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MR Imaging of Reversible Cyclosporin A-Induced Neurotoxicity

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Neurotoxicity is a recognized complication of cyclosporin A (CsA) therapy in patients undergoing organ transplantation. It is most commonly manifested by fever, seizures, and altered mental status. Cortical blindness and speech and motor disturbances can also occur. Changes seen in cerebral white matter on imaging studies are nonenhancing areas of hypoattenuation on CT and T2 prolongation on MR. We report three cases of CsA-induced neurotoxicity in which reversible changes were observed in the cerebral white matter. In the first patient, CsA neurotoxicity occurred 1 week following orthotopic liver transplantation. In the second patient, CsA neurotoxicity coincided with an episode of severe systemic hypertension 4 weeks after cardiac transplantation. The third patient experienced seizures 1 month after heart/lung transplantation for cystic fibrosis. A current theory postulates a relationship between diminished serum cholesterol and CsA neurotoxicity. This theory, however, does not satisfactorily address all cases of CsA neurotoxicity. In particular, serum cholesterol measurements were normal in cases 2 and 3 and probably were normal in case 1, despite diminished cholesterol levels preoperatively.

Although the matter of CsA-induced neurotoxicity remains unresolved, we suggest that endothelin, a newly described neuropeptide that causes intense vasoconstriction and that has been implicated in cerebral vasospasm, may potentiate CsA-induced damage to endothelium and promote CsA neurotoxicity.

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Cyclosporin A (CsA)-induced neurotoxicity has been reported to occur in up to 35% of patients undergoing orthotopic liver transplantation [1, 2]. It has also been reported in patients undergoing renal, bone marrow, and cardiac transplantation [1, 2]. It is most commonly manifested by seizures and altered mental status [1, 3, 4]. Cortical blindness and speech and motor disturbances can occur also [2, 5-7]. Changes seen in cerebral white matter on imaging studies include areas of hypoattenuation on CT and T2 prolongation on MR [1, 2, 5, 6]. We report three cases of CsA-induced neurotoxicity in which reversible changes were observed in the cerebral white matter.

Case Reports

Case 1

A 50-year-old woman with cryptogenic cirrhosis and overt, chronic hepatic encephalopathy underwent orthotopic liver transplantation. Postoperatively, she was treated with 750 mg of CsA orally twice a day until postoperative day 3, when the dose was increased to 1 g orally twice a day. Bile drained via a T tube was refeed via a nasogastric tube. IV magnesium sulfate was given on postoperative days 3, 4, 5, and 7 to compensate for hypomagnesemia, as noted in Table 1. An initial dose of methylprednisolone, 750 mg, was given intraoperatively. This was followed by a postoperative regimen of prednisone, 40 mg four times a day for the first 6 days, which was subsequently tapered. Other medications included azathioprine,

TABLE 1: Pre- and Postoperative Laboratory Values in Case 1

Day	BP (mm Hg)	Temp. (°C)	Hct. (%)	CsA (μg/l)	Mg ⁺⁺ (mg/dl)	Chol. (mg/dl)	Alk. Phos. (U/dl)	Bilirubin (mg/dl)	AST (U/l)	Creatinine (mg/dl)
-88					2.3 ^a	46	241 ^a	2.7 (1.4) ^a	91 ^a	1.6 ^a
-87						40	198 ^a	2.5 (1.4) ^a	76 ^a	1.6 ^a
-86						44	195 ^a	2.4 ^a	73 ^a	1.5 ^a
-80					2.0	58				1.5
-14							220	2.9	91	1.3
0	140/80	35.8 R	21.2		2.1		245	14.9	76	2.1
1	170/90	37.2 R	22.7	<25	1.3, 1.2 ^b		52, 54 ^b	1.7, 2.2 ^b	600, 727 ^b	1.6, 1.4, 1.5, 1.7, 1.7 ^b
2	165/90	37.2 R	21.5	<25	1.2		76	2.9	785	1.4, 2.0, 2.0, 2.0 ^b
3	180/80	37.2	28.2	37	1.0		66	3.8	960	1.7, 1.8, 1.6, 1.6 ^b
4	185/90	36.9	29.7	48	1.6		105	6.1 (5.2)	355	1.6, 1.8 ^b
5	185/90	37.0	33.0	78			147	5.8	88	1.6
6	180/90	36.9	32.6	253			167	7.1	88	1.6
7 ^c	160/86	36.7	34.9	401	1.1		194	8.6 (6.5)	57	1.5
	180/110	37.2								
8										1.4
9				75			213	3.6	34	1.2
10				178			256	3.2	34	1.3
11				64			246	2.6	29	1.2
12				231			259	1.9	27	1.3
21				220			358	1.1	40	1.4

Note.—Day 0 = day of operation; -88 = 88 days before surgery. Values for blood pressure (BP) and oral or rectal (R) temperature (Temp.) are the highest recorded during that 24-hr period. Hematocrit (Hct.) values are the lowest recorded during that 24-hr period. Cyclosporin A (CsA) was measured by high-performance liquid chromatography, whole blood; the therapeutic range is 50–400 μg/dl. Normal ranges for magnesium (Mg⁺⁺), alkaline phosphatase (Alk. Phos.), total bilirubin (values for direct bilirubin are in parentheses), aspartate transferase (AST), and creatinine are 1.6–2.7 mg/dl (magnesium), 41–133 U/l (alkaline phosphatase), 0.1–1.2 mg/dl (total bilirubin), 0.1–0.3 mg/dl (direct bilirubin), 7–39 U/l (aspartate transaminase), and 0.5–1.4 mg/dl (creatinine). Chol. = cholesterol. Albumin measured 3.2 mg/dl on day 9 and 3.9 mg/dl on day 21 (normal, 3.4–4.7 mg/dl).

^a These values were measured at an outside laboratory. Normal values were 1.9–2.5 mg/dl (magnesium), 39–177 U/l (alkaline phosphatase), 0.1–1.2 mg/dl (total bilirubin), 0.1–0.25 mg/dl (direct bilirubin), 0–31 U/l (aspartate transaminase), and 0.5–0.9 mg/dl (creatinine).

^b Serial values, same day, in chronologic order.

^c First set of data was obtained on the ward, before seizures; the second set was obtained after seizures.

Minnesota antilymphocyte globulin, gancyclovir, sucralfate, nystatin, multivitamins, folate, thiamine, morphine sulfate, nifedipine, acetaminophen, and diphenhydramine. T-tube cholangiographic findings on postoperative day 6 were normal. The following day, the patient had two focal seizures, manifested by head jerking to the right and staring episodes. No visual changes were reported. On the day of the seizures, the patient was afebrile and normotensive. The seizures were treated with standard doses of IV phenytoin and diazepam. Serum CsA was 401 μg/l, as measured by whole-blood, high-performance liquid chromatography assay. Although at the upper limit of the therapeutic range for CsA, the level had risen precipitously over 2 days, from 78 to 401 μg/l.

CT revealed bilateral, nonenhancing areas of hypoattenuation in the occipital white matter (Fig. 1A). MR the following day demonstrated bilateral nonenhancing areas of T2 prolongation in the occipital white matter (Fig. 1B). No petechial hemorrhage was apparent. Because the clinical findings and imaging features suggested CsA-induced neurotoxicity, CsA was withheld for 2 days. No further seizures occurred, and CsA was restarted on postoperative day 9 at 200–300 mg orally twice a day. There were no further complications. Peak blood pressure and temperature and preoperative and postoperative laboratory values are listed in Table 1. Of note, preoperative serum cholesterol measurements ranged from 40 to 58 mg/dl. No postoperative cholesterol measurements were obtained. However, fresh frozen plasma was administered during the perioperative period. Postoperative serum creatinine values were normal. On postoperative day 23 (16 days after the seizures), T2-weighted MR examination revealed complete resolution of the white matter lesions (Fig. 1C).

Case 2

A 36-year-old man underwent cardiac transplant following 19 months of refractory dilated cardiomyopathy due to cardiac sarcoidosis. The peri- and postoperative periods were unremarkable until 4 weeks after transplantation, when the patient awoke with confusion, headache, change of vision, and anxiety. The day before admission, he had felt well and had walked the 18 holes of a golf course. The patient's medications included 400 mg of CsA twice a day, acyclovir, prednisone, diltiazem, captopril, magnesium supplement, ranitidine, aspirin, ferrous sulfate, Colace, clotrimazole, and trimethoprim/sulfamethoxazole.

In the emergency department, the patient was found to be markedly hypertensive (210/110 mm Hg) and was noted to have a gaze palsy. He had a generalized seizure that was treated with phenytoin. Nifedipine was administered for control of blood pressure. Clinically, the history of hypertension, confusion, and seizures suggested CsA neurotoxicity. The CsA level on admission was 348 μg/l; 4 days earlier, it was 392 μg/l. CsA was withheld, and the levels promptly decreased to 271, 188, and 169 μg/l, respectively, over the next 3 days. Serum cholesterol, magnesium, and creatinine were normal. Laboratory data and vital signs are listed in Table 2.

Ophthalmologic evaluation on the day of admission revealed subtle bilateral central scotomata that were diminished on reexamination 3½ hr later. Unenhanced CT revealed bilateral foci of decreased attenuation involving occipital white matter. MR the following day revealed nonenhancing areas of T2 prolongation in the same areas (Figs. 2A–2C). Minimal cortical involvement was suggested as well. The CT and MR findings were consistent with the clinical suspicion

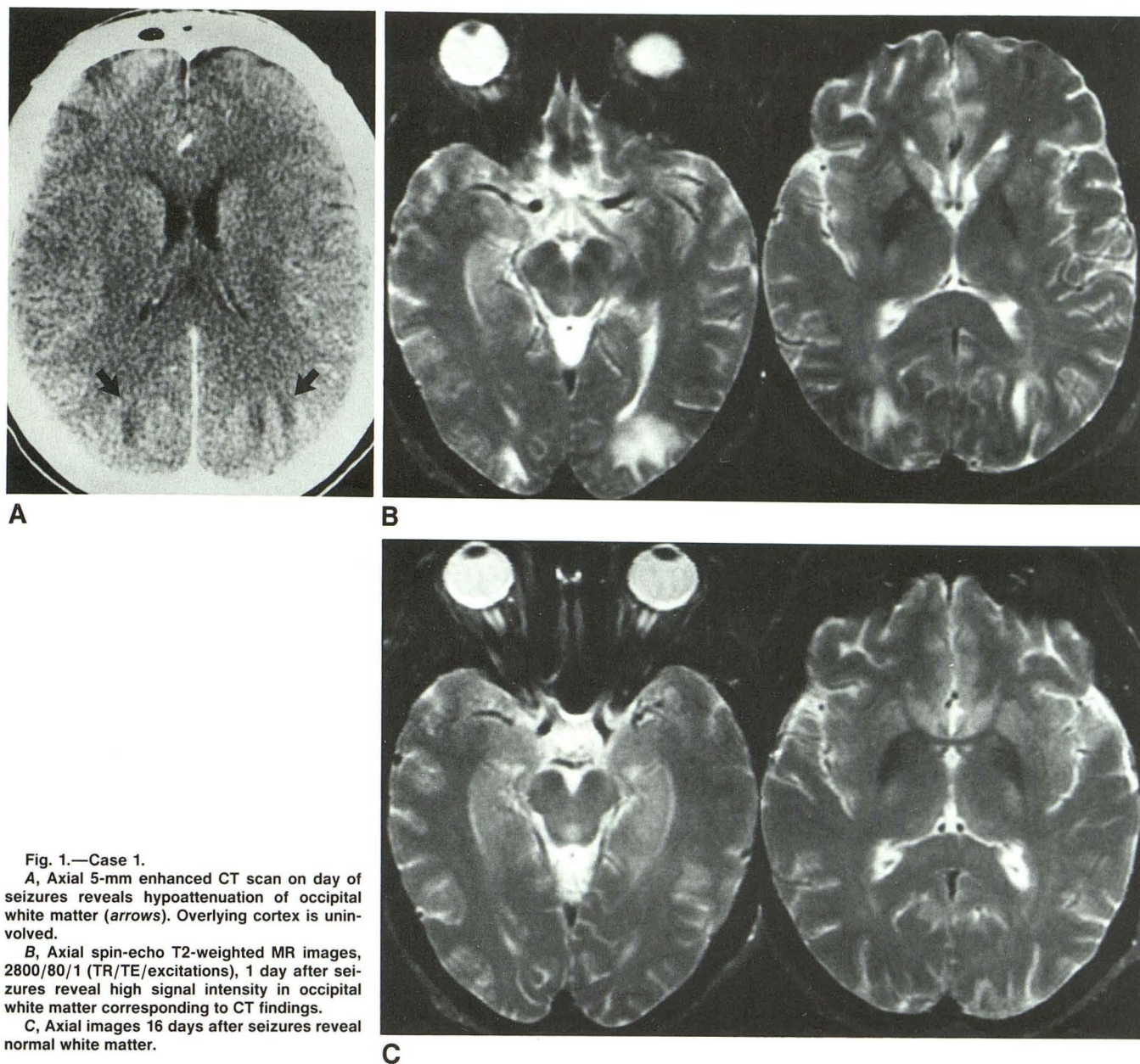


Fig. 1.—Case 1.

A, Axial 5-mm enhanced CT scan on day of seizures reveals hypoattenuation of occipital white matter (arrows). Overlying cortex is uninvolved.

B, Axial spin-echo T2-weighted MR images, 2800/80/1 (TR/TE/excitations), 1 day after seizures reveal high signal intensity in occipital white matter corresponding to CT findings.

C, Axial images 16 days after seizures reveal normal white matter.

of CsA neurotoxicity. Follow-up T2-weighted images 3 days later revealed nearly complete resolution of the abnormalities (Figs. 2D–2F).

Case 3

A 33-year-old woman underwent heart/lung transplantation for cystic fibrosis. Intraoperatively, a prolonged period of cardiopulmonary bypass was needed. The postoperative course was unremarkable except for an episode of moderate cardiac rejection and of mild pulmonary rejection on postoperative day 5; these were treated with methylprednisolone. The patient had no history of seizures. Medications included 100 mg of CsA three times a day, Imuran, prednisone, Pancrease, ranitidine, terfenadine, metoclopramide, magnesium supplementation, nystatin, and albuterol inhaler.

On postoperative day 29, the patient experienced generalized seizures with right arm involvement that were preceded by severe headache. Blood pressure at that time was 125/81 mm Hg, and CsA level was 636 $\mu\text{g/l}$. (Therapeutic CsA at that institution was 75–300 $\mu\text{g/l}$). Phenytoin therapy was instituted with a loading dose and was maintained at 300 mg orally every night. CsA was temporarily withheld. Admission CT demonstrated multiple areas of hypoattenuation in the cerebral white matter. MR 4 days later, on postoperative day 33, confirmed the CT findings (Figs. 3A–3C). Follow-up MR 12 days later revealed nearly complete resolution of the white matter lesions (Figs. 3D–3F). Phenytoin therapy was continued until postoperative day 63. Over the ensuing weeks, CsA levels were elevated sporadically (511 and 742 $\mu\text{g/l}$ on postoperative days 66 and 72, respectively, as noted in Table 3). No seizures occurred during this period, although the patient did experience headaches.

TABLE 2: Pre- and Postoperative Laboratory Values in Case 2

Day	BP (mm Hg)	Temp. (°C)	Hct. (%)	CsA (μg/l)	Mg ⁺⁺ (mg/dl)	Chol. (mg/dl)	Alk. Phos. (U/l)	Bilirubin (mg/dl)	AST (U/l)	Creatinine (mg/dl)
-5			37.6	321	1.7					1.1
-1			38.0	392	1.6		83	0.8	29	1.4
0	210/110	37.1	39.3	348	1.6					1.2
1	200/90	36.6	36.3	271	1.8					1.1
2	180/80	36.9	40.6	188	1.8	181 ^a	91	0.5	25	1.1
3	120/80	36.5		169						1.3
4	110/75	37.3	43.9	225			102	0.7	24	1.2
5	135/75	37.0	36.8	231	22.3, 1.8 ^b				22	1.1
6	135/65	37.0	36.1	161	1.7				28	0.9

Note.—Day 29 = day of cyclosporin A toxicity. Values for blood pressure (BP) and temperature (Temp.) are the highest recorded during that 24-hr period. Hematocrit (Hct.) values are the lowest recorded during that 24-hr period. Cyclosporin A (CsA) was measured by high-performance liquid chromatography, whole blood; the therapeutic range is 50–400 μg/l. Normal ranges for magnesium (Mg⁺⁺), alkaline phosphatase (Alk. Phos.), total bilirubin, aspartate transaminase (AST), and creatinine are 1.6–2.7 mg/dl (magnesium), 41–133 U/l (alkaline phosphatase), 0.1–1.2 mg/dl (total bilirubin), 7–39 U/l (aspartate transaminase), and 0.5–1.4 mg/dl (creatinine). Chol. = total cholesterol.

^a High-density lipoprotein cholesterol = 51 mg/dl; low-density lipoprotein cholesterol = 105 mg/dl.

^b Serial values, same day, in chronologic order.

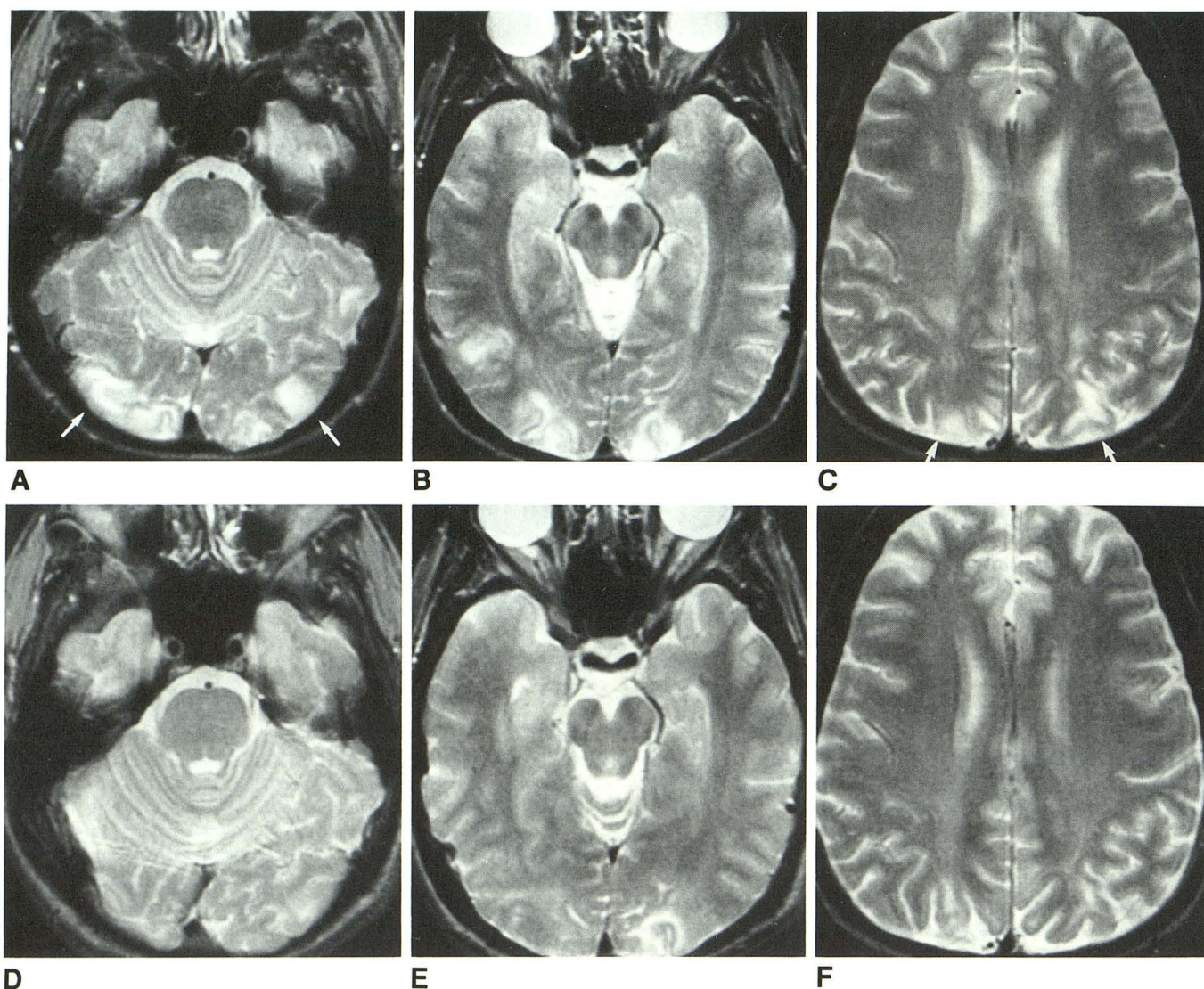


Fig. 2.—Case 2.

A–C, Axial spin-echo T2-weighted MR images, 2800/80/1 (TR/TE/excitations), 1 day after admission reveal hyperintense signal in occipital and to a lesser extent posterior temporal and parietal white matter (arrows). No abnormalities were detected on T1-weighted images (not shown), either before or after administration of contrast material. Unenhanced CT scans (not shown) on day of admission revealed similar lesions.

D–F, Follow-up images 3 days later show nearly complete resolution of white matter abnormalities.

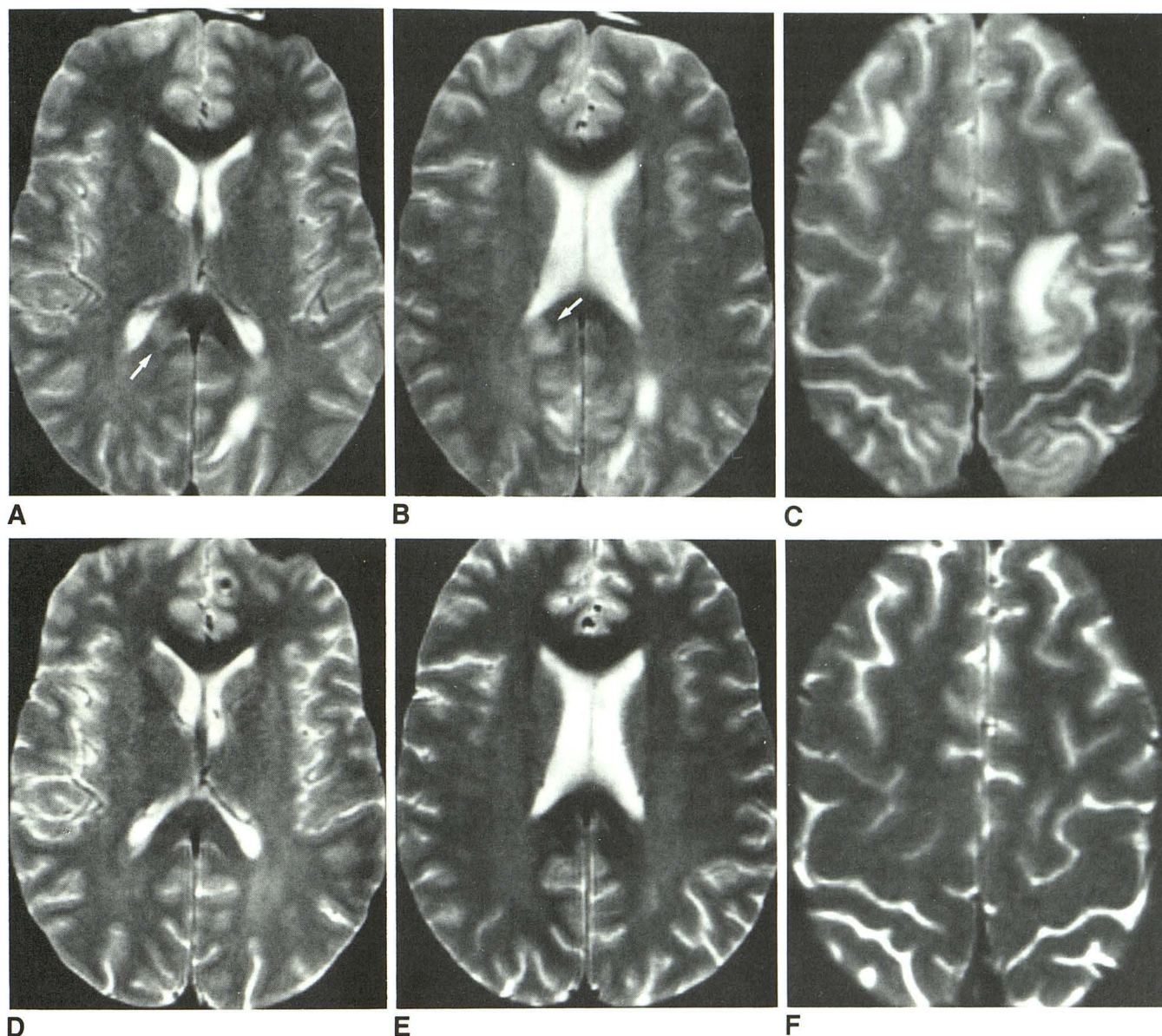


Fig. 3.—Case 3.

A–C, Axial spin-echo T2-weighted MR images, 2500/80/1 (TR/TE/excitations), 4 days after initial episode of cyclosporin A neurotoxicity reveal multiple foci of hyperintensity in subcortical white matter, as well as in right splenium (arrows).

D–F, Follow-up T2-weighted images (2308/80/1) 12 days later reveal complete resolution of white matter abnormalities.

On postoperative day 84, the patient had a generalized tonic clonic seizure, again with right arm involvement. The CsA level was 116 $\mu\text{g/l}$ at the time of readmission. MR revealed recurrent subcortical white matter lesions of the cerebral hemispheres, as well as new lesions of the corpus callosal genu and splenium and the midbrain and pons (Figs. 4A–4C). Smudgy enhancement of some of the lesions was suggested on enhanced images. Phenytoin therapy was reinstituted. No further seizures occurred, but headache persisted. Given the therapeutic levels of CsA, it was unclear whether these seizures were related to CsA or to some other clinical condition, including infection and hypoxic-ischemic insult due to the long duration of cardiopulmonary bypass. Blood and CSF analyses were negative, and infection was excluded as the source of the seizures and MR findings. Finally, follow-up MR on postoperative day 99 revealed complete resolution

of the white matter changes (Figs. 4D and 4E). A few questionable foci of either pial or cortical contrast enhancement were still apparent.

Discussion

The introduction of CsA in the late 1970s has resulted in a substantial decrease in the rate of rejection of organ transplants. Its use, however, is not without significant adverse effects. Most common are dose-related nephrotoxicity and hypertension. Neurotoxicity has been reported as well, and usually manifests as seizures, visual impairment, confusion, quadriparesis, drowsiness, or coma [7–12]. Although CsA

TABLE 3: Postoperative Laboratory Values in Case 3

Day	BP (mm Hg)	Temp. (°C)	Hct. (%)	CsA (μg/dl)	Mg ⁺⁺ (mEq/dl)	Chol. (mg/dl)	Alk. Phos. (U/l)	Bilirubin (mg/dl)	AST (U/l)	Creatinine (mg/dl)
24				176	2.0	122	87	0.7	100	0.9
29	125/81	36.8	31.1	636		146	113	0.7	14	1.2
30	100/60	37.2	28.5	64		139	97	0.5	14	0.8
31	120/70	36.7	34.7	49	1.9	151	114	0.6	11	0.8
32	115/70	36.8	32.5	110						0.8
33	130/90	36.5	34.2	126						0.9
34	134/84	36.6	31.4	279						0.6
35	120/70	36.9	31.4	190	1.1	183	120	0.4	<7	0.6
42			31.6	104		181	121	0.2	8	0.6
63	140/90		32.4	121		199	116	0.2	23	0.6
66				511						
70	130/90		35.5	165		239	94	0.3	14	0.9
72				742						
73				108						
79				351						
84			38.5	116		263	102	0.7	24	1.0
96			32.1	187						

Note.—Day 29 = day of cyclosporin A toxicity. Values for blood pressure (BP) and temperature (Temp.) are the highest recorded during that 24-hr period. Hematocrit (Hct.) values are the lowest recorded during that 24-hr period. Cyclosporin A (CsA) was measured by fluorescent polarization, serum; the therapeutic range is 75–300 μg/l. Normal ranges for magnesium (Mg⁺⁺), alkaline phosphatase (Alk. Phos.), total bilirubin, aspartate transaminase (AST), and creatinine are 1.6–2.7 mg/dl (magnesium), 43–122 U/l (alkaline phosphatase), 0.2–1.0 mg/dl (total bilirubin), 5–35 U/l (aspartate transaminase), and 0.5–1.4 mg/dl (creatinine). Chol. = cholesterol.

neurotoxicity typically occurs within the first month of therapy, toxicity may appear within the first hours to days or several months after the onset of CsA therapy.

Several reports of CsA neurotoxicity have included neuroimaging findings [1, 2, 5, 6]. Typical findings include white matter hypoattenuation on CT and hyperintensity on T2-weighted MR images. Less commonly, hemorrhage has been reported. Wilson et al. [5] reported a case of reversible cortical blindness due to CsA neurotoxicity. CT revealed bilateral hypoattenuation of the occipital white matter that was also apparent on follow-up MR 3 weeks later. Their patient ultimately succumbed to transplant rejection, and autopsy was performed. Pathologic specimens revealed mild pallor of the white matter and a few scattered macrophages among nerve fibers. Irregular swelling of myelin sheaths and mild astrogliosis were evident. Additionally, these investigators reported small resolving petechiae and a few minute demyelinating lesions characteristic of progressive multifocal leukoencephalopathy. Their description, however, reflects the findings 8.5 months following transplantation and, in particular, 3.5 months following a completely normal ophthalmologic examination.

As the findings of Wilson et al. [5] reflect only subtle foci of demyelination within a broader picture of myelin pallor, it is unlikely that acute demyelination is the source of the CT and MR signal abnormalities. One explanation would involve an acute toxic insult of undetermined origin resulting in axonal swelling and increased water. This is supported by the hypoattenuation seen on CT, the prolonged T2 relaxation seen on MR, and the absence of gadopentetate dimeglumine enhancement on MR and iodinated contrast enhancement on CT. Alternatively, vascular spasm might initiate mild, reversible ischemia. This is supported by the occasional incomplete reversal of white matter changes as well as the infrequent

reports of hemorrhagic lesions associated with CsA-induced neurotoxicity.

Another interesting question relates to the site of predilection for CsA neurotoxicity. Although scattered reports suggest that CsA neurotoxicity can occur in almost any location within the brain, including the posterior fossa and supratentorial white matter, a frequent region of insult is the occipital white matter, resulting in seizures or reversible changes in visual acuity, sometimes severe enough to cause reversible cortical blindness [1, 2, 4–7]. Although watershed ischemic changes may be related, it is possible that an as yet undefined selective vulnerability of the occipital white matter is responsible for the frequent association of CsA neurotoxicity with occipital lesions. As similar findings have been noted in *cis*-platinum-induced neurotoxicity, eclampsia, and acute hypertensive encephalopathy, it is possible that selective vulnerability of the occipital white matter plays a role in these disorders as well [13–15].

Some reported cases of CsA neurotoxicity have been correlated with elevated levels of CsA and/or its metabolites. However, many cases occur in the face of apparently normal (therapeutic) blood CsA levels [4, 16]. In light of these more problematic cases, several authors have sought to correlate CsA neurotoxicity with other factors, including hypomagnesemia, aluminum overload, high-dose methylprednisolone therapy, and elevated levels of CsA metabolites [8, 10–12, 16, 17]. To date, these theories have not been substantiated.

Another theory was suggested by de Groen et al. [4], who noted an inverse relationship between CsA neurotoxicity and serum cholesterol, which binds CsA in the serum. Within the blood, the vast majority of CsA either is carried by erythrocytes or is bound to lipoproteins, especially low- (LDL) and high-density lipoproteins [18]. Only a small fraction (<10%) of CsA is unbound. Thus, a small shift of the equilibrium between

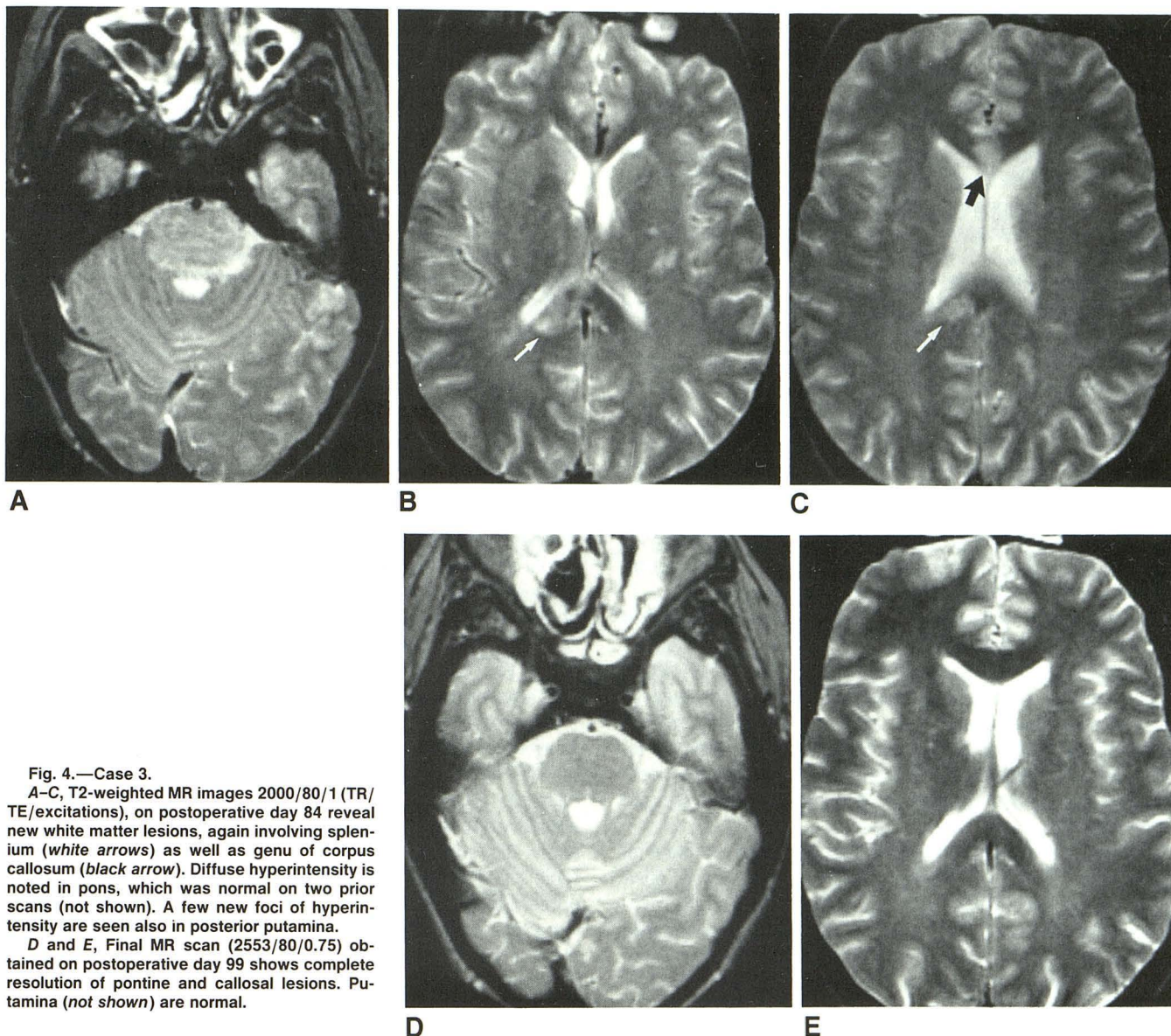


Fig. 4.—Case 3.

A–C, T2-weighted MR images 2000/80/1 (TR/TE/excitations), on postoperative day 84 reveal new white matter lesions, again involving splenium (white arrows) as well as genu of corpus callosum (black arrow). Diffuse hyperintensity is noted in pons, which was normal on two prior scans (not shown). A few new foci of hyperintensity are seen also in posterior putamina.

D and E, Final MR scan (2553/80/0.75) obtained on postoperative day 99 shows complete resolution of pontine and callosal lesions. Putamina (not shown) are normal.

erythrocyte-CsA, LDL-bound CsA, and free CsA could significantly alter the small fraction of free CsA. Such a change is suspected in cases of depressed cholesterol, where a diminished binding capacity would be present. In the face of a depressed binding capacity, de Groen et al. suggested an increased fraction of unbound (unmeasured) CsA would be present. As the current clinical assays of CsA measure total concentration, any increase in the free fraction would be undetected by routine testing.

In a subsequent report, however, de Groen [19] revised part of this theory, noting that dedicated assays of unbound CsA had failed to correlate with changes in total serum cholesterol. Instead, he hypothesized an increased concentration of bound CsA per LDL particle (in the case of diminished LDL), resulting in increased delivery of CsA to astrocytes, accounting for neurotoxicity. This theory also invokes diminished cholesterol as the underlying factor in CsA neu-

rotoxicity. However, not all patients with CsA neurotoxicity have diminished serum cholesterol levels.

Our first patient (case 1) had presumed CsA neurotoxicity in temporal association with several factors. Serum magnesium levels were chronically depressed, despite replacement therapy and fairly constant serum creatinine levels. CsA levels rose precipitously between postoperative days 5 and 7 to a level of 401 mg/dl, most likely consequent to increased absorption of CsA. Despite the rapid rise, a concentration of 401 mg/dl is often a nontoxic level in the immediate postoperative period of liver transplantation. No serum cholesterol measurements were obtained during the hospitalization period, although markedly diminished preoperative serum cholesterol was noted. In most liver transplantation patients, serum cholesterol rapidly reaches normal levels within the first few postoperative days because of the large perioperative infusions of plasma. Nevertheless, we cannot know

whether the serum cholesterol in this patient remained depressed or had increased to normal levels by postoperative day 7, the day of CsA neurotoxicity.

In case 2, serum CsA levels were within the therapeutic range, and the serum cholesterol, creatinine, and magnesium levels were normal. In case 3, although serum CsA was elevated at the time of initial neurotoxicity, serum cholesterol, creatinine, and magnesium levels were not depressed. It is unlikely, therefore, that the cholesterol hypothesis applies to these cases.

The second patient had systemic hypertension at the time of CsA neurotoxicity, although not to the levels seen in acute hypertensive encephalopathy (HE). In HE, diastolic blood pressure measurements typically surpass 130 mm Hg [15]. HE is hypothesized to result from a loss of cerebral autoregulation, focal vasodilatation, and breakdown of the blood-brain barrier (BBB) with extravasation of serum proteins and water [15, 20–22]. CsA neurotoxicity, on the other hand, occurs at lower blood pressures, even if elevated. As a result, loss of cerebral autoregulation most likely does not apply. Rather, we suggest that CsA neurotoxicity may be consequent to focal vasoconstriction, which may be mediated by the release of endothelin (ET), a new neuropeptide.

ET is a potent diffusible vasoconstrictive substance, first characterized in 1988 [23]. ET is a 21-amino acid peptide elaborated by endothelial cells that appears to act on vascular smooth muscle. It may have a significant role in the development of vasospasm, and may play a pivotal role in CsA neurotoxicity. Specific binding sites for ET have been identified in several areas of the human brain, including the cerebellum, hippocampal formation, diencephalon, and choroid plexus [24–26].

Clinically, increased plasma ET levels correlate with several conditions, including cardiogenic shock, hypertension (case 2), orthotopic liver transplantation (case 1), and acute myocardial infarction [27]. Conditions in which ET is postulated to play a role include sepsis, coronary artery spasm, vasculitis, toxemia of pregnancy, and CsA nephrotoxicity [27]. ET has also been implicated in vasospasm following subarachnoid hemorrhage, as it has been isolated in the CSF of patients with subarachnoid hemorrhage [28, 29]. We suspect that ET also may be involved in the development of CsA neurotoxicity and that a similar mechanism may be operative in the reversible CNS effects of eclampsia.

In the kidney, CsA has been shown to disrupt endothelial integrity, which induces increased release of ET [30]. Two *in vitro* studies have reported the stimulatory effect of CsA on ET release [30, 31]. In addition, CsA-induced increases in ET-1 binding site density in mice cardiac cell membranes have been reported [32]. Given the significant cerebral vasoconstrictive properties of ET, it is not unreasonable to suggest similar effects of CsA on CNS release and binding of ET.

In the CNS, integrity of the BBB normally restricts movement of both CsA and ET. However, in many patients on CsA, conditions exist that disrupt the BBB and permit access of both CsA and ET to otherwise protected sites in the CNS. Under conditions of hepatic encephalopathy, an increase in the permeability of the BBB has been observed experimentally

[19]. Clinically, the patient described in case 1 had multiple episodes of overt hepatic encephalopathy before transplantation.

A possible mechanism of BBB disruption involves elevation of plasma cholestanol, consequent to a deficiency of the hepatic enzyme 26-hydroxylase [19]. Increased cholestanol may alter the integrity of the BBB. Princen et al. [33] recently found potent inhibition of the same hepatic enzyme by CsA in rats. It is possible that such a mechanism disrupts the BBB in CsA neurotoxicity; if so, it could help explain CsA neurotoxicity in nonhepatic transplant patients, as in cases 2 and 3.

If endothelial integrity were disrupted, CsA could gain access to astrocytes, ET could gain access to cerebral vascular smooth muscle resulting in vasoconstriction and vasospasm, and elevated circulating ET could promote systemic hypertension. Under such conditions, local ischemia, and consequent white matter edema, would be possible. If severe enough, petechial or confluent parenchymal hemorrhages could ensue. Since the white matter lesions seen in CsA neurotoxicity are not seen after subarachnoid hemorrhage, vasospasm alone would seem to be inadequate to promote such lesions. We suspect a synergistic effect of both ET and CsA may be operative in CsA neurotoxicity. Unfortunately, ET assays are not yet readily available at our institution. As a result, we do not as yet have direct evidence of elevated ET at the time of CsA neurotoxicity.

Three cases of CsA-induced neurotoxicity are reported. Analysis of these cases fails to support the suggested relationship between diminished serum cholesterol and CsA neurotoxicity. The notion that underlying chronic hepatic encephalopathy increases permeability of the BBB may, however, apply. Elevated levels of ET during the first week after orthotopic liver transplantation may have contributed to the development of vasospasm in case 1. In case 2, severe systemic hypertension, perhaps consequent to CsA therapy and coupled with elevated levels of ET, may have resulted in cerebral vasoconstriction and/or vasospasm. In other words, CsA-induced hypertension, coupled with disruption of the BBB, could promote local ischemia with the development of white matter edema. In the third case, markedly elevated levels of serum CsA correlate with the initial episode of CsA neurotoxicity. Although systemic hypertension was not present, the markedly elevated levels of CsA may have promoted ET-mediated cerebral vasospasm resulting in neurotoxicity.

Despite numerous theories, including our hypothesis, the matter of CsA-induced neurotoxicity remains unsettled. We recognize the speculative nature of our hypothesis about the relationship between CsA and ET, particularly without direct evidence of elevated levels of ET at the time of neurotoxicity. We are hopeful that further study will offer additional insights into this fascinating and, fortunately, transient disorder.

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