

ROLE OF THE TACROLIMUS IN POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Elif Kocasoy Orhan¹, Hale Alpsan¹, Nerses Bebek¹, Binnur Pınarbaşı², Sabahattin Kaymakoğlu², İlgin Özden³, Oğuzhan Çoban¹

¹Istanbul University, Istanbul Medical Faculty, Department of Neurology, Istanbul

²Istanbul University, Istanbul Medical Faculty, Department of General Medicine, Istanbul

³Istanbul University, Istanbul Medical Faculty, Department of General Surgery, Istanbul

ABSTRACT

Posterior reversible encephalopathy syndrome (PRES), is a group of disorders which may present with headache, seizures, visual changes, altered mental status or focal neurological deficits. Many different conditions and diseases, which include tacrolimus treatment, may cause this syndrome. We present a 55 year old woman presented with PRES possibly due to tacrolimus treatment for liver transplantation. The patient stabilized after tacrolimus dose was decreased, and antihypertensive and antiepileptic treatments were started. PRES is one

of the neurological complications developing after solid organ transplantation. Early diagnosis and treatment is important for the patient's life as these patients are immunosuppressive and prone to many complications of transplantation. Here we present a case of PRES, possibly due to tacrolimus use after a living donor liver transplantation and discuss briefly the possible mechanisms of PRES.

Keywords: PRES, tacrolimus, hypertensive encephalopathy, reversible posterior cerebral oedema, seizure, headache, immunosuppression *Nobel Med 2015; 11(3): 80-83*

POSTERİOR GERİ DÖNÜŞÜMLÜ ENSEFALOPATİ SENDROMUNDA TACROLİMUS'UN ROLÜ

ÖZET

Posterior reversible ensefalopati sendromu (PRES) baş ağrısı, nöbet, görmeye ait değişiklikler, mental durum değişiklikleri ya da fokal nörolojik defisit ile ortaya çıkabilen bir hastalık grubudur. Takrolimus tedavisinin de içinde olduğu birçok farklı durum ya da hastalık bu sendroma neden olabilir. Bu bildiriye karaciğer transplantasyonu nedeniyle takrolimus tedavisi alan ve muhtemelen bu nedenle PRES gelişen 55 yaşında bir kadın hasta sunulmaktadır. Hasta takrolimus dozu düşürüldükten ve antihipertansif, antiepileptik teda-

vi başladıktan sonra stabilize olmuştur. PRES solid organ transplantasyonu sonrasında gelişen nörolojik komplikasyonlardan biridir. İmmünesupresif olup ve transplantasyonun birçok komplikasyonuna açık olan bu hastalarda erken tanı ve tedavi hayati önem taşımaktadır. Bu yazıda muhtemelen karaciğer transplantasyonu sonrası kullanılan takrolimusa bağlı olarak gelişen PRES olgusu sunulmakta ve kısaca olası PRES mekanizmaları tartışılmaktadır.

Anahtar kelimeler: PRES, takrolimus, hipertansif ensefalopati, reversible posterior serebral ödem, nöbet, baş ağrısı, immünesupresyon *Nobel Med 2015; 11(3): 80-83*

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES), hypertensive encephalopathy, and reversible posterior cerebral edema are all terms describing a group of disorders presenting clinically with headache, seizures, visual changes, altered mental status and occasionally focal neurological signs. There are many causes of this condition including infections, sepsis, shock, autoimmune diseases, chemotherapy, eclampsia and carotid endarterectomy. Furthermore the syndrome is typically noted after solid organ transplantations.^{1,2} Although the etiology remains to be elucidated, hypertension appears to be the primary cause of the syndrome.

Tacrolimus (FK 506), which is originally a macrolide antibiotic, is an immunosuppressive drug, primarily used after solid organ transplantation. Neurotoxicity secondary to tacrolimus has been well described particularly in solid organ transplant recipients. The spectrum of neurotoxicity ranges from relatively mild, presentations as tremor, insomnia, nightmares, headache, vertigo, dysesthesia, photophobia, mood disturbance to moderate to severe problems such as, seizures, focal deficits, cortical blindness, akinetic mutism, encephalopathy or psychosis. Moderate to severe neurotoxicity has been reported in 21-32% of the patients.³

PRES associated with tacrolimus use after solid organ transplantation, and allogenic hematopoietic stem cell transplantation have been reported in a few cases and overall incidence is estimated to be 1.6%.^{2,4,5} Median range time between initiation of treatment and onset of symptoms is reported as 61 days.⁵ Our aim here is to report a case who developed PRES possibly due to tacrolimus use after a living donor liver transplantation and discuss the possible mechanisms underlying the condition briefly.

CASE

A 55-year-old woman underwent living donor liver transplantation for decompensated cirrhosis due to hepatitis B and D. She received a right lobe from her daughter. The recipient portal vein wall contained a wide area of recanalized thrombus which caused difficulty in the construction of the anastomosis. Tacrolimus and methyl-prednisolone were used for initial immunosuppression.

The postoperative course was complicated by persistent ascites and two attacks of primary peritonitis that required prolonged antibiotic therapy. She was discharged on tacrolimus postransplantation. The tacrolimus through levels were maintained at moderate-low levels (between 5-8 ng/mL). She has

had no neurologic problems except for fine tremor in the early postoperative period. One month after discharge the patient started having rhinorrhea and flu like symptoms. She was also hypertensive (BP: 170/90 mmHg) and reported having blurred vision which lasted for several hours during this period. Her gastroenterologist put her on antihypertensive medication.

Two days after the symptoms recurred and the patient complained again blurring in her vision. Subsequently she became confused. She was uncooperative and disorientated at the admission to the hospital. During emergency evaluation, she was hypertensive (BP: 160/80 mmHg) and she had headache, blurred vision and two consecutive generalized tonic-clonic seizures without gaining consciousness, after which she had to be intubated and was admitted to the intensive care unit. She had no hypercalcemia, hypomagnesemia or hypocholesterolemia. Levetiracetam (1000 mg/day) was started as an antiepileptic treatment. Blood pressure of the patient remained within normal limits during hospitalization under antihypertensive therapy. The dose of tacrolimus was decreased from 4 to 3 mg/day.

The patient was extubated after 6 hours, and was fully conscious, she only complained of blurred and double vision. Her EEG revealed diffuse slowing accompanied with fast rhythms and low amplitude. T2-weighted and FLAIR MRI performed on the day of admission showed hyperintense lesions in bilateral occipital, parietal and left temporal lobe, centrum semiovale regions and also in mesencephalon and right brachium pontis (Figure). The neurologic status and complaints of the patient recovered completely within 24 hours. Three days after her full recovery, another MRI was performed; it showed the same lesions. She had a follow up MRI three weeks after the beginning of the symptoms. It showed normal findings except for slight enlargement of the cortical sulci and fissures in both cerebral hemispheres. She did not have another seizure during the follow up period and her control EEG was normal. The clinical diagnosis of the patient was reversible posterior leukoencephalopathy due to immune-suppressive treatment drugs of the patient. We considered that the hypertensive period at the beginning of the symptoms was also a facilitating factor. The dose of tacrolimus was decreased to 2 mg/day, and 1000 mg/day mycophenolate mofetil (MMF) was added. An effective hypertensive treatment was also prescribed. She has not had any symptoms for four years and her neurologic examination was normal.

DISCUSSION

Posterior reversible encephalopathy syndrome after calcineurin-inhibitor (CNI) treatment is a rare complication

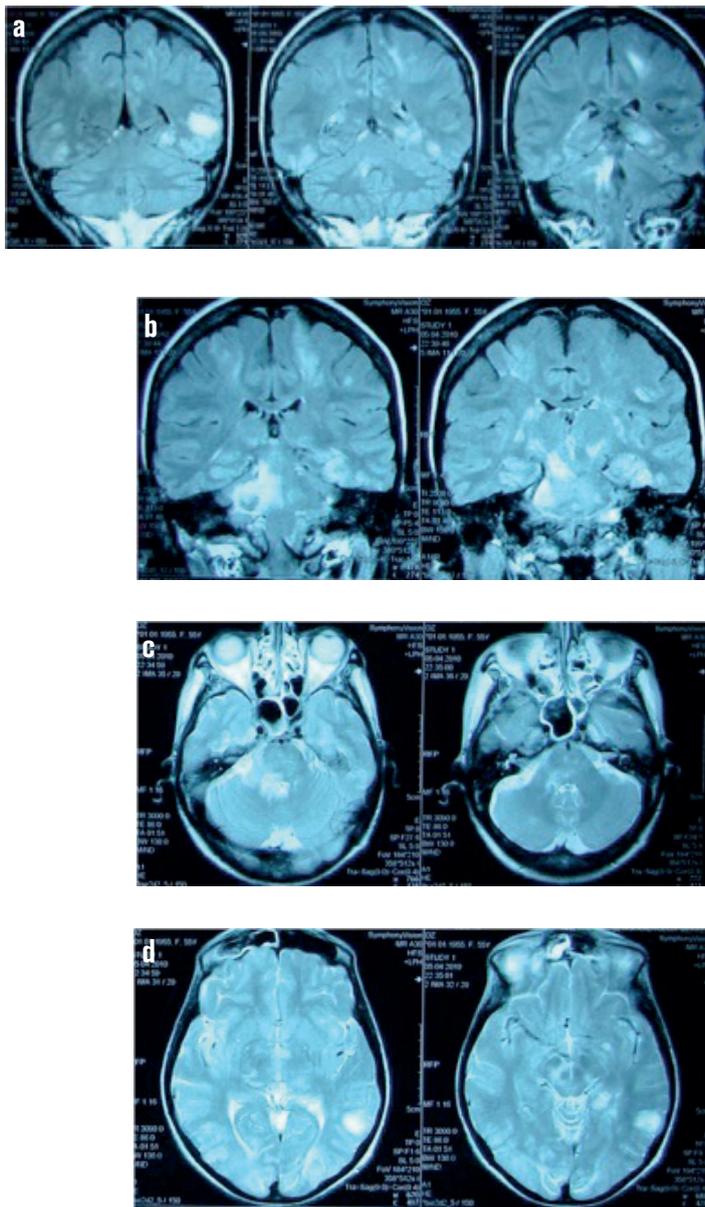


Figure. FLAIR Coronal (1a-1b) and T2 axial (1c-1d) sections MRI show hyperintense lesions in bilateral occipital, parietal and left temporal lobe, and also in mesencephalon and right brachium pontis.

with immunosuppressive agents (mostly after a liver or kidney transplantation and especially higher among liver transplantation patients compared to heart and lung transplantation patients).^{3,6} It was initially described by Hinchey et al. in 1996.⁷

The incidence of PRES ranges from 1% to 6% in transplant patients and occurs in 80% within the first 90 days after the initiation of CNI therapy. This syndrome develops most often after liver transplantation and, seems to be more often in female and elderly population.⁸ The mortality rate associated with the condition is about 1%-2%.⁹ Prompt recognition of the condition is essential to prevent morbidity and mortality, as most of the patients will experience complete recovery by reduction of drug dosage or by changing the immunosuppressive agent.²

This complication develops sometimes due to high drug levels but is mostly unrelated to drug levels and dosage.^{3,10} Although blood levels of CNI tend not to correlate with PRES, however it has been showed that medication withdrawal has often resulted in amelioration of neurotoxicity.^{11,12}

Immunosuppressant blood levels do not appear to correlate with severe neurotoxicity or PRES, but immunosuppressant discontinuation or switch usually results in clinical improvement.¹³⁻¹⁷ Although the etiopathogenesis of neurotoxicity with PRES remains controversial, in most of the cases, predisposing factors such as rejection, infection, hypertension, hypocholesterolemia, hypomagnesemia, hepatic encephalopathy, and drugs like high-dose methylprednisolone that inhibit tacrolimus metabolism may be found.³ Hypertension, which is a common complication of tacrolimus therapy, is commonly present, but patients may also be normotensive (20% to 30%).¹ Systemic hypertension was found to be common in patients who develop PRES after renal transplantation but uncommon after heart, lung, or liver transplantation.^{16,18} After liver transplantation, PRES typically occurs early (within two months after transplantation), blood pressure tends to be normal, and the extent of brain edema is significant.¹¹

Hypertension is also an additional risk factor for developing seizures during the course of the condition. Hyperperfusion syndrome is another term which is used to describe all of these clinical entities and excess cerebral blood flow is considered to be the main pathophysiological factor underlying these conditions. Endothelial cells are the most important component of blood brain barrier and when these are damaged by toxins, severe hypertension, eclampsia or drugs like cyclosporine A, autoregulation is impaired and threshold of autoregulatory breakthrough is lowered. When the lesion is confined to edema, this situation is reversible but intraparenchymal hemorrhage or infarction may also occur and it may cause a permanent sequelae⁶

In a retrospective study, 27 patients who developed PRES after solid organ transplantation were identified from the database. Clinical presentations of the patients included isolated seizure (seven patients) or a combination of headache, confusion, altered mentation, vision change alone (eighth patients) or progression to generalized seizure (12 patients). Mean arterial blood pressure during acute toxicity was within normal limits in eight patients (MAP=105 mmHg), mildly elevated in six (MAP, 106-115 mmHg), and severely elevated in 13 (MAP= 116 mmHg).¹

Calcineurin, the primary target of tacrolimus in the lymphocytes, is also widely found distributed in the

central nervous system. Inhibition of calcineurin alters sympathetic outflow during drug mediated hypertension.³ Sympathetic outflow is known to be an important factor in cerebral autoregulation, and breakdown in such a regulation results in vasogenic edema. This mechanism can also explain why the posterior regions are mostly affected because of the relatively sparse sympathetic innervation of the vertebrobasilar circulation.²

This condition primarily affects white matter but the cortex may also be involved. Pathophysiologic mechanisms underlying, still remain mostly unknown. Vasogenic edema is the predominant feature of the condition and postmortem studies after death due to tacrolimus neurotoxicity, showed multiple cerebral infarction, possibly due to vasculitis.⁹ To diagnose PRES during therapy after transplantation, differential diagnosis has extreme importance because the patient is immunosuppressive and prone to many complications of transplantation and bacterial and viral infections, as well as vascular, metabolic, and neoplastic processes must be ruled out. Most sensitive method seems to be MRI scanning which shows mostly subcortical white matter changes secondary to potentially reversible vasogenic edema. Due to these accompanying factors, late toxicity is associated with severe infections and multiple organ failure which have mostly lethal outcome in 50% of the patients. There are such fulminant cases which presented in a late course after liver transplantation.¹⁹

Decreasing the dose of the drug and administration of an antihypertensive drug with an antiepileptic was apparently the right choice for our patient. After this treatment was initiated patient recovered quickly in days and was discharged without residual neurological symptoms or signs. In our case we decreased the dose and added MMF to the therapy as soon as the diagnosis was suspected. Support therapy and elimination of the predisposing factors is also important, so we also prescribed an antihypertensive and an antiepileptic drug.

This case was a possible complication of tacrolimus therapy after liver transplantation and with an early diagnosis and change of the treatment plans, despite the severe condition of the patient which required intubation and intensive care unit admission, patient was discharged without any neurological deficits. PRES possibly due to tacrolimus treatment after solid organ transplantation should be kept in mind in case of headache, seizures, visual changes, altered mental status and focal neurological signs.

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Elif Kocasoý Orhan and Hale Alpsan contributed equally to the case report.

* The authors declare that there are no conflicts of interest.



C	CORRESPONDING AUTHOR: Elif Kocasoý Orhan İstanbul Üniversitesi, İstanbul Tıp Fakóltesi, Nöroloji Anabilim Dalı 34390 İstanbul, Turkey. elifkorhan@yahoo.com
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REFERENCES

- Bartynski WS, Tan HP, Boardman JF, et al. Posterior reversible encephalopathy syndrome after solid organ transplantation. *Am J Neuroradiol* 2008; 29: 924-930.
- Hodnett P, Coyle J, O'Regan K, et al. PRES (posterior reversible encephalopathy syndrome), a rare complication of tacrolimus therapy. *Emerg Radiol* 2009; 16: 493-496.
- Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; 13: 313-326.
- Nakamura M, Fuchinoue S, Sato S, et al. Clinical and radiological features of two cases of tacrolimus-related posterior leukoencephalopathy in living related liver transplantation. *Transplant Proc* 1998; 30: 1477-1478.
- Wong R, Beguelin GZ, De Lima M, et al. Tacrolimus-associated posterior reversible encephalopathy syndrome after allogeneic haematopoietic stem cell transplantation. *Br J Haematol* 2003; 122: 128-134.
- Feske SK. Posterior reversible encephalopathy syndrome: a review. *Semin Neurol* 2011; 31: 202-215.
- Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996; 334: 494-500.
- Singh N, Bonham A, Fukui M. Immunosuppressive-associated leukoencephalopathy in organ transplant recipients. *Transplantation* 2000; 69: 467-472.
- Kilinc M, Benli S, Can U, et al. FK 506-induced fulminant leukoencephalopathy after kidney transplantation: case report. *Transplant Proc* 2002; 34: 1182-1184.
- Wijdicks EFM, Wiesner RE, Dahlke LJ, et al. FK5060 induced neurotoxicity in liver transplantation. *Ann Neurol* 1994: 498-501.
- Bartynski WS. Posterior Reversible Encephalopathy Syndrome, Part 1: Fundamental Imaging and Clinical Features. *AJNR Am J Neuroradiol* 2008; 29: 1036-1042.
- Jain A, Brody D, Hamad I, et al. Conversion to neoral for neurotoxicity after primary adult liver transplantation under tacrolimus. *Transplantation* 2000; 69: 172-176.
- Furlong T, Storb R, Anasetti C, et al. Clinical outcome after conversion to FK 506 (tacrolimus) therapy for acute graft-versus-host disease resistant to cyclosporine or for cyclosporine-associated toxicities. *Bone Marrow Transplant* 2000; 26: 985-991.
- Gijtenbeek JM, Van Den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. *J Neurol* 1999; 246: 339-346.
- Reece DE, Frei-Lahr DA, Shepherd JD, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. *Bone Marrow Transplant* 1991; 8: 393-401.
- Shimono T, Miki Y, Toyoda H, et al. MR imaging with quantitative diffusion mapping of tacrolimus-induced neurotoxicity in organ transplant patients. *Eur Radiol* 2003; 13: 986-993.
- Zimmer WE, Hourihane JM, Wang HZ, et al. The effect of human leukocyte antigen disparity on cyclosporine neurotoxicity after allogeneic bone marrow transplantation. *AJNR Am J Neuroradiol* 1998; 19: 601-610.
- Wijdicks EF. Neurotoxicity of immunosuppressive drugs. *Liver Transpl* 2001; 7: 937-942.
- Heidenhain C, Puhl G, Neuhaus P. Late fulminant posterior reversible encephalopathy syndrome after liver transplant. *Exp Clin Transplant* 2009; 7: 180-183.