Case Report

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Posterior reversible encephalopathy syndrome in systemic lupus erythematosus

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Introduction

Neurologic or psychiatric abnormalities can occur frequently in patients with systemic lupus erythematosus (SLE). The American College of Rheumatology have already described a wide variety of neuropsychiatric syndromes associated with SLE [1]. Posterior reversible encephalopathy syndrome (PRES), which can be associated with various underlying diseases including SLE, is probably an under-diagnosed syndrome in nephrology departments. We present three cases of PRES in SLE patients (table 1), then summarize and discuss all reported cases.

Cases

Case 1

A 47-year-old Asian woman, with a 13-year history of SLE that included stage III proliferative glomerulonephritis 5 years previously, presented with diffuse oedema, proteinuria and haematuria. She was treated with prednisone and furosemide. Laboratory investigation revealed haemoglobin 67 g/l, serum creatinine 77 µmol/l, haaptoglobin 0.14 g/l, serum albumin 19.4 g/l, C3 279 mg/l, C4 60 mg/l, CH50 40%, indirect immunofluorescence against anti-nuclear antibodies 1/800 and anti-DNA antibodies 92% (Farr test, N < 20%). Anticardiolipin antibodies and anti-beta2GP1 antibodies were negative. No schizocytes were present. Twenty-four hours after having received two packed red blood cells transfusion, she developed high blood pressure (BP: 199/90 mmHg), diffuse headache, photophobia and vomiting. Neurologic examination revealed no other abnormalities. Funduscopy was normal. Cranial T2 fluid attenuated inversion recovery (FLAIR)-weighted MRI revealed bilateral parietal and occipital white matter hyperintensities, which were more pronounced on the left side. Diffusion-weighted imaging (DWI) scans showed increased apparent diffusion coefficient (ADC), suggestive of vasogenic oedema. Cerebrospinal fluid examination was normal (protein concentration: 0.34 g/l, glucose concentration: 2.8 mmol/l, no elements, negative gram stain and bacteriological cultures). She was treated with nicardipine and urapidil with normalization of the BP and resolution of all symptoms within a few days. Renal biopsy disclosed a WHO Class IV lupus nephritis (LN), and she received intravenous pulses of methylprednisolone and cyclophosphamide. Repeat MRI 12 days later revealed complete resolution of the parietal and occipital oedema.

Case 2

A 17-year-old woman was admitted to hospital with high blood pressure, headaches and vomiting. She had been diagnosed with SLE 4 years earlier when she developed a nephrotic syndrome, related to a Class IV–V LN. She had presented SLE pericarditis, cutaneous vasculitis and high grade fever resistant to high-dose corticosteroids, and had received rituximab (last infusion 5 months before hospitalization) and subsequently intravenous cyclophosphamide (last infusion 10 days before hospitalization). Renal biopsy 2 months before hospitalization showed persistent Class IV LN. On admission, blood pressure was 172/110 mmHg and neurologic examination was normal. Tonic–clonic seizure occurred a few hours after hospitalization and was spontaneously resolved. Serum creatinine was 112 µmol/l, haemoglobin 9.3 g/dl and platelets 283 G/l. Cranial T2-weighted MRI showed several cerebellar, occipital and parietal lobe cortical hyperintensities. Brainstem was also involved. DWI scans showed an increased ADC in these regions (Figure 1). Cerebrospinal fluid examination revealed no abnormality (protein concentration: 0.66 g/l, normal glucose concentration, no elements, negative gram stain and bacteriological cultures). Electroencephalography demonstrated diffuse slow waves and no paroxystic activity. She was hospitalized in the intensive care unit because of...
Fig. 1. Brain MR scan of patient 2: FLAIR images showing brainstem, cerebellum and bilateral occipital lobes involvement (A, C); complete resolution 11 days later (B, D). Initial DWI scan (E) and ADC measures (F): DWI shows hyperintense signal (1) whereas ADC values were slightly increased in the involved regions (3) compared to normal area (4).
persistent altered consciousness, which required intubation and mechanical ventilation during 3 days. Pericarditis was evacuated. Treatment with nicardipine, urapidil, amlodipine and furosemide was started. Sodium valproate was prescribed orally (1 g a day) for 15 days. Blood pressure and consciousness normalized within a few days. Repeat MRI 11 days later showed complete resolution of the abnormalities (Figure 1).

Case 3

A 28-year-old woman, with a 1-year history of WHO Class IV lupus glomerulonephritis treated with prednisone and cyclophosphamide, rituximab (last infusion 4 months before admission) then with mycophenolate mofetil (stopped 1 month before hospitalization), was admitted to hospital with headache, vomiting and blindness. Chronic dialysis therapy had been started 1 month earlier. On admission she was hypertensive (190/120 mmHg), with a severe headache. Neurologic examination revealed bilateral myosis and cortical blindness. Laboratory investigations revealed haemoglobin 9.6 g/dl, haptoglobin 1.40 g/l, platelets 157 G/l, indirect immunofluorescence against anti-nuclear antibodies 1/100, anti-DNA antibodies 96% (Farr test, N < 20%), C3 326 mg/l, C4 66 mg/l and CH50 10%. Cranial T2-weighted MRI showed bilateral occipital cortical and subcortical hyperintensities. DWI scans showed no abnormality. Shortly after admission she presented tonic–clonic seizures, which resolved under intravenous clonazepam (2 mg). A few hours later, the seizures recurred. Treatment with intravenous sodium valproate (4 g a day then 1 g a day per os) and oral clobazam (30 mg a day) controlled the seizures, and nicardipine, urapidil, ramipril and acebutolol allowed blood pressure and neurologic normalization within few days. Complete resolution of the hyperintense lesions was noted on repeat MRI, performed 12 days after the first symptoms.

**Literature review**

We performed a Medline search of the English language literature published between 1966 and April 2007, using the following keywords: SLE and PRES, reversible posterior cerebral oedema, leukoencephalopathy or occipital parietal encephalopathy (Table 2) [2–18].

All cases but one were women, and all but one were less than 40 years old, which is consistent with lupus flares epidemiology. SLE had been diagnosed from 2 months to 13 years before the occurrence of PRES. Patients had usually received recent treatment with corticosteroids and cyclophosphamide. In two cases [2,8], patients were under cyclosporine A, and symptoms resolved after discontinuation of this treatment. One patient developed PRES after receiving rituximab infusions on three successive occasions [5]. In two cases, no high blood pressure (HBP) was present [2,8] but one was treated with cyclosporine. Renal failure was present in most evaluable cases, as well as a history of LN. The most frequent symptoms were headache, seizures and visual changes (blurring, diplopia, hemianopsia or cortical blindness). On imaging, white matter changes occurred predominantly in occipital and parieto-temporal lobes. Frontal lobes, cerebellum, basal ganglia and brainstem were less frequently involved (Table 3).

**Discussion**

In 1996, Hinchey *et al.* reported a clinico-radiological picture they called reversible posterior leukoencephalopathy syndrome (RPLS) [4]. They described 15 patients with a reversible, predominantly posterior leukoencephalopathy. There has been a controversy about what should be the proper term for this syndrome. In 2000, Casey *et al.* proposed the term posterior reversible encephalopathy syndrome (PRES) for RPLS, to stress the common involvement of both the grey and the white matter [19]. Actually, it is probably a misnomer; PRES is not always reversible, and not necessarily confined to the posterior regions of the brain. Several other names have been proposed, such as reversible occipitoparietal encephalopathy, hyperperfusion encephalopathy, hypertensive encephalopathy, posterior leukoencephalopathy, reversible posterior cerebral oedema syndrome or potentially reversible encephalopathy.

**Table 1. Main characteristics of cases 1, 2 and 3**

<table>
<thead>
<tr>
<th>Case</th>
<th>Main treatments</th>
<th>Blood pressure</th>
<th>Creatinine (µM)</th>
<th>Main clinical findings</th>
<th>Main radiological findings</th>
<th>Renal biopsy</th>
<th>Main characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Transfusion</td>
<td>199/90</td>
<td>77</td>
<td>Headache, vomiting, photophobia</td>
<td>T2-weighted parietal and occipital hyperintensities</td>
<td>Class IV lupus nephritis</td>
<td>Prednisone, Cyclophosphamide, MMF stopped 1 month earlier</td>
</tr>
<tr>
<td>2</td>
<td>Prednisone</td>
<td>172/110</td>
<td>112</td>
<td>Headache, vomiting, seizures, altered consciousness</td>
<td>T2-weighted hyperintensities of cerebellar, parietal, occipital lobes and brainstem</td>
<td>Class IV lupus nephritis</td>
<td>Prednisone, Haemodialysis, Cerebral oedema, leukoencephalopathy, bilateral occipital hyperintensities</td>
</tr>
<tr>
<td>3</td>
<td>Prednisone</td>
<td>190/120</td>
<td>110</td>
<td>Headache, vomiting, seizures, cortical blindness</td>
<td>T2-weighted bilateral occipital hyperintensities</td>
<td>Class IV lupus nephritis</td>
<td>Haemodialysis, Headache, vomiting, seizures, cortical blindness</td>
</tr>
</tbody>
</table>

*Main treatments* Transfusion, prednisone, cyclophosphamide, MMF stopped 1 month earlier.

*Main clinical findings* Headache, vomiting, photophobia.

*Main radiological findings* T2-weighted parietal and occipital hyperintensities.

*Renal biopsy* Class IV lupus nephritis.
The pathophysiology of PRES involves cerebral oedema with diffusion of plasma proteins and cells into the extracellular space. However, the mechanisms of this process remain unclear. Two distinct theories have been proposed: the vasogenic theory and the cytotoxic theory.

The cytotoxic theory is that a sudden and severe increase in blood pressure causes cerebral vasoconstriction with cerebral ischaemia, hypoxic endothelial cell damage, vasospasm and cytotoxic oedema formation [20, 21]. The reversibility of the lesions with rapid treatment argues against this hypothesis. The vasogenic theory holds that HBP

### Table 2. Clinical characteristics and neuroimaging results of SLE patients with PRES

<table>
<thead>
<tr>
<th>Patient, reference</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>Clinical findings</th>
<th>Neuroimaging</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>47/f</td>
<td>Class IV LN, anaemia and transfusion, HBP</td>
<td>Headache, photophobia</td>
<td>MRI T2-weighted bilateral parietal and occipital white matter hyperintensities</td>
<td>Urapidil, nicardipine, IV methylprednisolone, IV cyclophosphamide</td>
</tr>
<tr>
<td>Patient 2</td>
<td>17/f</td>
<td>Class IV LN, HBP</td>
<td>Headache, seizures, altered consciousness</td>
<td>MRI T2-weighted cerebellar, occipital, parietal lobes and brainstem hyperintensities</td>
<td>Urapidil, nicardipine, furosemid, amiodipine, valproate</td>
</tr>
<tr>
<td>Patient 3</td>
<td>28/f</td>
<td>Class IV LN, haemorrhagic, HBP</td>
<td>MRI T2-weighted bilateral occipital cortical and subcortical hyperintensities</td>
<td>MRI T2-weighted bilateral occipital hyperintensities</td>
<td>Midazolam, phenytoin, anti-hypertensives, cyclosporine discontinuation, phenytoin, IV cyclophosphamide, IV methylprednisolone</td>
</tr>
<tr>
<td>Kur [2]</td>
<td>23/f</td>
<td>Pancreatitis, Class IV LN no HBP</td>
<td>Headache, blurred vision, seizures</td>
<td>T2-weighted bilateral occipital, cerebellar and right corticospinal tract hyperintensities</td>
<td>Anti-hypertensives, anti-convulsivants Plasmapheresis, IV cyclophosphamide, IV methylprednisolone</td>
</tr>
<tr>
<td>Primavera [3]</td>
<td>22/f</td>
<td>HBP, membranous nephritis with diffuse proliferative lesions</td>
<td>Headache, blurred vision, seizures, left hemiparesis, confusion</td>
<td>T2-weighted frontotemporal and cerebellar hyperintensities</td>
<td>Anti-hypertensives, anti-convulsivants, haemodialysis IV cyclophosphamide, IV methylprednisolone</td>
</tr>
<tr>
<td>Primavera [3]</td>
<td>30/f</td>
<td>HBP, LN (no biopsy)</td>
<td>Headache, blurred vision, seizures, confusion</td>
<td>T2-weighted occipital and parietotemporal hyperintensities</td>
<td>Anti-hypertensives</td>
</tr>
<tr>
<td>Hinchey [4]</td>
<td>30/f</td>
<td>HBP, LN</td>
<td>Headache, blurred vision, seizures, confusion</td>
<td>Occipital lobe (bilateral), posterior parietal lobe (bilateral), posterior temporal lobe (right), frontal lobe (left), thalamus (right) involvement</td>
<td>Anti-hypertensives</td>
</tr>
<tr>
<td>Hinchey [4]</td>
<td>39/f</td>
<td>HBP, LN</td>
<td>Headache, right hemianopia, seizures, confusion</td>
<td>Occipital lobe (left), posterior parietal lobe (bi-lateral), posterior temporal lobe (left), frontal lobe (left), pons (left) involvement</td>
<td>Anti-hypertensives</td>
</tr>
<tr>
<td>Mavragani [5]</td>
<td>38/f</td>
<td>Class IV LN, anti-phospholipid syndrome, HBP</td>
<td>Headache, blurred vision, seizures</td>
<td>T2-weighted bilateral occipital, parietal, and temporal lobes hyperintensities</td>
<td>Anti-hypertensives, anti-convulsivants, IV cyclophosphamide, IV methylprednisolone, plasmapheresis Rituximab discontinuation</td>
</tr>
<tr>
<td>Thaipsuttikul [6]</td>
<td>20/f</td>
<td>LN, HBP</td>
<td>Headache, blurred vision, seizures</td>
<td>T2-weighted bilateral occipital, parietal, and temporal cerebellar hyperintensities</td>
<td>Anti-hypertensives, phenytoin, oral prednisolone, IV methylprednisolone, azathioprine</td>
</tr>
<tr>
<td>Yong [7]</td>
<td>39/f</td>
<td>SLE/Systemic sclerosis overlap, Class IV LN, HBP</td>
<td>Blindness, seizures</td>
<td>T2-weighted bilateral occipital and cerebellar hyperintensities</td>
<td>Anti-hypertensives, mycophenolate mofetil</td>
</tr>
<tr>
<td>Shin [8]</td>
<td>24/f</td>
<td>Immune thrombocytopenia, no HBP</td>
<td>Headache, seizures</td>
<td>T2-weighted bilateral occipital, parietal and frontal hyperintensities</td>
<td>Diphenylhydantoin, prednisolone, vincristine, Cyclosporine discontinuation Phenytoin, nifedipine, Discontinuation of cyclosporine</td>
</tr>
<tr>
<td>Ozyurek [9]</td>
<td>13/f</td>
<td>HBP, LN</td>
<td>Headache, vomiting, seizures, HBP</td>
<td>MRI T2-weighted bilateral occipital and posterior parietal hyperintensities</td>
<td>Anti-hypertensives</td>
</tr>
</tbody>
</table>
results in impaired cerebral autoregulation, leading to cerebral vasodilatation, increased vascular permeability, disruption of the blood/brain barrier and vasogenic cerebral oedema.

However, HBP is not always noted in PRES [2,8]. A direct toxic effect produced by immunosuppressive or cytotoxic agents (especially cyclosporine or cyclophosphamide, as in two of our three patients), even when drug levels remain within the therapeutic range, may result in endothelial damage, reduced tissue perfusion and cytotoxic oedema, but also blood brain barrier disruption and vasogenic oedema. Interestingly, vasogenic oedema could become cytotoxic and lead to cerebral infarction [22].

Endothelial dysfunction may occur in SLE due to autoimmune or ischaemic (thrombosis, vasculitis) complication. Cytotoxic drugs used in SLE could also induce endothelial toxicity, which may trigger cytotoxic and vasogenic cerebral oedema. Fluid retention and HBP associated with SLE nephritis may also promote vasogenic cerebral oedema. Both theories (cytotoxic and vasogenic) could explain PRES susceptibility of SLE patients.

The parietal and occipital localization of this oedema seems to be the result of the differences in autonomic innervation between the anterior and posterior regions of the brain [1,4,7,10,23]. Autopsy studies have shown vascular alterations (fibrinoid necrosis or thrombosis of arterioles) and parenchymal lesions (microinfarcts, petechial haemorrhages, cerebral oedema) in the deep white matter and at the grey–white matter junction of posteriors areas. However, these findings may not be the representative of those present in surviving patients [24]. Further research is needed in order to improve our understanding of the pathophysiology of PRES.
Conditions commonly associated with PRES include hypertensive encephalopathy, pre- eclamptic toxemia and eclampsia, renal failure, transfusion, volume overload, use of immunosuppressive or cytotoxic drugs (cyclosporine, tacrolimus, rituximab, intravenous immunoglobulins, RAF kinase inhibitors), as well as SLE and other connective tissue diseases, or porphyria [4,25–29]. Solid organ transplantation, thrombotic thrombocytopenic purpura, hypercalcaemia or EPO use, which are commonly encountered in patients admitted in nephrology departments, have also been associated with PRES [29,30].

Because of the multisystemic involvement of SLE, several associated causes may lead to PRES in SLE patients.

The main presenting symptoms of PRES are headache, altered mental status, seizures (usually generalized) and visual loss, with an acute to subacute neurological presentation. Focal neurological signs can be occasionally noted. Altered consciousness leads to coma in extreme cases. HBP is frequent, but not always present [2,8].

Typically, imaging shows T2-weighted and FLAIR bilateral subcortical and cortical hyperintensities of the white and grey matter with a predominantly posterior distribution [19]. However, involvement in areas such as frontal lobes, brainstem, basal ganglia and thalamus has been reported [24,31]. DWI and apparent diffusion coefficient (ADC) analysis reveal vasogenic cerebral oedema in the majority of cases of PRES, with increased ADC and hypo-intense, iso- intense or sometimes hyperintense signals on DWI (the T2 effect remaining in DWI may induce hyperintense lesions on DWI scans despite normal or increased ADC values). Low ADC values lesions are rarely present. Lesions with high ADC values are most often reversible, whereas those with decreased ADC values (indicative of cytotoxic cerebral oedema) may progress secondarily to infarction [24,32]. Consequently, T2-weighted imaging, DWI signals changes and ADC values allow early differential diagnosis between PRES and acute cerebral infarction. Whether or not they may have a prognostic value in PRES is still under debate [22,24,33]. Perfusion-weighted MRI studies in PRES are rare. A recent study suggests that cerebral oedema might be caused by an elevation of capillary hydrostatic pressure mediated by venous constriction [21].

Bilateral ischaemic strokes in the posterior cerebral artery territory are the main differential diagnosis of PRES. This distinction is crucial because management of PRES includes rapid control of BP, whereas BP should not be aggressively treated in the case of cerebrovascular infarction. PRES can also mimic various diseases such as central venous sinus thrombosis, demyelinating disorders, lupus encephalitis, cerebral vasculitis and infectious or metabolic encephalopathy [25,34]. MRI findings and reversibility are the main elements to distinguish PRES from different diagnoses and avoid unnecessary additional work-up.

Treatment must be started as soon as possible. BP should be rapidly controlled with parenteral anti-hypertensive medications, with a close monitoring of BP to prevent hypoperfusion and worsening of the cerebral damages. A goal of mean arterial BP between 105 and 125 mmHg has been proposed, as well as the use of nimodipine, a calcium channel blocker potentially useful in preventing cerebral vasospasm [35]. Haemodialysis may be necessary in cases of severe fluid retention. Complicated cases need supportive care in intensive care units. Recent observations report on the efficacy and safety of intravenous sodium valproate (ivVPA) in treatment of status epilepticus (SE) [36,37]. Furthermore, Servillo et al. reported the successful use of ivVPA in two eclamptic patients with PRES and SE [35]. The usefulness of ivVPA under this condition seems to be promising.

When PRES is promptly diagnosed and treated, clinical symptoms are rapidly reversible whereas radiological abnormalities improve less rapidly. However, delayed diagnosis and treatment may result in permanent damage. Even with adequate therapy, recovery is not always complete. Cases of cerebral infarction, subarachnoid haemorrhage, coma or death have been described [11,22,35]. Focal epilepsy could occur [25]. In children, cognitive impairment is reported, and white matter oedema can evolve into leukomalacia [38].

PRES is an under-recognized cause of CNS abnormalities in SLE patients. It is of particular concern in patients with HBP, renal involvement or immunosuppressive therapy. PRES requires the particular attention of nephrologists because of its severity and its potential severe consequences. A prompt diagnosis and treatment are mandatory for a full recovery of abnormalities.

Conflict of interest statement. None declared.

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7. Yong PF, Hamour SM, Burns A. Reversible posterior leukoencephalopathy in a patient with systemic sclerosis/systemic lupus
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