CASE REPORT

Tacrolimus-induced encephalopathy and polyneuropathy in a renal transplant recipient

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SUMMARY

Tacrolimus is an immunosuppressant frequently used following solid organ transplantation, including renal transplantation. Peripheral neuropathy is an uncommon neurological side effect of tacrolimus and has rarely been reported in renal transplantation. We report a patient who received a living-related donor kidney transplant and presented with altered mental status and new-onset bilateral foot drop. Laboratory tests including cerebrospinal fluid tests excluded infection, and MRI of the brain showed chronic microvascular ischaemic changes. Electromyography and nerve conduction study confirmed bilateral common peroneal nerve demyelination. He was also found to have inadvertently overdosed on tacrolimus at home. After switching from tacrolimus to cyclosporine, the patient's symptoms improved within 5 months. His renal function was maintained with an immunosuppressant regimen of cyclosporine, prednisone and mycophenolic acid. The prompt recognition of tacrolimus as a potential neurotoxic drug in a patient with renal transplant and substituting tacrolimus with a different immunosuppressant may prevent permanent neurological damage.

BACKGROUND

Tacrolimus, also known as FK 506, is a calcineurin inhibitor and macrolide antibiotic that is frequently used as an immunosuppressant following solid organ transplantation. Use of tacrolimus for initial immunosuppression in kidney transplant recipients has increased from 25.9% in 1998 to 87.8% in 2009 (Scientific Registry of Transplant Recipients data 2010).[1] Unfortunately, the use of tacrolimus has been associated with moderate or even severe neurological side effects. One uncommon side effect of tacrolimus is peripheral neuropathy.

We report a case of tacrolimus-associated neurotoxicity due to tacrolimus overdose, manifesting as mildly altered mental status and bilateral foot drop. Electromyography and a nerve conduction study confirmed demyelinating polyneuropathy affecting the common peroneal nerves bilaterally. Recovery of neurological function of the affected limbs occurred 5 months after tacrolimus immunosuppression was discontinued and switched to cyclosporine.

CASE PRESENTATION

The patient was a 69-year-old man with a medical history significant for transient ischaemic attack, coronary artery disease status post four coronary stents, monoclonal gammopathy of undetermined significance and end-stage renal disease secondary to hypertension. He received a living donor kidney transplant from his daughter. The transplant was a 1-haplotype match with negative pre-transplant flow cytometry cross matches. The patient's early post-transplant course was uneventful. The serum creatinine improved to 1.23 mg/dL by 7 days post-transplant. The patient did not receive any antibody induction therapy. He was immunosuppressed with high-dose intravenous methylprednisolone for the first 2 days (500 mg and then 250 mg), which was then converted to oral prednisone at 30 mg twice daily. He was also started on oral tacrolimus (5 mg twice daily), with an initial trough goal of 8–12 ng/mL and mycophenolic acid (720 mg twice daily). The prednisone was tapered by approximately 10 mg every week, with an eventual goal maintenance dose of 5 mg daily.

Twenty days after transplantation, the patient was seen for a routine follow-up visit in the transplant clinic and was noted to be mildly confused with a new-onset bilateral foot drop. The 12 h tacrolimus trough level was 48.1 ng/mL. On further questioning, it was found that due to confusion, the patient was inadvertently taking doses of the tacrolimus that were much higher than prescribed. The tacrolimus was then stopped. Five days later, the tacrolimus level had decreased to 12.8 ng/mL. Eight days after stopping, the tacrolimus was resumed in low doses at 0.5 mg twice a day. The tacrolimus level then ranged from 12.1 to 13.5 ng/mL. The patient's foot drop and confusion, however, worsened over the next several days, and he fell several times at home.

Because of his worsening neurological status, the patient was brought to the hospital by his family and admitted for further evaluation, 30 days after transplantation. On neurological examination, the patient was alert, awake, oriented to person and place but disoriented to time. Cranial nerve functions were all preserved. The gait was unsteady due to bilateral foot drop. Sensory examination was normal. Muscle strength of arms, hands and proximal lower extremities was normal. Weakness was present in distal portion of both legs with marked impairment in feet dorsiflexion (3/5 on both feet).

INVESTIGATIONS

Various tests were performed to rule out vascular or metabolic causes of his confusion and foot drop. CT of the head excluded acute bleeding, mass or hydrocephalus. MRI of the brain showed chronic microvascular ischaemic changes. Serum lead, mercury, zinc, thyroid stimulating hormone, vitamin B_{12} and B_6 and folic acid levels were all

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within normal limits. Hepatitis panel was negative. Serum protein electrophoresis was consistent with acute inflammation but had no M spike. Lumbar puncture showed that the opening pressure was within normal range. Amounts of red blood cell, white cell count, total protein and glucose in the cerebrospinal fluid (CSF) were normal. CSF tests for Epstein-Barr virus, West Nile virus, herpes simplex virus 6, *Borrelia burgdorferi* and acid-fast bacilli by PCR were all negative. Lyme antibody (IgM and IgG) and Venereal Disease Research Laboratory screen tests were negative. CSF cultures, including fungal cultures, were also negative. The electromyography and nerve conduction studies were carried out 1 month later. These studies showed bilateral common peroneal nerve demyelination.

DIFFERENTIAL DIAGNOSIS

Although the patient's serum tacrolimus level was high suggesting tacrolimus toxicity, his symptoms did not improve with decreasing the dose or temporarily holding the medication. Hence, we explicitly tried to exclude other diagnoses, including infectious, vascular, inflammatory or metabolic causes. Based on the clinical picture and the laboratory investigations, we excluded infection, vascular or metabolic reasons. The inflammatory causes included acute inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy and polyneuropathy due to renal disease or diabetes mellitus. The patient did not have any acute event following transplantation that could have caused acute inflammation or chronic inflammatory neuropathy. The patient did not have diabetes mellitus before transplantation nor a history of alcoholic abuse. Although the patient had a history of kidney failure, he did not have any neuropathic symptom prior to transplantation. His symptoms did improve slowly after switching the tacrolimus to cyclosporine, and this improvement supported the diagnosis of tacrolimus neurological toxicity.

TREATMENT

Tacrolimus dose was reduced to 0.5 mg and the tacrolimus trough level trended down to 3.4 ng/mL. Prednisone dose was also reduced to 5 mg daily. However, the patient's mental status and foot drop barely improved. Therefore, the tacrolimus was switched to cyclosporine 175 mg twice a day which was later reduced to 50 mg twice a day on discharge. The cyclosporine trough level ranged 127–187 ng/mL. The patient was discharged at 37 days post-transplant to a rehabilitation facility, with bilateral ankle foot orthoses.

OUTCOME AND FOLLOW-UP

One month after discharge, on follow-up examination, the patient's mental status had improved to his baseline level. By approximately 5 months after stopping tacrolimus, the patient's foot drop had dramatically improved. He was able to walk without any ankle foot orthoses. The serum creatinine level remained in the range 1.1–1.3 mg/dL with an immunosuppressant regimen of cyclosporine 50 mg twice a day, prednisone 5 mg daily and mycophenolic acid 720 mg twice a day.

DISCUSSION

Tacrolimus-induced neurological side effects

Between 25% and 31% of patients who receive tacrolimus experience some form of neurotoxic adverse events.[2 3] Approximately 20% of patients have mild neurotoxicity including tremor (most common finding), insomnia, headache, vertigo, dysaesthesia, photophobia and mood disturbance. They tend to be most prominent shortly after transplantation. In one prospective study of 294 patients, major neurological side effects were identified in 16 (5.4%) of the patients. These side effects generally occurred within the first 30 days following transplantation and were related in many instances to high plasma levels of tacrolimus.[2]

Peripheral neuropathy is rare but can be a severe side effect of tacrolimus. About 3 of 1000 patients develop severe multifocal demyelinating sensorimotor polyneuropathy 2–10 weeks after initiation of tacrolimus therapy.[4] Two patients with orthotopic liver transplantation were reported developing motor axonopathy with flaccid quadriparesis and hyporeflexia. The symptoms resolved 5 days after reducing or stopping the tacrolimus.[5] A retrospective study found two cases of disabling peripheral neuropathy in 50 patients with orthotopic liver transplantation. One patient had sensorimotor neuropathy prior to the transplant which was getting worse after transplantation. The other patient had a new-onset peripheral neuropathy post-transplant. The tacrolimus level was in the normal range in both patients, but the neurological symptoms and signs improved significantly or recovered completely after stopping the tacrolimus.[6]

Risk factors for tacrolimus-induced neurotoxicity

In patients treated with cyclosporine, several factors appear to increase the risk of neurotoxicity. Some of these factors include advanced liver failure, hypertension, hypocholesterolaemia, elevated drug blood levels, hypomagnesaemia, intravenous administration of drug or administration of other drugs that inhibit metabolism of the cyclosporine.[7] Among patients on tacrolimus, investigators did not find clear relationship between hypocholesterolaemia or hypomagnesaemia and neurotoxicity.[2] But similar effects such as intravenous administration of drug and blood drug levels are showed in patients treated with tacrolimus. Cyclosporine and tacrolimus are both substrates of CYP3A4, which plays an important role in drug interactions. Azole antifungals, which are CYP3A4 inhibitors, increase the blood level of cyclosporine and tacrolimus. For example, itraconazole was reported to induce cyclosporine neurotoxicity.[8] Nefazodone, a substrate of CYP3A4, also increases the tacrolimus level and was reported to induce encephalopathy in a renal transplant recipient.[9]

Tacrolimus-induced neurotoxicity in renal transplantation

The risk of neurotoxicity from tacrolimus may vary according to the type of solid organ transplant received. Major neurological side effects are much more common in liver transplantation than in heart or lung transplantation (3.6%).[2 10] They are rare in renal transplantation. One literature review study reported eight leukoencephalopathy cases in renal transplantation.[10] In few single case reports, tacrolimus-induced severe central nervous system or peripheral nervous system toxicity in adult or paediatric renal transplantation were reported.[11–13]

Pathogenesis

The cellular basis for neurotoxicity associated with tacrolimus has not been conclusively identified. It may have a common mechanism with cyclosporine based on their similar characteristics including imaging findings with CT and MRI.[14] Both tacrolimus and cyclosporine mediate their immunosuppressive effects via inhibition of calcineurin. This inhibition provokes a complete block off in the translocation of the cytosolic component of the nuclear factor of activated T cells, resulting in a failure to activate the genes regulated by the nuclear factor of activated T-cells transcription factor. Tacrolimus and cyclosporine can decrease the expression of *p*-glycoprotein, as drug efflux pump, in brain endothelial cell and cause the dysfunction of the blood–

brain barrier which results in vasogenic oedema. Prolonged exposure also leads to apoptosis of capillary endothelial cells.[15] Patients treated with cyclosporine and tacrolimus have nerve membrane depolarisation which may reduce the threshold for action potential generation and facilitate the development of neuropathic symptoms, including paresthesias and cramps.[16] However, at least one study showed that neurotoxicity improved after switching the tacrolimus to cyclosporine in 19 of 23 patients with persistent neurotoxicity.[17] Also six patients were converted back to tacrolimus because of ongoing rejection, retransplantation or persistent nausea and vomiting without a recurrence of the original neurological complication. It implied that a mechanism other than common calcineurin inhibition also took important effect on neurotoxicity. In the cases described by Wilson *et al*, the improvement of symptoms followed by plasmapheresis or intravenous immunoglobulin suggesting an immune-mediated cause. The immune-mediated demyelination may be related to enhanced T-cell activation by tacrolimus or elevated T cells reacting with autoantigens by altering T-cell subsets.[4] Allergic neuritis induced by low dose of cyclosporine A has a similar effect on T cell subsets to tacrolimus.[18]

TREATMENT

In patients with neurotoxicity from tacrolimus, there are several treatment options. First, the tacrolimus dose can be reduced. Some patients, like ours, do not improve despite such dose reduction. Second, the patient can be switched to a different calcineurin inhibitor, such as cyclosporine. In our patient, converting from tacrolimus to cyclosporine resulted in slow improvement of his symptoms. Third, the patient can be converted to a calcineurin inhibitor-free immunosuppressive regimen. For example, the tacrolimus can be switched to sirolimus or everolimus or the patient can receive monthly infusion of belatacept.[6 13 19]

Switching from tacrolimus to cyclosporine can also improve the tacrolimus-induced neurological adverse effects, even though tacrolimus and cyclosporine have common immunosuppressive mechanisms as aforementioned. Tacrolimus has a different chemical structure from cyclosporine. Switching to cyclosporine would allow the clearance of tacrolimus and its metabolites. At the same time cyclosporine can still provide adequate immunosuppression to prevent allograft rejection. Neoral is the microemulsion formulation of cyclosporine which has pharmacological advantages over conventional cyclosporine in terms of more reliable and consistent absorption, particularly its absorption in the absence of bile.[17]

Learning points

- Tacrolimus-induced encephalopathy and peripheral neuropathy presenting with confusion and bilateral foot drop is rare in patients who underwent renal transplantation.
- The diagnosis of tacrolimus neurotoxicity should exclude other neuropathies caused by vascular, infectious, inflammatory or metabolic reasons.
- Reducing the dosage, temporarily holding the dose of tacrolimus, switching to cyclosporine or calcineurin inhibitor-free immunosuppressant are the treatment options, which can prevent permanent damage and decrease the risk of rejection.

CONCLUSION

The prompt recognition of tacrolimus as a potentially neurotoxic drug and substituting it with a different immunosuppressant can prevent permanent damage and decrease the risk of rejection. Cyclosporine and tacrolimus are both calcineurin inhibitors sharing the same immunosuppressive pathway. Nevertheless, some cases of tacrolimus neurotoxicity may improve when the tacrolimus is switched to cyclosporine. In summary, neurological complications in patients receiving tacrolimus that fail to improve after a reduction in dosage can be managed safely with cyclosporine.

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Unexpected outcome (positive or negative) including adverse drug reactions