic cholangitis that can be difficult to predict in early phases (2). Cellular rejection is generally reversible, either spontaneously or with additional immunosuppressive therapy. Because clinical and laboratory tests are unreliable for the detection of acute rejection, the purpose of this study was to compare biochemical abnormalities associated with a rejection episode in a group of patients receiving living related liver transplantation versus the same patients who were disease free.

METHODOLOGY
From Aug. 1994 to Nov. 2000, 101 cases received orthotopic liver transplantation (OLT), which included 53 patients with living related liver transplantation (LRLT) in our series. The patient profiles are shown in Table 1. Complete liver functions including aspartate transferase (AST), alanine transferase (ALT), bilirubin total/direct (Bil.T/D), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) were collected by retrospective chart review with attention to the peak level when acute rejection was observed.
diagnosed by liver biopsy (Figure 1). The best data on the same patients after rejection had cleared were analyzed using paired samples t test. All patients had regular evaluation from the time of transplantation through a follow-up period of at least 6 months. Evaluation for clinical or biochemical evidence of rejection was performed at least monthly for the first 6 months after transplantation and then at least every 3 months for 1 year. Baseline immunosuppression consisted of the following: cyclosporine (CyA) 600mg/m2/d (Neoral) in pediatric patients, 15mg/kg/d in adults; intravenous methylprednisolone or oral prednisolone when tolerated; and azathioprine 2mg/kg/d then discontinued provided that the patient had not experienced an episode of severe rejection in the preceding 6 months. All of the acute rejections were reversed with steroid pulse therapy, and two cases were converted to FK506. No steroid-resistant rejection episodes or chronic rejections were observed in this series. The statistical analysis used an independent-samples t test and paired-samples t test. P values less than 0.05 were considered significant. Calculations were performed using statistical software (SPSS for Windows, release 10.0.0, standard version; Copyright c SPSS Inc., 1989-1999. All rights reserved).

RESULTS

In the patients with LRLT, 17 acute rejection episodes were observed in 13 patients. The incidence of histologically proven acute rejection episodes was 12.9% (13/101) in OLT and 24.5% (13/53) in LRLT. Among the liver function tests, GGT (p<0.0001), ALT (p=0.001), total bilirubin (p=0.005), direct bilirubin (p=0.006), AST (p=0.012), and INR (p=0.028) were the significant biochemical predictors of an acute rejection episode (Table 2). The ratio of AST/ALT showed a significant difference in the LRLT patients with AR versus those without AR (0.9918±0.4185 vs. 1.5259±0.4633, p<0.0001) (Table 3). Alkaline phosphatase (ALP) was not significantly different in our series. The severity of the histological change did not correlate with the elevation of liver enzymes. The other factors including age, sex, rejection in the first month, original disease diagnosis and viral related disease did not contribute to the severity of the acute cellular rejection among patients with LRLT. All of the AR episodes were reversible, either spontaneously or with additional immunosuppressive therapy.

DISCUSSION

In the present study, liver biochemical tests including GGT, ALT, Bil.T/D, AST, INR were significant and sensitive predictors of an acute rejection episode in patients receiving LRLT. Because ALP activity is not specific for the liver (and may come from...
a bony source), it was not directly influenced by acute rejection attack in our series particularly since most of our patients were young children. The use of the AST/ALT ratio has been proposed as a possible means of differentiating acute rejection among orthotopic liver transplantation patients. However, this phenomenon was also found in the patients with icteric hepatitis (3) and post-necrotic non-alcoholic liver cirrhosis (4). The severity of acute rejection based on the histopathologic change was not related to the degree of liver enzyme elevation. The acute rejection episodes after LRLT in our patients fulfilled the criteria of the accepted pathologic classification (2), particularly since liver biopsy is an important tool for the diagnosis of acute rejection after LRLT (5). All of the acute rejection episodes were reversible; there was no chronic rejection, possibly due to detection in the initial phase of acute rejection. Even weekly liver biopsies in the LRLT pediatric recipients have been suggested by the investigators when there are abnormalities liver enzymes including AST/ALT ratio.

CONCLUSION

Complete liver function tests including the ratio of AST/ALT, GGT, ALT, Bil.T/D, and AST proved to be sensitive predictors of an acute rejection in a group of patients receiving living related liver transplantation. The severity of acute rejection is based on the histopathologic change but is not related to the degree of liver enzyme elevation itself. Overall there are excellent outcomes of acute rejection in living related liver transplantation.

REFERENCES