that case external beam radiotherapy combined with high dose corticosteroid treatment is indicated (*14*).

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Reversible Cerebral Perfusion Abnormalities Associated with Cyclosporine Therapy in Orthotopic Liver Transplantation

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A 60-yr-old woman experienced several episodes of generalized seizures following 2 wk of immunosuppressive therapy with cyclosporine for orthotopic liver transplantation. CT showed low density in the white matter of the parieto-occipital lobes. A ^{99m}Tc-HMPAO brain SPECT showed diminished perfusion in the parieto-occipital cortex bilaterally. Although the cyclosporine was discontinued, the patient's neurologic status initially worsened and then improved over the next several days. Repeat perfusion brain SPECT showed resolution of most of the perfusion abnormalities, while repeat CT showed persistent white matter changes in the parieto-occipital lobes. We report the presence of reversible cortical perfusion abnormalities in conjunction with cyclosporine therapy. The findings suggest that perfusion brain SPECT may be a sensitive monitor of cyclosporine-induced neurotoxicity.

Key Words: cyclosporine; liver transplantation; seizures; brain SPECT

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Orthotopic liver transplantation is associated with neurologic complications in 19%–47% of the cases (*1–4*). The clinical presentations include alterations of consciousness, seizures, myoclonus, tremor, headache, quadriplegia, cerebellar dysfunction and polyneuropathy (*4*). Cyclosporine has been used in humans for immunosuppression after transplantation and has reduced the rate of allograft rejection substantially. Cyclosporine, however, is implicated as a major cause of drug-induced neurotoxicity (*5*). Blood levels of cyclosporine do not correlate clearly with neurologic toxicity. CT and MRI may show a characteristic abnormality in the brain. These changes, however, are not invariably present nor does their resolution parallel clinical improvement (*6*). Cerebral blood flow scintigraphy using ^{99m}Tc-HMPAO and SPECT imaging is a readily available and accurate technique for detection of perfusion abnormalities in patients with cerebrovascular and neurological abnormalities. We present the findings of brain perfusion studies in a case of transient cyclosporine-induced neurotoxicity that showed good temporal correlation with the clinical course of the disease.

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CASE REPORT

A 60-yr-old woman with cirrhosis, secondary to chronic hepatitis, underwent an uncomplicated liver transplantation. Six weeks after discharge, she was readmitted with signs of rejection and treated with intravenous and oral cyclosporine. Her trough cyclosporine blood levels were monitored daily, using the fluorescent polarization immunoassay with monoclonal antibodies. She subsequently received a second liver transplantation. Five days after surgery the patient experienced a grand mal seizure which was controlled with intravenous diazepam and phenytoin. At that time, the cyclosporine trough level was 378 ng/ml (normal value <350 ng/ml). Her serum magnesium level was 1.1 mg/dl (normal 1.5–2.5 mg/dl) and her cholesterol level was 121 mg/dl. A normal serum ammonia level of 31 mcg/dl (normal 15–50 mcg/dl) and a normally functioning liver after transplantation excluded the possibility of hepatic encephalopathy. Noncontrast head CT performed on the same day showed low density in the white matter of parieto-occipital regions bilaterally (Fig. 1A).

Brain perfusion SPECT imaging was performed using a dual-head gamma camera equipped with a low-energy, high-resolution collimator. Imaging began 30 min after intravenous injection of 740 MBq ^{99m}Tc-HMPAO. Ninety-six frames of 30 sec were acquired. The images were prefiltered using a Butterworth filter

(Cutoff frequency = 0.2 cycles/cm; power factor - 5). Transaxial, coronal and sagittal slices 1 pixel thick were reconstructed and displayed on a 128 × 128 matrix. No attenuation correction was used. The SPECT images demonstrated moderately decreased perfusion to both parieto-occipital areas corresponding to the margins of low attenuation on CT (Fig. 1B). The cyclosporine was discontinued, but over the next two days, the patient became confused and agitated and had two additional episodes of generalized seizures (cyclosporine level 151 ng/ml). The patient improved clinically over the next 2 wk and a repeat brain HMPAO-SPECT study (Fig. 2B) showed complete resolution of the perfusion abnormality in the right parieto-occipital lobe and minimally reduced perfusion in the left occipital region. Repeat CT at that time (Fig. 2A) showed only mild resolution of the changes noted previously. The patient continued to improve and was discharged.

DISCUSSION

Cyclosporine A, introduced in 1978 for immunosuppression in organ transplantation, has produced a significant decrease in the rate of organ rejection, predominantly through its inhibition of lymphokine production and secretion by helper T-cells. Its use is complicated by frequent and diverse adverse effects. Most common are nephrotoxicity and hypertension, both dose-related and usually reversible with discontinuation of cyclosporine. Neurotoxicity has been reported to occur in up to 47% of patients with orthotopic liver transplantation (*1–4*). It typically presents as an alteration in mental status and seizures, but blindness, visual blurring, motor and sensory deficits, quadriparesis, coma, ataxia, spasticity, psychosis, headache and incontinence have been reported (*1,5,6*). Cyclosporine-induced

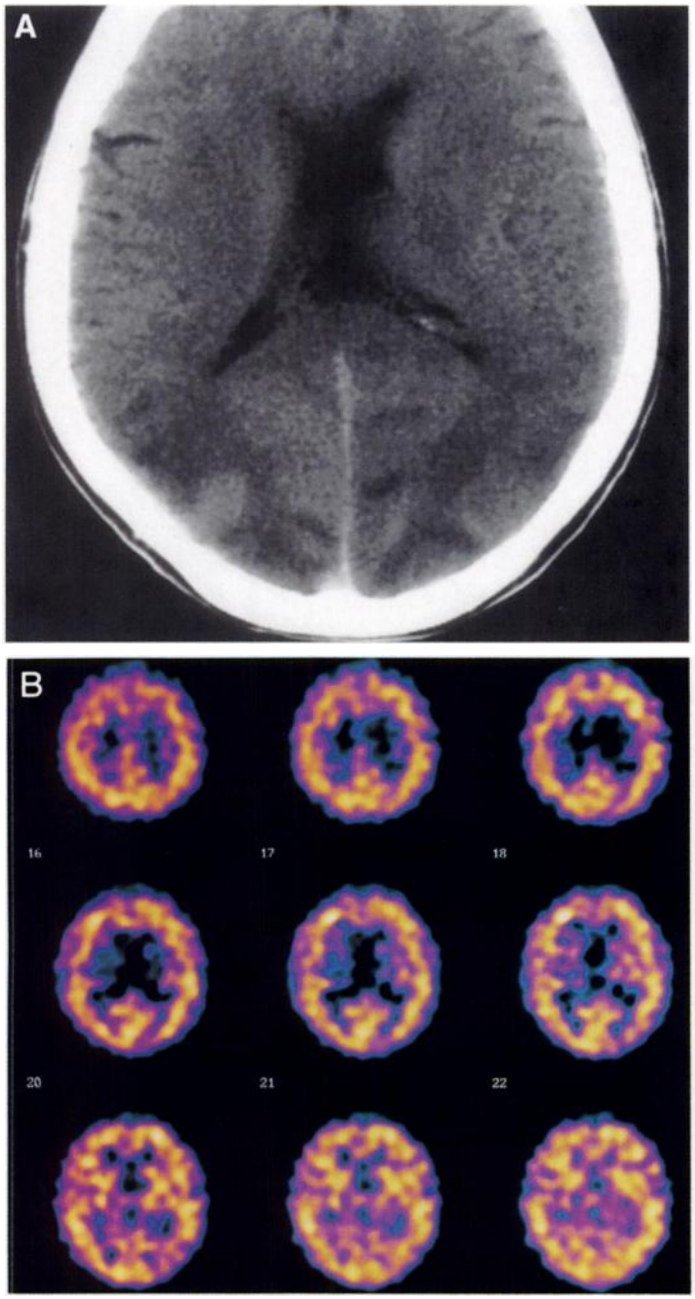

FIGURE 1. (A) Noncontrast CT shows symmetrical low density in the white matter of the parieto-occipital regions bilaterally. (B) Representative transaxial slices from the initial ^{99m}Tc-HMPAO SPECT performed 4 days later show moderately and symmetrically reduced perfusion to both parieto-occipital lobes.

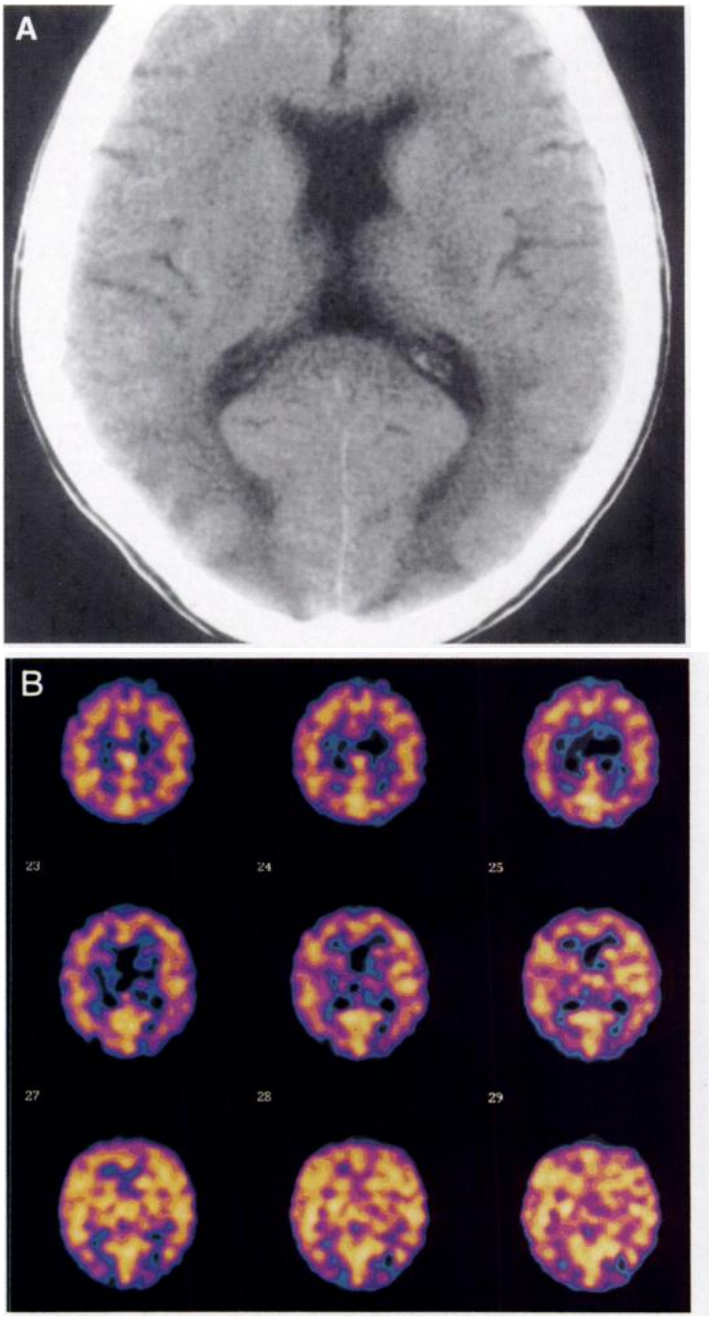

FIGURE 2. (A) Noncontrast CT performed 2 wk later reveals only minimal resolution of white matter abnormality in parieto-occipital area. (B) Representative transaxial slices from the follow-up ^{99m}Tc-HMPAO study show almost complete resolution of the previous abnormalities with only mildly reduced perfusion in the left occipital lobe.

neurotoxicity typically occurs within the first month of therapy, but it has been identified several months into the course of treatment. Cyclosporine-induced neurotoxicity is not dose-related and has been identified in patients with normal levels (*1,6*).

A constellation of CT and MRI findings has been reported by several authors to be characteristic of cyclosporine-induced neurotoxicity (*5,6*). CT typically demonstrates symmetrical regions of nonenhancing low density within the white matter of the posterior parietal and occipital lobes, with little mass effect. MRI will show symmetrical areas characterized by signal hyperintensity on T2-weighted images, signal hypointensity on T1-weighted images, and by absence of enhancement on postcontrast images. Occasionally, hemorrhage has been reported within such lesions (*5,6*). While involvement of the parieto-occipital lobes is most frequently encountered, reports suggest that white matter in any part of the brain may be affected. These findings may persist for several months despite discontinuation of cyclosporine treatment, and in the face of clinical improvement (*6*).

The presence of the characteristic findings on CT/MR imaging in combination with the most typical clinical manifestations may yield a correct diagnosis; however, the actual incidence of these typical findings remains unknown. Vogt et al. reported that in 40% of patients postliver transplantation, CT was interpreted as normal (*4*). A normal CT or a CT scan which demonstrates a nonspecific white matter abnormality of indeterminate age is not unusual. In such patients, whose neurological presentation may be atypical and whose cyclosporine levels may fall within the normal range, the neurological differential may be problematic.

The demonstration of perfusion abnormalities on SPECT imaging may permit identification of those patients with cyclosporine-induced neurotoxicity and normal CT and MRI studies. The more rapid resolution of the perfusion abnormalities, in comparison with the abnormalities on CT, more accurately paralleled the patient's clinical course. Our patient presented with hypomagnesemia and hypocholesterolemia at the onset of symptoms. Although these abnormalities as well as hypertention and steroid administration have been identified as exacerbating conditions, cause and effect have not been established (*1,3,5,6*), and the etiology of cyclosporine-induced neurotoxicity remains obscure. Demyelination has been suggested as an explanation for the neuroimaging findings, however, scattered pathological reports have failed to support this theory (*6–7*). Truwit et al. have suggested that cyclosporine neurotoxicity may be the consequence of focal vasoconstriction producing usually mild and reversible ischemia. They propose that cyclosporine-induced neurotoxicity is mediated by the release of endothelin, a neuropeptide which is a potent vasoconstrictor (*6*). This claim is supported by the similarity found between the neuroimaging findings in patients with eclampsia and acute hypertensive encephalopathy (conditions in which endothelin is already postulated to have a role) to those neuroimaging findings described in patients with cyclosporine-induced neurotoxicity (*6*). Alternatively, Stein et al. suggest that cyclosporine may produce cerebral vasoconstriction by altering the balance between prostacyclin and thromboxane A_2 substances which have been found to be vasoactive elsewhere in the body (*3*).

CONCLUSION

The demonstration of moderately decreased perfusion on SPECT imaging corresponding to the regions of white matter abnormalities identified on CT and MRI examinations in our patient further supports the hypothesis that these abnormalities reflect an ischemic insult rather than demyelination. Assuming that the SPECT correlates better with the neurological symptoms, it may eliminate prolonged discontinuation of much-needed immunosuppression and the increased risk of organ rejection. Further studies are needed to determine whether SPECT may be used to identify cyclosporine-induced neurotoxicity in patients whose other imaging studies are nondiagnostic.

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Reversible Extraskeletal Uptake of Bone Scanning in Primary Hyperparathyroidism

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Metastatic calcification within soft tissue, such as the lung and stomach, is associated with hyperparathyroidism, chronic renal failure, hemodialysis, metastatic neoplasm and hypervitaminosis D. Bone scanning agents variably accumulate within these extraskeletal metastatic calcifications. We report a patient with primary hyperparathyroidism whose bone scan revealed abnormal uptake in the liver, lung, stomach and parathyroid gland followed by complete resolution of extraskeletal uptake less than 1 wk after parathyroidectomy.

Key Words: metastatic calcification; hyperparathyroidism; bone scintigraphy

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Since the introduction of the ^{99m}Tc-phosphate compounds, unusual extraosseous accumulations have been reported, in which