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Tacrolimus-Induced Posterior Reversible Encephalopathy Syndrome (PRES)

Takrolimusa Bağlı Posterior Geri Dönüşümlü Ensefalopati Sendromu (PRES)

ABSTRACT

Since solid organ and hematopoietic stem cell transplantations have been performed increasingly recently, use of immunosuppressive agents such as cyclosporine and tacrolimus has also risen significantly. Posterior reversible encephalopathy syndrome (PRES) is known to be a serious complication of immunosuppressive therapy use following solid organ or stem cell transplants. Clinical findings of the syndrome involve headache, mental status changes, focal neurological deficits, as well as visual disturbances, which are also associated with characteristic imaging features of subcortical white matter lesions on computed tomography (CT) or magnetic resonance imaging (MRI). Despite the fact that the alterations in subcortical white matter might be secondary to potentially reversible vasogenic edema, conversion to irreversible cytotoxic edema has also been described. These imaging findings appear to be prevalent in the territory of the posterior cerebral artery. In most earlier studies, it has been reported that the neurotoxicity associated with tacrolimus may occur at therapeutic levels. The sypmtom complex in most cases in PRES can be reversed through decreasing the dosage or withholding the drug for a few days. PRES is an uncommon complication; however, it may lead to significant morbity and mortality if ir is not diagnosed instantly. The study sheds light on the importance of MRI in prompt recognition of this syndrome, which provides us with the best chance to avoid long-run sequelae. This report highlights the value of MRI in prompt recognition of this entity, which offers the best chance of avoiding long-term sequelae. We aimed to present our 9 year-old renal transplant patient in whom we observed PRES following tacrolimus treatment in the light of clinical and MRI findings. Similar findings did not recur after tacrolimus use. Drug was not changed.

KEY WORDS: Progressive reversible encephalopathy syndrome, Tacrolimus, Kidney transplantation, Children

ÖZ

Solid organ ve hematopoetik kök hücre nakli artan sayıda yapılmaktadır. Bu nedenle siklosporin ve takrolimus gibi immünsupresif ajanların kullanımında önemli artışlar olmuştur. Posterior geri dönüşümlü ensefalopati sendromu (PRES) solid organ veya kök hücre nakli sonrasında immünsupresif tedavi kullanımının ciddi bir komplikasyonudur. Baş ağrısı, mental durum değişiklikleri, fokal nörolojik ve/veya görme bozuklukları gibi klinik bulgular görülmektedir. Bilgisayarlı tomografi (BT) veya manyetik rezonans görüntüleme (MRG) subkortikal beyaz cevher lezyonlarına ait karakteristik görüntüleme bulguları vardır. Subkortikal beyaz cevher değişiklikleri, geri dönüşümlü vazojenik ödeme veya geri dönüşümü olmayan sitotoksik ödem ikincil olarak görülebilir. Bu görüntüleme bulguları posterior serebral arter kanlanma bölgelerinde görülür. Birçok çalışma, takrolimus nörotoksisite ile ilişkili terapötik seviyelerde ortaya olabileceğini göstermiştir. PRES septomları çoğu durumda, ilaç dozunun azaltılması ya da birkaç gün boyunca ilaç yapılmayarak tersine çevrilebilir. PRES nadir bir komplikasyon olmasına rağmen süratle önemli morbidite ve mortalite ile ilişkilidir. MR PRES tanımak için en hassas görüntüleme tekniğidir. Takrolimus tedavisi sonrasında PRES gözlemlediğimiz 9 yaşındaki renal transplant olgumuzu klinik ve MRI bulguları eşliğinde sunmak istedik. Benzer bulgular ilaç kullanımından sonra tekrarlamadı. İlaç değiştirilmedi.

ANAHTAR SÖZCÜKLER: Posterior geri dönüşümlü ensefalopati sendromu, Takrolimus, Böbrek nakli, Çocuklar

Seçil CONKAR
Caner KABASAKAL
Sevgi MİR

Ege University Faculty of Medicine, Department of Pediatric Nephrology, İzmir, Turkey

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Correspondence Address:
Seçil CONKAR
Ege Üniversitesi Tıp Fakültesi, Çocuk Nefroloji Bilim Dalı, İzmir, Turkey
Phone : + 90 554 539 05 01
E-mail : secilcankar@yahoo.com.tr

INTRODUCTION

Tacrolimus (also FK-506 or Fujimycin) is an immunosuppressive drug. Its primary role is to prevent graftversus- host disease in the post-allogenic organ transplant patients, and recently the drug seems to have been employed increasingly as an immunosuppressive agent in solid organ and hematopoietic stem cell transplantation (1,2). Neurotoxicity secondary to tacrolimus has been well described particularly in solid organ transplant recipients (3). Patients typically present with the symptoms such as altered mental status, headache, focal neurological deficits, visual disturbances, and seizures. Posterior reversible encephalopathy syndrome (PRES) is a relatively new clinicoradiological entity first described as PRESS in 1996, characterized by headaches, altered mental status, seizures, and visual loss, which can be most sensitively detectec by MRI (16). It is crucial to recognize this symptom complex promptly, since most case will make complete recovery through reducing dosage or withholding the immunosuppressive agent.

We aimed to present our 9-year-old renal transplant patient in whom we observed PRES following tacrolimus treatment in the light of clinical and MRI findings. Similar findings did not recur after tacrolimus use. The drug was not changed.

CASE REPORT

A nine-year-old boy had been followed up in our peritoneal dialysis unit for 5 years due to posterior-urethral valve-related chronic renal insufficiency. The patient was transplanted a kidney from cadaver. His immunosuppressive treatment was arranged as tacrolimus (0.1 mg/kg/day, bid), mycophenolate mofetil (600 mg/m2, bid), and prednisolone. The patient was given antithymocyte immunoglobulin for the first 7 days according to CD3 count. The patient was started tacrolimus on the 2nd day of transplantation as his creatinine value decreased below 2.5 mg/dl. Tacrolimus was administered as 0.1 mg/kg/day in two equal doses. The patient experienced mild headache following the first dose of tacrolimus. The blood pressure was evaluated as stage I (110/70 mmHg) and followed up closely. His headache became severe after the second dose of tacrolimus, and the blood pressure was consistent with stage II (150/110 mmHg), he described blurred vision. Hypertensive retinopathy was not detected. He was learned to have personality changes from his family. Afterwards, bilateral tonic- clonic seizure developed especially in the upper extremity. No neurological findings suggestive of intracranial hemorrhage were detected on his physical examination at that moment. Fever, meningeal irritation findings and neck stiffness suggestive of encephalitis were not detected. Blood electrolytes and blood glucose levels studied in the course of convulsion were found to be normal. Convulsions recurred three times within 3 hours. A tendency to sleep was observed in the postictal period and continued for approximately 30 minutes. The patient completely recovered after the seizures and no medical treatment was administered as the seizures lasted less than 5 min. He was administered a phenytoin loading dose of 15 mg/kg once after the third seizure. When his family was interviewed and anamnesis was deepened, the patient was learned to have personality changes like headache, jealousy, unhappiness beginning from the first dose of tacrolimus. He was detected to have complaint of blurred vision 20-30 min after the first dose of the drug.

Cranial MRI and electroencephalography (EEG) were performed. Deceleration was observed in the parietooccipital part of the right hemisphere in awake EEG. Sleep EEG was normal and no epileptic discharges were observed. On cranial MRI, areas showing diffusion restriction secondary to multifocal mild vasogenic edema in the right cerebellar hemisphere and cerebral hemispheres were observed (Figure 1). The case was interpreted as PRES in light of the clinical findings. When we evaluated the patient together with the literature, the diagnosis

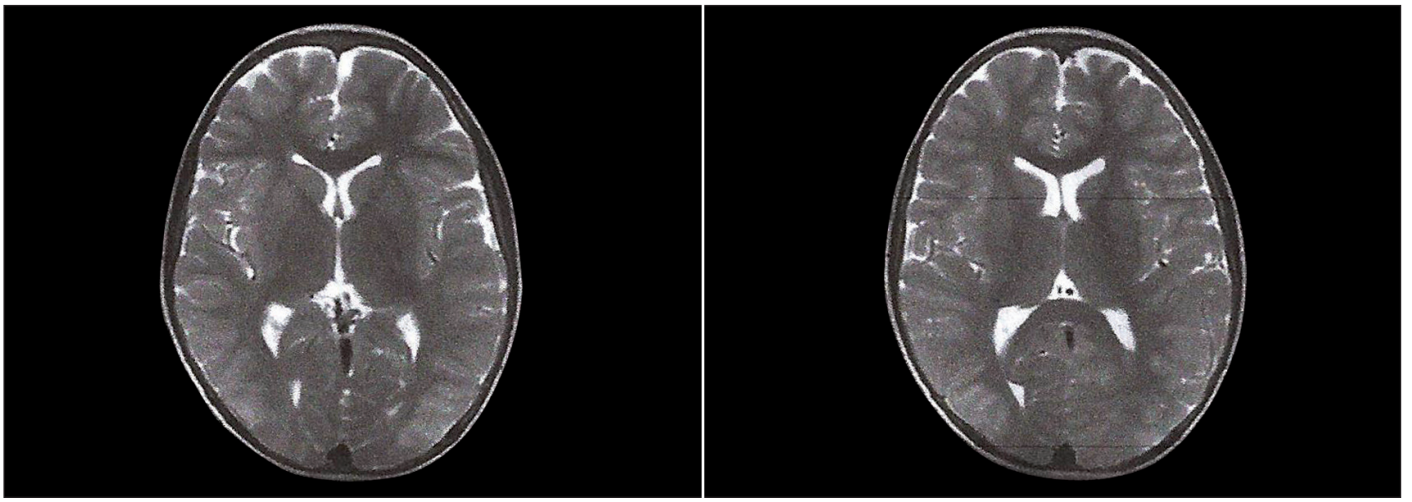

Figure 1: *Vasogenic edema in the right occipital lobe on T2A cranial MR imagings.*

of PRES was strengthened as the vasogenic edema detected on cranial MRI was especially in the posterior hemispheres and multifocal, and hypertension accompanied these findings.

Convulsions did not recur during follow-up. Antiepileptic or antihypertensive treatment was not started. Blood pressure returned to normal within 2-3 hours. The tacrolimus level examined in the course of a convulsion was found to be <2 ng/ml The patient is being followed up and receiving the triple treatment of tacrolimus, steroids, and MMF. Similar findings did not recur after tacrolimus use. The drug was not changed. Clinical findings returned to normal within a couple of days without permanent injury. MRI and EEG findings were completely normal when the tests were repeated three months later.

DISCUSSION

Posterior reversible encephalopathy syndrome is an increasingly recognized neurologic disorder with a multitude of diverse clinical entities (1,4). Among known associated causative agents are immunosuppressives such as tacrolimus (1,5), cyclosporine (1,6), cisplatin (1,7), and erythropoietin (1,8), with the conditions in such presentations as pre eclampsia and eclampsia, acute glomerulonephritis, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome (1,9). PRES consists of reversible vasogenic edema in posterior circulation territories, although conversion to irreversible cytotoxic edema has also been documented (1,10). PRES, hypertensive encephalopathy, and reversible posterior cerebral edema are all terms used to describe a group of disorders presenting clinically with headache, seizures, visual changes, altered mental status, and occasionally focal neurological signs (1,11).

PRES clinically presents with seizures, severe headaches, and mental and visual changes. Risk factors comprise hypertension and calcineurin inhibitor administration, fluid retention, renal failure, and alteration in vascular permeability (1,3).

Convulsion, headache, mental and visual findings were observed in our case as reported in the literature. Of the risk factors mentioned in literature, our patient had high blood pressure, calcineurin inhibitor treatment, and intensive fluid supplementation as he was on the second day of transplantation.

Withholding tacrolimus may be considered to be diagnostic tool, if symptoms persist or other complications require this approach. The drug was not changed as neurotoxic findings did not continue, and the plasma level of the drug was low.

Diagnosis of PRES is made through MRI findings and was also made with cranial MRI findings in our patient. The abnormalities primarily affect white matter but the cortex can also be involved. Therefore, MRI of the brain is the most sensitive diagnostic means. MRI findings include subcortical white matter and grey matter lesions on FLAIR, and T2- weighted sequences predominantly located posteriorly. Typically, the lesions of PRES reported in the literature are symmetrical in distribution (1,12).

Characteristic lesion locations such as the inferior temporal-occipital junction, superior frontal sulcus, and parietal/ occipital region are likely to represent junctional expression between second-order branches or distal hemispheric branches.

A continuum is noted between diminutive and extensive expression of PRES; and partial, asymmetric, or mixed forms of these patterns may be encountered (12). Localized mass effect and subtle enhancement within lesions have been described but are not seen consistently. Previous studies have shown that vasogenic edema accounts for the changes observed in PRES(1,14).

Cranial MRI findings were not symmetrical in our case unlike those described in the literature. More explicit findings were detected in the left posterior region. A breakdown in cerebral autoregulation results in the leakage of fluid into the interstitium, which is detected as vasogenic edema. The predilection for involvement of posterior circulation territories is generally accepted to result from the relatively sparse sympathetic innervation of the vertebrobasilar circulation. In healthy subjects, cerebral autoregulatory mechanisms that have both myogenic and neurogenic components maintain normal perfusion. In patients with PRES, the myogenic response is blunted by either passive over distension of the vessels due to elevations in blood pressure or direct toxic effects on the endothelium (15). Neurotoxicity may occur even at therapeutic levels of tacrolimus and thus serum levels of the drug cannot be maintained as reliable diagnostic markers of severe neurotoxicity induced by tacrolimus. Neurological findings were observed with the first dose of the drug before the effective plasma tacrolimus level was reached in our case.

In a study involving a large series of patients with immunosuppressant- induced PRES, most cases were observed to be reversible following the reduction of dosage of the drug or witholding it for a few days(1). Our case, who presented with sudden onset of neurologic symptoms, hypertension, and psychiatric symptoms after tacrolimus adminstration showed improvemnet upon discontinuation of tacrolimus and keeping the blood pressure under control.

Personality changes, headache and blurred vision are the initial complaints of tacrolimus neurotoxicity. Neurotoxicity should be considered if these complaints develop after tacrolimus treatment. We believe that keeping the blood pressure within the normal range, and close monitorization of volume load could prevent PRES development. The convulsions and hospitalization in the intensive care unit caused severe trauma for the child and the family although PRES itself is reversible.

In conclusion, solid organ transplantations and utilization of immunosuppressive treatments are gradually increasing. The fact that severe neurologic side effects may occur following

the first dose of tacrolimus should be kept in mind in these patients. It should not be forgotten that neurological side effects of tacrolimus are not correlated with the plasma level of the drug. Blood pressure, headache, personality changes should be followed up closely in the period that calcineurin inhibitors were started on the first days posttransplantation that intensive fluid treatment is applied. Immunosupressive treatment should be done carefully when needed.

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