Abstract

Purpose: Tacrolimus-related neurotoxicity is a serious complication. Posterior reversible encephalopathy syndrome (PRES), which is severe neurotoxicity after pediatric living donor liver transplantation (LDLT), is a medication-induced complication related to calcineurin inhibitors. The purpose of this study was to evaluate the long-term outcome of tacrolimus-related neurotoxicity after pediatric LDLT.

Methods: Pediatric patients who underwent LDLT between 2007 and 2020 at our institution who developed neurological symptoms with tacrolimus were included in the study. Tacrolimus-related encephalopathy was defined as encephalopathy that resolved after tacrolimus was stopped. All patients received tacrolimus and a steroid for immunosuppression starting just after LDLT.

Results: During the study period, 128 patients underwent LDLT. All patients received tacrolimus and a steroid. Six patients (5%) developed tacrolimus-related encephalopathy. The median age at transplant was 1.6 years. The original diseases were biliary atresia (n=5) and progressive familial intrahepatic cholangiopathy type 2 (n=1). Patients developed encephalopathy at a median of 9 days after LDLT. All patients recovered with conversion to cyclosporine. PRES was confirmed by magnetic resonance imaging in 3 patients. The mean tacrolimus level at encephalopathy was 11 ng/dL (range, 5.6 to 14.6 ng/dL). White blood cell

count elevation was observed in all patients. One patient died of pancreatitis. Surviving patients (n=5) were followed for a median of 9 years. All patients resumed tacrolimus a median of 8 months from onset. No neurological complications were observed after resuming tacrolimus.

Conclusions: We observed tacrolimus-induced encephalopathy in 5% of patients after pediatric LDLT. Patients can resume tacrolimus safely without further neurological symptoms.

Introduction

Neurological complications were recently recognized as long-term survival improved after liver transplantation. The main types of neurological complications include encephalopathy, seizure, immunosuppressant-related neurotoxicity, and peripheral nerve damage [1, 2].

Tacrolimus (TAC)-related neurotoxicity is a serious neurological complication. One type of TAC-related neurotoxicity is encephalopathy. Posterior reversible encephalopathy syndrome (PRES), which is severe encephalopathy after pediatric living donor liver transplantation (LDLT), is a medication-induced neurotoxicity related to calcineurin inhibitors (CNIs), including TAC. The cause of neurotoxicity with PRES remains controversial, especially in pediatric patients. Pediatric cases and long term outcome were rarely reported. The purpose of this study was to evaluate acute laboratory data changes and the long-term outcome of TAC neurotoxicity, especially TAC-related encephalopathy after pediatric LDLT.

Methods

Pediatric patients who underwent LDLT between 2007 and 2020 at our institution and who developed neurological symptoms with TAC were included in the study. TAC-related encephalopathy was defined as encephalopathy that resolved after TAC was stopped. All

patients received TAC and a steroid for immunosuppression starting just after LDLT. Patients were tapered from TAC-based immunosuppression and steroids (Methylprednisolone and Predonisolone) according to our protocol. The standard protocol for TAC tapering was as follows: the target TAC trough level was 10–15 ng/mL for the first month after transplantation, which was tapered to 3–5 ng/mL thereafter. All patients initially received steroids. Steroids were usually tapered off by 4 months after transplantation.

White blood cell (WBC) and platelet counts were assessed with a daily complete blood count test. WBC and platelet counts on the day before symptom onset versus on the day of symptom onset were compared.

Data were analyzed using the JMP software package, version 11 (SAS, Cary, NC, USA). Continuous variables are presented as medians with ranges or as mean with standard deviation (SD). They were compared using Student's t-test. Linear regression was performed. A *P* value less than .05 was considered to be statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Congress and the Istanbul declaration regarding donor source regarding donor source. Donors must not be from prisoners, or from those individuals who are coerced or

paid.

Results

During the study period, 128 patients received LDLT. Six patients (5%) developed TAC-related encephalopathy. The median age at transplant was 1.6 years (range, 0.9 to 8.2 year old). The original diseases were biliary atresia (n=5) and progressive familial intrahepatic cholangiopathy type 2 (n=1). Patients developed encephalopathy at a median of 9 days (range, 6 to 661 days) after LDLT. The symptoms were seizure (n=3) and drowsiness (n=3). Immunosuppressive agents at the time of onset were TAC and a steroid (Methylpredonisolone).

All patients recovered with conversion to cyclosporine (CYA) except for 1 patient. PRES was confirmed by magnetic resonance imaging (MRI) in 3 patients A typical image of patient 2 was shown in Fig. 1 (a). The median serum TAC level at onset of encephalopathy was 11 ng/dL (range, 5.6 to 14.6 ng/dL).

One patient did not respond to the switch to CYA because seizure continued. Therefore, CYA was switched to everolimus. The patient developed blindness. Ultimately, he passed away from necrotizing pancreatitis. The other 5 patients recovered fully after conversion to CYA.

The surviving patients (n=5) were followed for a median of 9 years (range, 7.7 to 14 years). All patients resumed TAC a median of 8 months (range, 0.8 to 113 months) after onset of encephalopathy. No neurological complications were observed after switching back to TAC. A summary of the patients is shown in Table 1.

WBC and platelet count change of patient 5 were shown in Fig. 1(b). WBC count elevation was observed in all patients at the time of encephalopathy onset. Mean WBC count was 18,500/mm^3 (SD: 65000/mm^3), which was a 2.8-fold increase compared with 2 days before the episode of TAC-related encephalopathy in **Fig. 1(c)**. WBC and eosinophil counts were elevated at the time of onset of encephalopathy. Platelet count was elevated in 5 patients. Mean platelet count was 150,000/mm^3 (SD: 32000/mm^3), which was a 2.1-fold increase, similar to the WBC count in **Fig. 1(d)**.

Discussion

PRES is a rare neurologic adverse effect of CNIs with poorly understood clinical features. Symptoms are typically reversible and include confusion, headache, visual disturbances, seizures, loss of consciousness, paresthesia, insomnia, and tremor. However, these symptoms are not obvious in pediatric patients.

After liver transplantation, patients experience neurologic complications because of

poor clinical condition, presurgical encephalopathy, and complex surgery. In addition, CNIs play a direct role in PRES in liver transplant recipients [3]. Bernhardt et al reported that the incidence of PRES ranges from 0.5% to 7% in adult cases [4]. Cruz et al reported that PRES comprises only 1% of neurologic complications in adults after deceased donor liver transplantation [5]. In our pediatric LDLT patients, 5% of pediatric LDLT patients had suspected PRES. The prevalence of TAC-related encephalopathy was similar to that in previous reports.

Cruz et al reported that the risk of PRES peaks 3 months after liver transplantation in an adult series [5]. Bartynski et al reported that medication-induced PRES is most frequently reported soon after transplantation [6]. Liu reported that PRES occurs 10 days after adult liver transplantation [7]. In our patients, onset mostly occurred within 10 days, except for 1 case.

The etiology of PRES is not well understood. TAC reduces the expression of p-glycoprotein in the endothelium of the brain, leading to dysfunction of the blood-brain barrier and vasogenic edema [8]. TAC-related PRES needs to be rapidly diagnosed after transplantation as delayed diagnosis can cause permanent neurological problems. MRI with diffusion-weighted sequences provides a powerful means of diagnosing PRES [9].

In the acute phase, vasogenic edema in the subcortical parietal-occipital white matter

is a classic feature, best demonstrated with MRI. Therefore, MRI is the most sensitive imaging test for detection. However, it is difficult to perform in pediatric patients because it requires deep sedation.

The pathophysiological mechanism underlying PRES is not fully understood. Hypotheses include medication-induced endothelial damage and hyperperfusion due to disruption of the cerebral autoregulation system. Endothelial dysfunction is a key factor [10] that may be related to WBC and platelet counts. In our series, patients had elevated WBC and platelet counts, suggesting that WBCs might play a role in TAC-related encephalopathy, and that WBC count might be useful for early detection of TAC-related encephalopathy. WBC and platelet counts might help detect PRES without MRI.

In patients with TAC-related PRES, the dose of TAC is reduced or discontinued. TAC-related PRES is unrelated to drug levels. Some patients have experienced permanent or even fatal neurologic damage even after dose reduction or discontinuation [11]. TAC should be promptly switched to other immunosuppressive agents, including CYA. Most patients recovered. However, PRES induced by everolimus has also been reported [12]. Once a patient has recovered, TAC can be resumed safely in our experience.

CNI-related PRES has a good prognosis with early diagnosis and changes to immunosuppressive agents [13]. Actually, most of our patients had a favorable long-term

prognosis, except for 1 patient who did not improve.

Conclusions

We observed TAC-related encephalopathy in 5% of patients after pediatric LDLT. Patients can resume TAC safely without further neurological symptoms.

References

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