Dear Editor:

The calcineurin-inhibitor tacrolimus (FK506) is widely used to prevent rejection and graft loss in solid organ transplantation. It induces immunosuppression by inhibiting interleukin 2 and interferon-gamma production. Tacrolimus is metabolized in the liver via CYP3A4 and has high inter-and intra-personal variability [1]. Moreover, tacrolimus has a very narrow therapeutic index, requiring constant increase for success of solid organ transplantation while reducing its adverse effects. Therefore, monitoring tacrolimus blood trough concentration is mandatory to optimize treatment after organ transplantation. The most common side effects of tacrolimus are neurotoxicity, nephrotoxicity, and electrolyte abnormalities. Neurologic complications occur in 8.2% of patients who have undergone liver transplantation, with encephalopathy being the most common. Herein, we report for the first time an infant who underwent living donor liver transplantation (LDLT) and developed chorea due to tacrolimus neurotoxicity. Written informed consent was obtained from the patient’s parents.

A 45-day-old boy presented with biliary atresia, for which he underwent a Kasai portoenterostomy at 80 days of age. Biliary drainage was achieved, but his course was complicated by recurrent cholangitis episodes and ascites. He was not thriving and developed portal vein thrombosis. Therefore, LDLT was planned. At 10 months of age, weighing 6 kg, LDLT was performed with a liver from his father. A reduced left lateral segment graft weighing 180 g was implanted following thrombectomy and portal vein reconstruction with patch venoplasty. The graft weight-to-body weight ratio was 3%. Postoperative anti-rejection therapy initially consisted of corticosteroid and tacrolimus. Tacrolimus was adjusted to maintain trough blood level within the range of 10–12 ng/ml. The targeted tacrolimus level was between 5–6 ng/ml. On post-transplant day 5, mycophenolate mofetil (MMF) was added.

The early postoperative course was uneventful except for atelectasis. On postoperative day 6, the patient developed choreiform movements, which were non-repetitive, irregularly timed, spontaneous movements in both arms. No obvious reason for these movements could be found. He was on methylprednisolone (0.3 mg/kg/day), tacrolimus (0.125 mg/kg/day), and MMF (530 mg/m²/day). The tacrolimus blood trough level was 16.1 ng/ml. After starting MMF, the tacrolimus blood level target was decreased from 10–12 ng/ml to 5–6 ng/ml. However, during follow-up, the blood drug level started to increase. The tacrolimus dose, which was started at 0.25 mg/day, was continued at 0.5 mg in the morning and evening according
to the drug level. On the 6th day after transplantation, the tacrolimus blood level was 16.1 ng/ml, and the tacrolimus dose was skipped. On the 7th day, a single dose of 0.25 mg/day was given. No seizures were observed until the 8th day after transplant when the tacrolimus level was 6 ng/ml without the daily dose, encephalopathy increased and generalized tonic-clonic seizure activity was observed. Immediate administration of intravenous midazolam at 0.1 mg/kg during the seizure led to its rapid resolution, after which the patient was put on levetiracetam for seizure control. The patient’s electrolytes were within normal reference values, except magnesium and calcium. That day, the patient experienced brief, semi-directed, irregular movements of the upper extremities. These movements were explained as chorea on pediatric neurology consultation. Chorea, encephalopathy, and seizures were attributed to tacrolimus neurotoxicity, and the drug was withheld until blood trough level was below the target level. The patient was conscious but apathetic and experienced truncal hypotonia. Neurological examination revealed normal cranial and peripheral nerves and motor systems but meningeal irritation. Post-seizure biochemical parameters were calcium 6.5 mg/dl, ionized calcium 0.7 mmol/L, and magnesium 1.1 mg/dl. However, the calcium and magnesium values measured 8 hours prior were within the normal reference values. All electrolyte abnormalities were resolved. Computerized cranial tomography was not ordered because the patient showed no focal neurologic findings. The next day when tacrolimus blood trough level reduced to 3.9 ng/ml, his choreiform movements resolved, his encephalopathy improved, and seizure did not repeat. Tacrolimus was restarted with a target blood trough level of 4–5 ng/ml. The patient was discharged from the pediatric intensive care unit 13 days after LDLT with normal vital signs, neurologic findings, and graft function. He was still doing well at 30 days post-transplant when the tacrolimus level was 6 ng/ml without the daily dose neurotoxicity. Hemodialysis is not useful in tacrolimus toxicity since tacrolimus is lipophilic and mostly bound to plasma proteins and erythrocytes. Tacrolimus has a high distribution volume and its blood concentration is 10 to 30 times higher than plasma concentration. Therefore, red blood cell exchange is the only reliable option to address tacrolimus toxicity.

Vasospasm resulting in brain hypoperfusion was demonstrated in tacrolimus users by magnetic resonance angiography. That study indicated that tacrolimus can cause PRES via reversible vasospasm resulting in brain hypoperfusion [3]. Furthermore, tacrolimus can induce encephalopathy by hypomagnesemia, which can lead to vasoconstriction. Thus, in our patient, chorea, seizure, and encephalopathy occurred due to low magnesium level.

To the best of our knowledge, there is only one case report describing chorea in a 14-year-old girl who was given tacrolimus following renal transplantation. However, blood tacrolimus trough level at the time of chorea was not included in that case report [4]. The authors report that the chorea symptoms resolved by maintaining a tacrolimus blood trough concentration at 4–5 ng/ml [4]. Similarly, in our patient, choreiform movements regressed when tacrolimus blood trough level decreased. If tacrolimus neurotoxicity occurs, the first step is to reduce or skip the dosage. Phenytoin, which is a strong CYP3A4/5 inducer, can be used to increase the metabolism of tacrolimus to combat neurotoxicity. Hemodialysis is not useful in tacrolimus toxicity since tacrolimus is lipophilic and mostly bound to plasma proteins and erythrocytes. Tacrolimus has a high distribution volume and its blood concentration is 10 to 30 times higher than plasma concentration. Therefore, red blood cell exchange is the only reliable option to address tacrolimus toxicity [5].

In conclusion, neurotoxicity is a serious adverse effect of tacrolimus, and the precise mechanism of action is not understood. To prevent adverse effects, electrolyte disturbances and blood trough levels above the therapeutic range should be avoided, especially in infants receiving tacrolimus.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.
Tacrolimus toxicity-related chorea

AUTHOR CONTRIBUTIONS

Conceptualization: FK, AG, EB. Data curation: AG, OB. Formal analysis: FK. Methodology: TK, MK, ZK, DB. Project administration: FK, TK, ZK. Visualization: FK. Writing—original draft: FK, AG, MK, DB, AK. Writing—review & editing: TK, EB, MK, OB, ZK, DB, AK.

REFERENCES


