Tacrolimus-Induced Optic Neuropathy After Multivisceral Transplantation

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Transplantation Direct 2020;6: e516; doi: 10.1097/TXD.0000000000000960. Accepted 25 October 2019.

The patient is a 51-year-old man who underwent an MVTx (stomach, liver, pancreas, duodenum, and small bowel) for a postalcoholic liver cirrhosis complicated by a complete portomesenteric thrombosis. Indication for transplantation was recurrent episodes of gastrointestinal bleeding, hepatic decompensation, and hepatorenal syndrome. He received a graft from a blood group–compatible, brain dead donor (31-y-old man, body mass index = 26 kg/m²). Due to irreversible hepatorenal syndrome, the patient also received a kidney from the same donor. Induction therapy with basiliximab was followed by maintenance therapy with tacrolimus, azathioprine, and corticosteroids, according to our previously described protocol.13 The postoperative course was complicated by bleeding requiring revision after 15 days. Immunosuppressive therapy had been tapered to tacrolimus 2 mg BID (immediate-release formulation, Prograft; Astellas, at trough levels: 4–5 µg/L), azathioprine 50 mg and methylprednisolone 4 mg.

Three and a half years after MVTx, the patient developed progressive, bilateral vision loss over a period of 2 weeks. He was admitted on day 15 for further investigations. The tacrolimus level was measured at 4.4 µg/L (target 4–5 µg/L). Trough levels were measured every month and never exceeded 5.7 µg/L in the last 12 months. The patient did not use any medication known to interact with tacrolimus nor did he have any reason for reduced absorption (ie, gastrointestinal disease). Ophthalmological examination revealed a bilateral, severe decline in visual acuity (VA), down to counting fingers at a 2-m distance. The peripheral visual field examination was normal, apart from a central scotoma. Except for known lens opacification on the right eye, bilateral dilated fundus examination, fundus autofluorescence, and optical coherence tomography revealed normal optic discs and retina. Pupillary reflexes were symmetric (both direct and indirect). Pattern visual evoked potentials revealed absent amplitude in responses bilaterally (Figure 1A). There were no systemic or other neurological complaints. Serological blood tests were...
negative for infections. Cerebrospinal fluid also did not reveal abnormalities on cytology, cultures, and biochemistry. His nutritional state was adequate and stable with a body mass index of 18 kg/m² (54 kg at 174 cm height). Albumin and total serum protein levels were in the normal range (42 g/L [normal range: 35–52 g/L] and 75 g/L [normal range: 66–88 g/L], respectively). Magnetic resonance imaging (MRI) showed diffuse inflammation of both optic tracts including the optic chiasm (Figure 2A). There were no signs of ischemia or PRES. As a result, a tentative diagnosis of TION was made.

Therapy was started on day 17 after onset of symptoms (see Figure 3). Tacrolimus dosage was reduced to reach trough levels of around 2–3 µg/L. To prevent rejection, a mammalian target of rapamycin inhibitor (Everolimus) was added (target trough level 2–3 µg/L). Given the severe inflammation seen on the MRI, pulse therapy of intravenous corticosteroids (3 d—1000 mg per d) was started in addition to a 5-day course of intravenous immunoglobulins (IVIGs) at 0.3 mg/kg per day. The intravenous corticosteroid therapy was tapered as follows: 3 days, 1000 mg; 3 days, 500 mg; and 3 days, 250 mg. This was followed by switch to oral methylprednisolone at 64 mg per day. The corticosteroid therapy was slowly tapered over the course over 3 months to 4 mg per day (dosage was halved every 2 wk). The patient noted a subjective improvement of vision within 4 days after start of therapy (d 21). However, ophthalmological examination

**FIGURE 1.** Pattern visual evoked potential (pVEP). A, At time of vision loss showing bilateral severely diminished amplitude in responses. B, One year after treatment: complete recovery.

**FIGURE 2.** Magnetic resonance imaging (MRI) of the brain. A, At time of vision loss showing severe a thickened optic chiasm (asterisk) and high signal in both optic tracts (arrows). B, One year after treatment: complete recovery.
on day 23 showed minimal objective improvements in VA testing. The patient was discharged from the hospital on day 27 and seen regularly on an outpatient basis. VA gradually improved over the next few months. At 3 months after start of therapy, vision had recovered to pre-TION levels (right eye: 20/50 to 20/30 with stenopeic hole [cataract eye]; left eye: 20/20).

The patient subsequently underwent phacoemulsification with intraocular lens implantation to treat the cataract on the right side. He had no rejections or organ dysfunction during this period. Immunosuppression was continued with low-dose tacrolimus (Prograft, BID), everolimus, and prednisolone. Follow-up pattern visual evoked potential and MRI made 1 year after treatment (Figures 1B and 2B, respectively) demonstrated a complete recovery from the TION.

FIGURE 3. Timeline of case, including implemented treatment. CS, corticosteroids; IVIG, intravenous immunoglobulin; MVTx, multivisceral transplant.

DISCUSSION

We report a case of severe TION after MVTx that was successfully treated by reduction of tacrolimus, addition of everolimus, and anti-inflammatory therapy.

The pathophysiology of TION is currently not fully understood. The first potential mechanism is direct neurotoxicity with damage to the oligodendrocytic cells leading to demyelination.6 Direct evidence for this theory was provided in a report from Venneti et al5 after an optic nerve biopsy was taken in a TION case. The second hypothesis focuses on the vascular complications of tacrolimus. Neurotoxicity may be caused by vasoconstriction in cerebral microvasculature.6 This phenomenon is also thought to play a central role in PRES, another rare but devastating neurological complication of tacrolimus.4 Tacrolimus has been demonstrated to induce microvascular damage through Toll-like receptor 4–mediated inflammation.14

Diagnosis of TION remains difficult with variable presentations reported in the literature (Table 1). Patients presented at various times after transplantation, ranging from 3 months to 5 years. Tacrolimus levels were in the normal range, demonstrating that TION is not related to a particular tacrolimus level. In our case, all trough levels were below 6 µg/L. Of note, all cases occurred at least 3 months after transplantation when tacrolimus had already been tapered. This means that various factors can lead to toxic accumulation of tacrolimus in individuals. One factor may be genetic variations in tacrolimus elimination mechanisms from the central nervous systems.13 There is also a relatively high incidence of neurotoxicity after liver transplantation, which may be due to changes in tacrolimus metabolism leading to cumulative toxicity.6 Neurotoxicity also occurs more frequently in men, which may again be related to differences in tacrolimus pharmacokinetics.3,4 Interestingly, TION has also been described in a nontransplant case receiving tacrolimus for nephrotic syndrome.16 This demonstrates that the neurotoxic properties of tacrolimus are not necessarily related to changes in metabolism after organ replacement.

We did not obtain an area under the curve measurement for tacrolimus in our patient. This is because previous studies have shown that tacrolimus trough levels correlate highly to area under the curve (correlation coefficients of 0.78–0.98).17 We utilize the immediate-release formulation of tacrolimus (Prograf) in all ITx patients. Recently, several other formulations have become available such as the slow-release version (Advagraf; Astellas) and the extended-release version (Envarsus; Veloxis). The principal advantages are the once-daily formulation and lower variation of serum levels.18 However, how these medications are absorbed in ITx patients remains unclear which is why we prefer the immediate-release formulation in this specific population. In liver transplant patients, a nonrandomized study showed a slightly lower incidence of early neurotoxicity in patients receiving slow-release tacrolimus compared with immediate-release formulation.19 However, in a large randomized controlled trial in >600 de novo kidney transplant recipients receiving either Advagraf or Prograf, no differences were found in neurotoxic complications.20

Vision loss after TION is severely debilitating (20/125 to hand motion) and occurs over the course of several days. Fundoscopic findings of the optic nerve varied depending on
Table 1. Published cases of tacrolimus-induced optic neuropathy cases after solid-organ transplantation

| Patient no. | Publication Year | Organ(s) | Tacrolimus therapy | Other therapy | MRI | Ophthalmological examination | Other treatment | Outcome |
|-------------|-----------------|----------|--------------------|---------------|-----|-----------------------------|----------------|---------|
| 1           | Brazis et al 7   | Liver    | Discontinued       | None          | Normal | Optic disk swelling, lower light reactivity left | None | No recovery |
| 2           | Lake et al 8     | Pancreas | Discontinued       | None          | Normal | Sluggish response to light, bilateral optic pallor, no hemorrhage | None | Partial recovery |
| 3           | Kessler et al 9  | Islet    | Discontinued       | IV CS and IVIG| Normal | Optic disc atrophy, sluggish response to light | IV CS | Partial recovery |
| 4           | Venneti et al 5  | Heart and kidney | Discontinued | None | Optic disc pallor, delayed filling | IV CS, IVIG | Full recovery |
| 5           | Yun et al 10     | Liver    | Reduced            | IV CS         | Normal | No fluorescence filling in the optic disc bilaterally | None | No recovery |
| 6           | Ascaso et al 11  | Liver    | Continued          | None          | 2.6    | Normal | Optic disc atrophy, bilateral delayed filling | None | Partial recovery |
| 7           | Shao et al 12    | Intestine| Discontinued       | None          | 4.4    | Normal | Bilateral inflammation of the optic tract | None | No recovery |

Tacrolimus level at time of transplantation (µg/L): 3 mo; 3 y; 5 mo; 6 mo; 8.8; 6.2; 13.9; 2.6; 13.9; 4.4.

Patient age (years): 58; 38; 51; 63; 54; 56; 54; 56; 51.

Gender: Male; Male; Female; Male; Male; Female; Male; Male; Male.

Other treatment options for TION that have been described include corticosteroids in pulse therapy and IVIG. In our patient, given the severe demyelinating inflammation visible on MRI, we—pragmatically—decided to administer both therapies. This treatment has already been described in patients with tacrolimus-induced polyneuropathy and optic neuritis in systemic inflammatory diseases such as multiple sclerosis. We hypothesize that prompt and aggressive control of inflammation prevented permanent demyelination, ischemia, and secondary atrophy of the optic tract and led to full recovery of vision in our patient. In 2 other TION cases, anti-inflammatory therapy was used unsuccessfully. However, these patients had late-stage TION with irreversible optic nerve atrophy. Therefore, anti-inflammatory treatment is only effective in early-stage TION.

**CONCLUSIONS**

TION is a rare complication after transplantation. It can occur at any tacrolimus level and at any time after transplantation. TION must be promptly recognized and treated to prevent severe and permanent vision loss. Tacrolimus should be stopped if possible. If not, tacrolimus can safely be reduced if everolimus is added to maintain adequate immunosuppression. In addition, we recommend prompt and aggressive control of inflammation by steroids and IVIG.

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