AJNR

# Quantitative MR Diffusion Mapping and Cyclosporine-Induced Neurotoxicity

Stuart C. Coley, David A. Porter, Fernando Calamante, Wui K. Chong and Alan Connelly

*AJNR Am J Neuroradiol* 1999, 20 (8) 1507-1510
http://www.ajnr.org/content/20/8/1507

*AJNR Am J Neuroradiol* 20:1507–1510, September 1999

**Case Report**

# Quantitative MR Diffusion Mapping and Cyclosporine-Induced Neurotoxicity

Stuart C. Coley, David A. Porter, Fernando Calamante, Wui K. Chong, and Alan Connelly

**Summary: Apparent diffusion coefficient maps of two patients with cyclosporine-induced neurotoxicity showed areas of increased diffusion that corresponded to the characteristic regions of signal change on routine T2-weighted sequences. The majority of lesions subsequently resolved without residual T2 or diffusion signal alteration. These findings suggest that, in our patients, the neurotoxic effects of cyclosporine resulted in a partially reversible extravasation of fluid into the cerebral interstitium and were not associated with acute ischemia.**

Cyclosporine (CSA)-induced neurotoxicity is well described and is characterized by cerebral edema within the cortex and juxtacortical white matter of the posterior cerebral hemispheres (1–4). Previous theories regarding the mechanism of neurotoxicity include neuropeptide-mediated ischemia and high-pressure failure of cerebral autoregulation (3, 4). We present the results of quantitative diffusion MR imaging of two patients with CSA-induced neurotoxicity, discuss the implications of these findings with regard to the pathogenesis of this syndrome, and highlight the clinical usefulness of the technique.

## Case Reports

### *Case 1*

A 4-year-old male patient underwent bone marrow transplantation for severe combined immunodeficiency disease. On day 30 after bone marrow transplantation, he suffered two left-sided motor seizures lasting approximately 6 minutes and was left with a residual hemiparesis that resolved over several hours. Two days before the seizure, a regimen of orally administered steroids was commenced in addition to the routine bone marrow transplantation prophylactic regimen that included orally administered CSA. At the time of seizure, the patient was normotensive and all hematologic and biochemical parameters (including serum magnesium) were normal. The next day, he suffered a further focal seizure.

November 16, 1998; accepted after revision, December 16.

From the Department of Neuroradiology (S.C.C., W.K.C.), Great Ormond Street Hospital for Children NHS Trust, and the Radiology and Physics Unit (D.A.P., F.C., A.C.), Institute of Child Health, University College London Medical School, London, England.

Address reprint requests to Stuart C. Coley, MD, Department of Neuroradiology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, England.



EEG showed nonspecific abnormalities in the parieto-occipital regions. Serum levels of CSA were not elevated on two occasions (145 and 99 mcg/L), and the drug was continued at a slightly lower dose. The results of a CSF examination were normal. CT of the brain performed immediately after the first seizure revealed peripheral low-density change in the parieto-occipital regions.

MR imaging was performed using a 1.5-T system and included axial T2- and diffusion-weighted imaging. The latter was performed using single-shot spin-echo echo-planar imaging, with an inversion prepulse used to suppress signal from fluids (5). Diffusion gradients were applied in turn along each of three orthogonal axes. The b-values used were 0 and 606 s/mm$^2$, from which apparent diffusion coefficient (ADC) maps were calculated for each of the three directions. These were then combined, as described previously (6), to produce maps of the trace of the diffusion tensor, which were therefore rotationally invariant. MR imaging was performed within 24 hours of the seizure and showed bilateral regions of T2-weighted prolongation confined to cortex and juxtacortical white matter of the occipital and parietal lobes (Fig 1A). The T2-weighted signal abnormalities corresponded to regions of increased diffusion on the ADC map (Fig 1B).

The patient recovered fully within 3 days. Consent for further MR imaging, however, was not obtained.

### *Case 2*

A 9-year-old male patient with homozygous sickle cell disease presented with nephrotic syndrome, possibly secondary to parvovirus. After a poor response to steroids, CSA was administered in addition to ciprofloxacin, fluconazole, penicillin V, folic acid, ranitidine, magnesium, and potassium supplements and 45 mg of prednisolone.

Four days after commencing CSA, the patient suffered a generalized seizure that was terminated by intravenous diazepam after 10 minutes. He was normotensive at the time of seizure, and subsequent hematologic and biochemical parameters were normal except for an HbS of 15% and a low serum (Mg) of 0.5 mmol/L. Serum levels of CSA were acceptable on each occasion (<100 mcg/L). During the next 3 weeks, the patient's level of consciousness continued to fluctuate and he suffered several further generalized seizures. The diagnostic dilemma at this stage was whether this encephalopathic illness was a result of sickle cell disease requiring exchange transfusion.

Several sessions of EEG were performed, and each showed frequent multifocal discharges associated with subclinical seizures. A technetium-99m–hexamethylpropyleneamine oxime single-photon-emission CT (SPECT) on day 10 showed no reduction in regional perfusion. The isotope examination was conducted during a period of further clinical deterioration that required readmission to the intensive care unit for assisted ventilation. Analysis of the CSF was normal.

MR imaging of the brain with diffusion-weighted imaging and quantitative ADC mapping (as described for case 1) was conducted on days 2, 6, 21, 31, and 49 after the initial seizure. The MR images obtained on day 2 showed diffuse and focal areas of T2-weighted prolongation within the cortex and jux-

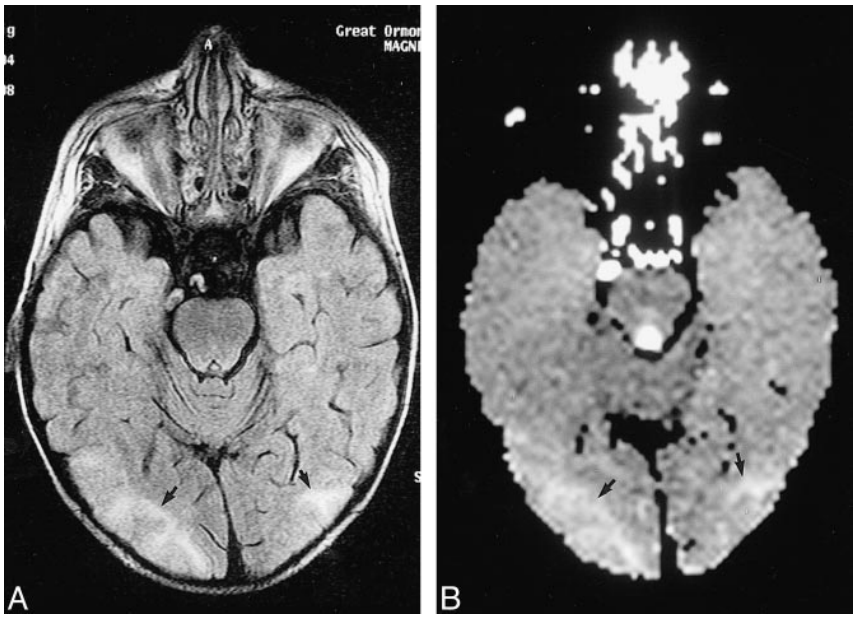


FIG 1. Axial MR images of a 4-year-old patient (case 1) obtained on day 30 after bone marrow transplantation. The patient presented with lethargy and focal seizures secondary to CSA therapy. The T2 signal abnormalities corresponded to areas of increased diffusion, suggesting that these areas of cerebral edema were caused by extravasation of fluid and not cerebral ischemia.

*A,* A fluid-attenuated inversion-recovery image shows confluent cortical and juxtacortical signal alteration in both occipital lobes (*arrows*).

*B,* The ADC map at the same level reveals increased diffusion in the regions of prolonged T2 signal (*arrows*). (Normal brain = $1.00 \times 10^{-3}$ mm²/second, abnormal areas = 1.42.)

tacortical white matter of the occipital and parietal lobes and also similar focal lesions in the frontal lobes. Each region of T2 signal abnormality was matched by an area of increased diffusion on the ADC map (Fig 2A and B). Repeat MR imaging performed on day 6 revealed further juxtacortical lesions in the parietal lobes and further confluent signal alteration in the corona radiata. Once more, each area was associated with increased diffusion (Fig 2C and D). By days 31 and 49, the majority of the lesions had resolved on the T2- and diffusion-weighted sequences without any residual abnormality. Certain areas of increased T2-weighted signal did, however, persist and remained as high-signal areas on the ADC maps (Fig 2E and F).

## Discussion

CSA is a potent immunosuppressant that is used widely in bone marrow and organ transplantation. Neurotoxicity is well documented and presents with lethargy, headache, seizures, visual impairment, confusion, or coma (1, 2, 7–9). Symptoms usually occur within the first month of commencing CSA but may occur within the first few hours or after several months of treatment (3). No clear relationship between CSA levels and neurotoxicity has been established (10).

Although the clinical presentation of CSA-induced neurotoxicity is diverse, the pattern of radiologic abnormalities is relatively characteristic. MR imaging shows signal change within the cerebral cortex and juxtacortical white matter of the occipital lobes, often with involvement of the posterior temporal, parietal, and frontal lobes (1–4). The radiologic changes are usually, but not invariably, reversible (11). Very similar abnormalities are reported in hypertensive encephalopathy, eclampsia, and other chemotherapeutic neurotoxicities (eg, cisplatin neurotoxicity) (4, 12–14). Because these disease processes also share common clinical denominators with CSA-neurotoxicity, namely acute seizure, hypertensive crisis, or both, these conditions are considered causes of a ''reversible posterior cerebral edema syndrome'' (15).

It has been proposed that the characteristic appearance of lesions within the posterior cerebral circulation results from regional differences in the distribution of intracranial adrenergic receptors (4). The vertebrobasilar circulation has a sparse sympathetic innervation and is therefore poorly equipped to initiate protective vasoconstriction in response to systemic increases in blood pressure (16). If cerebral perfusion continues to increase unchecked, high-pressure failure of cerebral autoregulation occurs and results in disruption of the blood-brain barrier and passive extravasation of fluid into the interstitium. Because hypertension associated with CSA is thought to be caused by activation of the sympathetic nervous system, even small additional increases in blood pressure may be sufficient to precipitate posterior cerebral edema in the setting of a chronically activated sympathetic system (4, 17).

Neurotoxicity also occurs in normotensive individuals, such as the two patients described herein, suggesting that additional causative factors are present. CSA is known to have profound effects on vascular endothelium and to cause the release of potent vasoconstrictors such as endothelin, prostacyclin, and thromboxane A2 (3, 9, 18). An alternative hypothesis, therefore, is that CSA-induced neurotoxicity results from neuropeptide-mediated ischemia in the presence of a disrupted blood-brain barrier (3, 11). The endothelial damage caused by CSA also may be accompanied by the release of cytokines in the context of acute graft-versus-host disease, and these agents may further contribute to vascular injury and disruption of the blood-brain barrier.

Diffusion-weighted imaging provides a means by which ischemic cytotoxic edema can be differ-

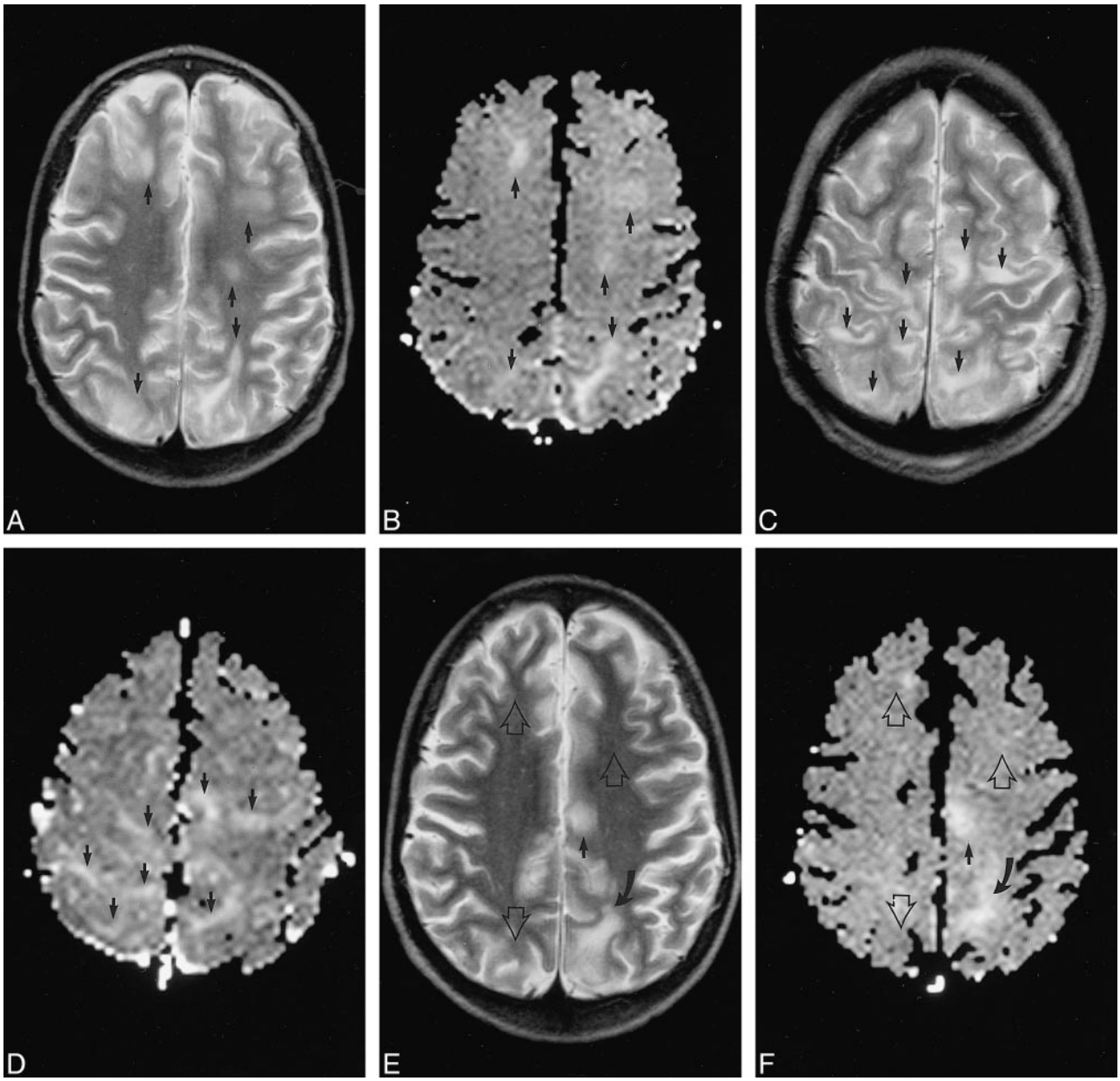


FIG 2. Axial MR images of a 9-year-old patient (case 2) with sickle cell disease and a viral-induced nephrotic syndrome. The patient developed a generalized seizure 4 days after commencing CSA therapy and experienced prolonged impairment of higher neurologic function. Regions of increased diffusion matched all the areas of T2 signal change. Many of the areas resolved without any residual T2 or diffusion abnormality. These findings suggest that the neurotoxic effects of CSA were associated with a partially reversible extravasation of fluid into the brain.

*A,* A T2-weighted image (day 2 after seizure) shows cortical and juxtacortical signal alteration within both frontal and parietal lobes (*arrows*).

*B,* The ADC map (day 2) reveals increased diffusion in all areas of T2 abnormality (*arrows*). (Normal brain = 1.02, abnormal areas = 1.33.)

*C,* A T2-weighted image (day 6) shows new, more superior abnormalities (*arrows*).

*D,* The ADC map (day 6) again reveals that all of the T2-weighted abnormalities correspond to areas of increased diffusion (*arrows*). (Normal brain = 0.93, abnormal areas = 1.48.)

*E,* A T2-weighted image (day 49), obtained at the same level as the images presented in *A* and *B,* shows complete resolution of most of the lesions that were present on day 2 (*open arrows*). A new lesion is present in the left posterior frontal lobe (*solid arrow*). A preexisting abnormality in the left parietal lobe (*curved arrow*) is essentially unchanged.

*F,* The ADC map (day 49) reveals increased diffusion in the new area of T2 prolongation (*solid arrow*). No diffusion abnormality, however, is present where the lesions have resolved (*open arrows*). (Normal brain = 0.93, *open arrows* = 0.92, *solid arrow* = 1.34, *curved arrow* = 1.36.)

entiated from interstitial edema and can therefore determine whether CSA-induced neurotoxicity is caused by ischemia or failure of cerebral autoregulation (19). Cytotoxic edema caused by acute cerebral ischemia is associated with reduced diffusion that is thought to reflect failure of sodium membrane pumps. In contrast, vasogenic edema is associated with increased diffusion and appears as high-signal areas on ADC maps.

In both of our cases, the signal alteration on T2-weighted images clearly corresponded to regions of increased diffusion, indicating that the cerebral edema was extracellular. None of the T2-weighted hyperintensities were associated at any stage with restricted diffusion. Many of the lesions in case 2 resolved, as revealed by diffusion-weighted and T2-weighted imaging, without evidence of residual diffusion abnormality, supporting the theory that the lesions were not ischemic but represented areas of resolving interstitial edema. Certain T2 lesions, however, failed to resolve and corresponded to areas of increased diffusion that were unchanged on serial images. It was assumed that at least some of the residual cortical/juxtacortical hyperintensities represented areas of established injury, but at no point could they be matched to regions of restricted diffusion. Therefore, the diffusion imaging did not suggest that ischemia was responsible for either the reversible or irreversible lesions. The diffusion data are supported by the normal SPECT study; the latter was performed when the clinical and radiologic abnormalities were greatest. Similar diffusion-weighted imaging findings have been described in cases of hypertensive encephalopathy, suggesting that cerebral edema in this condition is also of vasogenic origin (19).

The diffusion-weighted imaging findings were of particular value in the clinical management of case 2. Cerebral ischemia secondary to sickle cell disease also was considered as an alternative explanation for the T2-weighted appearances, but because the diffusion data did not indicate the presence of ischemia, exchange transfusions were not performed to lower the blood sickle concentration.

## Conclusion

The results of the MR diffusion-weighted imaging in this report suggest that CSA-induced cerebral edema is mediated by reversible fluid extravasation, not acute cytotoxic ischemia. Several factors may act synergistically to precipitate interstitial edema, and the pathogenesis of CSA-induced neurotoxicity is likely to be multifactorial in most instances. Contributory factors include the integrity of the blood-brain barrier (neuropeptides, cytokines, and hepatic encephalopathy), intracranial hemodynamics (hypertension, seizures, hypoalbuminemia, and response to corticosteroids), and levels of unbound CSA (hypercholesterolemia, drug interactions, and cytochrome p450 activity).

## Acknowledgment

We thank the Wellcome Trust for financial support.

## References

1. Lane RJM, Roche SW, Leung AAW, Greco A, Lange LS. **Cyclosporin neurotoxicity in cardiac transplant recipients.** *J Neurol Neurosurg Psychiatry* 1988;51:1434–1437
2. Reece DE, Frei-Lahr DA, Shephard JD, et al. **Neurologic complications in allogenic bone marrow transplant patients receiving cyclosporin.** *Bone Marrow Transplant* 1991;8:393–401
3. Truwit CL, Denaro CP, Lake JR, DeMarco T. **MR imaging of reversible cyclosporin A-induced neurotoxicity.** *AJNR Am J Neuroradiol* 1991;12:651–659
4. Schwartz RB, Bravo SM, Klufas RA, et al. **Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy. CT and MR findings in 16 cases.** *AJR Am J Roentgenol* 1995; 165:627–631
5. Hajnal JV, Bryant DJ, Kasuboski L, et al. **Use of fluid attenuated inversion recovery (FLAIR) pulse sequences in MRI of the brain.** *J Comput Assist Tomogr* 1992;16:841–844
6. Calamante F, Porter DA, Gadian DG, Connelly A. **Correction for eddy current induced B0 shifts in diffusion-weighted echo-planar images.** *Magn Reson Med* 1999;41:95–102
7. Ghany AM, Tutschka PJ, McGhee RB, Avalos BR, Cunningham I. **Cyclosporin-associated seizures in bone marrow transplant recipients given busulfan and cyclophosphamide preparative therapy.** *Transplantation* 1991;52:310–315
8. De Groen PC, Aksamit AJ, Rakela J, Forbes GS, Krom RAF. **Central nervous system toxicity after liver transplantation. The role of cyclosporine and cholesterol.** *N Engl J Med* 1987; 317:861–866
9. Rubin AM, Kang H. **Cerebral blindness and encephalopathy with cyclosporin A toxicity.** *Neurology* 1987;37:1072–1076
10. Kunzendorf U, Brockmoller J, Jochimsen F, Keller F, Walz G, Offermann G. **Cyclosporin metabolites and central-nervous system toxicity.** *Lancet* 1988;1:1223
11. Zimmer WE, Hourihane JM, Wang HZ, Schriber JR. **The effect of human leukocyte antigen disparity on cyclosporine neurotoxicity after allogeneic bone marrow transplantation.** *AJNR Am J Neuroradiol* 1998;19:601–608
12. Hauser RA, Lacey DM, Knight MR. **Hypertensive encephalopathy. Magnetic resonance imaging demonstration of reversible cortical and white matter lesions.** *Arch Neurol* 1988;45:1078–1083
13. Hinchey J, Chaves C, Appignani B , et al.**A reversible posterior leukoencephalopathy syndrome.** *N Engl J Med* 1996;334:494–500
14. Sanders TG, Clayman DA, Sanchez-Ramos L, Vines FS, Russo L. **Brain in eclampsia. MR imaging with clinical correlation.** *Radiology* 1991;180:475–478
15. Dillon WP, Rowley H. **The reversible posterior cerebral edema syndrome.** *AJNR Am J Neuroradiol* 1998;19:591
16. Beausang-Linder M, Bill A. **Cerebral circulation in acute arterial hypertension. Protective effects of sympathetic nervous activity.** *Acta Physiol Scand* 1981;111:193–199
17. Scherrer U, Vissing SF, Morgan BJ, et al. **Cyclosporine induced sympathetic activation and hypertension after heart transplantation.** *N Eng J Med* 1990;323:693–699
18. Zoja C, Furci L, Ghilardi F, Zilio P, Benigni A, Remuzzi G. **Cyclosporine-induced endothelial cell injury.** *Lab Invest* 1986;55: 455–462
19. Schwartz RB, Mulkern RV, Gudbjartsson H, Jolesz F. **Diffusion-weighted MR imaging in hypertensive encephalopathy. Clues to pathogenesis.** *AJNR Am J Neuroradiol* 1998;19:859–862