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Short Communication

Tacrolimus-induced severe headache associated with diffuse leukoencephalopathy: Evidence for an immune-mediated pathogenesis

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A B S T R A C T

Tacrolimus-induced encephalopathy presents with acute neurological symptoms such as headache, seizures, visual disturbances, hemiplegia, and altered mental status. A 60-year-old woman, presented to our clinic with a 4-month history of severe headache. She recently underwent kidney transplantation and was taking tacrolimus. MRI scan showed diffuse and symmetric alterations involving both supratentorial and infratentorial white matter. Cerebral spinal fluid assessment for infectious diseases were negative but elevated total protein level and oligoclonal bands positivity were reported. Treatment with steroid bolus, along with tacrolimus tapering, provided clinico-radiological improvement. This is the first case of tacrolimus-induced neurotoxicity strongly suggestive of an immune-mediated pathogenesis.

1. Introduction

Tacrolimus is an immunosuppressive agent widely used to prevent rejection after solid organ transplantation. Tacrolimus pharmacological effects are performed through calcineurin inhibition, a mechanism of action shared with several other immunosuppressive drugs (e.g. Cyclosporine), named Calcineurin Inhibitors (CNI).

Calcineurin is a serine/threonine protein phosphatase widely expressed within the central nervous system (CNS), involved in intracellular T-lymphocytes signaling pathway: its inhibition prevents the activation of the Nuclear Factor of Activated T-cells, providing down-regulation of T-cells activation cascade (Liu et al., 2013). Due to its greater efficacy compared with cyclosporine, tacrolimus has become one of the most used immunosuppressive drug within liver and kidney transplants. Minor neurological side effects such as headache, postural tremor, paresthesia and visual changes have been described after tacrolimus initiation. One rare but potentially severe complication is encephalopathy, presenting with acute neurological symptoms such as seizures, visual disturbances, hemiplegia and altered mental status (Bechstein, 2000). In these cases, brain imaging may reveal white matter lesions predominantly in the posterior cerebral regions, with features similar to Posterior Reversible Encephalopathy Syndrome (PRES) (Wu et al., 2010). In a minority of cases, tacrolimus-induced encephalopathy shows a more diffuse and heterogeneous cerebral involvement. Rarely, it can resemble tumor-like lesions, demyelinating disease or central pontine myelinolysis (Fukazawa et al., 2011). Cerebral spinal fluid (CSF) assessment is useful to exclude CNS infectious diseases, with particular regard to those related to immunosuppressive treatment. Tacrolimus-induced encephalopathy frequently occurs within normal serum drug levels, although neurological complications due to drug overdose have also been described (Bersani et al., 2013). Variability in clinical presentation makes diagnosis of tacrolimus-induced encephalopathy extremely challenging and requires to rule out other possible neurological and systemic diseases, therefore extensive neurological examination, laboratory investigations and radiologic assessment should be performed. However, it is important to recognize tacrolimus-induced neurotoxicity since it can be reversible. According to literature, tacrolimus suspension or tapering are the best treatment options available at the moment. Switching to another immunosuppressive regimen might be needed in transplanted patients in order to prevent graft rejection (Schuuring et al., 2003). We report a case of extensive tacrolimus-induced leukoencephalopathy exclusively presenting with new onset, severe headache, showing evidence for an immune-mediated pathogenesis.

2. Case report

A 60-year-old woman presented to our clinic with a 4-month history of severe, analgesic-resistant headache. She had no previous history of headache, stroke or CNS autoimmune diseases and her family history

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was unremarkable.

Seven months before, the patient had undergone kidney transplantation for chronic renal failure due to autosomal dominant polycystic kidney disease. Immunosuppressive induction had been achieved with oral steroid, tacrolimus and mycophenolate mofetil combined treatment. Two months after surgery, mycophenolate mofetil was suspended due to severe leukopenia and immunosuppressive treatment was continued with tacrolimus and minor dosage of oral steroid. Tacrolimus serum level had been within normal range in the past 2 months before neurological examination.

Headache started 4 months after organ transplantation, while the patient was taking 3.5 mg of prolonged release tacrolimus (Advagraf™) once per day. Pain was described as bilateral, persistent and strongly disabling. It often started in the occipital region, with subsequent anterior irradiation, and was exacerbated by supine position. It was so severe to interfere with patient daily activities and quality of life. She also reported sleep disturbances and insomnia due to headache.

Neurological examination was normal. At the admission, blood pressure was 145/70 mmHg. Complete blood count, electrolytes, CRP, cholesterol level, liver and thyroid function tests were normal. Creatinine, urea and magnesium blood levels were within normal range. Tacrolimus blood level was within therapeutic range (7.7 ng/mL; N.V. 5–12 ng/mL). Serum antibodies for systemic autoimmune disease were all negative. Electroencephalography examination was normal.

Patient underwent MRI scan showing T2-weighted and FLAIR diffuse and symmetric hyperintensity widely involving supratentorial and infratentorial white matter, without alterations on diffusion-weighted MRI (DWI) and apparent diffusion coefficient (ADC) map (Fig. 1a, c). Serum and CSF analysis for infectious diseases, including T. Gondii, Borrelia spp. along with CSF protein chain reaction for TBE, CMV, EBV, HSV, VZV, HIV, HHV6, JCV were all negative.

Cell-based assays for antibodies directed towards typical and less typical neural surface antigens (NMDAR, LGI1, CASPR2, GABABR, AMPAR) were performed at the Udine University Hospital using commercial kits (Euroimmun, Lübeck, Germany), with negative results. Immunoblot analysis for the presence of onconeuronal antibodies (Euroimmun, Lübeck, Germany), including anti-Hu, Yo, CV2, Ri, Ma2, and amphiphysin, was also unrevealing. A CSF sample was sent to the Centre National de Référence pour les Syndromes Neurologiques Paranéoplasiques (Lyon, France) in order to perform immunofluorescence assays on rat brain hippocampus histological sections. No specific labelling was observed.

Notably, CSF analysis showed elevated total protein level (1.7 g/dL) and oligoclonal bands (pattern type 3) positivity was reported.

Diagnosis of tacrolimus-induced leukoencephalopathy was made. Treatment with intravenous steroid bolus (500 mg/day for 3 days followed by slow oral dosage tapering) along with tacrolimus tapering provided impressive clinical improvement right after the first 2 days of treatment. In order to prevent graft rejection, alternative immunosuppressive treatment with everolimus was initiated.

The patient was discharged with everolimus and oral steroid de-escalation therapy. At 5-month follow-up sustained clinical benefits and impressive neuroradiological improvements were reported (Fig. 1b, d).

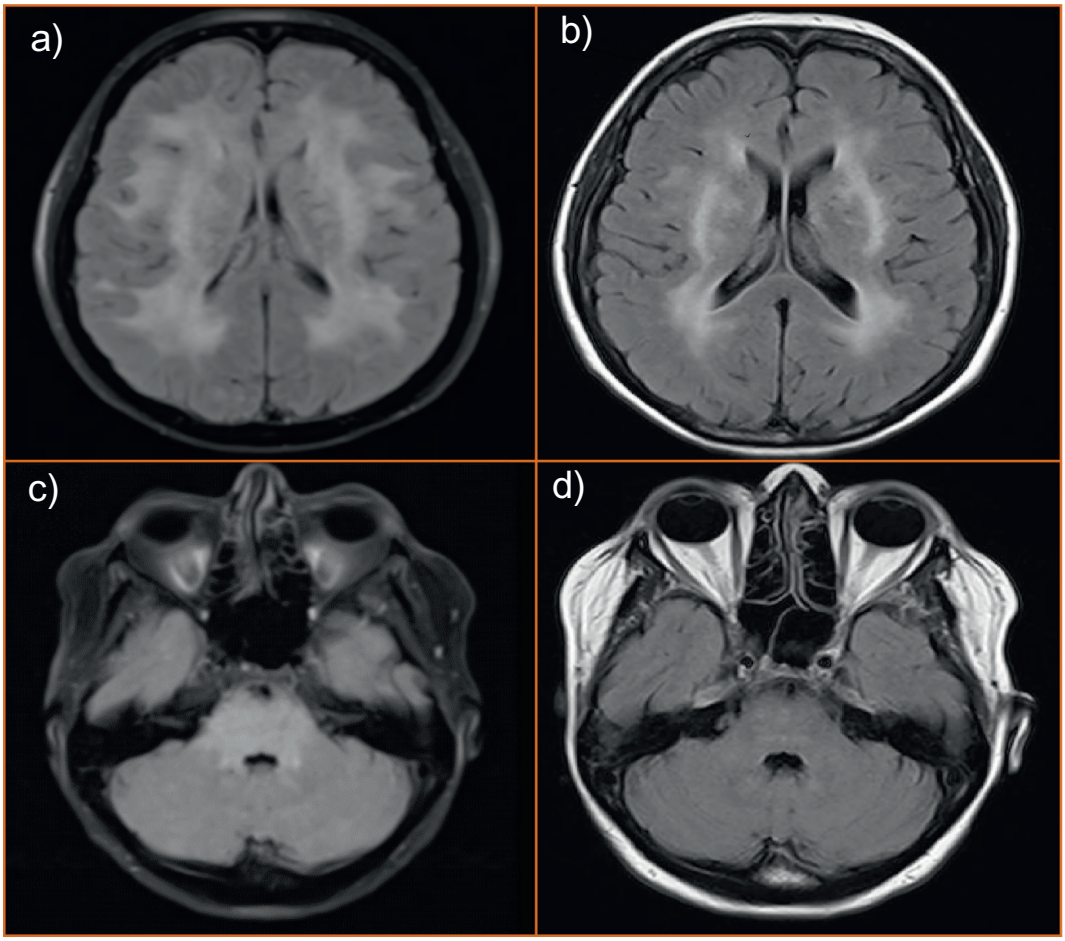

Fig. 1. T2-weighted FLAIR MRI pre (a, c) and post (b, d) IV steroid treatment and tacrolimus tapering; (a) diffuse and symmetric hyperintensity involving supratentorial white matter; (c) infratentorial white matter involvement with swelling of the pons; (b) and (d) T2-weighted FLAIR MRI scan 5 months after treatment.

3. Discussion

We report a case of extensive tacrolimus-induced leukoencephalopathy presenting with severe, disabling headache, showing evidence for an immune-mediated pathogenesis.

Tacrolimus-induced encephalopathy might present with a wide range of symptoms including headache, altered mental status, seizure, visual disturbances and focal neurological deficits (Bechstein, 2000). Headache represents a common clinical feature of tacrolimus encephalopathy and often co-occurs with more severe clinical manifestations. To our knowledge, this is the first case of tacrolimus neurotoxicity presenting exclusively with isolated headache.

Frequency of tacrolimus-induced neurotoxicity after solid organ transplantation varies from 7% to 32% among liver and renal receivers. Nevertheless, its exact pathophysiological mechanism remains widely unknown. Within the above-mentioned patient populations, several independent risk factors as well as differences in terms of timing onset from the immunosuppressive regimen initiation have been described. Brain imaging may reveal features compatible with PRES, but cases showing a more diffuse cerebral involvement have also been reported (Wu et al., 2010). The mechanism by which tacrolimus determines neuronal damage has been linked to its high lipophilicity, which allows tacrolimus to pass the blood brain barrier (BBB) easily and to distribute throughout the CNS.

Several hypotheses have been attempted to explain the biological mechanism of neurotoxicity induced by tacrolimus. The most current and popular theory refers to systemic hypertension which determines a transient disruption of BBB autoregulation mechanisms leading to cerebral vasodilatation and therefore to vasogenic edema. Alternatively, immunogenic processes with demyelinization (Horbinski et al., 2009), renal impairment (Ergün et al., 2008), hypomagnesemia (Thompson et al., 1984), vasospam with brain hypoperfusion and presumed ischemia (Lin et al., 2003) might partly contribute to tacrolimus-induced encephalopathy pathogenesis. Extravasation of fluid and its accumulation within the interstitial space determines characteristic MRI findings consisting of an increased diffusion on both DWI and ADC map, features highly suggestive of vasogenic edema. Therefore, DWI iso or hyperintense signal along with hyperintense signal on ADC map represent the most common MRI features of tacrolimus-induced encephalopathy along with bilateral and symmetric T2-weighted and FLAIR hyperintensity involving both cortical and subcortical regions of the parietal and occipital lobes. Notably, our case showed signal alterations widely involving supratentorial and infratentorial subcortical regions symmetrically, with a peculiar swelling of the pons and no alterations on DWI and ADC map were reported. Such neuroradiological findings along with normal blood pressure, renal function, and magnesium blood levels at admission and during patient's hospitalization do not support a diagnosis of hypertensive encephalopathy, nor a PRES.

Other differential diagnosis taken into account include graft-transmitted infectious diseases. According to international recommendations regarding the prevention of donor-to-recipient infection transmission through organ transplantation, complete donor evaluation including HIV, HBV, HCV, syphilis, CMV, and EBV tests was performed before surgery.

Additionally, serum and CSF analysis for infectious diseases, including T. Gondii, Borrelia spp. along with CSF protein chain reaction for TBE, CMV, EBV, HSV, VZV, HIV, HHV6, JCV were all negative in our patient, thus allowing us to rule out a CNS infectious disease.

Furthermore, an angiography-MRI scan showed no evidence of cerebral aneurysm in this case.

Treatment of tacrolimus-induced encephalopathy consists of suspending the drug, but in some cases it was reported that minor tapering of tacrolimus could be effective as well. Additionally, other non-CNI immunosuppressive agents (e.g. Everolimus, Sirolimus) might be initiated in order to maintain immunosuppression and prevent graft rejection (Schuuring et al., 2003).

In order to determine whether the headache reported by our patient and the above-mentioned MRI findings can be definitely attributed to a tacrolimus-associated serious adverse event (SAE), a re-challenge with the drug would be required.

However, a re-challenge test in this case may raise major clinical, scientific and ethical concerns.

First, given the brainstem involvement detected on brain MRI we could not exclude that a re-challenge test might pose the patient at risk of life-threatening complications.

Second, in the case of adverse reactions mediated by an immunological effect, as it is postulated in this case, the re-challenge could have unpredictable consequences (the usage of “low-doses” is not necessarily linked to a milder adverse event). Therefore, a re-challenge test with tacrolimus was not undertaken.

Our case presents interesting novelties compared to the literature series. Particularly, oligoclonal bands positivity and marked albuminocytologic dissociation in the CSF are unprecedented and strongly suggest a possible immune-mediated mechanism of tacrolimus-induced neurotoxicity. Furthermore, the marked clinical and radiological improvement at 5-month follow-up after intravenous steroid treatment is in line with a drug-induced autoimmune reaction.

4. Conclusion

We reported a peculiar case of tacrolimus-induced leukoencephalopathy showing symmetric and diffuse white matter involvement along with marked albuminocytologic dissociation and oligoclonal bands positivity in the CSF. There is a lack of understanding regarding the spectrum of clinical presentation of tacrolimus-induced leukoencephalopathy. An extensive literature review showed that PRES can be the more frequent and severe complication of tacrolimus treatment but other alterations widely involving cerebral white matter are possible. Mild to moderate headache has been described as tacrolimus-induced encephalopathy. Nevertheless, clinical presentation only with severe, disabling headache is unprecedented.

To our knowledge, this is the first case of neurotoxicity induced by tacrolimus showing clear evidence for an immune-mediated pathogenesis. Additionally, our findings suggest that tacrolimus-induced leukoencephalopathy could benefit from high-dosage steroid treatment. Further studies are needed in order to understand the exact pathophysiological mechanism underlying tacrolimus neurotoxicity.

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Conflicts of interest

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Ethics committee approval

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References

Bechstein, W.O., 2000. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl. Int. 13 (5), 313–326.

Bersani, G., Marino, P., Valeriani, G., Cuoco, V., Zitelli, C., Melcore, C., Bersani, F.S., 2013. Manic-like psychosis associated with elevated trough tacrolimus blood concentrations 17 years after kidney transplant. Case Rep. Psychiatry 2013, 926–933.

Ergün, T., Lakadamyali, H., Yilmaz, A., 2008. Recurrent posterior reversible encephalopathy syndrome in a hypertensive patient with end-stage renal disease. Diagn. Interv. Radiol. 14, 182–185.

Fukazawa, K., Nishida, S., Aguina, L., Pretto Jr., E., 2011. Central pontine myelinolysis (CPM) associated with tacrolimus (FK506) after liver transplantation. Ann. Transpl. 16 (3), 139–142.

Horbinski, C., Bartynski, W.S., Carson-Walter, E., Hamilton, R.L., Tan, H.P., Cheng, S., 2009. Reversible encephalopathy after cardiac transplantation: histologic evidence of endothelial activation, T-cell specific trafficking, and vascular endothelial growth factor expression. AJNR Am. J. Neuroradiol. 30, 588–590.

Lin, J.T., Wang, S.J., Fuh, J.L., Hsiao, L.T., Lirng, J.K., Chen, P.M., 2003. Prolonged reversible vasospasm in cyclosporin A-induced encephalopathy. AJNR Am. J. Neuroradiol. 24, 102–104.

Liu, F., Wang, Y.Q., Meng, L., Gu, M., Tan, R.Y., 2013. FK506-binding protein 12 ligands: a patent review. Expert Opin. Ther. Pat. 23 (11), 1435–1449.

Schuuring, J., Wesseling, P., Verrips, A., 2003. Severe tacrolimus leukoencephalopathy after liver transplantation. AJNR Am. J. Neuroradiol. 24 (10), 2085–2088.

Thompson, C.B., June, C.H., Sullivan, K.M., Thomas, E.D., 1984. Association between cyclosporine neurotoxicity and hypomagnesaemia. Lancet. 2 (8412), 1116–1120.

Wu, Q., Marescaux, C., Wolff, V., Jeung, M.Y., Kessler, R., Lauer, V., Chen, Y., 2010. Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation. Eur. Neurol. 64 (3), 169–177.