Int J Clin Exp Med 2016;9(8):16897-16900
www.ijcem.com /ISSN:1940-5901/IJCEM0020382

Case Report

Reversible posterior leukoencephalopathy syndrome caused by tacrolimus: a case report

Zhihua Si[1*], Ke Hu[2*], Aihua Wang[1], Jinzhi Liu[1]

Departments of [1]Neurology, [2]Emergency, Qianfoshan Hospital Affiliated to Shandong University, No. 16466, Jingshi Road, Lixia District, Jinan 250014, Shandong, China. [*]Equal contributors.

Received October 11, 2015; Accepted April 20, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Objective: Explore the clinical and imaging manifestation in one case of reversible posterior leukoencephalopathy syndrome (RPLS) after treatment with tacrolimus. Methods: The clinical and imaging data of this RPLS patient was retrospectively analyzed. Results: MR imaging showed abnormal signals bilaterally in both hemispheres of the cerebellum, the cortex, and in the subcortical area. Low signal was showed on T1-weighted images, high signal on T2-weighted images. The majority of the lesions had equal signals on diffusion weighted imaging (DWI) images, with only a few regions of the brain showing a slightly higher signal. After treatment, the patient recovered and the abnormal findings on MR imaging completely resolved. Conclusions: Tacrolimus can cause RPLS, the key for treatment is early diagnosis.

Keywords: Tacrolimus, RPLS

Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS) is known by its clinical and imaging characteristics. While a considerable amount of researches have been devoted to find the cause of RPLS, case reports of tacrolimus use being its primary cause are rare. In this study, we report a RPLS case caused by tacrolimus. We hope our research can strengthen clinician awareness of the relationship between tacrolimus and RPLS.

Case report

A 26-year-old male with fevers (37.9°C) and hypertension (160/90 mmHg) was sent to our hospital because of loss of consciousness and convulsions. These symptoms persisted for half an hour before remission; however, three similar attacks occurred in the days directly following admission. Neurological examination only revealed that the right Babinski sign was positive. The patient had a long history of treatment with the immunosuppressant tacrolimus due to his nephrotic syndrome and kidney failure. The EEG examination is normal; the tacrolimus concentration was 5.8 ng/ml and the creatinine level was 180 mmol/L after admission. MR imaging showed bilateral hypointensity on T1-weighted and hyperintensity on T2-weighted images in the cerebellar hemispheres, cortex, and subcortical area. The majority of the lesions had equal signal strength on diffusion-weighted imging (DWI) images, with only a few lesions showing a slightly higher signal (**Figure 1**). Thus, we speculated that the diagnosis may be RPLS caused by tacrolimus. For following treatment, the patient was placed on a regimen of the oral antihypertensive drug valsartan (Cap-sules) and lamotrigine as symptomatic treatment, while tacrolimus was discontinued. After 23 days of treatment, this patient recovered well and the MR imaging findings resolved (**Figure 2**). Based on these findings, we were able to make a definitive diagnosis of RPLS caused by tacrolimus. The patient's symptoms completely resolved after 1 month of treatment.

Discussion

PRLS was firstly found by Hinchey [1] and defined as a clinical syndrome that could be

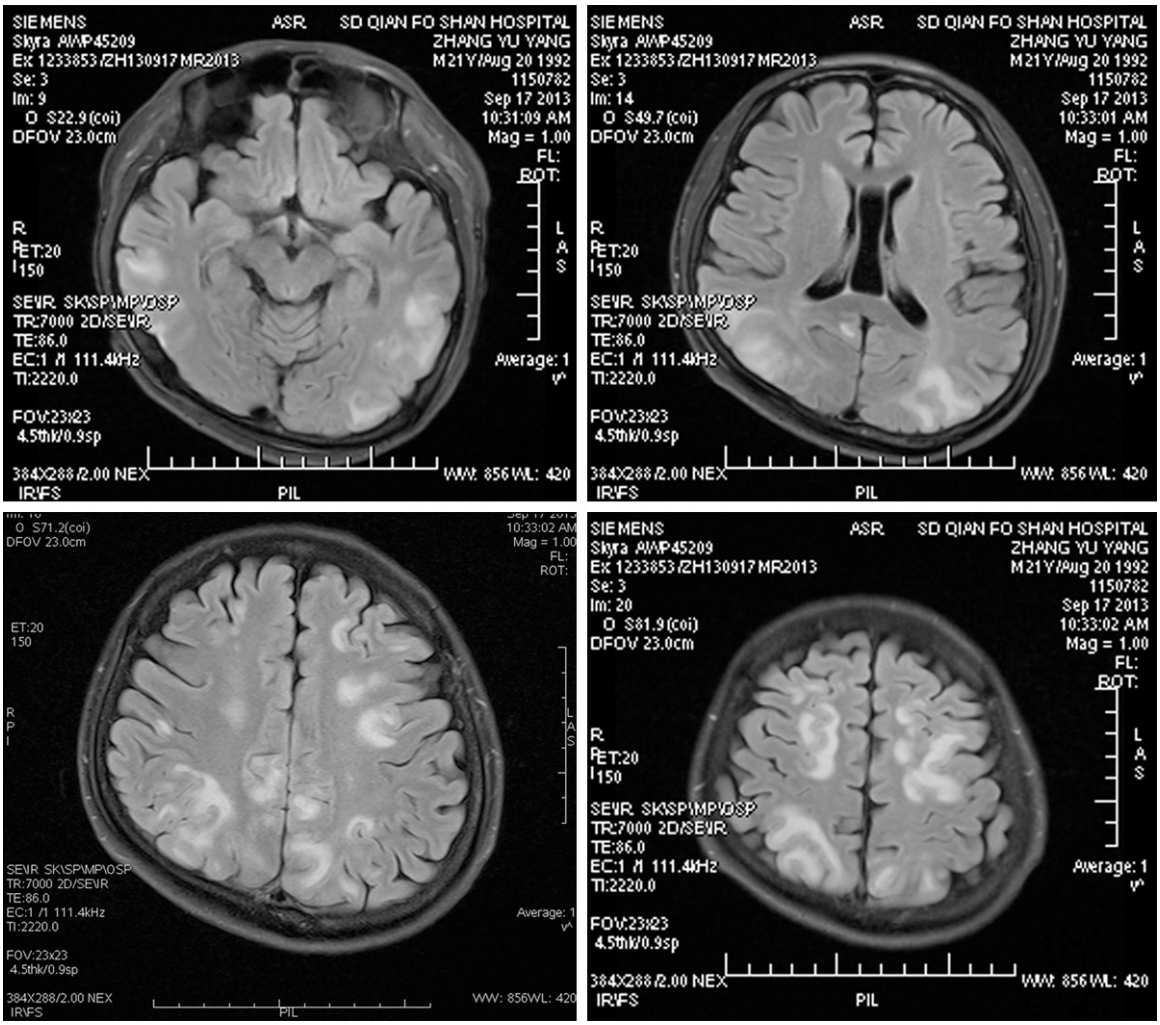

Figure 1. Multiple patchy T2FLAIR signal in bilateral frontal temporal-parietal occipital cortex and subcortical area.

diagnosed in part with imaging; it has multiple causes and is characterized by symmetric and reversible lesions in the posterior regions of the cerebra and cerebellum. The typical symptoms include headache, epilepsy, visual disorder and alterations in consciousness. Some of the main reasons for the onset of RPLS include hypertensive encephalopathy, eclampsia, renal failure, immunodepressants use and cytotoxic drugs. Rare causes include transplanttation, thrombocytopenic purpura, acquired immune deficiency syndrome, carotid endarterectomy, acute intermittent porphyria, and electrolyte imbalances [1, 2]. Although the pathogenesis of RPLS is inadequately understood, there are two kinds of hypotheses. The first theory is the breakthrough of cerebral perfusion pressure. Hinchey considered that the main pathogenic factors are the disorder in self-regulation of cerebral blood flow as well as the dysfunction of endothelial cells, which induce vasogenic edema under severe hypertension [1]. The second theory is related to damage to the vascular endothelial cells. In this theory, the bacterial toxin or immunosuppressant has a toxic effect on vascular endothelial cells, which then cause RPLS due to this damage [3, 4]. Moreover, some studies have shown that gamma globulin and linezolid could also lead to RPLS, possibly associated with the inhibition of monoamine oxidase. T2-weighted images, especially on fluid attenuation inversion recovery (FLAIR) imaging, demonstrate bilateral white matter reversible edema in the posterior region of the brain (lower signal on T1-weighted images and higher on T2-weighted images) [5, 6], while D-weighted imaging shows equal or slightly higher signals [1]. Part of the cerebral cortex

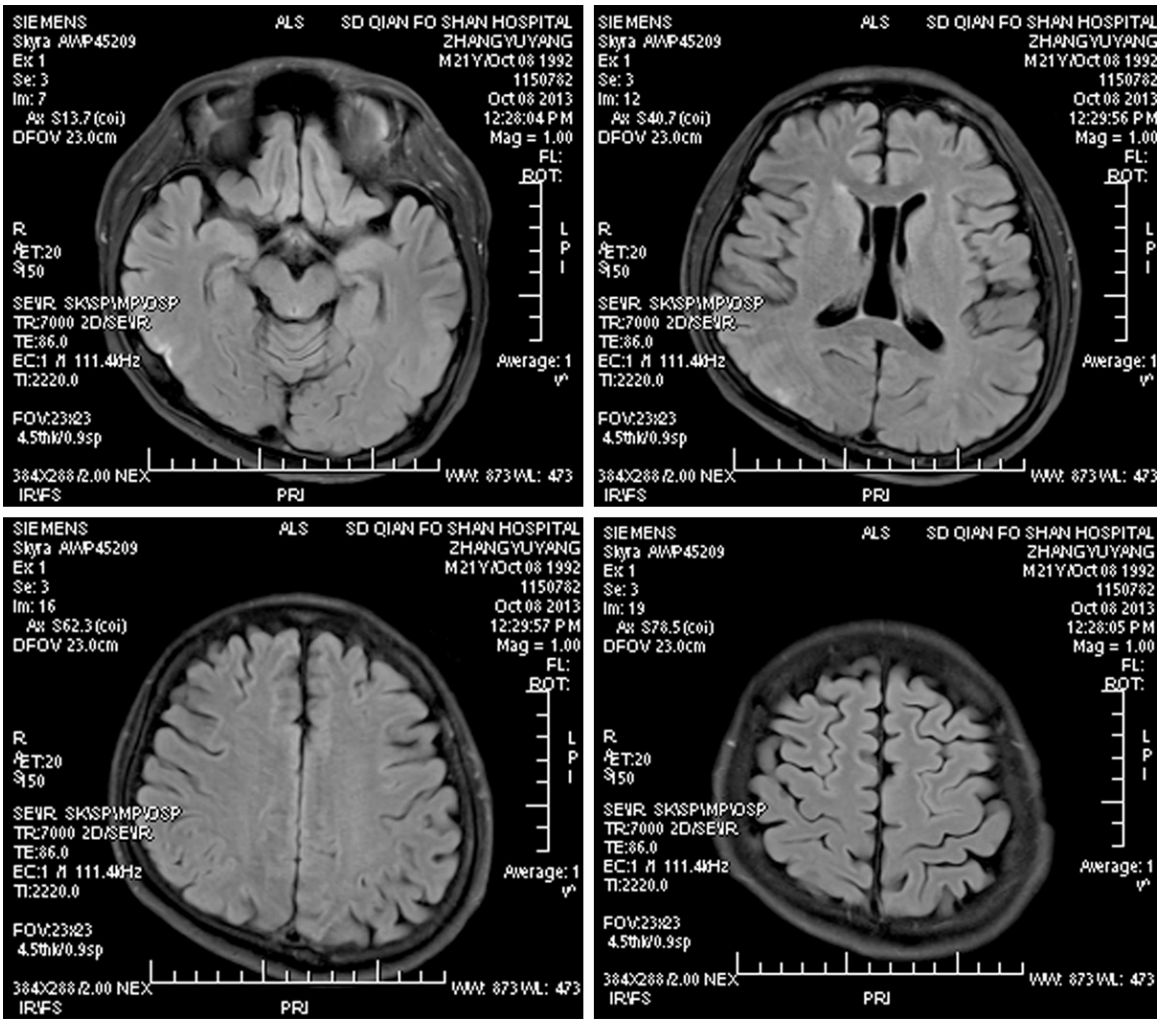

Figure 2. Lesions completely disappeared.

and the region in anterior circulation may also be involved, but the incidence is very low. The diagnosis of RPLS is mainly based on clinical manifestations, typical imaging and reversible course of disease. The key for treatment is early diagnosis. In the early stages, the patient experiences vasogenic cerebral edema that is reversible. Delayed treatment can lead to irreversible denaturation death of nerve cells. Treatments include: reduce blood pressure to normal level in several hours; control the seizures as much as possible; and discontinue or decrease the dose of cytotoxic drugs. As for the patients with severe basic diseases, timely symptomatic treatment must also be administered.

In this case report, there were two probable causes for the RPLS. First, severe hypertension caused by tacrolimus can lead to the dysfunction in self-regulation of cerebral blood flow; second, tacrolimus has a toxic effect on vascular endothelial cells.

Summary

Tacrolimus is a potential cause of RPLS that clinicians should be aware of. MR imaging, especially MR diffusion imaging, during the acute stage is crucial for definitive diagnosis and treatment. Early treatment is important to avoid serious neurological sequelae. Due to the reversability of the disorder, RPLS is distinct from other neurological diseases. Although the package insert for tacrolimus does not mention that tacrolimus can lead to RPLS in some cases, it is clearly a potential side effect and perhaps will be added to the label in the upcoming weeks or months.

Acknowledgements

This work was funded by the Shandong Provincial Natural Science Foundation, China (ZR2012HL28) and the Medical Science And Technology Development Plan of Shandong Province, China (2011HD009).

Disclosure of conflict of interest

None.

Address correspondence to: Ke Hu, Department of Emergency, Qianfoshan Hospital Affiliated to Shandong University, No. 16466, Jingshi Road, Lixia District, Jinan 250014, Shandong, China. Tel: +8615153184258; E-mail: raingodkeke@163.com

References

[1] Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, Pessin MS, Lamy C, Mas JL and Caplan LR. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996; 334: 494-500.

[2] Stott VL, Hurrell MA and Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. Intern Med J 2005; 35: 83-90.

[3] Yan GP, Wu HL and Y G. Conventional magnetic resonance imaging and diffusion-weighted mr imaging in eclampsia encephalopathy performance. Practical Journal of Medicine 2008; 24: 249.

[4] Mutter WP and Karumanchi SA. Molecular mechanisms of preeclampsia. Microvasc Res 2008; 75: 1-8.

[5] Huijgen W, van der Kallen B, Boiten J and Lycklama ANG. Unilateral reversible posterior leukoencephalopathy syndrome after coiling of an aneurysm. J Clin Neurol 2014; 10: 59-63.

[6] Myint ZW, Sen JM, Watts NL, Druzgal TJ, Nathan BR, Ward MD, Boyer JE and Fracasso PM. Reversible posterior leukoencephalopathy syndrome during regorafenib treatment: a case report and literature review of reversible posterior leukoencephalopathy syndrome associated with multikinase inhibitors. Clin Colorectal Cancer 2014; 13: 127-130.