Posterior reversible encephalopathy syndrome and systemic vasculitis: a report of six cases

B. Lioger[1,2], E. Diot[1], M. Ebbo[3], N. Schleinitz[3], L. Aaron[4], J.-M. Michot[5], O. Lambotte[5], R. Dhote[6], H. de Boysson[7], E. Ponce[1,2], F. Maillot[1,2]
On behalf of the Société Nationale Française de Médecine Interne (SNFMI) and the CRI (Club Rhumatismes et Inflammation)

[1]CHRU de Tours, Service de Médecine Interne, Tours, France; [2]Université François Rabelais, Tours, France; [3]CHU de la Conception, Service de Médecine Interne, Assistance Publique-Hôpitaux de Marseille, Aix-Marseille Université, Marseille, France; [4]CH Jacques Cœur, Service de Médecine Interne, Bourges, France; [5]CHU Kremlin Bicêtre, Service de médecine interne, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France; [6]CHU Avicenne, Service de Médecine Interne, Assistance Publique-Hôpitaux de Paris, Bobigny, France; [7]CHU de Caen, Service de Médecine Interne, Caen, France.

Bertrand Lioger, MD
Elisabeth Diot, MD, PhD
Mikael Ebbo, MD
Nicolas Schleinitz, MD, PhD
Laurent Aaron, MD
Jean-Marie Michot, MD
Olivier Lambotte, MD, PhD
Robin Dhote, MD, PhD
Hubert de Boysson, MD
Elodie Ponce, MD
François Maillot, MD, PhD

Please address correspondence and reprint requests to: Dr Bertrand Lioger, Department of Internal Medicine; University Hospital of Tours, 37044 Tours Cedex 9, France.
E-mail: bertrand.lioger@univ-tours.fr

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ABSTRACT

Objective. *Our objective was to describe the characteristics of posterior reversible encephalopathy syndrome (PRES) associated with systemic vasculitis.*

Methods. *A standardised questionnaire was used for a nationwide retrospective multicentre study in 2013 to collect clinical, radiological and outcome data about PRES associated with systemic vasculitis.*

Results. *We included six patients (all women; mean age 22.6±19.8 years (20-62)): two with polyarteritis nodosa and one case of each granulomatosis with polyangiitis, cryoglobulinaemic vasculitis, hypocomplementemic urticarial vasculitis, and Takayasu arteritis. PRES was the first manifestation of systemic vasculitis in three patients. Arterial hypertension was suspected to be the cause of PRES in five patients. Several other plausible causes including drugs, renal failure, and pneumonia were found in three patients. Clinical findings included headache, seizure, blurred or loss of vision, confusion, and altered cognition. Radiological study showed oedema in the occipital region in all patients, with a reversible state in MRIs performed one week to one month after the onset of PRES. Therapies used included antihypertensive therapy (n=5), immunosuppressive therapy (corticosteroids (n=5), cyclophosphamide (n=4), azathioprine (n=1), methotrexate (n=1), plasma exchange (n=1)), antibiotics (n=1), anticonvulsant therapy (n=2)), and analgesics. No relapse of PRES was reported during the follow-up period (mean: 47.5 ±29.9 months, 13–98); one patient continued to complain of vision loss.*

Conclusion. *Our study indicates that PRES is a rare condition associated with systemic vasculitis; which may be present at the onset vasculitis symptoms. Antihypertensive drugs should be prescribed if blood pressure is elevated. The impact of immunosuppressive therapy remains unclear.*

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare condition characterised by a reversible vasogenic brain oedema that can be detected by CT scan or magnetic resonance imaging (MRI) (1). Clinical manifestations include headache, confusion, nausea, vomiting, seizures, and visual disturbances secondary to bilateral grey and white matter oedema in cerebral posterior areas (2). Following specific therapies adapted to the cause of PRES, patients usually recover and radiological features resolve within days or weeks. As MRI is commonly available and sensitive to detect PRES, many conditions have been reported in association with PRES (1). Hypertension, eclampsia, sepsis, chronic kidney disease, organ transplantation and immunosuppressive therapy are the most frequently reported causes of PRES. In a recent study, autoimmune diseases have been identified in 45% of cases of PRES (3). PRES related to systemic lupus erythematosus (SLE) has also been reported in small retrospective series (4, 5). However, there are only limited descriptions of PRES associated with systemic vasculitis (SV) (6, 7). The case of a young girl with headaches, hypertension, seizures and MRI features of PRES was recently reported in association with Takayasu arteritis (TA) (7). Thus, the association of PRES with SV appears to be rare. Descriptions of additional cases of PRES related to SV are needed, as early recognition of PRES among patients presenting with CNS symptoms

and features of SV is still problematic. Identifying PRES in patients with SV may also influence therapeutic options. Our aim was to describe clinical and radiological characteristics of PRES associated with SV through a nationwide French multicentre observational study (PRESVAS study). The survey extended to cover therapeutic options and patients outcome.

Methods

Cases selection

We conducted a nationwide multicentre study during 12 months in 2013. Considering that PRES has been defined in 1996 (1), the PRESVAS study period for inclusions was 1996-2013. 2 344 members of the French Society of Internal Medicine and the "Club Rhumatismes et Inflammation" were asked to reply to an electronic survey about patients who developed PRES associated with SV (PRESVAS study) and a standardised protocol was also available on the CRI (www.cri-net.com) and SNFMI (http://www.snfmi.org/) websites. The PRESVAS study and database were declared to the *Commission Nationale Informatique et Libertés* and approved by the institutional review board of Tours University Hospital, and were in accordance with the Helsinki declaration.

Data were retrieved by clinicians from medical charts and collected retrospectively, using a standardised questionnaire. The following data was collected: sex, age, medical history (hypertension defined as blood pressure ≥140/90 mmHg, neurological disorder, renal failure, and pregnancy), SV characteristics (date of diagnosis, disease duration and activity, complications, immunological findings, therapy), information about PRES (date of diagnosis, neurological symptoms, blood pressure at baseline, biological evaluation, radiological findings, treatment and follow-up).

Diagnosis of PRES and SV

To be eligible, patients had to be aged 18 years or older. Diagnosis of PRES was based upon clinical and radiological (brain CT-scan or MRI) findings. PRES was defined as acute neurological change including headache, encephalopathy, seizure, visual disturbance, and focal deficit. Radiological features included oedema involving the white matter in the posterior portions of the cerebral hemispheres (1). The reversibility of cerebral oedema had to have been demonstrated by subsequent brain imaging. Neuroradiologists at each centre retrospectively reviewed brain MRIs. Complete recovery was defined as the absence of central neurological symptoms and normal MRI findings. Incomplete clinical recovery and/or persistent posterior signals on MRI were scored as partial response.

SV was diagnosed according to the diagnostic criteria proposed by the 2012 International Chapel Hill Consensus Conference Nomenclature (8) and the American College of Rheumatology criteria (9). Patients with cerebral vasculitis and/or reversible vasoconstriction syndrome were excluded. Vasculitis disease activity and prognosis were assessed with the Birmingham Vasculitis Activity Score 2003 (BVAS) as appropriate (10).

Statistical analysis

Descriptive statistics were used, as the study sample was small and heterogeneous. Continuous variables, means ± standard deviations (SD) and medians (interquartile ranges) were obtained using Excel Mac 2008.

Results

The study included six female patients diagnosed between 2005 and 2012 with PRES during the course of SV. One case of hypocomplementemic urticarial vasculitis (HUV) has been included, although this case has already been published as a single case report (11). All patients were women. The SV were polyarteritis nodosa (PAN) in two patients, and granulomatosis with polyangiitis (GPA), cryoglobulinaemic vasculitis (CV), HUV and TA in others. The mean age was 22.6±19.8 years (20-62). PRES occurred at the onset of vasculitis in three of the patients (namely cases 2, 3 and 6). None of the patients were pregnant. Patient characteristics at PRES onset are summarised in Table I.

Potential causes of PRES

The questionnaire asked clinicians caring for these patients to report suspected causes of PRES. Hypertension was suspected to be causative in five patients, although only four of them had high blood pressure (BP) on admission. Renal involvement, pseudo-ephedrine, and corticosteroids were reported to be associated and/or linked to hypertension. The patient (case 4) with normal BP had a history of pneumonia and chronic renal insufficiency, both conditions that have been reported in association with PRES (12, 13). Multiple causes were suspected in three patients, including drugs (intravenous steroids and pseudo-ephedrine) and renal failure. Finally, SV was suspected to be a potential cause of PRES, specifically in cases 1, 2, 3 and 6.

Radiological findings

Neurological symptoms and radiological findings are presented in Table II. Among four CT-scans available, two were considered to be normal (cases 4 and 5). Brain MRI was performed in all patients. Oedema and/or lesion of the occipital region were observed in all cases. Subsequent MRIs, between one week and one month after the onset of symptoms, were normal in all cases.

Treatment and follow up

The questionnaire collected data about both management of neurological symptoms (including treatment of headaches and seizures) and therapy of the suspected causes of PRES (Table I). Analgesics, including morphine in one case, were given to relieve headache, with a good outcome. Patients with seizures received various antiepileptic drugs. Three patients were admitted to an intensive care unit (cases 1, 2 and 3) because of seizure and stupor. Because of the initial high severity scores or relapses of SV, immunosuppressive drugs were prescribed to all patients. Corticosteroids were used in five patients, but not in case 6. Intravenous cyclophosphamide was administered to four patients (cases 1, 2, 3 and 5) and oral methotrexate to case 6. For the two patients with a previous history of vasculitis before the onset of PRES,

Table I. Characteristics of adults with PRES associated with vasculitis at PRES onset.

	1	2	3	4	5	6
Age (years)/Sex	57/W	49/W	22/W	62/W	20/W	20/W
Type of Vasculitis	PAN	PAN	GPA	Cryoglobulinemic vasculitis	Hypocomplementemic urticarial vasculitis	TA
Duration since onset of first clinical symptoms of vasculitis	3 days	0	0	6.3 years	5.1 years	0
BP at baseline m(mmHg)	160/70	130/75	170/96	135/70	130/70	160/70
Maximum BP (mmHg)	170/110	220/110	175/110	150/80	180/110	240/120
Neurological symptoms	H, N, AG, VS	H, N	H, N, AG, VS, D, S	AG, VS, D	H, N	H, AG, D, S
Organ involvement	Articular Peripheral Neuropathy	Pulmonary Renal Abdominal Cardiovascular	Cutaneous Articular Peripheral Neuropathy	Cutaneous Renal	Cutaneous Renal	Pulmonary Cardiovascular
BVAS	NA	47	23	NA	NA	14
Serum creatinine (µmol/L)	70	105	107	281	246	50
Immunological findings	_	_	ANCA (ELISA PR3+) Titer 1280 28 U/ML	Mixed cryoglobulinaemia type III Low complement	C1q antibody Low complement	_
Potential causes of PRES	Hypertension	Hypertension	Hypertension Corticosteroids	Pneumonia, Chronic renal insufficiency	Hypertension, Corticosteroids Pseudo-ephedrine Glomerulonephritis	Hypertension
Immunosuppressant treatments started following the onset of PRES	CT, CYC	IV CT, CYC, AZA	IV CT, CYC	CT	CT, CYC, PE	MTX
Additional treatments		AT	AT, AC	AT	AT, ATB	AT, AC

AC: anticonvulsant; AG: altered cognition; ANCA: anti-neutrophil cytoplasmic antibodies; AT: antihypertensive therapy; ATB: antibiotics; AZA: azathioprine; BP: blood pressure; BVAS: Birmingham vasculitis activity score; CT: corticosteroids; CYC: cyclophosphamide; D: delirium; GPA: granulomatosis with polyangiitis; H: headache; IV: intravenous; MTX: methotrexate; N: nausea (or vomiting); NA: non adapted; NP: not performed; PAN: polyarteritis nodosa; PE: plasma exchange; S: seizure; TA: Takayasu's arteritis; VS: visual symptoms; W: woman.

immunosuppressive treatment was not withdrawn. In addition, treatment for acute hypertension was required in five patients (cases 2, 3, 4, 5 and 6); two or three antihypertensive drugs were used, including combinations of calcium channel blockers, angiotensin-converting enzyme inhibitors, beta-blockers, alpha-blocking agents, centrally acting agents, and diuretics.

Overall, the outcome of PRES was satisfactory with a complete response to therapy in five patients. Case 1 complained of a persistent loss of vision. The response to multiple antihypertensive and immunosuppressive drugs was rapid among the patients with complete responses (median: 11 days, 2-413). Altered cognition was the last symptom to respond. No relapse of PRES was reported during the follow-up period (mean: 47.5±29.9 months, range 13–98).

Discussion

The present study reports six patients affected by PRES during the course of SV. Most cases of PRES associated with systemic autoimmune diseases have been reported in patients with SLE (4, 5), and less frequently with SV. Our nationwide multicentre study only identified 6 cases of PRES associated with SV among 2344 clinicians contacted through our survey. We estimate that this low rate of reply reflects the rarity of such an association, although some cases may have been missed due the inherent biases of selection cases linked to a retrospective study. In our centre, we have looked after 397 patients affected by SV during the last ten years and we have identified only one case (0.25%) of PRES among these patients. However, we estimate that PRES may be under diagnosed in patients with SV, as this association is not well known among physicians. The incidence of PRES associated with SV is probably underestimated. PRES has already been described in association with GPA, PAN, TA, Henoch-schönlein purpura, microscopic polyangiitis, and HUV (14). Our study is then the first to report a case of PRES associated with non-hepatitis C virus (HCV) CV. Indeed, a large study of this condition has been published without any description of PRES (15). Recently, PRES has been recognised in a patient with hepatitis C-associated cryoglobulinaemia (16). At first glance, cases of vasculitis included in our study appear to be heterogeneous, but five of the patients had SV characterised by small and/or medium-vessel involvement (8). The only exception was the patient with TA, which involves large

Table II. Radiological characteristics of PRES and neurological symptoms.

	Neurological symptoms	Brain CT-scan findings	Brain MRI
1	H, N, AG, VS	Diffuse cerebral oedema with multiple cortico-subcortical hypodensities in the bilateral parieto-occipital regions and the right frontal lobe	Recent ischaemic lesion in the right frontal lobe and bilateral hyperintensitites in the parieto-occipital regions and the semiovale centrum
2	H, N	NP	Posterior oedema of the occipital region with dissection of both the left vertebral artery and the right internal carotid
3	H, N, AG, VS, D, S	NP	Bilateral signal intensity of cortical and subcortical temporo-occipital regions
4	AG, VS, D	Small asymmetry of the left occipital white matter	Bilateral hyperintensities of the occipital region with encephalitic picture without oedema
5	H, N	Normal	Oedema of the cerebellar hemispheres and hyperintense lesions of the cortex of the occipital lobe and the brainstem
6	H, AG, D, S	Diffuse contrast-enhanced meningeal signal	Bilateral posterior subcortical lesions

AG: altered cognition; D: delirium; H: headache; N: nausea (or vomiting); NP: not performed; S: seizure; VS: visual symptom.

vessels. As only eleven other cases of TA have been reported in the literature as compared to more than thirty cases of Henoch-Schönlein disease, PAN, and GPA (7), we suggest that PRES may be mostly associated with SV of small and/or medium vessels.

The clinical features of PRES reported here are consistent with those described previously, including abrupt onset with headache, seizure, blurred or loss of vision, confusion, and altered cognition. Imaging is central to the diagnosis of PRES. As expected, we observed that MRI is more sensitive than CT scan. Indeed, one brain CT-scan was normal in case 5 and showed a small lesion of the white matter in case 4. In all cases, MRI findings were bilateral symmetric hyperintensities on T2-weighted images in the posterior parietal or occipital lobes that were not visible in diffusion-weighted imaging (2). Thus, atypical localisations and imaging manifestations involving the basal ganglia, the brain stem, and the deep white matter with ischaemic lesions and haemorrhage have already been described (17). In case 2, left carotid dissection may have been a potential cause of ischaemia. As our radiographic requirements for PRES was an oedema in the posterior portions of the cerebral hemispheres and PRES does not always involve the classical regions, we may have missed some cases. In case 3, brain MRI performed for mild headache four days before the onset of PRES was normal but a subsequent MRI showed bilateral signal intensity in the cortical and subcortical temporo-occipital regions (Fig. 1). This shows that MRI features of PRES may be absent before, and even during the onset of the disease; which could lead to a under diagnosis of PRES.

PRES was the first manifestation of SV in half of the patients in our series (cases 2, 3, and 6). Therefore, the issue of whether PRES should be considered to belong to the spectrum of CNS manifestations of SV has to be addressed. In the Five Factor Score (FFS) (18), CNS involvement in SV is associated with a poor outcome, as well as proteinuria >1g/24h, serum creatinine level >140 μmol/L, and specific gastrointestinal or cardiac involvements. If one of these features is present, FFS is ≥1, which indicates a significantly high risk of mortality at five years and therefore identifies patients who require immunosuppressive agents in addition to corticosteroids. Including PRES as a

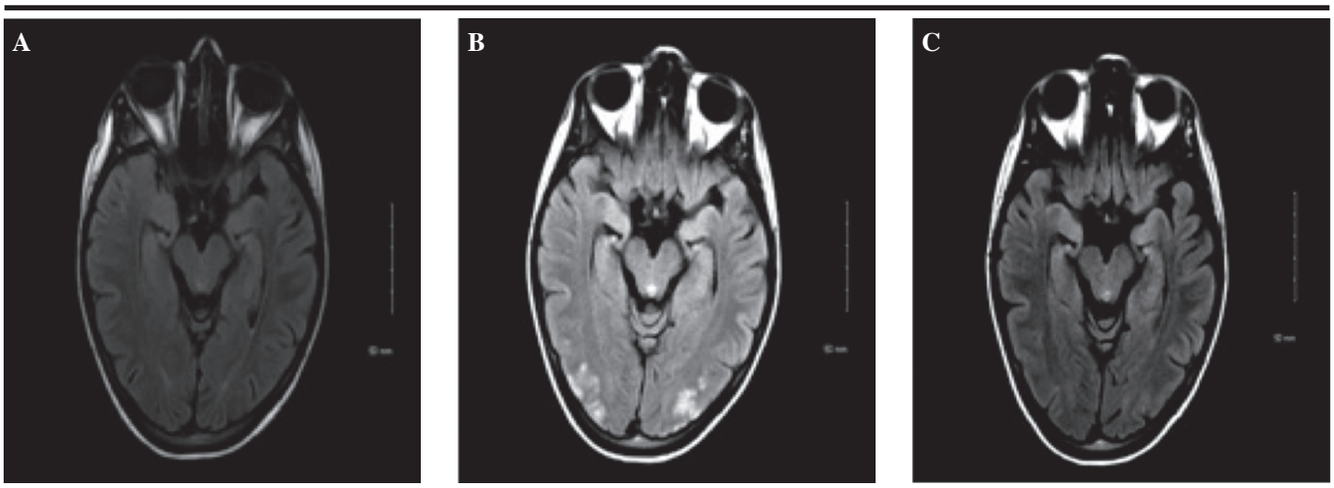

Fig. 1. MRI (T2-FLAIR) of brain of case 3. The patient was a 22-year-old woman without previous medical history. Four days before the onset of PRES, she complained of headache with a high suspicion of cerebral vasculitis. The brain MRI was considered to be normal (**A**). Because of seizures, a new MRI was performed showing bilateral signal intensity of cortico-subcortical temporo-occipital regions (**B**). One month later, the signal intensity had regressed (**C**).

neurological manifestation of SV would affect FFS and then therapeutic choices. However, it is unclear whether PRES affects the outcome of SV. Indeed, outcomes were good in our patients as well as those reported in the literature (6, 7, 13, 14). Various therapeutic options have been proposed for the treatment of PRES. Hypertension is frequent among patients with PRES; so multiple antihypertensive drugs have been proposed, as was the case with our patients. Patients who benefit from antihypertensive drugs should be monitored with regular or automated blood pressure measuring to ensure immediate antihypertensive efficacy. If necessary, antiepileptic drugs and antibiotics are prescribed (2). The value of specific immunosuppressive therapy for cases of PRES associated with vasculitis needs to be considered, as cases of PRES secondary to cyclophosphamide have been described (19). This controversial issue is illustrated in our series. On the one hand, corticosteroids were suspected to be involved in the onset of PRES in patients 3 and 5 leading to withdrawal. On the other hand, immunosuppressive agents including high dose corticosteroids, cyclophosphamide, and methotrexate have also been prescribed with good outcome. Because of the small number of patients and the heterogeneous nature of SV in the patients included in our study, it is difficult to draw conclusions about the influence of immunosuppressive therapy. As PRES was the initial manifestation of the vasculitis in most of our patients, an initial aggressive strategy may be effective.

The pathophysiology of PRES is partly understood. Severe hypertension may lead to dysfunction of autoregulatory vasoconstriction of small cerebral vessels. A breakthrough of the blood-brain barrier is then responsible for fluid leakage and vasogenic oedema (2). In our study, hypertension was present at PRES onset in four patients, and was considered to be the main cause of PRES in five patients. In contrary to case 4, BP was normal, as in 20-30% of patients with PRES (20). A brain capillary leak due to endothelial dysfunction secondary to cytotoxic or immunosuppressive drugs or infection has also been proposed as a mechanism of PRES (20) as well as direct targeting of the endothelial wall by antibodies linked to SV. In clinical practice, several mechanisms may be associated as in our case 4 in which both cryoglobulinaemia and sepsis may be the cause of PRES.

In conclusion, PRES may be the onset symptom of SV. We suggest that, SV should be investigated in all cases of PRES without obvious aetiology, even if BP is raised high. The outcome of PRES associated with SV appears to be favorable in most cases if the appropriate treatment is initiated quickly. Antihypertensive drugs should be prescribed if BP is elevated. Further work is needed to assess the consequences of immunosuppressive therapy on PRES associated with SV.

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