

A REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

JUDY HINCHEY, M.D., CLAUDIA CHAVES, M.D., BARBARA APPIGNANI, M.D., JOAN BREEN, M.D.,
LINDA PAO, M.D., ANNABEL WANG, M.D., MICHAEL S. PESSIN, M.D., CATHERINE LAMY, M.D.,
JEAN-LOUIS MAS, M.D., AND LOUIS R. CAPLAN, M.D.

Abstract *Background and Methods.* In some patients who are hospitalized for acute illness, we have noted a reversible syndrome of headache, altered mental functioning, seizures, and loss of vision associated with findings indicating predominantly posterior leukoencephalopathy on imaging studies. To elucidate this syndrome, we searched the log books listing computed tomographic (CT) and magnetic resonance imaging (MRI) studies performed at the New England Medical Center in Boston and Hôpital Sainte Anne in Paris; we found 15 such patients who were evaluated from 1988 through 1994.

Results. Of the 15 patients, 7 were receiving immunosuppressive therapy after transplantation or as treatment for aplastic anemia, 1 was receiving interferon for melanoma, 3 had eclampsia, and 4 had acute hypertensive encephalopathy associated with renal disease (2 with lupus nephritis, 1 with acute glomerulonephritis, and 1 with acetaminophen-induced hepatorenal failure). Altogether, 12 patients had abrupt increases in blood

pressure, and 8 had some impairment of renal function. The clinical findings included headaches, vomiting, confusion, seizures, cortical blindness and other visual abnormalities, and motor signs. CT and MRI studies showed extensive bilateral white-matter abnormalities suggestive of edema in the posterior regions of the cerebral hemispheres, but the changes often involved other cerebral areas, the brain stem, or the cerebellum. The patients were treated with antihypertensive medications, and immunosuppressive therapy was withdrawn or the dose was reduced. In all 15 patients, the neurologic deficits resolved within two weeks.

Conclusions. Reversible, predominantly posterior leukoencephalopathy may develop in patients who have renal insufficiency or hypertension or who are immunosuppressed. The findings on neuroimaging are characteristic of subcortical edema without infarction. (N Engl J Med 1996;334:494-500.)

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BOTH acute medical illness and treatment with immunosuppressive drugs are occasionally complicated by neurologic abnormalities, including altered mental function, visual loss, stupor, and seizures. These abnormalities appear to be the result of an acute encephalopathy that is probably related to edema within the brain, usually in the cerebral white matter.

The cerebral white matter is composed of myelinated-fiber tracts in a cellular matrix of glial cells, arterioles, and capillaries that makes this region susceptible to the accumulation of fluid in the extracellular spaces (vasogenic edema). Modern neuroimaging techniques are sensitive to changes in the distribution of water in the brain and make it possible to detect white-matter edema even in its early phases. Patients with hypertensive encephalopathy, hypertension associated with acute glomerulonephritis,¹⁻⁵ and eclampsia of pregnancy⁶⁻¹³ have been known to have edema in the brain, predominantly in the posterior portions of the cerebral white matter. Recently, patients treated with cyclosporine and other immunosuppressants have been reported to have similar findings on neuroimaging.¹⁴⁻²⁹

We have noted a variety of disorders associated with findings on neuroimaging that suggest white-matter edema, mostly in the posterior parietal-temporal-occipital regions of the brain. The clinical findings in these patients make up a recognizable syndrome characterized by headache, decreased alertness, altered mental functioning, seizures, and visual loss, including cor-

tical blindness. In our experience, the clinical signs and abnormalities on imaging are always reversible. This syndrome, which we call reversible posterior leukoencephalopathy, is unfamiliar to many. In this report we describe the clinical and neuroimaging features of the syndrome, which appears to involve capillary leakage and acute disruption of the blood-brain barrier.

METHODS

We searched the log books recording computed tomographic (CT) and magnetic resonance imaging (MRI) procedures performed at the New England Medical Center to identify patients evaluated from 1988 through 1994 who had prominent white-matter abnormalities. We reviewed all CT and MRI scans and charts for these patients and selected those with reversible clinical or radiologic lesions for further study. Our analysis of the charts included information about symptoms, concurrent medical illnesses, medications, findings on neurologic examination, and results of the analysis of cerebrospinal fluid, electroencephalography (EEG), and other neurologic evaluations. Abnormalities on imaging were defined as areas of low white-matter attenuation on CT scans and as T₁-weighted hypointense and T₂-weighted hyperintense areas on MRI scans that had partially or completely resolved on follow-up scanning, when subsequent images were available. These changes probably represent increased water in the white matter.³⁰

RESULTS

We identified 13 patients seen at the New England Medical Center in Boston, as well as 2 seen at Hôpital Sainte Anne in Paris, who had the characteristic clinical and imaging features of this syndrome. The 15 patients (13 female and 2 male) ranged in age from 15 to 62 years (average, 39). All underwent cranial imaging studies; 2 underwent only CT scanning, 3 only MRI scanning, and 10 both CT and MRI scanning. Clinical and imaging findings are summarized in Table 1.

Four patients (Patients 1, 2, 3, and 4) had hyperten-

From the Department of Neurology, New England Medical Center and Tufts University School of Medicine, Boston (J.H., C.C., B.A., J.B., L.P., A.W., M.S.P., L.R.C.), and the Service de Neurologie, Hôpital Sainte Anne, Paris (C.L., J.-L.M.). Address reprint requests to Dr. Caplan at the Department of Neurology, New England Medical Center, 750 Washington St., Boston, MA 02111.

sive encephalopathy; in two it was secondary to lupus nephritis, in one to idiopathic glomerulonephritis, and in one to acetaminophen-induced hepatorenal failure. Three patients (Patients 5, 6, and 7) had postpartum eclampsia, which developed 1, 4, and 13 days after delivery. Eight patients (Patients 8 through 15) were receiving immunosuppressive drugs for aplastic anemia or metastatic melanoma or after receiving kidney, liver, or bone marrow transplants; four were receiving cyclosporine, three tacrolimus, and one interferon alfa.

Eleven patients had had seizures. Visual abnormalities, noted in 10 patients, consisted of cortical blindness in 5, homonymous hemianopia in 3, and blurred vision and visual neglect (lack of attention to parts of the visual field) in 1 patient each. Headache and nausea or vomiting were present in eight patients. Lethargy was present in six, confusion in four, and abulia in one pa-

tient. The number of seizures varied; six patients had three seizures each, two had two seizures, and one had four seizures. One patient had only one seizure, and status epilepticus developed in one. Most patients (8 of 11) had focal seizures with secondary generalization; 3 patients had tonic-clonic seizures without focal onset. Except for the patients receiving tacrolimus, all had blood pressures above normal; the pressure was highest in those with hypertensive encephalopathy. All patients receiving cyclosporine and those with hypertensive encephalopathy ultimately had some degree of acute renal failure.

The most common location of the white-matter abnormalities on neuroimaging was the posterior regions of the cerebral hemispheres (this was the site in 14 of the 15 patients). The multifocal abnormalities included both hemispheres and were often symmetric. The

Table 1. Clinical Characteristics and Findings on Neuroimaging Studies of 15 Patients with Reversible Posterior Leukoencephalopathy.

PATIENT NO.	AGE (YR)/SEX	DIAGNOSIS OR DRUG TREATMENT	CLINICAL FINDINGS	HIGHEST BLOOD PRESSURE <i>mm Hg</i>	LESIONS ON CT OR MRI	HIGHEST SERUM CREATININE LEVEL* <i>mg/dl</i>
1	30/F	Systemic lupus erythematosus, hypertensive encephalopathy	Hypertension, headache, lethargy, vomiting, cortical blindness	200/110	Occipital lobe (bilateral), posterior parietal lobe (bilateral), posterior temporal lobe (right), frontal lobe (left), thalamus (right)	3.3
2	61/F	Acute nephritis, hypertensive encephalopathy	Hypertension, headache, vomiting, seizures, cortical blindness, confusion	200/100	Occipital lobe (bilateral), posterior temporal lobe (bilateral), posterior parietal lobe (bilateral)	3.9
3	27/M	Hepatorenal syndrome, hypertensive encephalopathy	Headache, vomiting, hypertension, visual hallucinations, confusion, cortical blindness	180/110	Occipital lobe (bilateral), posterior parietal lobe (right), frontal lobe (bilateral), posterior temporal lobe (right)	16.1
4	39/F	Systemic lupus erythematosus, hypertensive encephalopathy	Headache, seizures, hypertension, vomiting, confusion, right hemianopia	200/130	Occipital lobe (left), posterior parietal lobe (bilateral), posterior temporal lobe (left), frontal lobe (left), pons (left)	3.1
5	25/F	Puerperal eclampsia	Headache, hypertension, vomiting, seizures, visual neglect, right hemiparesis	170/100	Occipital lobe (bilateral), posterior parietal lobe (right), posterior temporal lobe (left), caudate (right)	0.9
6	15/F	Puerperal eclampsia	Headache, nausea, hypertension, seizures, left hemiparesis	150/104	Occipital lobe (bilateral), posterior parietal lobe (right)	0.4
7	28/F	Puerperal eclampsia	Headache, lethargy, vomiting, seizures, hypertension, visual blurring, left hemiparesis	160/100	Occipital lobe (bilateral), parietal lobe (bilateral), frontal lobe (bilateral)	0.1
8	62/F	Liver transplantation, treatment with cyclosporine	Hypertension, seizures, cortical blindness	142/95	Occipital lobe (bilateral), posterior temporal lobe (right), parietal lobe (bilateral)	2.7
9	47/F	Aplastic anemia, treatment with cyclosporine	Headache, hypertension, vomiting, seizures, cortical blindness	180/88	Occipital lobe (bilateral), posterior parietal lobe (bilateral), posterior temporal lobe (left)	1.5
10	47/F	Bone marrow transplantation, treatment with cyclosporine	Hypertension, seizures, lethargy, left hemianopia	150/80	Occipital lobe (bilateral), posterior temporal lobe (bilateral)	2.3
11	36/F	Renal transplantation, treatment with cyclosporine	Hypertension, seizures, confusion	210/110	Occipital lobe (bilateral), parietal lobe (bilateral), frontal lobe (bilateral)	5.3
12	50/M	Melanoma, treatment with interferon alfa	Hypertension, dizziness, status epilepticus, left hemiparesis, left hemianopia, bilateral dysmetria, lethargy	180/110	Occipital lobe (bilateral), posterior parietal lobe (right), cerebellum (bilateral)	0.9
13	48/F	Liver transplantation, treatment with tacrolimus	Abulia, left hemiparesis, dystonia of right arm	100/60	Frontal lobe (right), internal capsule (left), central white matter (bilateral)	0.7
14	20/F	Liver transplantation, treatment with tacrolimus	Lethargy, asterixis, seizure	120/80	Occipital lobe (bilateral), posterior temporal lobe (left), posterior parietal lobe (left), frontal lobe (left), centrum semiovale (bilateral)	1.2
15	57/F	Liver transplantation, treatment with tacrolimus	Lethargy, asterixis	130/80	Occipital lobe (bilateral), posterior parietal lobe (bilateral), pons	0.9

*To convert values for creatinine to micromoles per liter, multiply by 88.4.

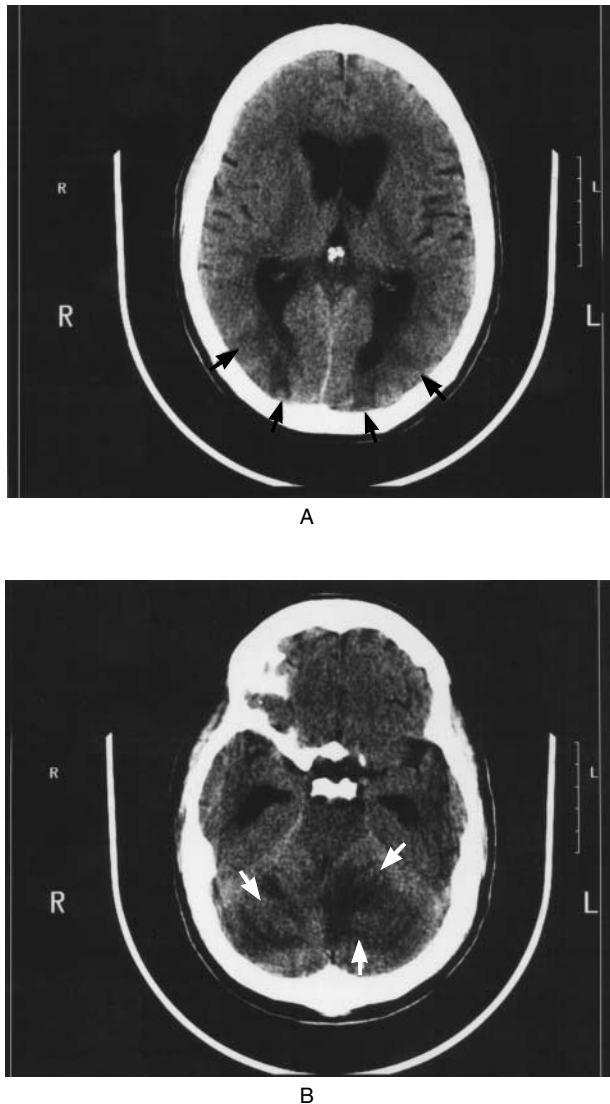


Figure 1. CT Scans of Patient 12.

Panel A shows areas of hypodensity in the parieto-occipital white matter (black arrows). In Panel B, abnormal hypodensity is also seen in the cerebellum (white arrows), with the abnormality larger on the left (L) than on the right (R).

involved areas were the occipital lobes in 14, the posterior parietal lobes in 13, the posterior temporal lobes in 9, the pons in 2, and the thalamus and cerebellum in 1 each. Figure 1 shows CT scans of a patient with typical posterior cerebral white-matter hypodensities who also had cerebellar abnormalities. Nine patients had additional anterior hemispheric lesions (seven frontal and one caudate). One patient (Patient 13) had only anterior hemispheric lesions.

The white-matter abnormalities in 12 patients encompassed more than one vascular territory, straddling border-zone regions between the posterior- and middle-cerebral-artery territories in 5 patients and between anterior- and middle-cerebral-artery territories in 1. Three

patients had relatively restricted white-matter lesions in areas perfused by either the posterior cerebral artery (in two) or the middle cerebral artery (in one). The cerebral cortex was also involved in four patients (Patients 1, 4, 6, and 9). Five patients underwent contrast-enhanced studies; in two, minimal cortical enhancement was observed in areas of abnormality on scans without contrast material. No enhancement was seen in the other three patients.

Follow-up scanning in eight patients (CT in two and MRI in six) showed complete resolution of the abnormalities in six patients and partial resolution in two. Resolution was noted within 8 days to 17 months after the first abnormal results, but follow-up scans were often obtained after the resolution of symptoms. In three patients the abnormalities resolved within three weeks. In seven patients symptoms and neurologic signs resolved completely but follow-up scans were not performed.

Patients were treated with antihypertensive agents (Patients 1 through 7) or decreased doses or withdrawal of the offending immunosuppressant (Patients 8 through 15). Resolution of neurologic signs occurred within two weeks in all patients, and within one week in most of them (10 of 15).

The typical features of this syndrome are illustrated by its course in three patients, described below.

Patient 2

Periorbital and hand edema developed in a 61-year-old, previously healthy woman three weeks before admission. On the day of admission, she had severe headache, nausea, and vomiting and one hour later could not see. Later she became confused and was brought to the hospital. Her blood pressure was 200/100 mm Hg. The general examination showed anasarca, and the neurologic examination showed slowed responses with confusion and cortical blindness. No retinal hemorrhages or cotton-wool spots were seen. She experienced a witnessed left focal seizure (with shaking of the left arm), followed by a generalized tonic-clonic seizure. Cranial T₂-weighted MRI showed increased signal intensity in the occipital lobes bilaterally, centered at the gray matter-white matter junction. T₁-weighted images showed hypointensities in these areas. The findings on cranial magnetic resonance angiography and magnetic resonance venography were normal. The cerebrospinal fluid contained 18,000 red cells and 13 white cells in tube 1, and 7800 red cells and 6 white cells in tube 4. The cerebrospinal fluid protein level was 37 mg per deciliter, and the glucose level was 75 mg per deciliter (4.2 mmol per liter). An echocardiogram was normal, the blood urea nitrogen level was 36 mg per deciliter (12.8 mmol per liter), the serum creatinine level 1.8 mg per deciliter (160 μmol per liter), and the urine contained 3+ protein and 3+ blood. A serologic test for vasculitis was negative.

The patient was treated with sodium nitroprusside,

phenytoin, and diuretics, and two days later the neurologic findings returned to normal. A renal biopsy showed focal crescentic glomerulonephritis without immune-complex deposits. The patient apparently had hypertensive encephalopathy secondary to idiopathic glomerulonephritis with the nephrotic syndrome. A follow-up MRI scan at 15 months was normal.

Patient 6

A 15-year-old girl who was 34 weeks pregnant was admitted to the hospital after 4 weeks of increasing blood pressure (140/100 mm Hg at admission), pedal edema, and proteinuria (3+) and a week of headache and nausea. Vaginal delivery was induced three days later, and magnesium sulfate therapy was begun. The patient felt well until nine hours after delivery, when she had a generalized tonic-clonic seizure. Her blood pressure at that time was 150/104 mm Hg; she was given more magnesium sulfate. The next day she had two generalized tonic-clonic seizures; at that time the blood pressure was 200/126 mm Hg. The patient was treated with intravenous labetalol, lorazepam, and phenytoin. The neurologic examination showed a slight left hemiparesis. Biochemical-test results were normal. A cranial CT scan without contrast material showed bilateral low-density areas involving the white matter of the parieto-occipital lobe with extension into the gray matter of the right posterior parietal lobe. Cranial MRI the same day confirmed these findings; the findings on magnetic resonance venography were normal. Two days later the patient's blood pressure improved and the neurologic examination was normal. A follow-up cranial CT scan one week later was normal.

Patient 11

A 36-year-old woman with end-stage, chronic glomerulopathy underwent kidney transplantation in December 1987. The immunosuppressive regimen included prednisolone, antilymphocyte globulin, and azathioprine. Signs of kidney rejection developed in October 1988 and April 1990 and were treated both times with bolus doses of corticosteroids and cyclosporine (2 mg per kilogram of body weight per day). In June 1992, she had two right-sided focal seizures followed by generalized seizures. The neurologic examination showed drowsiness and confusion. T₂-weighted MRI (Fig. 2A) showed severe diffuse hyperintensity of the hemispheric white matter. The electroencephalogram showed moderate generalized dysrhythmia. The cerebrospinal fluid contained 2 red cells per milliliter and 56 mg of protein per deciliter. Biochemical testing showed a blood urea nitrogen level of 67 mg per deciliter (24 mmol per liter) and a serum creatinine level of 5.3 mg per deciliter (470 μ mol per liter). The serum cholesterol and magnesium concentrations were normal, and the cyclosporine level was maintained within therapeutic ranges. After cyclosporine was withdrawn, the patient made a full, gradual recovery within two weeks. Cyclosporine

was not reintroduced. A follow-up MRI (Fig. 2B) one month later showed almost complete resolution of the brain lesions.

DISCUSSION

The clinical signs and findings on neuroimaging in patients with the reversible posterior leukoencephalopathy syndrome are consistent enough that this entity should be readily recognizable. Its causes are diverse, but common precipitants are acute elevations of blood pressure, renal decompensation, fluid retention, and treatment with immunosuppressive drugs.

Clinical Findings

The most common clinical symptoms and signs are headache, altered alertness and behavior ranging from drowsiness to stupor, seizures, vomiting, mental abnormalities including confusion and diminished spontaneity and speech, and abnormalities of visual perception. The onset is usually subacute but may be heralded by a seizure. Seizures are common at the onset of neurologic symptoms but can also develop later. Seizures may begin focally but usually become generalized. Multiple seizures are more common than single events. Most patients have a change in alertness and activity. Lethargy and somnolence are often the first signs noted. Temporary restlessness and agitation may alternate with lethargy. Stupor and frank coma may develop, but usually patients remain responsive to stimuli. The mental functions are slowed, and patients are often confused; spontaneity is decreased, and responses are slowed. Memory and the ability to concentrate are impaired, although severe amnesia is unusual. Abnormalities of visual perception are nearly always detectable. Patients often report blurred vision. Hemianopia, visual neglect, and frank cortical blindness may occur. Some cortically blind patients do not realize that they cannot see (Anton's syndrome). The tendon reflexes are often brisk, and some patients have weakness and incoordination of the limbs.

Abnormalities on Neuroimaging

The most common abnormality on neuroimaging in the patients we describe, as in previous reports,^{2,7,16} was edema involving the white matter in the posterior portions of the cerebral hemispheres, especially bilaterally in the parieto-occipital regions. The calcarine and parameian occipital-lobe structures are usually spared, a fact that distinguishes reversible posterior leukoencephalopathy from bilateral infarction of the posterior-cerebral-artery territory. Simultaneous bilateral infarction of the posterior-cerebral-artery territory occurs in patients with embolism to the rostral basilar artery, but with "top of the basilar" embolism the calcarine regions are invariably involved and often there are accompanying thalamic and midbrain infarcts.³¹ Involvement of additional areas of the brain in patients with the reversible posterior leukoencephalopathy syndrome, such as

the brain stem, cerebellum (Fig. 1B), basal ganglia, and frontal lobes, has also been reported.^{4,11,17}

Although the abnormalities in our patients tended to be symmetric, the degree of involvement and the clinical manifestations were often asymmetric. The gray matter was involved in four patients, a finding also described in other series.^{2,10,13} In all 12 patients in whom the first imaging study done was CT, the radiologic diagnosis of white-matter disease was apparent on the scan. Although MRI yielded a higher-resolution image, it was not necessary for the diagnosis of reversible posterior leukoencephalopathy. The only advantage of MRI was its ability to show small, focal abnormalities beyond the limits of resolution of CT. Signal enhancement was present in two patients and probably is explained by disruption of the blood-brain barrier.⁴ In all the patients who had follow-up CT or MRI scans, there was improvement or resolution of white-matter abnormalities, suggesting transient edema rather than infarction.⁵

Causes and Mechanisms

Hypertensive encephalopathy is the cause of this syndrome that has been most thoroughly studied both

clinically and experimentally. Sudden elevations in systemic blood pressure exceed the autoregulatory capability of the brain vasculature. Regions of vasodilation and vasoconstriction develop, especially in arterial boundary zones, and there is breakdown of the blood-brain barrier with focal transudation of fluid and petechial hemorrhages.³²⁻³⁵ Byrom showed that in rats that were made suddenly hypertensive, these signs disappeared within hours after hypertension was relieved, suggesting that functional vascular changes and edema were the chief causes, rather than infarction.³⁶ Patients with hypertensive encephalopathy have the same clinical signs as those with the reversible posterior leukoencephalopathy syndrome, and they also have rapid resolution of clinical and imaging abnormalities when blood pressure is lowered.

Most authorities believe that hypertensive encephalopathy and eclampsia share similar pathophysiologic mechanisms.³⁷⁻³⁹ In the patients we studied, the reversible posterior leukoencephalopathy syndrome occurred during the puerperium, rather than during pregnancy. The fluid accumulation often observed during this period may have accentuated the tendency for brain edema

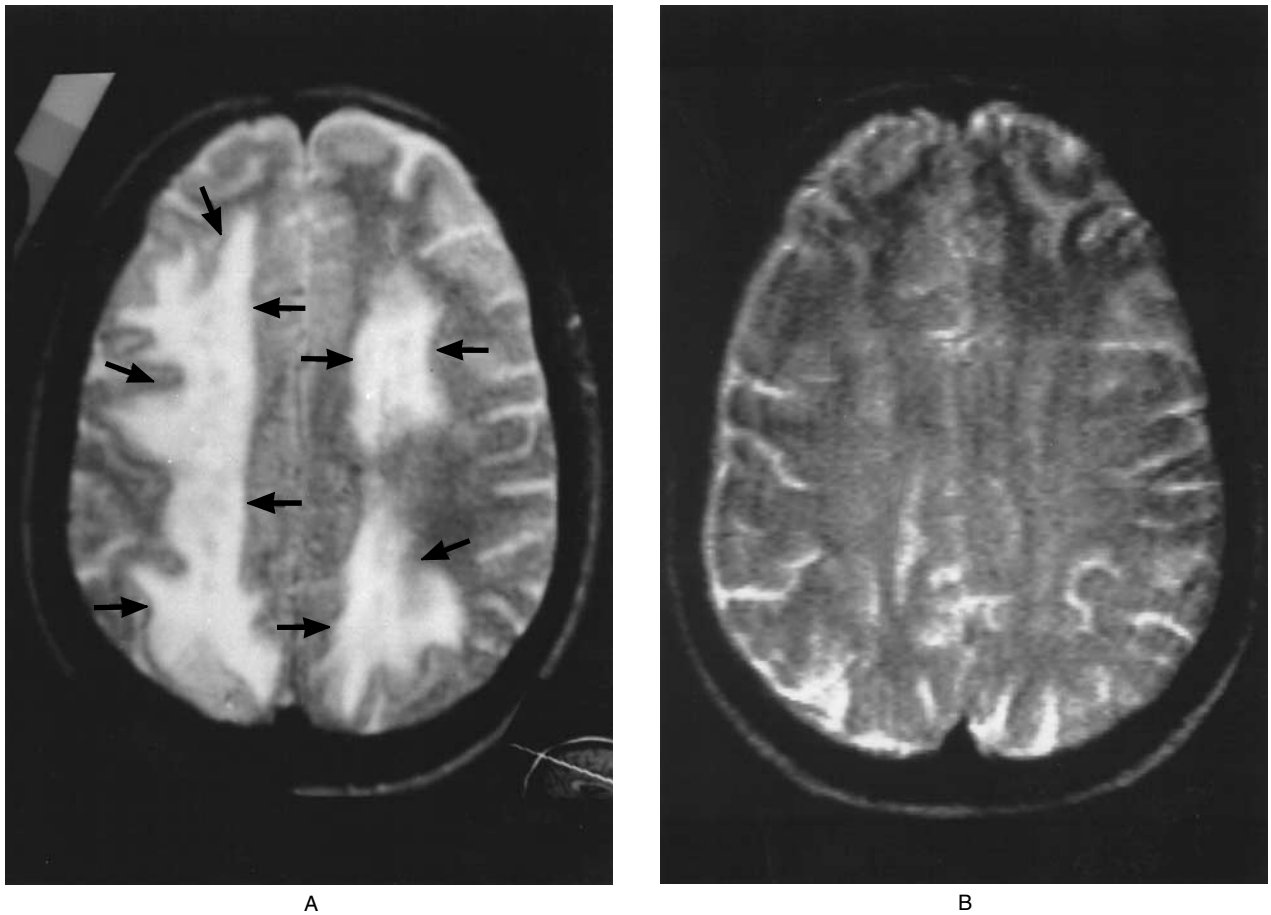


Figure 2. MRI Scans of Patient 11.

In Panel A, the initial image shows widespread white-matter signal abnormalities (arrows). A follow-up scan (Panel B) is of poor quality but shows that the abnormalities have resolved.

to develop, as it does in patients with renal decompensation. The imaging findings and clinical features of postpartum eclampsia are identical to those of hypertensive encephalopathy. The pathologic process is also characterized by cerebral edema and petechial hemorrhages, especially in the parieto-occipital and occipital lobes. Microscopically, these petechiae are ring hemorrhages around capillaries and precapillaries that are occluded by fibrinoid material.³⁹ The susceptibility of the posterior portion of the brain to the lesions seen in hypertensive encephalopathy and eclampsia is recognized, although poorly understood.^{1,4,7} Altered vascular reactivity has been posited to result from an increased sensitivity to normally circulating pressor agents, a deficiency of vasodilating prostaglandins, and endothelial-cell dysfunction. These abnormalities have all been reported in eclampsia.^{39,40} Some of these changes preceded clinical symptoms in our patients. Endothelial dysfunction may cause profound vasospasm and reduced organ perfusion, activation of the coagulation cascade, and loss of fluid from the intravascular compartment.⁴⁰

The mechanism by which immunosuppressive therapy can cause the reversible posterior leukoencephalopathy is less clear. Hypocholesterolemia, hypomagnesemia, high-dose methylprednisolone treatment, aluminum overload, and drug levels above the therapeutic range are some factors posited to explain the neurotoxicity of cyclosporine.^{14-16,18-20} Adverse neurologic events have been reported, however, in patients with therapeutic serum levels of cyclosporine and none of these risk factors.¹⁵ In all but one of our patients who were taking cyclosporine, the drug levels were in the therapeutic range. The direct effect of cyclosporine on the central nervous system has not been established; however, the identification of cyclosporine and its metabolites and of tacrolimus in cerebrospinal fluid from liver-transplant recipients and a patient with Behçet's syndrome suggests a perturbation of the blood-brain barrier.^{21,23,41} Sloane et al.⁴² found abnormalities of the blood-brain barrier at autopsy in two bone marrow-transplant recipients with cyclosporine neurotoxicity. Others have suggested that cyclosporine toxicity occurs only in patients whose blood-brain barrier has been previously disturbed. This hypothesis is based on the observation that liver-transplant recipients who have more episodes of encephalopathy before transplantation are the most susceptible to the toxic effects of cyclosporine and tacrolimus.^{21,24,43,44} Tollemar et al.⁴³ saw cyclosporine toxicity only in patients with prior damage to the blood-brain barrier due to infection, perhaps because of exposure of the brain to cyclosporine.

No direct effect of these drugs on the endothelium is known, but cyclosporine can cause vasculopathy⁴⁵⁻⁵¹ and has direct toxic effects on vascular endothelial cells.⁵²⁻⁵⁴ Cyclosporine also causes endothelial cells to release endothelin, prostacyclin, and thromboxane A₂ by a direct cytotoxic effect.^{52,53,55} The role of endothelin, a potent vasoconstrictor, in hypertensive encephalopathy is being investigated.³⁹ Increases in thromboxane and prostacy-

clin may cause microthrombi and a syndrome resembling the hemolytic-uremic syndrome, which has been observed in transplant recipients treated with cyclosporine.^{45,51,56,57} Immunosuppressive agents could damage the blood-brain barrier by various means: direct toxic effects on the vascular endothelium; vasoconstriction caused by elaboration of endothelin, with results similar to eclampsia; and microthrombosis, as in the hemolytic-uremic syndrome.

Hypertension and nephrotoxicity often accompany cyclosporine-related central nervous system symptoms.^{18,58} The four patients in our study who were taking cyclosporine had increased blood pressure and renal failure before the onset of neurologic symptoms. Both factors may be related to the development of neurologic symptoms in our series. We believe that hypertension associated with fluid overload in patients with an altered blood-brain barrier best explains the acute, reversible white-matter changes that characterize this syndrome.

The mechanism of tacrolimus neurotoxicity is probably similar to that of cyclosporine.^{23,26,59} The only risk factor detected among the three patients who were receiving tacrolimus was a high drug level in one patient. The mechanism of the reversible posterior leukoencephalopathy syndrome in the patient receiving interferon alfa is unknown; the development of hypertension before the neurologic event, as well as neurologic improvement after the discontinuation of the drug, suggests a mechanism similar to those with the other two immunosuppressants. In our experience, limb edema and neurologic signs similar to those of the reversible posterior leukoencephalopathy syndrome have been known to develop in patients treated with interleukins for cancer, but neuroimaging studies were not available in these cases.

Other conditions can also occasionally cause the reversible posterior leukoencephalopathy syndrome. Two patients with acute intermittent porphyria were reported to have cortical blindness and seizures and had reversible, predominantly posterior white-matter abnormalities on imaging.⁶⁰

The cause of the reversible posterior leukoencephalopathy syndrome is multifactorial. The syndrome should be promptly recognized, since it is reversible and readily treated by controlling blood pressure and discontinuing the offending immunosuppressive agent or decreasing the dose. The mechanism of the syndrome is probably a brain-capillary leak syndrome related to hypertension, fluid retention, and possibly the cytotoxic effects of immunosuppressive agents on the vascular endothelium.

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