



Case report

FK506-induced intractable leukoencephalopathy following allogeneic bone marrow transplantation

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Summary:

FK506-related leukoencephalopathy has been reported to be reversible and readily treated by discontinuation or reduction of FK506. We describe two pediatric cases of FK506-related leukoencephalopathy following allogeneic bone marrow transplantation, which could not be readily controlled. These cases show that FK506-related leukoencephalopathy is not always reversible, and patients may develop epilepsy. *Bone Marrow Transplantation* (2000) **25**, 331–334.

Keywords: FK506; leukoencephalopathy; bone marrow transplantation

FK506 (tacrolimus) is an immunosuppressive drug, and more potent than cyclosporine (CsA). However, the clinical usefulness of FK506 is limited by its severe adverse effects including neurotoxicity. FK506-related leukoencephalopathy has been reported to be reversible and readily treated by discontinuation or reduction of FK506.^{1–7} The signs and symptoms are usually resolved within 1 to 2 weeks with discontinuation of the drug or even reduction of its dose. We describe two pediatric cases of FK506-related leukoencephalopathy following allogeneic bone marrow transplantation, which could not readily be controlled.

Case reports

Case 1

A 15-year-old girl was diagnosed as having chronic myelogenous leukemia in August 1993. She underwent allogeneic bone marrow transplantation (BMT) in March 1996, with marrow from an unrelated HLA-matched donor, following conditioning with cyclophosphamide and total body irradiation. Prophylaxis for graft-versus-host disease (GVHD) consisted of CsA and short-term methotrexate

(MTX). On day 19, she developed acute GVHD grade II. FK506 was substituted for CsA, because GVHD was uncontrollable in spite of high-dose methylprednisolone (mPSL). GVHD symptoms were resolved in a few days and FK506 was discontinued on day 114. However, FK506 and mPSL were readministered because of recurrent GVHD. She recovered gradually and FK506 was tapered off in January 1997. Five months after FK506 discontinuation, she developed chronic GVHD. FK506 and prednisolone were readministered.

In October 1997, she complained of severe headache, and developed generalized tonic–clonic convulsions, confusion, and left hemiparesis 3 months after FK506 readministration (Figure 1a). She was afebrile. Her blood pressure was 142/90 mmHg. The pupillary reflexes and fundi were unremarkable. Platelets had decreased to $73 \times 10^9/l$ and the hemoglobin level was 14.0 g/dl. No red blood cell fragmentation was observed in a peripheral smear. The reticulocyte level was not increased (2.6%). She exhibited normal renal function. The serum concentrations of lactate dehydrogenase and bilirubin had increased to 744 IU/l (upper normal, 243 IU/l) and 1.92 mg/dl. The level of von Willebrand factor (vWF) was high (336%, NR 50–150%). The whole blood FK506 level was 5.6 ng/ml. The cerebrospinal fluid (CSF) contained 0/ml white blood cells, 37 mg/dl protein and no leukemic blasts. The CSF FK506 level was 3.0 ng/ml. Polymerase chain reaction (PCR) analysis demonstrated no cytomegalovirus (CMV), human herpes virus (HHV)-6, or HHV-7 in the CSF. An MRI scan 5 days later demonstrated an abnormally high signal in T2-weighted images (WI) in the bilateral occipital lobes, parietal lobes, frontal lobes, caudate nucleus, putamen and globus pallidus (Figure 2). No abnormal enhancement was seen with intravenous contrast medium on MRI. Electroencephalography (EEG) showed diffuse slow activity. A diagnosis of FK506-related leukoencephalopathy with microangiopathy was made. FK506 was discontinued immediately. She received phenytoin for status epilepticus, and mPSL for both chronic GVHD and microangiopathy. Hypertension resolved spontaneously within 12 h after admission. She recovered with no neurologic deficit within 2 weeks. A follow-up MRI 9 days later showed almost complete resolution of the brain lesions, but persistence of a small focal abnormality. Twenty days after the first seizure, she experienced a left-sided facial focal seizure without FK506 readministration.

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Received 4 June 1999; accepted 14 October 1999

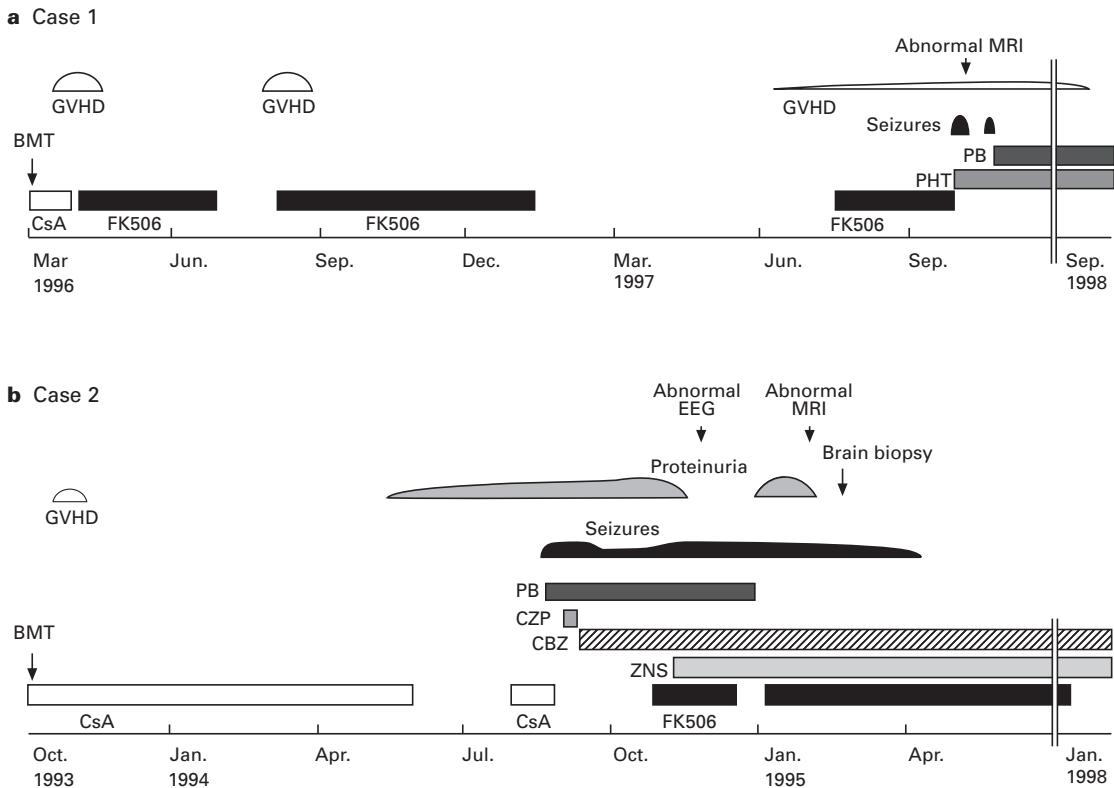


Figure 1 Clinical courses of the patients.

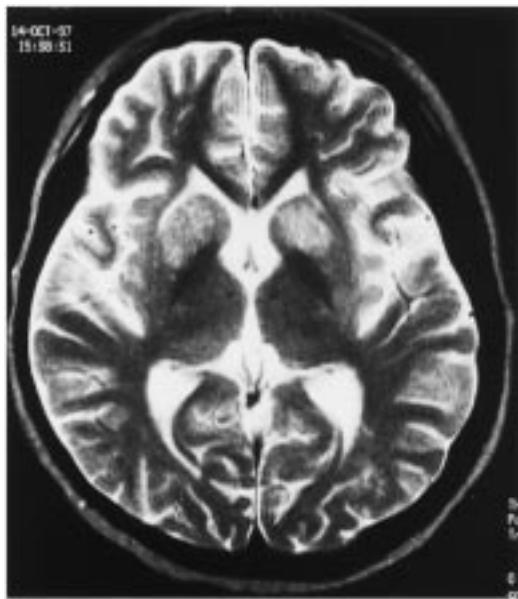


Figure 2 MRI scans in case 1. T2-weighted MRI scans obtained at the onset of symptoms show abnormally high signals in the bilateral caudate nucleus, putamen, and globus pallidus.

Phenobarbital was administered in addition to phenytoin. No further seizures have occurred. Currently, she is alive and well at 3 years post BMT.

Case 2

A 4-year-old boy was diagnosed as having acute myeloid leukemia FAB M4E in January 1992. He had no history of epilepsy, but a cousin of his father had epilepsy. In October 1993, 20 months after achieving complete remission, he underwent allogeneic BMT following a radiation-free preparative regimen of busulfan, etoposide and cyclophosphamide. He received 12 doses of intrathecal MTX and Ara-C as CNS prophylaxis prior to transplantation. GVHD prophylaxis consisted of CsA, short-term MTX, and anti-lymphocyte globulin. On day 7, he developed acute GVHD grade II and then received high-dose mPSL. Subsequently, he recovered and CsA was discontinued in June 1994.

In May 1994, proteinuria and microscopic hematuria appeared, while prednisolone was maintained. He apparently developed nephrotic syndrome, which was related to chronic GVHD. A renal biopsy revealed membranous nephropathy. Nineteen days after CsA readministration, he developed generalized tonic-clonic convulsions. He was afebrile and not hypertensive. His CsA trough level was 95–155 ng/ml. He exhibited normal renal function. The CSF contained 0/ml white blood cells, 8 mg/dl protein, and no leukemic blasts. At that time, MRI was normal. CsA was discontinued and prednisolone was increased to 2 mg/kg/day. The seizures persisted despite discontinuation of CsA, and resisted both phenobarbital and clonazepam. Carbamazepine was effective for the seizures, but only transiently (Figure 1b). Two months later, nephrotic syndrome was progressive after CsA discontinuation, and FK506

treatment was begun. Thereafter, proteinuria decreased. FK506 was discontinued because EEG showed diffuse multi-spike and wave bursts 1 month later (Figure 3a). However, FK506 had to be readministered because of recurrent massive proteinuria. Three weeks after FK506 readministration, brain MRI revealed areas of increased signal intensity in T2-WI in the bilateral occipital and parietal lobes (Figure 3b), although the frequency of the seizures was decreasing. No abnormal enhancement was seen with intravenous gadolinium contrast medium. The FK506 trough level was maintained below 10 ng/ml. The blood pressure was not elevated. CSF contained 21/ml white blood cells, 15 mg/dl protein, and no leukemic blasts. Although the seizures became gradually less frequent after zonisamide administration, the number of abnormal areas on MRI increased. In addition to FK506 neurotoxicity,

other disorders such as CNS relapse, lymphoma, viral infection and GVHD were considered in the context of the clinical picture. A brain biopsy demonstrated increased numbers of macrophages in brain and perivascular tissues. The perivascular infiltrating cells were positively stained with the CD68, a marker of macrophage-monocyte (Figure 3c). Neither neoplastic cells nor lymphoid cells were found. No microorganisms were detected on PAS, Ziehl-Neelsen, Grocott, or Gram staining. PCRs for CMV, HHV-6, and HHV-7 in brain tissue were negative. A repeat MRI scan, performed 6 weeks after the initial abnormal study, showed decreases in the size and intensity of the white-matter lesions, although low doses of FK506 were administered continuously. No seizures have occurred since April 1995. In January 1998, FK506 was discontinued. He was doing well at 5 years post BMT.

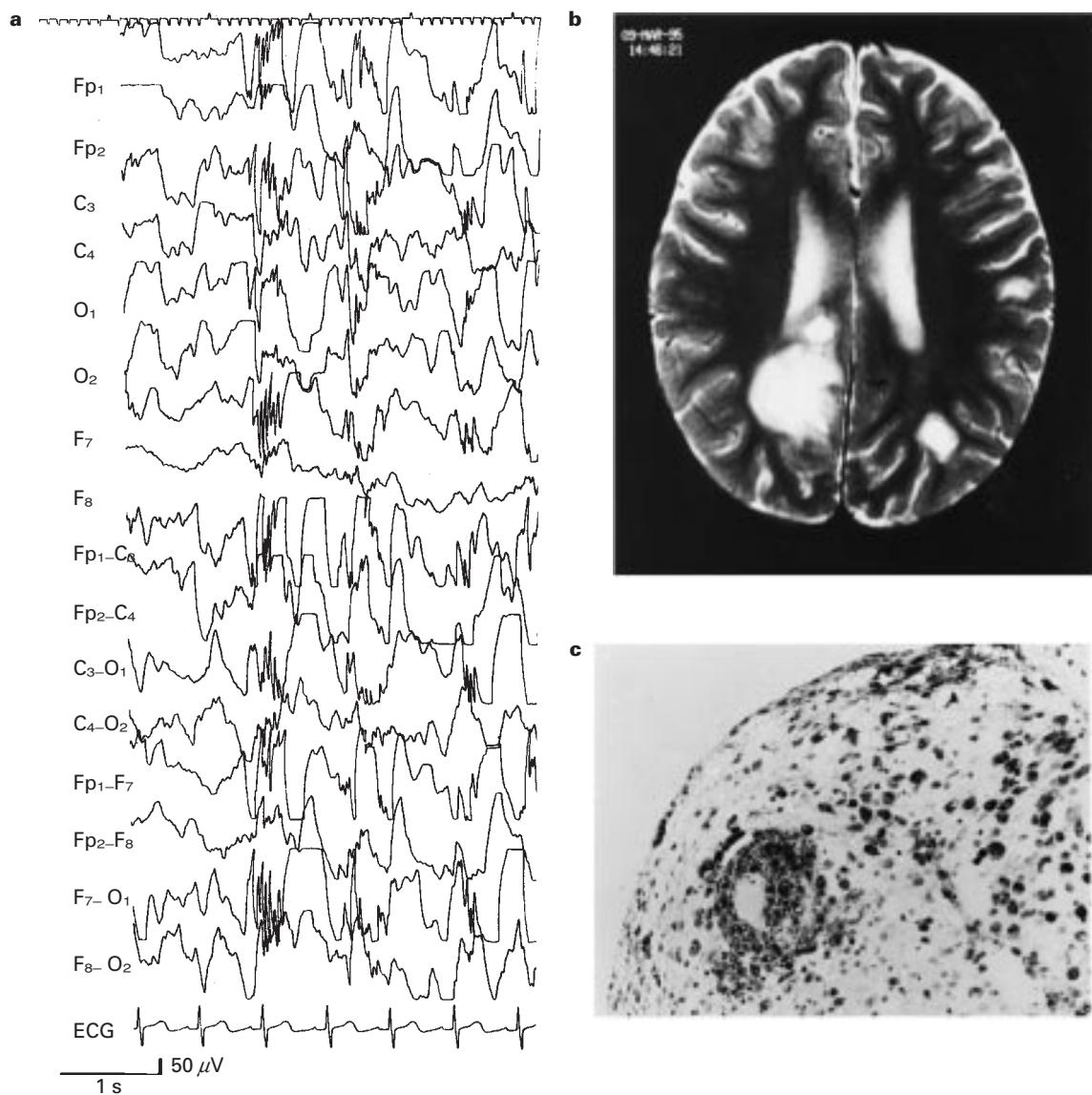


Figure 3 EEG in case 2(a). EEG 1 month after FK506 administration shows diffuse multi-spike and wave bursts (left side dominant). MRI scans in case 2(b). T2-weighted MRI scans obtained 3 weeks after FK506 readministration show abnormally high signals in the bilateral occipital lobes. Histopathological analysis in case 2(c). Immunostaining for the CD68 antigen shows increases in the numbers of macrophages in brain and perivascular tissues. Original magnification $\times 100$.

Discussion

The precise mechanism of FK506- or CsA-associated leukoencephalopathy remains unknown. FK506 and CsA share several common features including lipophilic properties and hepatic metabolism. The high lipid content of myelin in the brain would make it an attractive binding site for these agents because both FK506 and CsA have lipophilic properties. Breakdown of the blood-brain barrier (BBB) may allow increased passage of lipophilic agents such as FK506 and CsA. The identification of CsA and its metabolites, and FK506 in the CSF suggests perturbation of the BBB.¹ Alteration in the BBB due to endothelial damage is one of several hypotheses explaining the mechanism of this leukoencephalopathy. Endothelial injury is thought to underlie the pathogenesis of both FK506- or CsA-induced leukoencephalopathy and microangiopathy.⁸ In case 1, there was an elevated vWF level, a marker of endothelial damage. Furthermore, the presence of GVHD increases the probability of endothelial damage. In case 1, leukoencephalopathy occurred after readministration of FK506 for chronic GVHD, but not during the first administration for acute GVHD. In case 2, there was also chronic GVHD when seizures occurred. Our cases suggest chronic GVHD may be a risk factor of late onset leukoencephalopathy.

Although the number of histopathological studies on FK506- or CsA-induced leukoencephalopathy is small, disruption of the BBB due to endothelial damage, non-specific demyelination, and cerebral vasculitis has been reported.²⁻⁵ There have only been two previous studies in which a brain biopsy was performed. The others involved autopsies. One of the findings on brain biopsy was nonspecific demyelination,² and the other was microglial and astrocytic activation.³ The histological findings in our case are similar to those in the latter, and demyelination or endothelial damage was not evident. Neither CD3-positive cells shown in brain GVHD⁹ nor abnormal cells had infiltrated, but CD68-positive cells had. Macrophages might infiltrate in response to local inflammation.

A neuroprotective effect of FK506 has been reported in experimental cerebral ischemia.¹⁰ Although the cellular mechanism underlying this neuroprotective effect also remains uncertain, pharmacological data have confirmed the importance of immunophilin binding and suggested a role for calcineurin. FK506 mediates its activity through binding to an immunophilin (FKBP). FK506 binds to FKBP to form an active FK506-FKBP complex. This complex inhibits calcineurin, thereby leading to its effect. It has been reported that the level of FKBP is 10–40 times higher in brain than immune tissues.¹¹ FK506 toxicity has frequently

been observed in organs with high FKBP contents, such as the brain and kidneys. The FKBP in the brain may be related to this FK506-induced leukoencephalopathy, which seems to be contrary to reported experimental neuroprotective effects. There was no relationship between the onset of seizures and elevated levels of FK506. The leukoencephalopathy may be associated with FKBP rather than levels of FK506.

FK506-induced leukoencephalopathy has been described to be reversible neurologically and readily treated by discontinuation of FK506. Our cases illustrate that deficits due to posterior leukoencephalopathy may be not readily controlled and may persist, even if FK506 is discontinued or reduced. Furthermore, chronic GVHD might be a risk factor for intractable leukoencephalopathy.

References

- 1 Freise CE, Rowley H, Lake J et al. Similar clinical presentation of neurotoxicity following FK506 and cyclosporine in a liver transplant recipient. *Transplant Proc* 1991; **23**: 3173–3174.
- 2 Small SL, Fukui MB, Bramblett GT, Eidelman BH. Immunosuppression-induced leukoencephalopathy from tacrolimus (FK506). *Ann Neurol* 1996; **40**: 575–580.
- 3 Thyagarajan GK, Cobanoglu A, Johnston W. FK506-induced fulminant leukoencephalopathy after single-lung transplantation. *Ann Thorac Surg* 1997; **64**: 1461–1464.
- 4 Shutter LA, Green JP, Newman NJ et al. Cortical blindness and white matter lesions in a patient receiving FK506 after liver transplantation. *Neurology* 1993; **43**: 2417–2418.
- 5 Pizzalato GP, Sztajzel R, Burkhardt K et al. Cerebral vasculitis during FK506 treatment in liver transplant patient. *Neurology* 1998; **50**: 1154–1157.
- 6 Hinckey J, Chaves C, Appignani B et al. A reversible posterior leukoencephalopathy syndrome. *New Engl J Med* 1996; **334**: 494–500.
- 7 Steg RE, Kessinger A, Wszolek ZK. Cortical blindness and seizures in a patient receiving FK506 after bone marrow transplantation. *Bone Marrow Transplant* 1999; **23**: 959–962.
- 8 Pettitt AR, Clark RE. Thrombotic microangiopathy following bone marrow transplantation. *Bone Marrow Transplant* 1994; **14**: 495–504.
- 9 Iwasaki Y, Sako K, Ohara Y et al. Subacute panencephalitis associated with chronic graft-versus-host disease. *Acta Neuropathol* 1993; **85**: 566–572.
- 10 Sharkey J, Butcher SP. Immunophilins mediate the neuroprotective effect of FK506 in focal cerebral ischaemia. *Nature* 1994; **371**: 336–339.
- 11 Steiner JP, Dawson TM, Fotuhi M et al. High brain densities of the immunophilin FKBP colocalized with calcineurin. *Nature* 1992; **358**: 584–587.