Posterior Reversible Encephalopathy Syndrome — An Underrecognized Manifestation of Systemic Lupus Erythematosus

JASON K. KUR and JOHN M. ESDAILE

ABSTRACT. ***Objective.*** Posterior reversible encephalopathy syndrome (PRES) is a rare, recently described neurologic condition identifiable by clinical presentation and magnetic resonance image (MRI) appearance. It is associated with renal insufficiency, hypertension, and rheumatologic diseases. Patients present with headache, seizures, loss of vision and altered mental function, and a pattern on imaging studies of predominantly transient, posterior cerebral hyperintensities on T2-weighted MRI. There is a high likelihood of presentation of this syndrome to a rheumatologist.

Methods. Three recent cases of systemic lupus erythematosus (SLE) with PRES, along with 9 previously reported cases, are reviewed.

Results. All 3 patients presented with seizures and subacute visual changes in association with lupus nephritis. The first presented with hypertension, complete visual field loss, and status epilepticus 2 weeks after starting oral cyclosporine therapy for refractory lupus nephritis. The second patient was normotensive and presented with seizures and visual symptoms while in hospital with SLE-related pancreatitis and nephritis. The third patient had headache and seizures with severe lupus disease activity including nephritis, pancytopenia, and pulmonary hemorrhage. Cranial MRI showed predominantly posterior signal abnormalities on T2-weighted images, which resolved after cessation of cyclosporine in the first case, treatment with IV cyclophosphamide in the second case, and treatment with cyclophosphamide and plasmapheresis in the final case. Literature review showed that PRES is a manifestation of SLE or a consequence of therapy with calcineurin inhibitors or rituximab. The hallmark features are visual loss and seizures. Severe hypertension (> 170/110 mm Hg) and renal failure were present in the majority of previously identified cases of SLE and PRES. Our second case was normotensive but had marked lupus disease activity. PRES can lead to cerebral infarction.

Conclusion. With increasing availability of MRI, PRES will be identified more frequently. Swift action to identify potential offending agents, controlling hypertension, and treating active disease can lead to reversal of radiologic and neurologic findings. (First Release Sept 1 2006; J Rheumatol 2006;33:2178-83)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS SEIZURES ENCEPHALOPATHY HYPERTENSION

Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition identifiable by clinical presentation and magnetic resonance imaging (MRI) appearance. It is associated with renal insufficiency, hypertension, and rheumatologic diseases, and has also been reported in cases of eclampsia, post-transplant immunosuppression, and intraoperative blood pressure fluctuation[1]. Patients present with headache, altered mental function, seizures and loss of vision, and a pattern on imaging studies of predominantly transient, posterior cerebral hyperintensities on T2-weighted MR scans. Subsequent diffusion-weighted images reveal an increased diffusion coefficient indicating vasogenic edema. Several names have been proposed for this clinical entity, including reversible posterior cerebral edema and posterior leukoencephalopathy; however, PRES best describes the clinical and neuroradiologic presentation of this condition. With advances in radiologic imaging, there is a high likelihood of presentation of this syndrome to a rheumatologist. It is important to recognize the condition early in order to minimize potential for irreversible central nervous system damage.

We summarize all reported cases of systemic lupus erythematosus (SLE) and PRES. PRES has been described rather infrequently in patients with lupus and never before in a normotensive SLE patient from lupus disease activity.

MATERIALS AND METHODS

We describe 3 recent cases of SLE with PRES seen by the Division of Rheumatology consultation service at the Vancouver General Hospital, Vancouver, between 2004 and 2005. In addition we performed a Medline

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search of the English language literature published 1966 to 2005, searching for SLE presenting as PRES, reversible posterior cerebral edema, leukoencephalopathy, or occipito-parietal encephalopathy.

CASE REPORTS

Case 1: SLE and cyclosporine A. A 29-year-old Asian woman, with a 6-year history of SLE that included recurrent active mixed membranous and focal proliferative glomerulonephritis, presented with generalized tonic clonic seizures and complete bilateral blindness 14 days after starting cyclosporine. She was hypertensive (206/135 mm Hg) with mild malar erythema. Neurologic examination revealed normal papillary responses and normal funduscopy and cranial nerve examination. Laboratory investigations revealed hemoglobin 99 g/l, creatinine 136 μmol/l, C3 of 0.44 g/l (reference range 0.80 to 1.80 g/l) and C4 of 0.07 g/l (reference range 0.12 to 0.36 g/l). Cyclosporine level was 129 μg/l (reference range 75 to 340 μg/l). Cranial T2-weighted MRI revealed posterior edema in the occipital regions predominantly (Figure 1A). Diffusion-weighted imaging (DWI) scans showed increased diffusion coefficient, suggestive of vasogenic edema.

She was treated conservatively with cessation of cyclosporine and control of hypertension. Seizures were controlled initially with a loading dose of intravenous midazolam and phenytoin. Visual acuity gradually returned to normal within weeks and no further seizure activity was noted. Repeat MRI 3 weeks after presentation showed improvement of posterior vasogenic edema (Figure 1B).

Case 2: SLE, pancreatitis, and nephritis. A 23-year-old Asian woman was admitted to hospital with a flare of SLE including fever, arthritis, and epigastric pain secondary to pancreatitis. She had been diagnosed as having SLE 2 years earlier and treated initially with prednisone and hydroxychloroquine. At admission she was anemic, with hemoglobin 78 g/l, sedimentation rate 60 mm/h, and lipase 1869 U/l (normal 0–265 U/l). During hospital admission for pancreatitis and subsequent treatment with corticosteroids, she developed worsening headache, blurred vision, confusion, and focal seizures (localized to the occipital lobe, starting with visual hallucinations) that became secondarily generalized. Neurologic examination revealed a bilateral central scotoma, normal visual acuity, and otherwise unremarkable remainder of the cranial nerve examination. Laboratory investigations revealed hemoglobin 78 g/l, creatinine 99 μmol/l, sedimentation rate 60 mm/h, C3 of 0.24 g/l and C4 of 0.04 g/l. She had new-onset WHO Class IV lupus nephritis on renal biopsy. Maximal recorded blood pressure was 140/90 mm Hg. Cranial T2-weighted MRI revealed bilateral cerebellar edema, posterior edema in the occipital regions, and a hyperintense lesion in the right posterior limb of the internal capsule (Figure 2A). DWI scans showed diffusion was increased in these regions, consistent with vasogenic edema. The findings on cranial MR angiography and venography were normal.

Seizures were initially controlled with phenytoin. She was treated with intravenous cyclophosphamide and intravenous pulse methylprednisolone. Repeat MRI 4 weeks after starting therapy revealed complete resolution of the vasogenic edema in all regions previously involved, including the lesion of the right corticospinal tract (Figure 2B). Headaches, blurred vision, and pancreatitis all resolved in the ensuing months.

Case 3: SLE, nephritis, and pulmonary hemorrhage. A 23-year-old Southeast Asian woman was admitted to hospital with a flare of SLE including acute renal failure, pancytopenia, and transaminitis. She had been diagnosed as having SLE 3 years earlier and was treated initially with azathioprine. During hospital admission she received oral prednisone and mycophenolate mofetil. She was discharged briefly, however, returned 3 days later with worsening headache, blurred vision, confusion, and hemoptysis. She subsequently had a generalized tonic clonic seizure in the emergency department. Visual acuity was not tested. Laboratory investigations revealed hemoglobin 63 g/l,

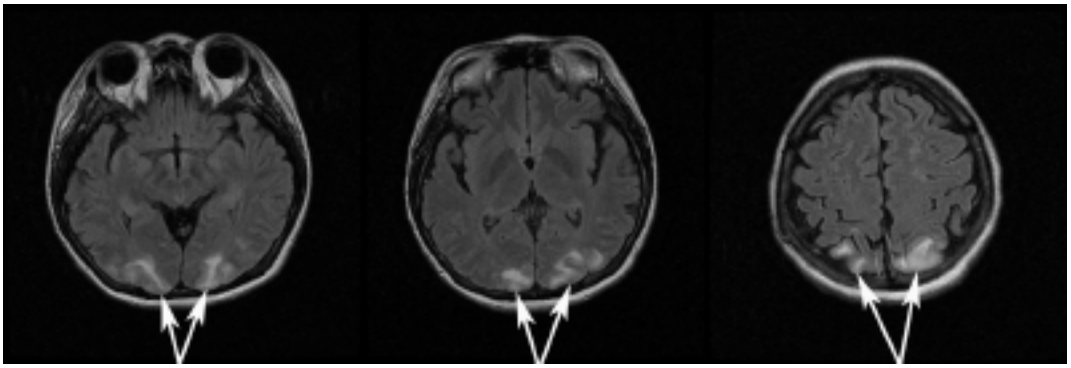

Figure 1A. Brain MRI scans of Patient 1 show increased T2 fluid-attenuated inversion recovery (FLAIR) predominantly in the white matter of the occipital lobe (arrows).

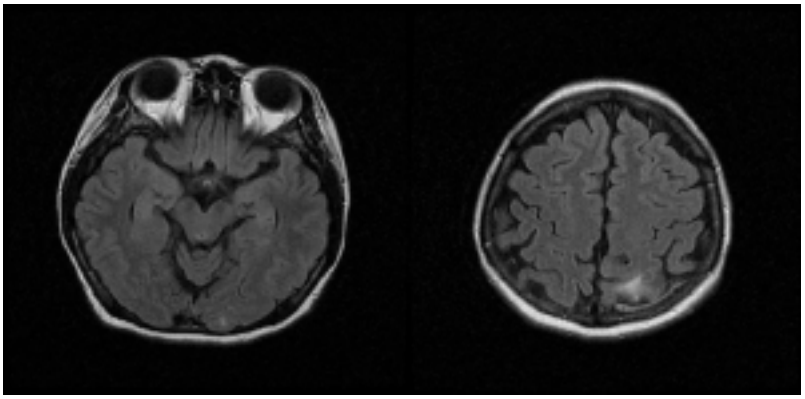

Figure 1B. Brain MRI scan of Patient 1 three weeks after cessation of cyclosporine. T2 FLAIR imaging shows near-complete resolution of high signal intensities compared with Figure 1A.

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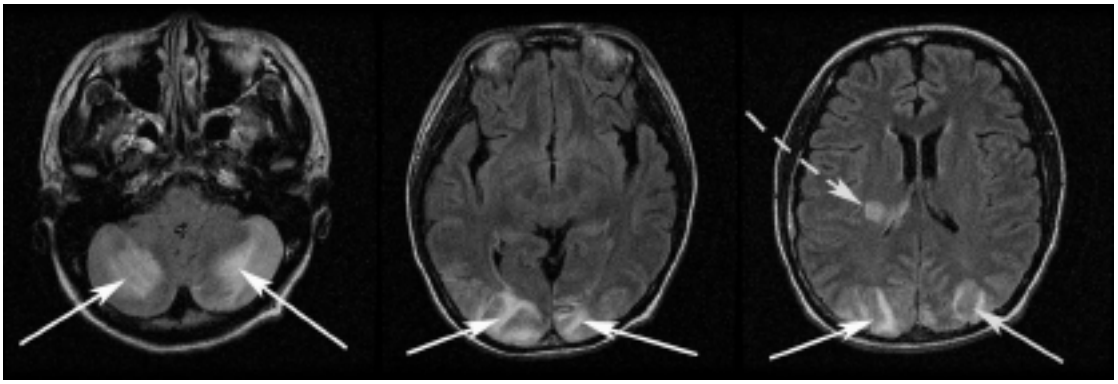

Figure 2A. Brain MRI scans of Patient 2 show increased T2 FLAIR intensity in the cerebellar hemispheres and occipital lobes bilaterally (arrows). In addition there is a hyperintense lesion in the right posterior limb of the internal capsule (broken arrow).

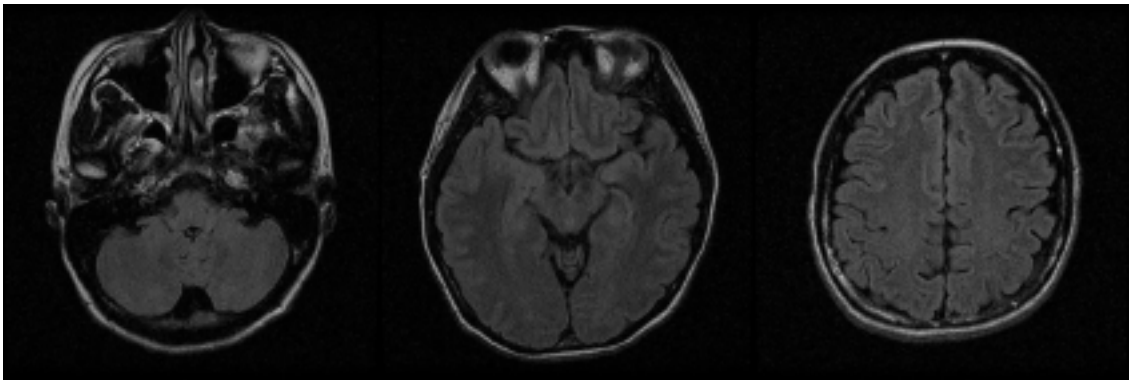

Figure 2B. Brain MRI scans of Patient 2 four weeks after treatment with intravenous cyclophosphamide. T2 FLAIR imaging shows complete resolution of all high signal intensities compared with Figure 2A.

platelets 71×10^9/l, white blood cell count 2.4×10^9/l, creatinine 154 μmol/l, C3 of 0.57 g/l and C4 of 0.10 g/l. Cranial T2-weighted MRI revealed left frontal, parietal, bilateral occipital, and right cerebellar hyperintensities (Figure 3A). The findings on cranial MR angiography and venography were normal. She was also subsequently found to have new-onset WHO Class IV lupus nephritis on renal biopsy and pulmonary hemorrhage.

She was treated with anticonvulsants, plasmapheresis, intravenous cyclophosphamide, and intravenous pulse methylprednisolone. Repeat MRI 4 weeks later showed complete resolution of the edema in all regions previously involved (Figure 3B). Renal function stabilized and pulmonary hemorrhage abated in the ensuing weeks.

RESULTS

Nine cases of SLE with posterior reversible encephalopathy were found in the literature, in addition to the 3 cases described here. Table 1 summarizes the main clinical and epidemiologic data.

All patients were female and less than 40 years of age, with mean age 28 years (range 20–39 yrs). The mean duration of SLE disease activity, available for 10 of the patients, was 5.5 years (range 1–10 yrs). All patients developed a reversible syndrome consisting of headache, seizures, or visual changes. Seizures, headache, and visual changes, manifesting as blurring, hemianopsia, or cortical blindness, were present in 11/12 patients (92%). Also, 11 patients (92%) had a history of new or previously diagnosed lupus nephritis. One patient (8%) had immune thrombocytopenia purpura (ITP) and SLE with iatrogenic PRES 7 days after commencement of cyclosporine[2]. Severe hypertension (blood pressure > 170/110 mm Hg) was a presenting feature in 10 of the cases (83%), except one SLE patient with ITP and Case 2 described here. The latter is the first description of PRES in a normotensive lupus patient in the absence of a therapeutic induced cause (e.g., calcineurin inhibitors). In addition, one patient had reversible encephalopathy in association with an overlap syndrome of lupus and systemic sclerosis[3]. The encephalopathy features recurred in a patient with poorly controlled renal disease[4].

Three had PRES attributed to an immunosuppressive agent (cyclosporine = 2; rituximab = 1). Mavragani, *et al*[5] reported recurrent headache, seizures, and visual changes in an SLE patient hours after receiving rituximab infusions[5]. On 3 occasions, 6–8 hours after rituximab infusion, a constellation of symptoms suggestive of PRES developed, which resolved over days after infusion. MRI findings consistent with PRES were present, but had resolved at 45 days.

The most common location of white matter changes was involvement of the occipital lobes in all cases. Other involved areas included the parieto-temporal lobes in 9/12 patients

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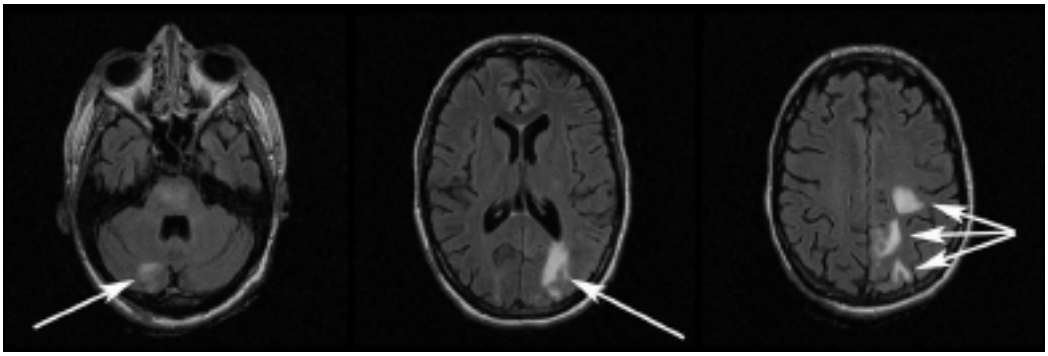

Figure 3A. Brain MRI scans of Patient 3 show increased T2 FLAIR intensity in left parietal, occipital, and right cerebellar regions (arrows).

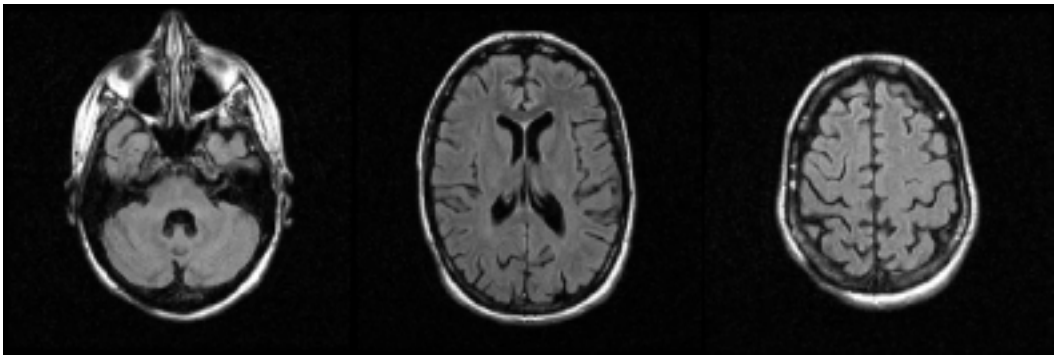

Figure 3B. Brain MRI scans of Patient 3 four weeks after treatment with intravenous cyclophosphamide and plasmapheresis. T2 FLAIR imaging shows complete resolution of all high signal intensities compared with Figure 3A.

(75%) and the cerebellum in 5/12 (42%). In this series of lupus patients, all clinical changes were reversible. Where repeat imaging was available, 8/10 (80%) had complete resolution of cranial imaging findings and 2/10 (20%) had near complete resolution.

DISCUSSION

Posterior reversible encephalopathy syndrome (PRES) was first described by Hinchey, *et al*[1] in a retrospective series of 15 patients. There has been one other case series in rheumatologic patients that describes 3 patients with SLE and PRES[6], and 4 other case reports in the SLE population[2-5]. The constellation of presenting symptoms includes headache, altered mental function, seizures (usually generalized), and visual alterations (ranging from blurred vision and hemianopia to cortical blindness). In addition to the clinical presentation, diagnosis is supported by hyperintensity in T2-weighted MR images of parieto-occipital white matter. DWI scans, which reveal the net movement of water molecules, show increased diffusion in PRES, consistent with vasogenic edema.

In general, the causes of PRES are diverse, but it is most common in patients with acute hypertension, acute renal failure, or those taking immunomodulatory drugs. In the setting of SLE, PRES can be a manifestation of lupus disease activity or a consequence of immunomodulatory therapy, making the diagnosis and treatment challenging. In this series, cyclosporine and rituximab were implicated; however, other immunomodulatory agents such as tacrolimus and intravenous immunoglobulin have been reported to cause PRES in subjects without SLE. Since cyclosporine neurotoxicity was first described in 1984 in a bone marrow transplant patient[7], there have been many cases of cyclosporine-induced PRES. Most of these patients were hypertensive and had an onset of symptoms averaging 14 days after starting cyclosporine[8].

Most studies have postulated that PRES is a manifestation of hypertensive encephalopathy resulting in vasogenic edema. Dysregulation of brain perfusion by sympathetic innervation has been implicated as a proposed etiology[1,9]. In fact, Byrom[10] has shown in rat models that sudden hypertension can reproduce PRES changes that resolve hours after resolution of hypertension. The predominantly posterior distribution of white matter changes has been attributed to differences in cerebral autoregulation. The antero-posterior gradient of sympathetic cerebral arterial innervation makes the posterior circulation more susceptible to variations in blood pressure[11]. Indeed, severe hypertension was a significant feature in 83% of the lupus cases (Table 1). However, our Patient 2 represents one of the few normotensive cases of PRES and indeed the only example to our knowledge of PRES as a manifestation of SLE disease activity. It was suspected that factors relating to lupus disease activity, such as the new-onset nephritis and an absolute increase in blood pressure, may have contributed to

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Table 1. Clinical characteristics and neuroimaging results of 12 SLE patients with PRES.

PATIENT NO.	AGE (YR)/ SEX	DIAGNOSIS	CLINICAL FINDINGS	HIGHEST BLOOD PRESSURE (mmHg)	LESIONS ON CT OR MRI	HIGHEST SERUM CREATININE (μmol/L)	TREATMENT
1 Kur	29/F	SLE, hypertension, membranous / proliferative glomerulonephritis	Headache, cortical blindness, seizures	206/135	MRI: T2 weighted bilateral occipital hyperintensities	136	Cyclosporine discontinuation, IV midazolam, IV phenytoin and antihypertensives
2 Kur	23/F	SLE, pancreatitis, serositis, Class IV nephritis	Headache, blurred vision, seizures, confusion	140/90	MRI: T2 weighted bilateral occipital, bilateral cerebellar and right corticospinal tract hyperintensities	119	Phenytoin, IV cyclophosphamide and IV methylprednisolone
3 Kur	23/F	SLE, hypertension, Class IV nephritis, pancytopenia, pulmonary hemorrhage	Headache, blurred vision, seizures, confusion, nausea	194/126	MRI: T2 weighted left frontal, left parietal, bilateral occipital and right cerebellar hyperintensities	227	Antihypertensives, anticonvulsants, IV cyclophosphomide, IV methylprednisolone and plasmapharesis
4 Primavera[6]	22/F	SLE, hypertension, membranous nephritis with diffuse proliferative lesions	Headache, blurred vision, seizures, confusion, left hemiparesis	200/130	MRI: T2 weighted frontal, occipital, parietotemporal, and cerebellar hyperintensities	390	Antihypertensives, clonazepam, IV cyclophosphamide and IV methylprednisolone
5 Primavera[6]	22/F	SLE, hypertension, lupus nephritis (not biopsy proven)	Headache, blurred vision, seizures, confusion, vomiting	170/110	MRI: T2 weighted occipital and parietotemporal hyperintensities	340-840	Antihypertensives, anticonvulsant, hemodialysis, IV cyclophosphamide and IV methylprednisolone
6 Primavera[6]	30/F	SLE, hypertension, lupus nephritis	Headache, blurred vision, seizures, confusion	210/125	CT: occipital and temporal hypodensities	550	Diazepam, sodium nitroprusside and hemodialysis
7 Hinchey[1]	30/F	SLE, hypertension, lupus nephritis	Headache, cortical blindness, lethargy, vomiting	210/110	Left frontal, right thalamic, right posterior temporal, bilateral parietal and bilateral occipital involvement	291	Antihypertensives
8 Hinchey[1]	39/F	SLE, hypertension, lupus nephritis	Headache, right hemianopia, seizures, confusion, vomiting	200/130	Left frontal, left temporal, bilateral parietal, left pons and left occipital involvement	274	Antihypertensives
9 Mavragani[5]	38/F	SLE, Class IV nephritis, antiphospholipid syndrome	Headache, blurred vision, seizures	210/120	MRI: T2 weighted bilateral occipital, parietal and temporal lobe hyperintensities	Not reported	Rituximab discontinuation, antihypertensives, anticonvulsant, plasmapharesis, IV cyclophosphamide and IV methylprednisolone
10 Thaipisuttikul[4]	20/F	SLE, lupus nephritis	Headache, blurred vision, seizures	200/100	MRI: T2 weighted bilateral occipital, parietal, temporal and cerebellar hyperintensities	195	Antihypertensives, phenytoin, high dose oral prednisolone, IV methylprednisolone and azathioprine
11 Yong[3]	39/F	SLE / Systemic sclerosis overlap, Class IV nephritis	Cortical blindness, seizures	170/100	MRI: T2 weighted bilateral occipital and cerebellar hyperintensities	Not reported	Antihypertensives and mycophenolate mofetil
12 Shin[2]	24/F	SLE, immune thrombocytopenia	Headache, seizures	130/80	MRI: T2 weighted bilateral frontal, parietal and occipital hyperintensities	Not reported	Cyclosporine discontinuation, diphenylhydantoin, high dose prednisolone and vincristine

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the development of PRES in Patient 2. The pathogenesis of PRES in the lupus population is probably due to multiple factors including lupus disease activity, hypertension, nephritis, and/or medications.

Management of PRES in SLE is dependent on etiology, which because of multiple possible offending agents may not always be clear. In drug-induced PRES, prompt cessation of the offending agent and management of seizures and severe hypertension are the mainstay of therapy. When PRES is a manifestation of lupus disease activity, with or without active lupus nephritis, intravenous methylprednisolone and cyclophosphamide are the most frequently used interventions. While required initially to control seizures, longterm anticonvulsant therapy was not required in the 3 described cases once imaging findings had resolved.

PRES is not always reversible, as shown by Stott, *et al*[12]. Permanent deficits have included residual visual loss and cognitive impairment[12]. Severe cases of PRES can result in cerebral infarction, making prompt recognition of this syndrome particularly important. However, all patients with lupus described here had reversible neurologic changes.

PRES may be a feature of disease activity with nephritis and hypertension or a result of immunosuppressive therapy in patients with lupus. With increasing availability of MRI, PRES will be identified more frequently in patients with connective tissue diseases. Swift action to identify potential offending agents, control hypertension, and treat active disease can lead to reversal of radiologic and neurologic findings in patients with lupus.

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