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Cortical Hyperintensity on Proton Density–Weighted Images: An MR Sign of Cyclosporine-Related Encephalopathy

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PURPOSE: To describe cortical hyperintensities in proton density–weighted images in six patients with presumed cyclosporine-induced neurotoxicity. **METHODS:** In six patients with clinical evidence of cyclosporine-related encephalopathy, MR imaging was performed after the onset of symptoms and signs (mean, 24 days after liver transplantation). Five of these patients had serial MR imaging for a period that varied from 2 to 20 months. Along with the imaging studies, the patients' clinical status was evaluated and various laboratory parameters, including blood pressure and levels of cyclosporine, cholesterol, and magnesium, were monitored. **RESULTS:** In all six patients, initial MR studies showed hyperintensity of several cerebral gyri that was unequivocal only on proton density–weighted images. Although in five patients these signal abnormalities were limited to the cortex, one patient had increased signal in the subjacent white matter as well. In one patient, the images were also remarkable for areas of cortical hyperintensities on T1-weighted images. In another patient, cortical enhancement occurred after administration of gadopentetate dimeglumine, with a normal cortical signal on the precontrast images. The abnormal cortical signal began to fade after cyclosporine reduction, but in two patients it remained visible for at least 20 months. The neurologic symptomatology associated with cyclosporine-induced neurotoxicity included seizures (three patients), speech disorder (three patients), and disturbance of consciousness (three patients). **CONCLUSION:** Cyclosporine-induced neurotoxicity occurring in patients after liver transplantation appears to affect the cerebral cortex preferentially. Because its MR equivalent resembles changes resulting from hypoxic injury or cortically centered vasculitis, we suspect the underlying mechanism may be a vascular injury that results in cortical hypoperfusion.

Since its introduction in 1978, cyclosporine has become the primary drug for immunosuppression in solid-organ transplantation because it substantially lowers the allograft rejection rate. Although it is well known that cyclosporine is nephrotoxic and may also cause hypertension and diabetes mellitus, neurotoxic effects have been reported only recently (1–3). The

frequency of neurotoxic side effects related to cyclosporine is thought to be 10% to 25% (1, 4), depending on diagnostic criteria. In solid-organ transplantation, neurotoxicity seems to occur more often with liver transplantation than with heart or renal transplantation (2, 5, 6). In most cases, neurologic signs and symptoms, such as seizures, confusion, or coma, occur within the first few days after transplantation. The existence of cyclosporine-related encephalopathy is supported by the appearance of white matter changes on computed tomography (CT) scans and magnetic resonance (MR) images obtained during treatment with the drug (1, 7). The mechanism by which cyclosporine causes dysfunction of the brain remains unclear, however (8). Our review of six patients with presumed cyclosporine toxicity showed hyperintensities on proton density–weighted images within the cortex, suggesting that this is a possible addi-

Fig 1. Patient 3: 16-year-old girl with generalized seizures and cortical amaurosis 30 days after liver transplantation and 25 days after onset of symptoms.

A and *B*, MR imaging shows circumscript hyperintensity of superficial cortical layers on proton density–weighted image (2200/20, *A*) in the frontal cortex and the cingulate gyrus (*arrows*). Signal abnormality is difficult to discern on T2-weighted image (2200/100, *B*) (*arrow*).

A

B
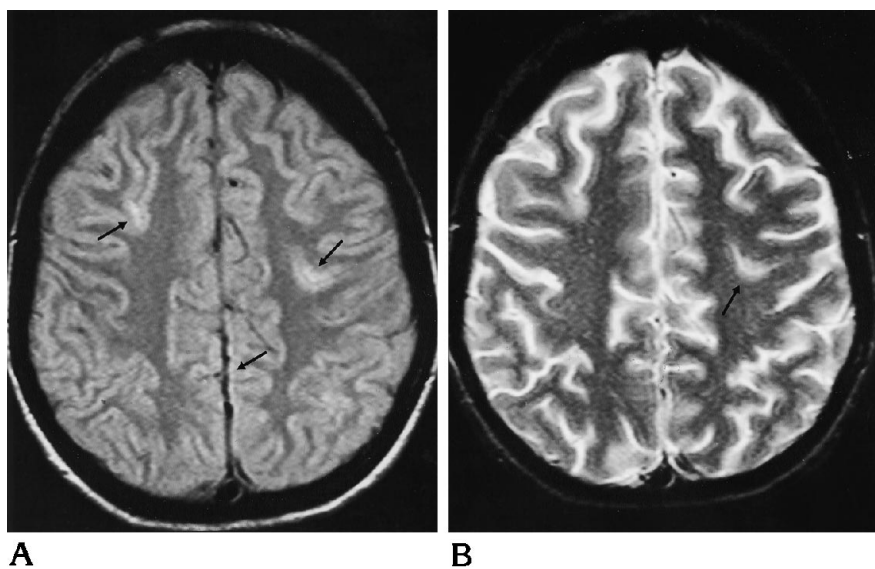
tional sign of cyclosporine-related encephalopathy.

Materials and Methods

From 1987 to 1994, 156 patients underwent orthotopic liver transplantation at our medical center. Retrospectively, 11 patients (7%) were identified in whom a cyclosporine-related dysfunction of the central nervous system (CNS) was thought to explain the occurrence of neurologic deterioration shortly after surgery. In all these patients, the onset of symptoms and signs was acute, and there was no evidence of CNS infection or significant metabolic derangement. The symptomatology disappeared or diminished when the cyclosporine dosage was reduced (3 to 11 patients) or when an alternative immunosuppression agent (ie, tacrolimus) was used (8 of 11 patients).

MR imaging was scheduled for all patients with evidence of cyclosporine-related neurologic symptoms in the postoperative period, but because of poor clinical condition some patients could not be transferred from the intensive care unit. Therefore, only 6 of the 11 patients with presumed cyclosporine-induced neurotoxicity underwent cranial MR imaging. These six patients are the subject of our report.

The three women and three men were 16 to 55 years old (mean age, 41 years). The onset of CNS symptoms and signs was 2 to 12 days (mean, 5 days) after transplantation. The first MR study was done 3 to 40 days (mean, 22 days) after transplantation, and the mean interval between onset of symptoms and signs and MR imaging was 18 days. Five of six patients were followed-up with serial MR imaging for up to 20 months. Thus, a total of 18 MR studies were available for analysis. All MR images were obtained on a 1.0-T scanner with a quadrature head coil. In all investigations T2-weighted (2400/20–100/1) (repetition time/ echo time/ excitations) and T1-weighted

(540/20/1) images were obtained in the transaxial plane. In 7 of 18 examinations additional sagittal T1-weighted images (520/20/1) were obtained. In two patients T1-weighted images in the transaxial plane were repeated after intravenous administration of contrast material (gadopentetate dimeglumine, 0.1 mmol/kg). Additionally, cranial CT was performed 3 to 23 days (mean, 9 days) after symptom onset in five of the six patients who had serial MR imaging. Blood pressure and several laboratory parameters, including those related to liver function as well as blood levels of cyclosporine (determined by means of monoclonal and polyclonal antibody assays), cholesterol, magnesium, and ammonia were monitored during the observation period. Neurologic examinations were performed daily during the hospital stay. Subsequently, the patients were examined neurologically at the time of MR imaging follow-up.

Results

MR Imaging Findings

In all patients, initial proton density–weighted images showed an abnormally increased signal of superficial cortical layers that involved several cerebral gyri (Fig 1). In five of the patients, these hyperintensities appeared like fine lines, 2 to 4 cm in length, that could be detected more readily in the gyral crest than in the depth of a sulcus. These laminar signal abnormalities were seen most frequently in the cingulate gyrus (4/6) and the occipital cortex (4/6); they were seen less frequently in the central and precentral cortex (3/6). Although hyperintensities were limited to the cortex in five patients, one patient had increased signal in the subjacent
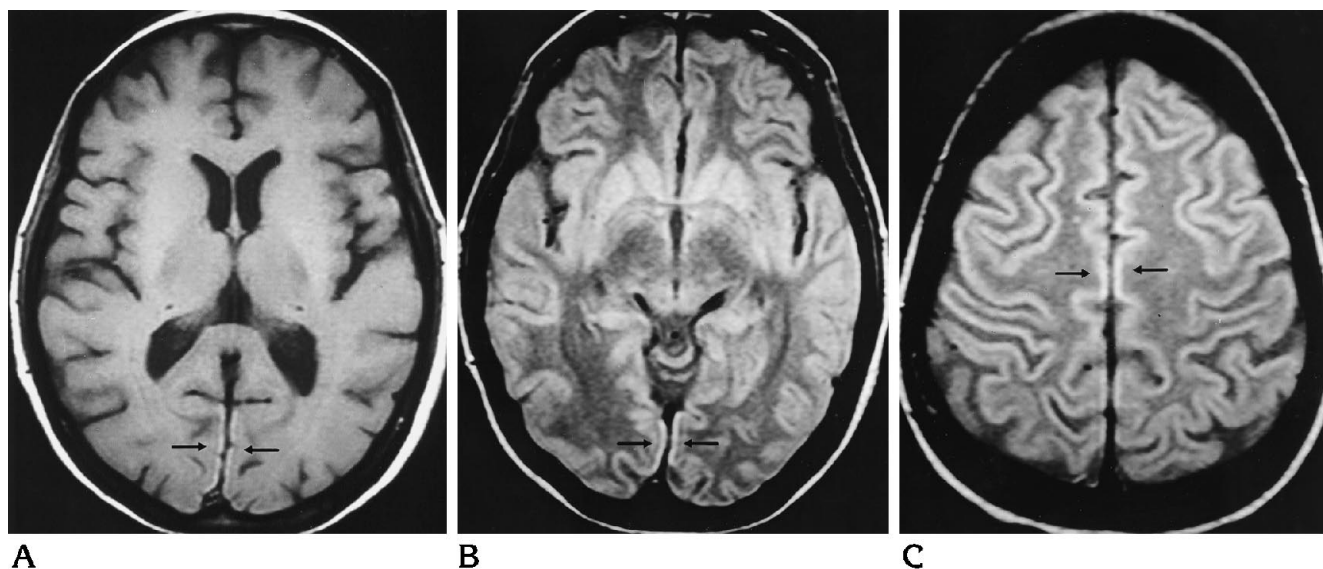
Fig 2. Patient 4: 49-year-old woman with speech deceleration and cortical amaurosis 24 days after liver transplantation.

A, T1-weighted image (640/20) shows laminar hyperintensity (*arrows*) in the occipital cortex bilaterally.

B and *C*, Proton density–weighted images (2200/20) show hyperintensity of the superficial cortical layers in the occipital cortex (*B*) and cingulate gyrus (*C*) (*arrows*).

white matter that was associated with a space-occupying effect.

In one patient, hyperintensities of the superficial cortical layers were seen on the initial T1-weighted images (Fig 2). These hyperintensities were in the same area as the signal abnormalities on the proton density–weighted images. Another patient had normal cortical signal on the precontrast images but focal cortical enhancement after administration of the paramagnetic contrast agent (Fig 3). This enhancement differed in location from the hyperintensities on the proton density–weighted image.

Serial MR-imaging showed that the abnormal cortical signal decreased over time in all patients. In one patient (patient 4), however, mild cortical hyperintensity remained visible on proton density–weighted images for up to 14 months; and the patient with additional white

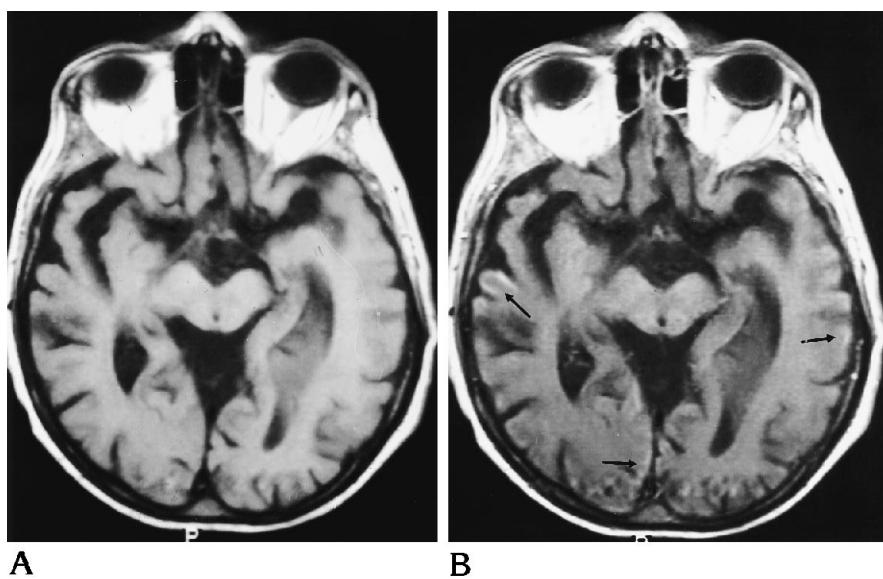Fig 3. Patient 2: 55-year-old man with seizures and confusion 30 days after liver transplantation.

A and *B*, T1-weighted precontrast (*A*) and postcontrast (*B*) images (640/20) show cortical enhancement in occipital and temporal cortex (*arrows*).
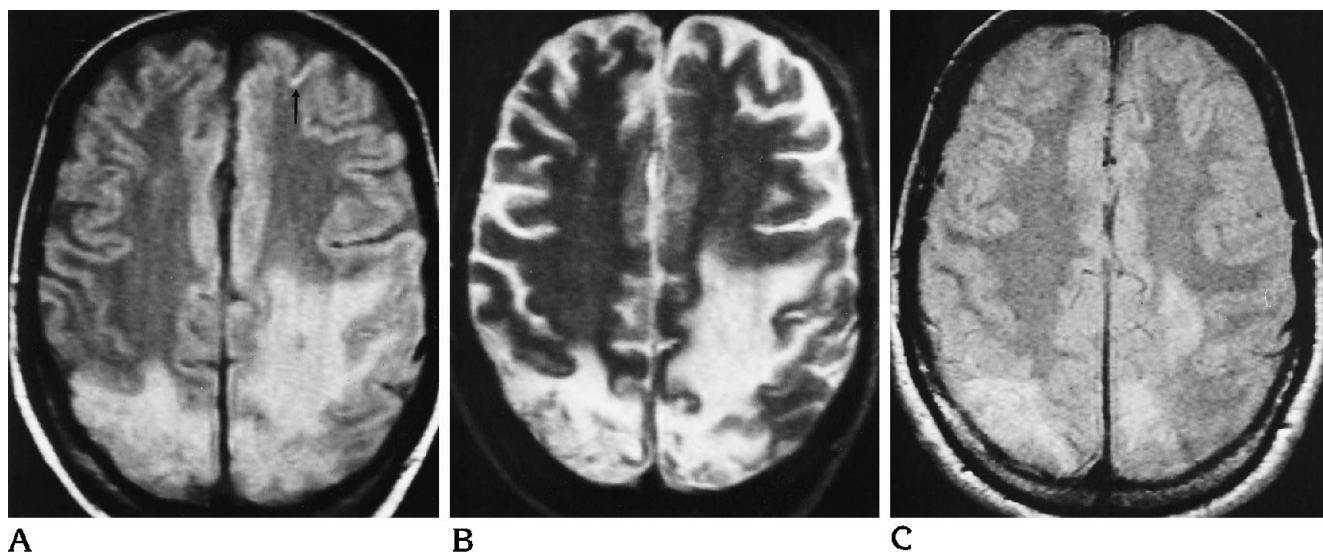
Fig 4. Patient 1: 40-year-old man with generalized seizures, right hemiparesis, and confusion 3 days after liver transplantation.

A and *B*, Proton density–weighted (2200/20, *A*) and T2-weighted (2200/100, *B*) images show parietal cortical hyperintensities, fingerlike hyperintensities of the subjacent white matter associated with a space-occupying effect, and cortical hyperintensities in cingulate and frontal gyrus (*arrow*).

C, Follow-up T2-weighted image (2200/20) after 20 months shows residual hyperintensities of the parietal cortex and subcortex.

matter lesions (patient 1) still had residual hyperintensity of both white matter and cortex 20 months later (Fig 4).

In five of the six patients, bilateral hyperintensity of the globus pallidus was seen on the initial T1-weighted images, as has been described in patients with chronic hepatic failure (9, 10). After liver transplantation, these changes gradually disappeared in all patients over a period of several months.

CT Findings

In three of five patients the initial CT scan showed no evidence of gyral or white matter disease. In one patient (patient 1), the CT scan showed bilateral hypodensity of the parietal and left frontal white matter and a small subcortical hemorrhage in the left frontal lobe. In another patient (patient 2), the CT scan showed bilateral hypodensities that involved both the occipital cortex and the subjacent brain parenchyma, whereas an MR image obtained 2 days later showed only cortical hyperintensity at the central and precentral sulci bilaterally.

Clinical Findings

Signs and symptoms began from 1 to 12 days (mean, 5 days) after administration of cyclosporine. In three patients these consisted of generalized seizures, aphasia or slurred speech, and disturbance of consciousness, respectively. Two patients had cortical blindness or visual hallucinations. The mean maximal blood level of polyclonal cyclosporine (toxic range, > 500 mg/L) was 770.8 mg/L (range, 619–889 mg/L), the mean level of monoclonal cyclosporine (therapeutic aim, 200 mg/L) was 223.4 mg/L (range, 122–380 mg/L), the mean level of cholesterol was 83.5 mg/dl (range, 67–380 dl), and the mean level of magnesium was 0.75 mmol/L (range, 0.59–0.98 mmol/L). During the onset of neurologic symptoms the mean blood pressure was 118 mm Hg (range, 90–155 mm Hg). In five of the six patients the immunosuppressive treatment with cyclosporine was replaced after an average of 8 days (range, 3–20 days), and another drug was chosen (tacrolimus); the remaining patients received steroids only. Follow-up neurologic examination revealed total or partial remission of CNS symptoms in five of the six patients. One patient remained unconscious and continued to have the same abnormal MR signal pattern, consisting of hyperintensity involving primarily the parietal subcortex and cortex. Abnormal signal also persisted in another patient who had only minor residual neurologic deficits. There was no correlation between the type and extent of signal changes and

the severity of CNS symptoms and signs. Also, there was no direct link between location of signal abnormalities and clinical findings.

Discussion

All our patients with cyclosporine-related encephalopathy had cortical hyperintensity on MR images that most commonly involved the cingulate gyrus and the occipital lobe, less commonly the parietal lobe and the frontal cortex. These changes consisted primarily of fine linear (laminar) cortical hyperintensities, which were most apparent on proton density–weighted images; they were difficult to discern on T2-weighted images.

We observed a frequency of cyclosporine neurotoxicity of 7%, which is lower than the reported frequency of 10% to 25% (1, 4). The difference may be explained in part by the retrospective identification of our patients, which makes it likely that not all patients with cyclosporine-induced neurotoxicity were found. Also, several authors, by including patients with nonspecific symptoms (such as tremors and irritability) in their studies, may have overestimated the frequency of cyclosporine-related encephalopathy.

Although the mean monoclonal cyclosporine-level approached the therapeutic level, the mean polyclonal cyclosporine-level moderately exceeded the accepted upper levels in our patients. In concordance with findings reported by other researchers (25), we presume that cortical abnormalities can also be seen in patients with cyclosporine-related encephalopathy and *therapeutic* blood levels of cyclosporine.

Most reports of CT and MR imaging findings in patients with cyclosporine-related neurologic symptoms describe only diffuse areas of white matter hyperintensity (1, 4, 7, 8, 11). We observed similar white matter hyperintensity in only one of our six patients, however, we saw predominantly cortical signal abnormalities. Observations of cortical changes are rarely reported in patients with cyclosporine-related encephalopathy. Lane et al (7) described MR imaging findings in patients with cyclosporine-induced neurotoxicity after cardiac transplantation and reported a hyperintense signal in the right occipital and left frontal cortex in three patients. A follow-up MR study 1 month after recovery revealed complete resolution of these cortical lesions. Estol et al (12) described the

neuropathologic findings in 21 patients with seizures after liver transplantation and found cortical laminar necrosis in three patients; in another 10 patients they found nonspecific neuronal ischemic changes. They suggested that these cerebrovascular abnormalities were due to poorly controlled generalized seizures and subsequent cerebral hypoxia, rather than being a feature of cyclosporine neurotoxicity. In our series, however, only three of six patients had generalized seizures (status epilepticus), and three patients had no seizures at all. Also, cortical signal abnormalities were not found in typical watershed areas or in the temporal lobe but primarily in the cingulate gyrus, followed by the occipital cortex. Additionally, no T2 signal abnormality was found in the basal ganglia and thalami; such abnormalities are often present after cerebral hypoxia. By contrast, in all our six patients cyclosporine-related neurologic symptoms coincided with cortical hyperintensity in proton density–weighted images. We also observed that all our patients improved neurologically and had fewer MR imaging findings when cyclosporine was reduced or replaced.

The above-described MR signal abnormalities—laminar cortical hyperintensities—strikingly resemble cortical alterations that have been described in patients with hypoxic brain damage (13), in whom cortical laminar necrosis with subsequent cytolysis and interstitial edema occurs initially. Later, during resorption, the edema subsides and macrophages start removing the necrotic tissue. Finally, after about 6 weeks, glial scarring can be observed. Although the abnormalities seen in patients with cyclosporine-related encephalopathy are somewhat more circumscript than the lesions in patients with hypoxic brain damage, they may be caused by a similar mechanism.

We hypothesize that initially in the evolution of cyclosporine-induced cortical lesions a focal cytotoxic edema with an additional vasogenic component due to disruption of the blood-brain barrier develops. The edema may be so small, however, that only the blood-brain barrier disruption can be detected on contrast-enhanced MR images, such as were seen in the initial examination of patient 2. Hyperintensity on unenhanced T1-weighted images, as observed in the examination of patient 4, usually indicates subacute hemorrhage (methemoglobin), fat, or high cellularity (13). We thus speculate that in cyclosporine-induced cortical lesions, microhe-

morrhages may occur along with acute blood-brain barrier disruption. Although white matter T2-hyperintensity is thought to be the predominant MR-imaging finding in cyclosporine neurotoxicity, a review of the literature further supports our pathophysiological concept that cyclosporine-induced disruption of the blood-brain barrier can cause hemorrhage. Intracerebral hemorrhage after liver transplantation and cyclosporine immunosuppression has been reported by Moreno et al (14) in 3 of 19 patients with neurologic symptoms. In one of these patients cyclosporine was discussed as a possible cause for the underlying vascular injury. De Groen et al (1) observed one subdural hematoma but also one cerebellar hematoma in 13 patients with cyclosporine neurotoxicity. In our study, one patient (patient 1) had cortical as well as white matter hyperintensity. Additionally, this patient had a subcortical hemorrhage in the left frontal lobe on one of the first CT scans obtained after transplantation. Clearly, these examples from the literature and our own observation do not *prove* our concept but do show that hemorrhages are seen with cyclosporine neurotoxicity and subcortical MR imaging abnormalities.

Alternatively, cortical T1 hyperintensity may be caused in part by fat-laden macrophages, which are found in laminar cortical necrosis with interstitial edema and cytolysis (15). Glial scarring results in long-standing or permanent hyperintensity on proton density–weighted images. If the interstitial edema and the glial scarring involve those layers of the cerebral cortex that are close to the subarachnoid space, T2-weighted images may appear unremarkable, because the high signal intensity of cerebrospinal fluid masks the cortical disease.

Regarding the pathophysiology of cortical injury in patients with cyclosporine-induced neurotoxicity, we presume that the cortical lesions observed in our group were caused by a cyclosporine-induced blood flow reduction in small pial vessels with subsequent cortical ischemia. Changes in the cerebral circulation may be caused either by cyclosporine-induced thrombogenicity with elevated platelet aggregation or factor VII activity (16, 17) or by direct endothelial damage of small pial vessels comparable to the cyclosporine effect on the renal vasculature (18). The latter hypothesis is supported by the work of Sloane et al (19), who were able to detect microvascular damage induced by cy-

closporine with toxic effects on the vascular basement membrane and blood-brain barrier disruption.

We believe that isolated cortical abnormalities occur in the early stage of cyclosporine-related encephalopathy, whereas in more severe cases, additional damage of subcortical vessels results in white matter edema. If prominent enough, these lesions can be visible not only on MR images but on CT scans as well.

In contrast to previously reported MR imaging findings in cyclosporine-induced neurotoxicity, only one of our patients had white matter hyperintensities whereas all six patients had cortical hyperintensities. Because patients who were in particularly poor clinical condition, including those with signs of severe cyclosporine toxicity, could not be transported to the MR imaging suite, the patients described in this study represent a selected group. The fact that primarily cortical abnormalities were observed in these patients supports our pathophysiological concept of cortical changes being early manifestations of cyclosporine neurotoxicity and subcortical injury occurring in the more severe cases.

Our observations of cyclosporine-induced cortical damage and its possible pathophysiology need confirmation by autopsy studies or by an adequate animal study. As yet, no animal studies have been done to investigate the influence of high-dose cyclosporine on the brain cortex. Famiglio et al (20) studied the CNS toxicity of cyclosporine in a rat model but did not find any cortical cerebral changes. Although the administered doses of cyclosporine were high (20 mg/kg per day, given over a period of 2 weeks), they may have been too low to simulate the situation in patients with preexisting hepatic encephalopathy. Patients with chronic hepatic failure have a blood-brain barrier that is pathologically permeable (21). In liver transplantation patients, perioperative cyclosporine medication is given intravenously. This route of administration results in temporarily high blood levels of cyclosporine. To study the effects of cyclosporine neurotoxicity that occur in liver transplant recipients in an animal model, very high cyclosporine doses along with disruption of the blood-brain barrier is necessary to imitate the situation of patients with chronic hepatic failure.

On the initial unenhanced T1-weighted MR images, five of our six patients had bilateral

hyperintensity of the globus pallidus and substantia nigra. These hyperintensities are known to be associated with chronic hepatic failure. After successful liver transplantation with good organ function, these hyperintensities disappear during the next few months (10). Although there is a correlation between the intensity of these signal changes and the duration of liver dysfunction, there is no direct correlation between the signal intensity and the grade of hepatic encephalopathy. Currently, these hyperintensities in the basal ganglia are thought to be caused by manganese deposition with associated elevated blood levels of this element, as seen in chronic liver disease (22, 23).

Cyclosporine-related encephalopathy is observed more frequently after liver transplantation than after cardiac or renal transplantation (2, 7). Although the elimination of cyclosporine is through hepatic metabolism by the P-450 cytochrome oxidase system (24–26), and the concentration of biologically active cyclosporine depends on the blood cholesterol level (1), cyclosporine neurotoxicity is especially likely to occur after liver transplantation in the early postoperative period, when the transplanted organ still shows functional impairment.

The rate of cyclosporine-related neurologic symptoms after liver transplantation is estimated to be about 10% to 25% (1, 25). The exact rate remains obscure, however, for the following reasons:

1. Most patients have additional neurologic symptoms and signs related to the underlying hepatic encephalopathy.
2. Alcoholic cirrhosis is the most common indication for liver transplantation; thus, many patients present with a severe degree of alcohol-related neurologic disease (26).
3. In the early postoperative period, detailed neurologic examination is difficult, and medications used to treat these patients may cause or exacerbate neurologic complications (27).
4. Normal cyclosporine blood levels may be associated with toxic levels of biologically active cyclosporine. Because there is a wide variation in absorption, metabolism, and elimination of cyclosporine among patients, there exists an individual "therapeutic window" for cyclosporine (26).
5. Cyclosporine metabolites may exert neurotoxicity and escape recognition on monoclonal antibody assays.

In conclusion, MR imaging, by making visible the described cortical lesions, helps to detect early signs of cyclosporine-related neurotoxicity after liver transplantation. As a possible pathomechanism, we suspect a cyclosporine-induced vascular injury that results in cortical hypoperfusion and cortical injury. MR imaging may support the clinical suspicion of cyclosporine intoxication in patients with seizures, disturbed consciousness, cortical blindness, or speech disorders in the early postoperative period. The validity of this MR imaging sign remains to be confirmed in a prospective study.

Acknowledgment

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