Posterior Reversible Encephalopathy Syndrome in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To study the clinical profile of posterior reversible encephalopathy syndrome (PRES) in patients with systemic lupus erythematosus (SLE) and analyze the risk factors and outcomes associated with it.

Methods. We identified patients with SLE and PRES from January 2006 to October 2010. Data were collected on demographic details, lupus characteristics, PRES-related features, laboratory abnormalities, treatment details, and outcomes.

Results. We studied 13 patients (all female) ages 14–37 years (median 23 yrs; 4 were aged < 18 yrs with juvenile SLE). Duration of lupus ranged from 1.5 to 36 months (median 6 mo). Six patients had PRES as a part of their initial presentation of lupus. All had active lupus and hypertension; 9 had nephritis. Four patients were on treatment with cyclophosphamide therapy when they developed PRES. Antihypertensives and antiepileptics were the mainstay of treatment along with supportive care. Immunosuppressive therapy was guided by lupus-related major organ manifestations. Two patients had focal neurological deficits; one had persistent hemiparesis at followup. One patient died.

Conclusion. PRES occurs in young lupus patients and in the early part of the disease. Focal deficits are not uncommon. It can be the presenting manifestation of lupus. Management is predominantly symptomatic. Immunosuppression is directed by other major organ manifestations. Early diagnosis and appropriate management is productive. (First Release May 15 2011; J Rheumatol 2011;38:1607–11; doi:10.3899/jrheum.101308)

Key Indexing Terms:
LUPUS LUPUS NEPHRITIS
NEUROPSYCHIATRIC LUPUS POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition identifiable by characteristic clinical manifestations and magnetic resonance imaging (MRI) features[1]. Reversible MRI hyperintensities compatible with PRES were reported as early as 1985 by Aisen, *et al* in lupus patients with neuropsychiatric manifestations[2]. Later, Sibbitt, *et al* described punctate or focal high-intensity lesions suggestive of edema that resolved with corticosteroid treatment[3]. The specific reversible quantitative MR relaxation properties of this syndrome and association with cerebral edema were described in 1995[4]. It was first denoted "PRES" in 1996 in a case series[1]. The term PRES is probably incorrect descriptively, as this entity frequently affects nonposterior portions of the brain as well. PRES is known to occur in a context of hypertension, eclampsia, renal failure, and immunosuppression. Patients typically present with headache, seizures, loss of vision, focal weakness, and altered mental function. Cases have been reported in patients with autoimmune diseases, particularly in systemic lupus erythematosus (SLE). It can present as a neurological emergency and without prompt treatment, may lead to permanent brain injury and sequelae. Awareness of this entity is vital as early recognition allows for early intervention and improved outcomes. We undertook this study to characterize the clinical features, risk factors, and outcomes of PRES in patients with lupus.

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Accepted for publication February 8, 2011.

MATERIALS AND METHODS

Patients who were diagnosed as having SLE (fulfilling the 1997 American College of Rheumatology criteria[5]) and PRES between January 2006 and October 2010 were identified in the Department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, India. The demographic and clinical profiling included age, sex, duration of lupus, present and past lupus-related manifestations, present clinical features, drugs used, laboratory data, and MRI details. Presence of renal failure, hypertension, and cytotoxic therapy was analyzed. Management and outcomes of these patients were recorded. PRES was diagnosed based upon the characteristic clinical and MRI features.

RESULTS

During the study period, 13 patients with SLE with PRES were diagnosed. All were women with ages ranging from 14 to 37 years (median 23 yrs). Four patients had juvenile lupus (age < 16 yrs).

Clinical features. The duration of SLE ranged from 1.5 to 36

months (median 6 mo). Six patients presented with symptoms attributable to PRES, while 7 developed PRES during the course of their hospital stay. These 7 patients were each admitted with mesenteric vasculitis, inferior vena cava thrombosis, nephritis, myositis, cutaneous flare, severe hypoalbuminemia, and pulmonary tuberculosis.

Eleven patients had seizures; 10 had headache; 7 had loss of consciousness and vomiting; 3 had transient vision loss; and one each had paraparesis and left hemiplegia. Hypertension[6] was seen in all 13 patients; 4 had stage 1 hypertension (systolic blood pressure 140–159 mm Hg or diastolic blood pressure 90–99 mm Hg according to US Joint National Committee classification 7[6]). Maximum blood pressure recorded was 220/120 mm Hg. PRES-related characteristics of patients are summarized in Table 1; other lupus-related disease characteristics have been summarized in Table 2. Eight patients were receiving corticosteroids and 4 (Cases 2, 5, 6, and 13) were taking monthly cyclophosphamide (CYC) therapy when they developed PRES.

Laboratory measures. Cerebrospinal fluid (CSF) analysis was done in 10 patients, of whom 3 provided abnormal results suggestive of aseptic meningitis. All patients had MRI findings consistent with PRES (Figure 1). The serological abnormalities are summarized in Table 3.

Treatment. Twelve patients were treated with antihypertensive drugs; 5 required more than 2 antihypertensive agents. Eight patients received antiepileptic drugs. All patients were treated with high-dose corticosteroids, of which 8 required pulse methylprednisolone (1000 mg); others received 1 mg/kg oral prednisolone. Eight patients received monthly CYC infusions. Two of 3 patients who were receiving CYC at the time of developing PRES continued with CYC. One patient (Case 4) was switched to mycophenolate mofetil in view of persistent disease activity. Treatment details are shown in Table 4.

Table 1. Clinical manifestations of PRES: all patients were female.

Case	Age, yrs	Duration of SLE, mo	Onset of PRES*	Maximum Blood Pressure, mm Hg	Seizure	Headache	Vomiting	LOC	Visual Abnormality	Recovery Time, days
1	14	3	Day 6	140/90	+	+	+	+	+	7
2	16	6	Day 1	140/100	+	+	+	+	+	4
3	16	1.5	Day 9	130/90	+	–	+	–	–	4
4	16	12	Day 14	190/130	+	+	+	–	–	2
5	19	9	Day 1	160/110	+	+	+	+	–	2
6	20	2	Day 6	150/100	–	–	–	–	–	3
7	23	36	Day 1	220/110	+	+	+	+	–	7
8	23	24	Day 6	160/80	+	+	–	–	–	2
9	25	3	Day 1	130/90	+	+	–	–	–	10
10	26	5	Day 7	140/80	+	–	–	+	–	–
11	35	4	Day 1	220/110	+	+	+	+	–	4
12	36	22	Day 6	160/100	–	+	–	–	–	2
13	37	36	Day 6	220/120	+	+	–	+	+	3

* At presentation. LOC: loss of consciousness.

Table 2. Treatment details, organ manifestations, and associated conditions of the patients with PRES.

Case	CYC	Corticosteroids, dose/day	Other Disease Manifestations
1	–	—	Nephritis, APS with IVC thrombosis, anemia
2	–	—	Nephritis, cutaneous, anemia, psychosis
3	–	PDN 60 mg	MNM, chorea, mesenteric vasculitis, anemia
4	+ (pulse 2)	PDN 30 mg	Nephritis, renal failure, steroid myopathy, anemia
5	–	—	Nephritis, anemia, thrombocytopenia
6	+	PDN 7.5 mg	Nephritis, anemia
7	–	PDN 60 mg	Nephritis, neuropsychiatric manifestation, PAH
8	–	—	myositis, leukopenia, lupus headache
9	–	—	Nephritis, aseptic meningitis, anemia
10	–	PDN 1 mg/kg	Nephritis, neuropsychiatric manifestations, myositis, serositis, pancytopenia
11	+ (pulse 3)	PDN 25 mg	Nephritis, cutaneous vasculitis
12	+	PDN 60 mg	Anemia, sclerodactyly
13	–	PDN 7.5 mg	Neuropsychiatric manifestations: seizures, hemiparesis

CYC: cyclophosphamide; PDN: prednisolone; MNM: mononeuritis multiplex; APS: antiphospholipid syndrome; IVC: inferior vena cava; PAH: pulmonary arterial hypertension.

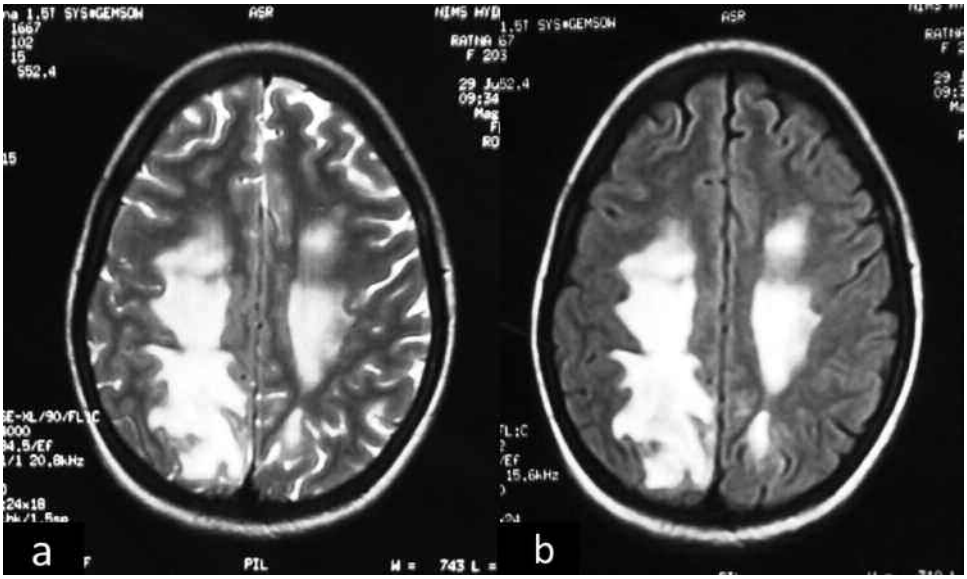

Figure 1. A representative brain MRI showing T2 (a) and FLAIR (b) hyperintensities in frontal, parietal, and occipital white matter.

Table 3. Laboratory abnormalities in patients with PRES.

Case	Serum Creatinine, mg/dl	Anti-dsDNA, > 30 U/l	aCL	C3	C4	CSF
1	1.1	154	+	N	N	N
2	1.1	95	ND	Low	Low	ND
3	1.0	86	+	N	N	ND
4	1.9	26	–	High	N	N
5	1.8	365	–	ND	ND	Abnormal
6	1.1	395	+	N	Low	N
7	2.1	90	ND	ND	ND	ND
8	0.7	16	–	N	N	N
9	1.4	143	–	ND	ND	Abnormal
10	1.0	211	ND	ND	ND	N
11	0.7	34	–	N	Low	N
12	0.7	86	ND	ND	ND	Abnormal
13	0.7	45	–	N	N	N

aCL: anticardiolipin antibodies; CSF: cerebrospinal fluid analysis; ND: not done; N: normal.

Outcomes. Twelve patients improved and were discharged; one patient died. The duration of hospital stay ranged from 5 to 26 days (median 14 days). Time for recovery from PRES was 2 to 10 days (median 3.5 days). Cause of death in the lone patient was pancytopenia, severe hypoalbuminemia, and disseminated candidiasis. Of the 2 patients who had neurological deficit (Table 1), the patient with paraparesis recovered completely at discharge. The patient with hemiparesis had residual weakness 4 months after the incident. Repeat MRI was done in 2 patients. There were reversals of T2 hyperintensities in both patients. Eight continued regular followup. Case 4 developed chronic kidney disease.

Risk factors. All the patients were young, with a median age of 23 years, and 4 were juveniles. Occurrence of PRES was seen in the early part of the lupus course — 9 of 13 patients had disease duration less than 1 year (median 6 mo). All had active lupus (Table 2) and nephritis was seen in 10 patients, with creatinine > 1.5 mg/dl in 3 patients. Hypertension was noted in all patients; 9 had stage 2 and 4 had stage 1 hypertension at the onset of PRES. It was observed that 4 out of 7 patients had a sudden elevation in blood pressure before occurrence of PRES. Four patients were receiving CYC therapy. In the 2 patients (Cases 7 and 8) who developed PRES a day after receiving CYC infusion, the possibility that PRES was related to CYC infusion cannot be ruled out.

DISCUSSION

Our study shows that PRES can be the presenting manifesta-

Table 4. Treatment given to SLE patients with PRES.

Case	CYC	Indications for CYC	Antihypertensives	Antiepileptics	Steroids
1	+	Nephritis	Prazosin, enalapril	None	+
2	+	Nephritis	Prazosin	Carbamazepine	+
3	+	Mesenteric vasculitis	Amlodipine	None	+
4	MMF	Nephritis	Prazosin, amlodipine, furosemide	Phenobarbitone	+
5	+	Nephritis	Nifedipine, prazosin, metoprolol	Phenytoin	+
6	+	Nephritis	Amlodipine, losartan, hydrochlorthiazide	None	+
7	+	NPSLE, nephritis	Furosemide, amlodipine	Clobazam	+
8	+	Overall severe disease	Amlodipine	Levetiracetam	+
9	–	—	None	Oxcarbazine, clobazam	+
10	+	Nephritis	Amlodipine	Phenytoin	+
11	+	Nephritis	Losartan, enalapril, amlodipine	Phenytoin	+
12	+	Nephritis	Enalapril	None	+
13	+	NPSLE, nephritis	Enalapril, losartan, amlodipine, metoprolol	None	+

CYC: cyclophosphamide; MMF: mycophenolate mofetil; NPSLE: neuropsychiatric lupus manifestations.

tion of SLE. Patients tend to present in the early stage of the disease. A quarter of our patients had juvenile lupus. Headache and seizures were the most common manifestations. Most patients had active lupus, with nephritis being the most common accompaniment. Hypertension is most often mild, and this is unlike the classical description in the setting of accelerated hypertension. Cerebrospinal fluid analyzed in a few patients showed aseptic meningitis.

Although PRES is increasingly being recognized now, due to its rarity, its incidence, etiopathogenesis, and management are not well studied. The proposed pathogenetic mechanisms are disordered cerebral autoregulation and endothelial dysfunction[1,7]. Because of the heterogeneity of the associations of this disorder, the exact pathogenesis in lupus is undetermined, as different mechanisms may etiologically be important in different clinical situations. This is probably the reason for occurrence of PRES in the setting of normal or mild elevation of blood pressures, where endothelial dysfunction may be due to cytotoxic therapy or vasculitis[8,9,10].

PRES may occur any time in the course of lupus; in a previous series[11] PRES was reported in established cases of SLE with mean disease duration of 61.8 ± 53.6 months, but in our series it occurred considerably early (12.2 ± 13.2 months) in the disease course of lupus. SLE is known to be aggressive during the early periods of illness[12].

Seizures and headache were the most common presenting features, and our study is comparable to previous observations in this regard[13,14]. In view of the diffuse expression of lesions and cortical involvement, the occurrence of seizure and the diffuse edema causing headache is well explained. NMDA NR2A or NR2B autoantibodies, some of which cross-react with double-stranded DNA, have been implicated in the occurrence of epilepsy in SLE[15]. PRES is associated with diffuse slowing on electroencephalography, consistent with diffuse encephalopathy[16]. Headache and seizures are the most common neuropsychiatric manifestations, which have a variety of etiologies, and PRES should always be a differential diagnosis in acute headache in appropriate clinical settings[17].

Renal failure and severe hypertension are known risk factors for the development of PRES[1]. However, in our series we found that severe hypertension is not an invariable association, indicating that it may not be an extended spectrum of hypertensive encephalopathy that may be seen in SLE with renal involvement. It is interesting that case reports of PRES in normotensive patients with SLE were ascribed to high doses of corticosteroids[1,8,10] or to cytotoxic therapy with CYC[18]. But in our series PRES was also seen in patients who were treatment-naive. Occurrence of PRES in normotensives and treatment-naive patients may explain the endothelial dysfunction due to disease activity playing an important pathogenetic role[19].

Renal failure with fluid overload state is a well known cause for PRES[1]. In the literature review by Leroux, *et al*[14], 91% of patients had renal involvement, with renal insufficiency in 84% of cases. That only one patient had renal failure in our series emphasizes that disease activity rather than fluid overload could be responsible for the occurrence of PRES.

Seven patients were receiving corticosteroids and 4 CYC when they developed PRES. The use of immunosuppressives is considered one of the risk factors; cyclosporine is one of the commonest immunosuppressants associated with PRES and is well studied[1,9]. The mechanism is thought to be mediated through mitochondrial dysfunction[20]. Corticosteroids are implicated in the occurrence of PRES by predisposing to hypertension and fluid overload[21]. The manner in which CYC predisposes to PRES is not clearly known. It can cause water toxicity in the first 2 days after infusion due to unknown action on renal function not explainable by antidiuretic hormone; a similar role may be implicated in PRES in our patients who developed it a day after infusion[22].

Three of 8 patients tested positive for anticardiolipin antibodies, in comparison to 12 of 17 cases in a previous

review[14]. One girl had antiphospholipid syndrome with inferior vena cava thrombosis. The relationship between PRES and the presence of antiphospholipid antibody is difficult to assess.

MRI predominantly show transient, white matter hyperintensities on T2-weighted images in PRES[1]. Diffusion-weighted images reveal an increased diffusion coefficient indicating vasogenic edema. The advent of MRI has increased the awareness of PRES. All patients with seizures usually do not undergo MRI and the decision to pursue MRI often is based on its availability and on knowledge about the disease. As knowledge about PRES becomes more widespread there might be increased recognition and reporting of it.

The mainstay of treatment is supportive care including appropriate control of hypertension and antiepileptics to control seizure. Patients were treated with corticosteroids and immunosuppression with CPA and mycophenolate mofetil as required for controlling disease activity (Table 4). Although the general recommendation is to withdraw the offending drug, after control of the acute episode was achieved, patients had no recurrences with use of CYC on followup. This reiterates that multiple etiologies may be responsible for occurrence of PRES in SLE patients already undergoing treatment with cytotoxic therapy.

Although PRES is considered benign and complete recovery can be expected, residual deficits are not uncommon, as noted in our patient in the form of hemiparesis, and as described in previous reports[11]. No patient had active infection at presentation.

We understand the limitations of our study, the most important being its retrospective design and small number of cases. Also, followup MRI was not available in the majority of cases, although clinical recovery was documented.

PRES occurs in young patients with lupus and in the early stage of the disease. Focal deficits are not uncommon. It can be the presenting manifestation of lupus. Management is predominantly symptomatic. Intensity of immunosuppression is directed by other major manifestations. Early diagnosis and management is productive. As it is always associated with active SLE, without any evidence of infections or severe hypertension, this might well be considered one of the neurological manifestations of SLE[23].

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