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Tacrolimus-Induced Optic Neuropathy After Multivisceral Transplantation

Emilio Canovai, MD,[1,2] Catherine Cassiman, MD,[3] Laurens J. Ceulemans, MD, PhD,[1,2] Philippe Demaerel, MD, PhD,[4] Mauricio Sainz-Barriga, MD, PhD,[1,2] Ina Jochmans, MD, PhD,[1,2] Diethard Monbaliu, MD, PhD,[1,2] Jacques Pirenne, MD, PhD,[1,2] and Tim Vanuytsel, MD, PhD[1,5]

Tacrolimus is currently the most commonly prescribed immunosuppressant.[1] Tacrolimus allowed intestinal transplantation (ITx) to become a clinical reality by significantly reducing rejection rates in this highly immunogenic organ.[2] Despite its effectivity, tacrolimus can cause severe neurological complications.[3] Specifically, tacrolimus can lead to neuropathy and posterior reversible encephalopathy syndrome (PRES).[4] The exact mechanism is not fully understood, but both direct neurotoxicity- and vasoconstriction-induced ischemic damage have been proposed.[5,6] One particular form, tacrolimus-induced optic neuropathy (TION) leading to severe visual loss, has been described after solid-organ transplantation.[5,7-12] The clinical course of TION can vary substantially, including the degree of vision loss, ophthalmological findings, and subsequent recovery. As there is no pathognomonic sign, the diagnosis is made after excluding other causes such as inflammatory diseases, stroke, infections, and metabolic problems.[4] The definitive diagnosis is often only made after clinical improvement following withdrawal of tacrolimus. This is possible in most solid-organ transplants but is particularly difficult after ITx where tacrolimus is vital to prevent rejection.[2] We describe a rare case of late-onset, severe, bilateral TION after multivisceral transplantation (MVTx) that was successfully treated while also avoiding rejection.

CASE DESCRIPTION

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/m^2). 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, Prograf; 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

Received 8 September 2019. Revision received 15 October 2019.

Accepted 25 October 2019.

[1] Leuven Intestinal Failure and Transplantation center (LIFT), University Hospitals Leuven, Leuven, Belgium.

[2] Department of Abdominal Transplantation Surgery and Coordination, University Hospitals Leuven, Leuven, Belgium.

[3] Ophthalmology Department, University Hospitals Leuven, Leuven, Belgium.

[4] Radiology Department, University Hospitals Leuven, Leuven, Belgium.

[5] Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium.

E.C., C.C., and T.V. participated in the collection of data, data analysis, and writing of the article. L.J.C., P.D., and J.P. participated in the collection of data, data analysis, and writing of the article. M.S.-B., I.J., and D.M. participated in data analysis and writing of the article. All authors gave final approval for the final version to be published and agreed to be accountable for all aspects of the work.

The authors declare no conflicts of interest.

T.V. is a senior clinical investigator of the Flanders Research Foundation (FWO Vlaanderen). J.P. holds named chairs at the Catholic University Leuven (Belgium) from the Institut Georges Lopez and from the "Centrale Afdeling voor Fractionering" (DGF-CAF).

Correspondence: Emilio Canovai, MD, Department of Abdominal Transplantation Surgery and Coordination, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. (emilio.canovai@uzleuven.be).

ISSN: 2373-8731

Transplantation Direct 2020;6: e516; doi: 10.1097/TXD.0000000000000960. Published online 24 December, 2019.

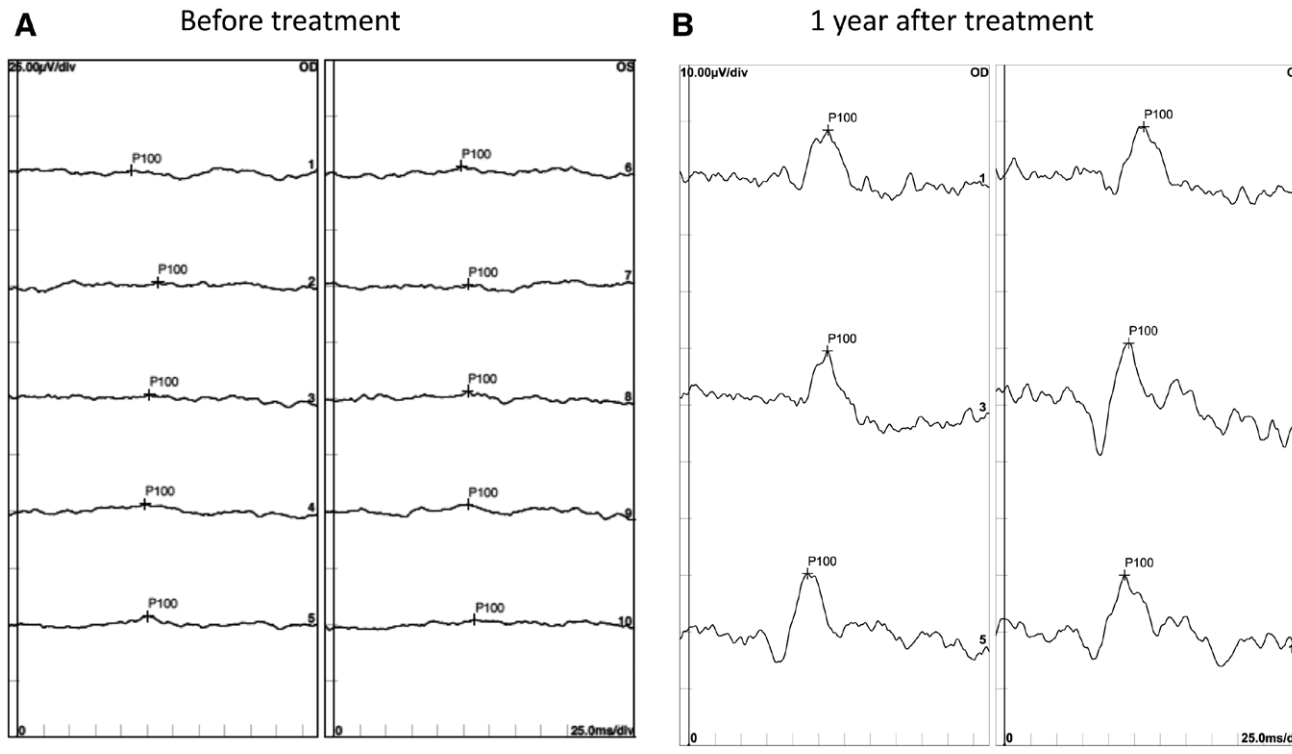

FIGURE 1. Pattern visual evoked potential (pVEP). A, At time of vision loss showing bilateral severely diminished amplitude in responses. B, One year after treatment: complete recovery.

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

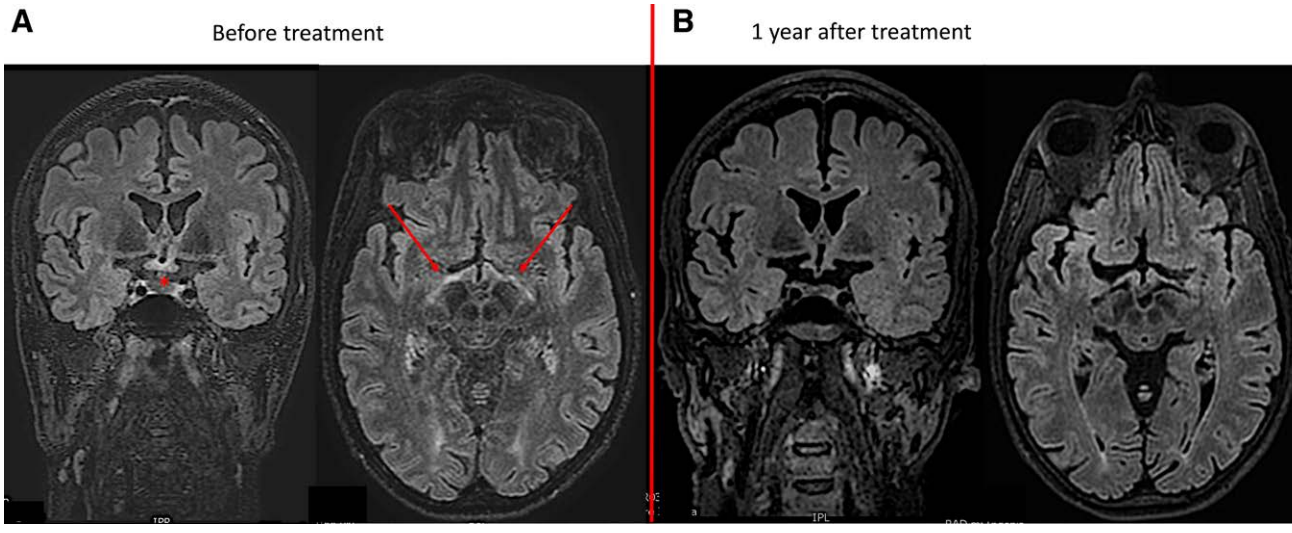

FIGURE 2. Magnetic resonance imaging (MRI) of the brain. A, At time of vision loss showing severe a thickened optic chiasm (asterisk) and high signal in both optic tracts (arrows). B, One year after treatment: complete recovery.

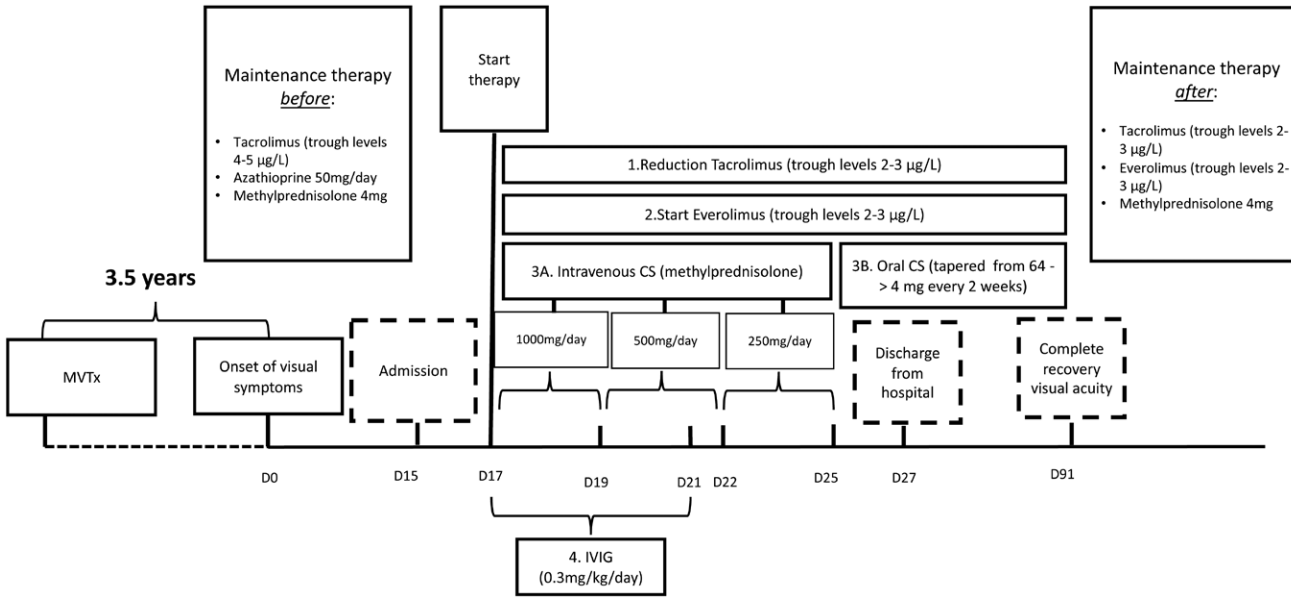

FIGURE 3. Timeline of case, including implemented treatment. CS, corticosteroids; IVIG, intravenous immunoglobulin; MVTx, multivisceral transplant.

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.

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 demyelinization.[6] Direct evidence for this theory was provided in a report from Venneti et al[5] 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.[15] There is also a relatively high incidence of neurotoxicity after liver transplantation, which may be due to changes in tacrolimus metabolization leading to cumulative toxicity.[3] Neurotoxicity also occurs more frequently in men, which may again be related to difference 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 metabolization 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 (Prograft) 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 Prograft, 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)	Patient age (years)	Gender	Onset after transplant	Tacrolimus level at time of symptoms (µg/L)	Ophthalmological examination	MRI	Tacrolimus therapy	Other treatment	Outcome
1	Brazis et al[7]	2000	Liver	58	Male	3 mo	Unknown	Optic disk swelling, lower light reactivity left	Some subcortical ischemic changes	Discontinued	None	No recovery
2	Lake et al[8]	2003	Pancreas	38	Male	3 y	Unknown	Sluggish response to light, bilateral optic pallor, no hemorrhage	Normal	Discontinued	None	Unknown
3	Kessler et al[9]	2006	Islet	51	Female	5 mo	3.4	Normal	Normal	Discontinued	None	Partial recovery
4	Venneti et al[5]	2010	Heart and kidney	63	Male	5 y	8.8	Optic disk atrophy, sluggish response to light	Left optic nerve inflammation	Discontinued	IV CS and IVIG	No recovery
5	Yun et al[10]	2010	Liver	54	Male	6 mo	6.2	No fluorescence filling in the optic disc bilaterally	Not available	Discontinued	None	Partial recovery
6	Ascaso et al[11]	2012	Liver	56	Female	6 mo	2.6	Optic disc pallor	Normal	Continued	IV CS	No recovery
7	Shao et al[12]	2012	Intestine	30	Male	3 mo	13.9	Optic disc pallor, hemorrhage, bilateral delayed filling	Normal	Reduced	None	Partial recovery
8	Canoval et al	2019	Multivisceralx and kidney	51	Male	3.5 y	4.4	Normal	Bilateral inflammation of the optic tract	Reduced	IV CS and IVIG	Full recovery

IV CS, intravenous corticosteroids; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging.

the stage of TION. In our case, as well as 1 previous report,[9] fundoscopic examination was normal. In contrast, most cases had advanced stages with optic disc edema or pallor. In 2 cases,[10,12] there was even abnormal retinal angiography. This is indicative of advanced TION, whereby persistent inflammation leads to irreversible ischemia of the optic nerve. Bilateral optic tract inflammation was clearly present in our case on MRI (Figure 2A). This is rare in the reported literature as significant anomalies were only seen on MRI in one other case.[5]

The primary treatment of TION is cessation of tacrolimus, which was performed in most cases. However, given the high risk of rejection in ITx, we were reluctant to completely stop tacrolimus.[2] Instead, tacrolimus was reduced (rough levels 2–3 µg/L) and everolimus was added. Using this regimen, rejection was avoided while safely reducing tacrolimus levels. In a case of PRES after MVTx, tacrolimus was discontinued in favor of sirolimus (mammalian target of rapamycin inhibitor).[21] However, this resulted in an acute cellular rejection requiring reintroduction of tacrolimus and caused a second episode of PRES. Eventually, the patient was switched to cyclosporine which has been shown to be less neurotoxic.[22] However, cyclosporine does increase the risk of rejection, especially in ITx.[23] This is why we chose an alternative strategy by lowering, but not discontinuing tacrolimus.

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[24] and optic neuritis in systemic inflammatory diseases such as multiple sclerosis.[25] 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.[5,11] 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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