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Brain Perfusion Imaging in Asymptomatic Patients Receiving Cyclosporin

Tarang N. Sheth, Masanori Ichise, and Walter Kucharczyk

BACKGROUND AND PURPOSE: Cyclosporin has neurotoxic effects in a significant number of transplant patients that are associated with characteristic findings on MR images. Focal abnormalities in cerebral perfusion have been implicated in the pathophysiology of cyclosporin neurotoxicity. In the clinically asymptomatic patient, however, it is not known whether any imaging evidence of cyclosporin's effect on the brain is demonstrable. Our hypothesis was that conventional MR imaging, perfusion MR imaging, and single-photon emission CT (SPECT) could enable detection of subclinical lesions in asymptomatic patients. The ability to detect such lesions might aid in the identification of persons most at risk for clinical neurotoxicity.

METHODS: Ten posttransplant patients being treated with cyclosporin were recruited prospectively. Imaging studies were performed within 3 weeks of transplantation. Patients were examined with MR imaging, using standard spin-echo and dynamic contrast-enhanced perfusion techniques, and SPECT scanning. Postprocessing of MR perfusion data was performed to obtain pixel-by-pixel maps of regional cerebral blood volume, peak height, and time-to-peak parameters.

RESULTS: The mean age of the patients was 45 ± 11 years. At the time of imaging, three patients had minor neurologic manifestations commonly associated with cyclosporin (ie, mild tremor, headache), but no patient had clinical neurotoxicity. Findings on conventional MR images, MR perfusion maps, and SPECT perfusion scans were normal in all patients.

CONCLUSION: Conventional MR imaging, dynamic perfusion MR imaging, and SPECT do not depict any lesions in asymptomatic patients on cyclosporin. Therefore, it may not be possible for imaging methods to aid in the identification of patients at risk for neurotoxicity. Our findings support previously published conclusions that the lesions visible in patients with clinical neurotoxicity are due to cyclosporin effects and not to preexisting coincidental abnormalities.

Neurotoxicity induced by cyclosporin is an important adverse effect of posttransplantation immunosuppressive therapy. The clinical syndrome is characterized by severe headaches, seizures, altered mental status, and visual disturbances. In most cases, the MR findings include lesions of increased signal intensity on T2-weighted images affecting the subcortical white matter, most frequently in the occipital lobes. Other regions that may be affected include the frontal, posterotemporal, and parietal

lobes. This clinical and radiologic correlation in cyclosporin neurotoxicity has been confirmed by numerous studies (1, 2). Several hypotheses regarding the pathophysiology of this syndrome suggest that abnormalities of cerebral perfusion may be involved (1, 2).

Although completely reversible, clinical neurotoxicity is often a traumatic and disturbing event for the posttransplant patient. It is not known whether MR imaging can help one detect abnormalities in asymptomatic patients or in patients with very subtle clinical changes before the development of neurotoxicity. Theoretically, detection of such lesions in patients receiving cyclosporin may allow prevention of neurotoxicity by alerting clinicians to modify the dosage or to change the drug. In order to investigate the possibility of preventing neurotoxicity by the use of imaging, it is necessary to investigate asymptomatic patients to determine whether current imaging techniques allow for the detection of subclinical lesions. All imaging studies

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From the Department of Medical Imaging, The Toronto Hospital and University of Toronto (T.N.S., W.K.); and the Department of Medical Imaging, Mount Sinai Hospital and University of Toronto (M.I.).

Address reprint requests to Walter Kucharczyk, MD, FRCP, Department of Medical Imaging, University of Toronto, Fitzgerald Building, Room 127, 150 College St, Toronto, Ontario, Canada M5S 3E2.

to date have described findings only in patients with neurotoxicity; a series of asymptomatic patients has not been studied. It is not known, therefore, whether any evidence of early neurotoxicity is demonstrable by imaging. Furthermore, it is not known whether asymptomatic patients have any alteration in cerebral perfusion.

The purpose of this study, therefore, was first to examine asymptomatic posttransplant patients receiving cyclosporin with MR imaging for the presence of subclinical parenchymal abnormalities, and second to use MR imaging and SPECT to study cerebral perfusion in this patient population.

Methods

Ten patients were recruited prospectively to participate in the study while in the immediate posttransplant period. Patients were included in the study if they were receiving cyclosporin, had not incurred neurotoxicity, had had transplant less than 3 weeks earlier, and were able to undergo the required investigations. Patients were excluded from the study if they had evidence of cerebrovascular disease as suggested by a history of previous transient ischemic attacks, cerebral infarction, or angiographic documentation of intracranial cerebrovascular disease. The study was approved by the research ethics committee, and all patients gave informed written consent.

Demographic data were collected at the time of enrollment. All patients underwent conventional MR imaging, dynamic contrast-enhanced perfusion MR imaging, and single-photon emission CT (SPECT). MR imaging and SPECT scanning were conducted within 3 weeks of transplant. A clinical neurologic examination was performed at the time of the MR study. Patients were followed up for a mean of 3 months to determine whether neurotoxicity developed.

MR Studies

Conventional MR imaging consisted of T2-weighted spin-echo sequences obtained before the infusion of contrast agent and T1-weighted spin-echo images obtained before and after infusion of contrast material.

Dynamic contrast-enhanced images were acquired for the MR perfusion technique (3). Contrast material was injected IV as a compact bolus through a 20- to 22-gauge needle over 3 seconds followed by 20 mL of saline flush. The dose of contrast agent was 0.2 mg/kg. A rapid imaging technique with spiral k-space sampling was used to image the transit of the contrast bolus. Two nearly contiguous oblique axial images were obtained in a rapid repetitive manner. The section locations for these images were selected from the precontrast spin-echo images as connecting the rostrum and genu of the corpus callosum to ensure imaging of the occipital and frontal lobes. These particular locations allowed for imaging of the common sites of neurotoxic lesions and, therefore, the most likely site for associated perfusion abnormalities. Imaging parameters for this acquisition were 160/40 (TR/TE), 34° flip angle, 1.6 seconds per frame (both sections), 5-mm section thickness, and 20-cm field of view.

Images from the perfusion MR studies were postprocessed on a Sun workstation using MRVision postprocessing software (Palo Alto, CA). Pixel-by-pixel maps of regional cerebral blood volume (rCBV), peak height, and time-to-peak parameters were generated and reviewed in conjunction with the conventional MR studies. The algorithm performed empirical measurement of bolus tracking perfusion data.

SPECT Studies

SPECT imaging of regional cerebral blood flow (rCBF) was performed using ^{99m}Tc -ethyl cysteinate dimer (ECD) (4). For the imaging study, each patient received an intravenous injection of 20 mCi of ECD with eyes closed and ears unplugged in a quiet room. SPECT scanning was started 30 minutes after injection. For each scan, 120 7.5-second project images were obtained over a period of 15 minutes using 3° angle intervals on a 128×128 matrix over 360° by rotating each head 120°. Images were reconstructed in three orthogonal planes, including transverse, coronal, and sagittal, using a stereotaxic standardization technique.

Data Analysis

Images resulting from the conventional MR, postprocessed perfusion MR, and SPECT studies were interpreted by a board-certified neuroradiologist and nuclear medicine specialist.

Results

Patient Demographics

In total, 10 patients were scanned. There were six men and four women with a mean age of 45 ± 11 years. Of the 10 patients, six had had liver transplants and four had had kidney transplants.

Clinical Presentation

Three patients reported minor neurologic signs or symptoms commonly associated with cyclosporin (ie, either a mild headache or tremor), but no patient had clinical neurotoxicity. In addition, no patient subsequently incurred neurotoxicity during the follow-up period of the study.

Imaging

Findings on spin-echo images were normal in all subjects. In particular, there was no evidence of cortical or subcortical white matter lesions on T2-weighted images.

The rCBV, peak height, and time-to-peak maps were normal in all cases. There were no areas of hyperperfusion or hypoperfusion suggestive of subclinical blood flow abnormalities.

SPECT scans were normal for cerebral perfusion in all patients. No regional variability was noted. Representative images are shown in Figure 1.

Discussion

Neurotoxicity induced by cyclosporin is an important adverse effect of posttransplantation immunosuppressive therapy. The clinical syndrome is associated with characteristic findings at imaging. These include, most commonly, lesions of increased signal intensity on T2-weighted images affecting the subcortical white matter of the occipital lobes.

Various hypotheses have been suggested to explain the pathophysiology of cyclosporin-induced neurotoxicity. One hypothesis implicates cyclo-

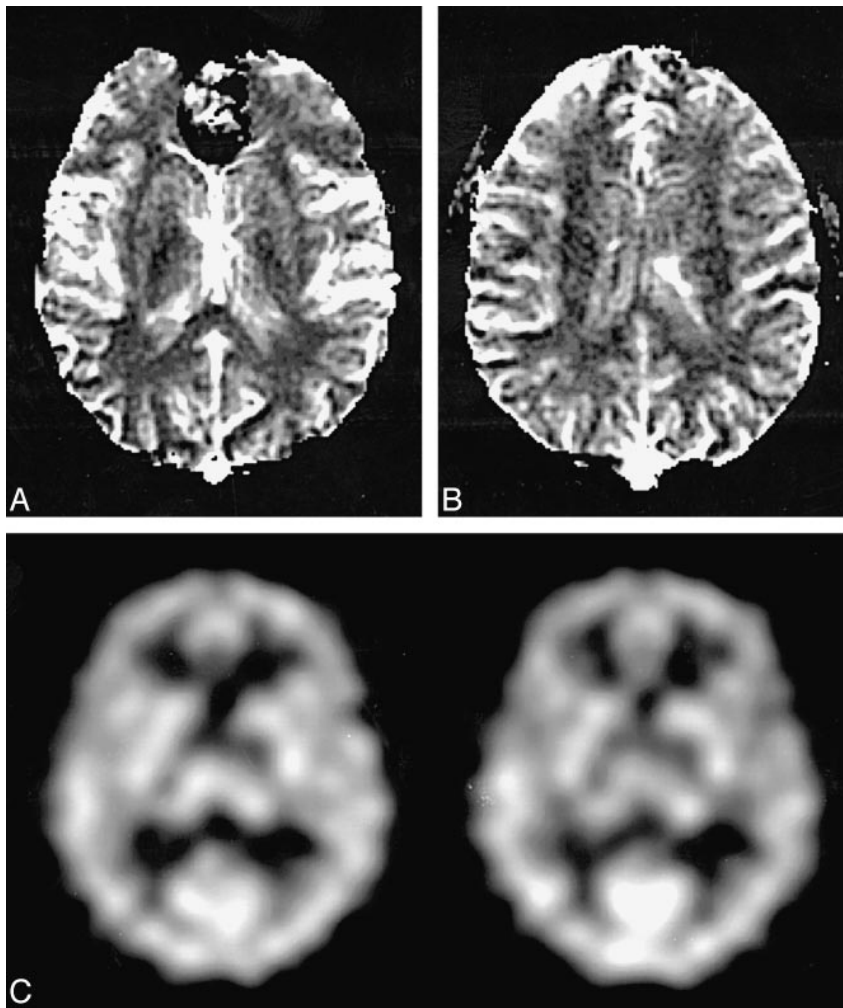


FIG 1. A, Postprocessed axial rCBV map at inferior section location shows no asymmetry or focal abnormality.

B, Postprocessed axial rCBV map at superior section location shows normal blood volume pattern.

C, Two axial SPECT scans at approximately the same section location as the rCBV maps. The superior section is shown on the left. Both images are normal.

sporin-induced hypertensive encephalopathy with blood-brain barrier compromise, extravasation, and focal cerebral edema (1). According to this hypothesis, a focal increase in cerebral perfusion would be expected in areas of neurotoxic lesions. An alternative hypothesis posits the role of cyclosporin-induced vasospasm leading to focal cerebral ischemia and the development of cytotoxic edema (2). In this case, a focal reduction in cerebral perfusion would be expected in the area of a neurotoxic lesion. Additional hypotheses implicate the role of hypocholesterolemia (5) and hypomagnesemia (6). These hypotheses do not suggest an alteration in CBF. Functional imaging techniques have been used to image symptomatic patients. In at least one case, hypoperfusion on SPECT scans was noted in the parietooccipital cortex bilaterally (7).

Recently, Casey et al (8) noted that numerous drug-related neurotoxicities have a common, relatively unique imaging appearance: predominantly bilateral parietooccipital T2 hyperintense lesions within the subcortical white matter and cortex. They have proposed posterior reversible encephalopathy syndrome (PRES) as a name for this syndrome. They indicated that most patients have hypertension and that most evidence supports

hyperperfusion and blood-brain barrier disruption leading to subcortical edema without infarction. They correlated results from advanced MR techniques such as fluid-attenuated inversion recovery, MR angiography, diffusion/perfusion, and proton spectroscopy with these theories as well as with literature from other imaging methods and experimental animal models. Their preliminary data support the contention that imaging findings in PRES are predominantly due to vasogenic edema without infarction.

The clinical manifestations of neurotoxicity, such as seizures and cortical blindness, can be difficult events for the posttransplant patient. It is appealing to explore the possibility of detecting the earliest manifestations of disease with modern neuroimaging methods. Nevertheless, before attempting to use imaging to screen for subclinical lesions and thus allow for the prevention of neurotoxicity, it is necessary to demonstrate that current techniques allow for their detection. Because a series of asymptomatic patients had not been studied, it was not known whether any evidence of early neurotoxicity is demonstrable by imaging.

In this study of asymptomatic posttransplant patients receiving cyclosporin, we found no paren-

chymal lesions on conventional MR images. The two techniques used to image cerebral perfusion did not reveal any focal or regional abnormalities.

The results of this study do not support the hypothesis that MR imaging can detect the subclinical effect of cyclosporin on the brain. Conventional MR studies, therefore, may not be of use in the identification of those at risk or in the prevention of neurotoxicity in this patient population. The fact that MR perfusion and SPECT studies do not reveal any perfusion abnormalities suggests that either these changes do not occur with cyclosporin administration in asymptomatic patients or that they are too subtle to detect with our techniques. In addition, by establishing the lack of lesions in asymptomatic patients, this study supports previously published conclusions that the lesions visible in patients with clinical neurotoxicity are due to cyclosporin effects and not simply to some preexisting coincidental abnormalities.

Our study has several limitations. First, our protocol for dynamic perfusion imaging was not optimal. With faster gradients, such as an echo-planar imaging system, it would have been possible to image more section locations with better temporal resolution. Therefore, although our section locations were placed through the region in which neurotoxicity has been reported most commonly, we cannot exclude the presence of lesions in other parts of the brain. Second, our patient sample size might be considered small to rule out the presence of subclinical lesions with high statistical certainty. It is possible that by imaging more patients we might have found an abnormality. Third, we studied patients in the immediate posttransplant period. The time from transplant is one risk factor for neurotoxicity. Hypertension, hypomagnesemia, and hypocholesterolemia have also been associated with neurotoxicity in retrospective studies. Perhaps by

studying posttransplant patients with one or more of these clinical abnormalities, and thus studying a group presumably at higher risk, we would have increased our chances of finding abnormalities. This should be considered in future investigations.

Conclusion

Cognizant of the above limitations, we suggest that imaging methods may not be able to help in detection of subclinical lesions in asymptomatic patients. It may not be possible, based on imaging criteria, to identify a subset of patients at risk for neurotoxicity. The role of imaging in patients receiving cyclosporin will most likely be limited to the evaluation of symptomatic patients.

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