Immunosuppression-induced Leukoencephalopathy from Tacrolimus (FK506)

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Tacrolimus (FK506) has recently been approved for immunosuppression in organ transplantation, although its use is accompanied by a wide spectrum of neurotoxic side effects. We describe the clinical, radiological, and pathological features of 3 cases of tacrolimus-related leukoencephalopathy. The syndrome of immunosuppression-related leukoencephalopathy is proposed as an uncommon neurological syndrome occurring in patients with organ transplants involving demyelination, in particular in the parieto-occipital region and centrum semiovale. Although the syndrome is not associated with a particular (absolute) serum level of tacrolimus, it resolves spontaneously upon decreasing the dose. The tacrolimus-related syndrome has a similar radiographic and pathologic appearance as the analogous syndrome that occurs in patients taking cyclosporine.

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Tacrolimus (formerly FK506) is a new immunosuppressant agent that has recently been approved by the Food and Drug Administration for use in liver transplantation [1]. Clinical trials of tacrolimus have shown it to be as effective as cyclosporine [2], although more adverse neurological effects have been reported [3]. We have previously reported an array of central nervous system (CNS) side effects from tacrolimus [4], including focal neurological abnormalities. Two patients had speech disturbances [5], 1 had hemiplegia, and 1 had cortical blindness. Magnetic resonance imaging (MRI) demonstrated focal abnormalities in the white matter [4]. Both clinical and MRI findings improved over time in each of these patients.

In the current study, we further define the neurological, radiological, and neuropathological features of this tacrolimus-related leukoencephalopathy. Data are presented from 3 patients with the clinical syndrome, including 2 patients with longitudinal neuroimaging and 1 with neuropathological diagnosis. The neuroimaging demonstrates the natural history of the syndrome, which undergoes spontaneous remission with removal of the offending agent. Brain biopsy during the acute illness demonstrates the histopathological finding of demyelination.

Case Reports

Three individual case studies are presented, demonstrating a clinical neurological disorder occurring in the context of organ transplantation, involving generalized seizures without a clear metabolic etiology. Two patients had orthotopic liver transplants and 1 had an orthotopic single lung transplant. Laboratory evaluation did not provide an explanation for the new onset of generalized seizures, including normal studies of serum electrolytes (sodium, calcium, and magnesium), serum glucose, hematological parameters, and cerebrospinal fluid (CSF). Clinical, radiographic, and neuropathological evaluation led to the conclusion that the seizures resulted from an immunosuppression-related demyelinating syndrome caused by tacrolimus.

The Table shows the serum levels of tacrolimus for the 2-month period prior to symptom onset (averaged), on the day of the presenting generalized seizure, and on the succeeding days (up to 2 months in the case of the 1 patient who remained on tacrolimus).

Case 1

A 34-year-old, left-handed male with alcohol-related hepatic cirrhosis (postnecrotic cirrhosis-ethanol related [PNC-E]) underwent orthotopic liver transplant. One year later, he developed severe, constant headaches, accompanied by nausea, vomiting, and fever, which lasted for 10 days until he had a seizure and was brought to a hospital. The seizure was thought to be a primarily generalized seizure and was treated with diazepam and phenytoin sodium. The patient was transferred to our institution. Medicines on transfer included ceftriaxone, tacrolimus, phenytoin, trimethoprim with sulfamethoxazole, lorazepam, and Mylanta. The patient had no seizures following initiation of phenytoin therapy.

The patient was alert and awake. He was afebrile. Blood

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Summary of Tacrolimus (FK506) Levels Correlated with Times of Symptom Presentation

Case	Prior to Seizure	Time of Seizure	After Seizure
1	0.82	0.3	0.4
2	1.32	1	0.53
3	14.1	17.9	5.3

Tacrolimus levels are summarized according to date of initial presentation with generalized seizures. Values are averaged up to 2 months prior to presentation and up to 2 months after presentation. Note that levels of Cases 1 and 2 are not comparable with those of Case 3 because of a change in measurement method (serum level compared with whole blood level: conversion factor is not reliable but generally measures between 8:1 and 10:1).

pressure, pulse rate, and respiratory rate were normal. Neck was supple. Mild jaundice was present. Mental state was normal. Cranial nerve examination was significant only for a slight left deviation of the tongue on protrusion. A right pronator drift was present, accompanied by mild right-sided weakness. Reflexes were brisk and symmetrical. No clonus was present. The right plantar response was extensor, the left flexor. Sensory examination was normal. Coordination was mildly dysmetric bilaterally. Serum evaluation showed slightly low magnesium. The CSF cell counts reflected a traumatic lumbar puncture and also demonstrated a slightly elevated protein level (63 mg/dl). These clinical and laboratory data were not thought to explain the seizure.

Neuroimaging

A computed tomographic (CT) scan of the brain was performed before and after the intravenous administration of nonionic contrast and showed low-density regions in the left parietal subcortical white matter. Coronal and sagittal reformatting was performed for subsequent biopsy of the right frontal lobe lesion.

MRI of the brain demonstrated multiple bilateral focal areas of hyperintensity on both the T2-weighted and proton density–weighted images, particularly prominent in the right posterior temporal lobe, the left occipital lobe, the bilateral corona radiata, and the subcortical white matter of the left parietal lobe (corresponding to the CT abnormality). Smaller lesions were seen in the right frontal, right occipital, left centrum semiovale, and right external capsular regions. These multiple areas of T2 bright signal were not associated with mass effect or contrast enhancement. The imaging findings suggested progressive multifocal leukoencephalopathy (PML), multiple sclerosis (MS), or a toxic drug effect.

Stereotactic Biopsy

In addition to PML, MS, or drug toxicity, other disorders considered in the context of the clinical picture included lymphoma or viral infection other than PML. Thus, the recommendation of both the neurology and neurosurgery services was to proceed with stereotactic biopsy to guide further management. A low-density lesion in the right frontal lobe was selected as the least invasive target for biopsy.

Neuropathological Examination

Gross neuropathological examination revealed abnormally soft tissue, white to pink in color, with focal hemorrhage. The Luxol fast blue–stained sections (Fig 1A) showed small areas of demyelination, which were associated with veins. Bielschowsky staining of adjacent sections (Fig 1B) revealed that there was relative sparing of axons in these areas and that the pathology was confined to a loss of myelin. The sections stained with hematoxylin-eosin revealed minimal reactive astrocytosis and an absence of viral inclusion bodies. The sections analyzed for SV40 immunoreactivity were negative for PML. The HAM56 sections did not identify excessive numbers of macrophages. Polymerase chain reaction–based testing for *Cytomegalovirus* DNA was negative. These findings in the white matter thus led to an imprecise neuropathological diagnosis of nonspecific demyelination.

Case 2

A 51-year-old man with postnecrotic cirrhosis secondary to hepatitis C (PNC-C) underwent orthotopic liver transplant. His immediate postoperative course was uncomplicated. Three months later, he developed an occipital headache, which progressively worsened and was associated with nausea and vomiting. He was initially admitted to an outside hospital for dehydration. It was reported that he had a focal seizure that progressed to a generalized seizure. He was treated with phenytoin sodium and transferred to our institution.

Admission medications included tacrolimus, prednisone, Mycostatin, phenytoin, azathioprine, famotidine, and trimethoprim/sulfamethoxazole. Physical examination revealed a well-nourished patient who was awake and alert. He was afebrile. Blood pressure, heart rate, and respiratory rate were normal. The sclerae were anicteric. Mental status examination was normal. Neurologic examination was normal, including visual fields. Laboratory evaluation was significant for an elevated CSF protein level (99 mg/dl) but again did not explain the seizures.

The MRI scan of the brain performed prior to transfer demonstrated abnormal signal intensity in the right occipital lobe on the T2-weighted images (Fig 2A), with enhancement after gadolinium administration (Fig 2B). Additional small lesions were seen in the left parietal and left frontal lobes.

The dose of tacrolimus was reduced but not stopped, and the serum level reflected this decrease, as shown in the Table. One day following admission, a CT scan of the head was performed, which was normal. Five days later, a repeat MRI scan of the brain was performed, which showed complete resolution of the lesions seen previously (Fig 2C).

Case 3

A 34-year-old, right-handed female underwent an orthotopic single lung transplant 3 months before admission for pulmonary fibrosis related to rheumatoid arthritis. Infectious complications included pulmonary aspergillosis and sepsis from *Pseudomonas aeruginosa.* The patient developed renal insufficiency, attributed to tacrolimus toxicity, for which she underwent hemodialysis three times per week. For the week before admission, she noted an occipital headache and a cough, treated with azithromycin. She had also noted some

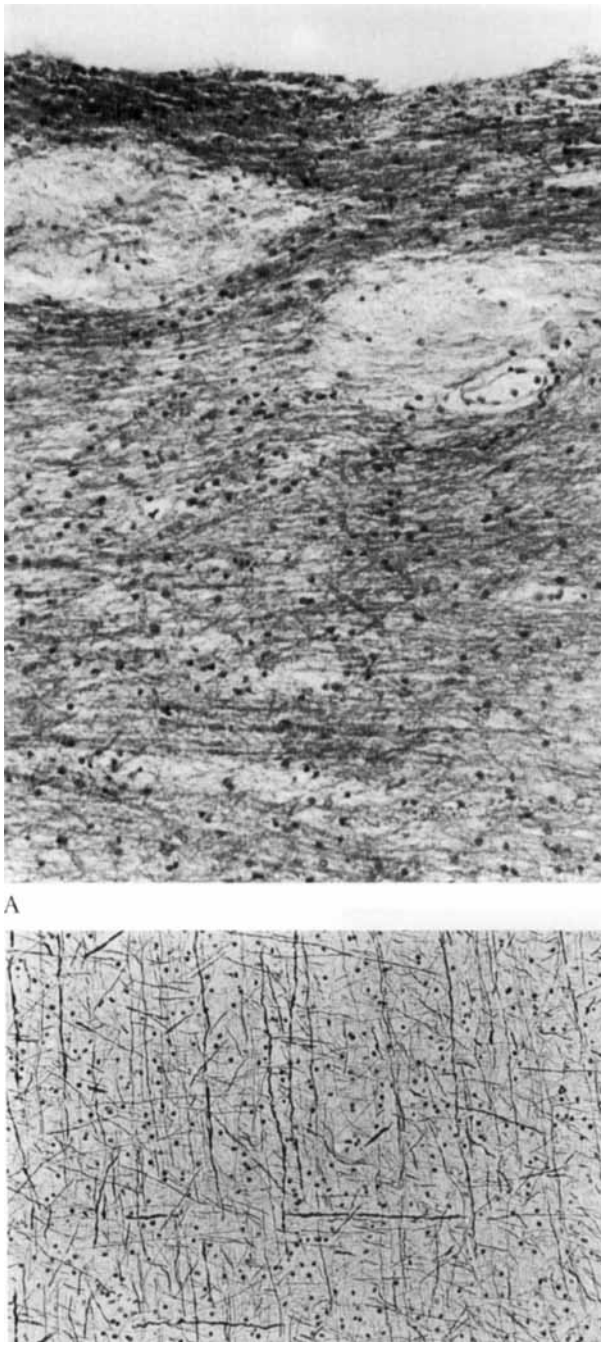

Fig 1. Histopathological analysis of Case 1. (A) Sections of the brain biopsy of Case 1 were stained for myelin with Luxol fast blue. This procedure revealed several foci of demyelination (the two light patches in the upper part of the figure) within the white matter. (B) Sections of the brain biopsy were stained by the Bielschowsky procedure. This region of the biopsy had foci of demyelination as seen in Figure 2A. This procedure shows that the rarefaction of white matter was not due to axonal damage, and that the pathology was confined to a loss of myelin.

deterioration in her visual acuity. On the night before admission, she awoke with a headache and developed unremitting nausea and vomiting. In the emergency room, she had a witnessed generalized seizure.

The patient's medications included prednisone, azathioprine, famotidine, trimethoprim-sulfamethoxazole, acyclovir, itraconazole, aluminum hydroxide, clonidine, hydralazine, warfarin sodium, and tacrolimus. On initial examination, the patient was awake and alert, with mildly injected and anicteric sclerae. Neurological examination was normal with the exception of diffuse hyperreflexia. Visual fields were full. Funduscopic examination was normal. Blood pressure was elevated (200/120 mm Hg) and the patient was tachycardic (108 beats/min). Respirations and temperature were normal. Laboratory evaluation was noncontributory. No explanation was found for the seizures.

A CT scan of the head was performed on admission. There were several foci of abnormal contrast enhancement in the right posterior parietal/occipital lobe and to a lesser extent on the left in the same region. Some surrounding edema with focal mass effect was also noted.

The patient stopped taking tacrolimus, and the serum level slowly declined as shown in the Table. A repeat CT scan was performed 2 days later, with and without nonionic intravenous contrast, and showed decreased enhancement of the bilateral parieto-occipital lesions. A third CT scan was obtained 10 days after symptom onset (i.e., initial seizure), and the previously described bilateral parieto-occipital abnormalities had resolved.

Discussion

A neurological syndrome characterized by cortical blindness occurring in association with MRI findings of signal abnormalities on T2-weighted images involving the posterior white matter has been described as a complication of cyclosporin A therapy. This syndrome, however, has not yet been well characterized clinically or radiographically with the use of tacrolimus, and histopathology has not previously been reported.

In this study, we present the imaging findings of 3 patients with clinical evidence of tacrolimus toxicity, 1 of which has pathologic correlation. Although the clinical findings of tacrolimus toxicity following liver transplantation have been described [4], the neuroimaging correlate of this syndrome has only been sporadically reported. This study describes for the first time the correlation between imaging abnormalities in the cerebral white matter and the histopathological finding of demyelination without evidence of other cause of leukoencephalopathy.

The radiology of this syndrome has only recently become clear. In a recent large case series of 14 patients with tacrolimus neurotoxicity, for example, "no structural abnormalities could be imaged unlike the well-described white matter changes seen in cyclosporine toxicity" [6]. On the other hand, several single case reports have described MRI findings in the white matter. Reyes and colleagues [5] described abnormal signal

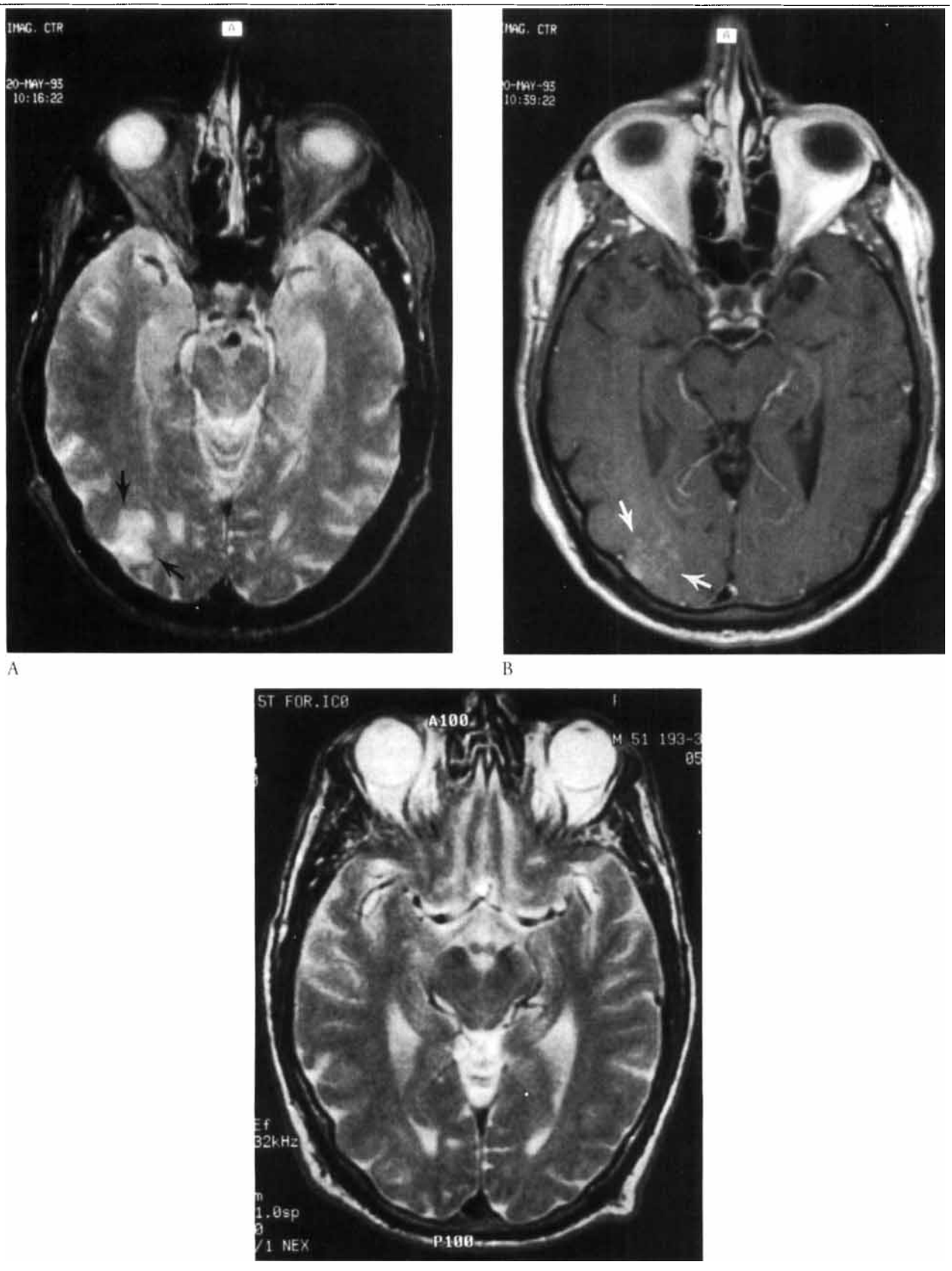
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Fig 2.

in the pons on T2-weighted images of 1 patient, and Shutter and associates [7] described a patient with cortical blindness and signal abnormality in the cortical white matter, most prominent posteriorly, which resolved after 7 weeks.

A similar syndrome that occurs in the context of cyclosporine administration has been well characterized clinically in both adults [8–12] and children [13, 14]. Imaging findings in this cyclosporine leukoencephalopathy comprise patchy signal abnormalities primarily in the posterior white matter [15]. CT or MRI scans show nonspecific white matter lucencies, in particular periventricularly, in the deep frontal white matter and in the occipital lobes. Other regions of the subcortical white matter have also been involved. This neuroradiological pattern is similar to that recently described with leukoencephalopathy from tacrolimus, and may be characteristic of a posterior leukoencephalopathy syndrome from a variety of causes [16].

Despite much investigation, the precise mechanism of cyclosporine-related leukoencephalopathy remains unknown. The neuropathology of the cyclosporine-related syndrome includes demyelination, reactive astrocytosis, and neuronal loss. However, the basic pathophysiology of the cyclosporine effect on myelin or neurons remains to be elucidated.

The radiological features of tacrolimus-related leukoencephalopathy include bilateral white matter lesions, which resolve over time [7]. A recent report has pointed out the similarity between the tacrolimus-induced syndrome and the better known syndrome associated with cyclosporine: A patient, switched from tacrolimus to cyclosporine because of seizures and focal neurological signs, subsequently developed the identical syndrome [17]. In both occurrences of the syndrome, parieto-occipital white matter lesions were present on neuroimaging.

The clinical features of tacrolimus-induced leukoencephalopathy are surprisingly similar within the 3 patients described here. At the onset of the toxic state, patients can have headaches, characteristically occipital, accompanied by nausea and vomiting. A short time later, patients have a generalized seizure, which can have a focal onset or be primarily generalized. Following the seizure and the postictal phase, patients can have normal or abnormal neurological examination, with focal sensorimotor findings, but with normal funduscopic examination. Serum and CSF studies should not reveal an infectious or metabolic cause of the symptoms.

In all 3 of our cases, imaging abnormalities demonstrated a predilection for the parietal and occipital lobes. The 2 patients who were imaged following resolution of the clinical syndrome also had resolution of imaging abnormalities on MRI or CT (Cases 2 and 3), which corresponded to reduced plasma levels of tacrolimus. The absolute tacrolimus levels associated with imaging findings were inconstant, although variability in tacrolimus levels is a feature of the clinical syndrome of tacrolimus neurotoxicity as well [6].

The neurological signs and symptoms should resolve on cessation of tacrolimus or on dose reduction. Since toxicity across individuals is not dose related, this dosage must be tailored individually for each patient. Although the differential diagnosis of tacrolimus toxicity includes some serious infectious, vascular, metabolic, and neoplastic processes, these can be evaluated quite easily, and do not require brain biopsy, as was performed in 1 of these cases before the syndrome was characterized. A combination of the typical clinical picture with MRI findings of signal abnormality in the cerebral white matter, in particular posteriorly, and no clinical or laboratory evidence of infection or metabolic abnormality should alert to the diagnosis.

Since the signs and symptoms resolve rapidly with elimination of the drug or even reduction of its dose, in cases without evidence of acute deterioration or concomitant infection, it is probably prudent to remove the offender and wait. If the patient does not improve with this approach, other causes of the problem, such as opportunistic infection (eg, PML) or neoplasm (eg, lymphoma) might demand consideration.

It is unclear why such a syndrome occurs with tacrolimus therapy. Tacrolimus (like cyclosporine) binds to specific intracellular protein ligands [18], which play a role in maintaining the stability of intracellular structures. Tacrolimus inhibits the activity of calcineurin [19], which is the key to its immunosuppressive effects. There appears to be some correlation between the toxic effects of tacrolimus and related compounds (including cyclosporine) and their ability to inhibit calcineurin activity [20], but the exact mechanism whereby this results in demyelination within the CNS has yet to be elucidated.

Fig 2. Magnetic resonance imaging (MRI) scan of Case 2 during the acute (symptomatic) phase and after resolution of symptoms. (A) Acute: The initial axial T2-weighted MRI scan (TR 2,500; TE 90) shows abnormal signal intensity in the right occipital lobe at the level of the midbrain (arrows). *(B) Acute: The axial T1-weighted MRI scan (TR 680; TE 22) enhanced with gadolinium at the same level shows enhancement within the right occipital lesion* (arrows). *(C) Subacute: MRI scan 5 days later when the tacrolimus level had diminished and symptoms had resolved. This axial T2-weighted MRI scan (fast spin echo TR 2,500; TE 104Ef) showed no abnormality.*

References

1. Tacrolimus (FK506) for organ transplants. Med Lett 1994:82–83
2. Porayko MK, Wiesner RH, Group USMFS. US multicenter prospective randomized trial comparing primary immunosuppression with FK506 vs cyclosporin (CyA) following liver transplantation. Gastroenterology 1994;104:A974 (Abstract)
3. European FK506 Multicentre Liver Study Group. Randomized trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. Lancet 1994;344:423–428
4. Eidelman BH, Abu-Elmagd K, Wilson J, et al. Neurologic complications of FK506. Transplant Proc 1991;23:3175–3178
5. Reyes J, Gayowski T, Fung J, et al. Expressive dysphasia possibly related to FK506 in two liver transplant recipients. Transplantation 1990;50:1043–1045
6. Wijdicks EFM, Weisner RH, Dahlke RN, et al. FK506-induced neurotoxicity in liver transplantation. Ann Neurol 1994; 35:498–501
7. 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
8. Berden JHM, Hoitsma AJ, Merx JL, et al. Severe central nervous system toxicity associated with cyclosporin. Lancet 1985; 1:219–220 (Letter)
9. Palmer BF, Toto RD. Severe neurologic toxicity induced by cyclosporin A in three renal transplant patients. Am J Kidney Dis 1991;XVIII:116–121
10. de Groen PC, Aksamit AJ, Rakela J, et al. Central nervous system toxicity after liver transplantation. N Engl J Med 1987; 317:861–866
11. Boon AP, Adams DH, Carey MP, et al. Cyclosporine associated cerebral lesions in liver transplantation. Lancet 1988;1: 1457
12. Hughes RL. Cyclosporin-related central nervous system toxicity in cardiac transplantation. N Engl J Med 1990;323:420–421
13. Rubin AM, Kang H. Cerebral blindness and encephalopathy with cyclosporin toxicity. Neurology 1987;37:1072–1076
14. Cilio MR, Danhaive O, Gadisseux JF, et al. Unusual cyclosporin related neurological complications in recipients of liver transplants. Arch Dis Child 1993;68:405–407
15. Truwit CL, Denaro CP, Lake JR, et al. MR imaging of reversible cyclosporin A-induced neurotoxicity. Am J Neuroradiol 1991;12:651–659
16. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494–500
17. Friese CE, Rowley H, Lake J, et al. Similar clinical presentation of neurotoxicity following FK506 and cyclosporin in a liver transplant recipient. Transplant Proc 1991;23:3173–3174
18. Cameron AM, Steiner JP, Sabatini DM, et al. Immunophilin FK506 binding protein associated with inositol 1,4,5-triphosphate receptor modulates calcium flux. Proc Natl Acad Sci USA 1995;92:1784–1788
19. Liu J. FK-506 and cyclosporin: molecular probes for studying intracellular signal transduction. Trends Pharm Sci 1993;14: 182–188
20. Dumont FJ, Staruch MJ, Koprak SL, et al. The immunosuppressive and toxic effects of FK-506 are mechanistically related: pharmacology of a novel antagonist of FK-506 and rapamycin. J Exp Med 1992;176:751–760