Cerebrospinal Fluid in Posterior Reversible Encephalopathy Syndrome: Implications of Elevated Protein and Pleocytosis

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Colin A. Ellis, MD¹, Andrew C. McClelland, MD, PhD²,
Suyash Mohan, MD², Emory Kuo, DO³, Scott E. Kasner, MD, MSCE¹,
Cen Zhang, MD⁴, Pouya Khankhanian, MD¹, and Ramani Balu, MD, PhD¹

Abstract

Background and Purpose: Patients with posterior reversible encephalopathy syndrome (PRES) sometimes undergo analysis of cerebrospinal fluid (CSF) to exclude alternative diagnoses. This study's objectives were to describe the CSF characteristics in patients with PRES and to identify clinical and radiologic findings associated with distinct CSF abnormalities. **Methods:** We identified a retrospective cohort of patients with PRES. We compared clinical and radiographic characteristics of those who did versus did not undergo lumbar puncture, described the observed range of CSF findings, and analyzed clinical and radiographic features associated with specific CSF abnormalities. **Results:** A total of 188 patients were included. Patients with ($n = 77$) and without ($n = 111$) CSF analysis had similar clinical and radiographic characteristics. Cerebrospinal fluid protein was elevated in 46 (60%) of 77, with median CSF protein 53 mg/dL (upper limit of normal 45 mg/dL). Protein elevation was significantly associated with radiographic severity ($P = .0058$) but not with seizure, time from symptom onset, radiographic evidence of diffusion restriction, or contrast enhancement. Five (7%) patients had elevated CSF white blood cells, all of whom had infarction and/or hemorrhage on neuroimaging, and 4 of whom had eclampsia. **Conclusion:** The CSF of most patients with PRES shows a mild protein elevation commensurate with radiographic severity. Cerebrospinal fluid pleocytosis may mark a distinct subtype of PRES with predisposition toward infarction and/or hemorrhage. These findings help clinicians interpret CSF findings in these patients and generate new hypotheses about the pathophysiology of this syndrome.

Keywords

posterior reversible encephalopathy syndrome, PRES, RPLS, eclampsia, cerebrospinal fluid

Introduction

The posterior reversible encephalopathy syndrome (PRES) presents with characteristic clinical symptoms (including headache, vision change, seizure, and confusion) and reversible vasogenic edema on brain imaging studies.^{1,2} Breakdown of the blood–brain barrier is thought to be central to the development of vasogenic edema and neurologic dysfunction.^{3,4} However, despite much speculation, the exact pathogenesis of PRES remains unknown.

A variety of clinical conditions, including malignant hypertension, immunosuppressive therapy, reversible cerebral vasoconstriction, sepsis, eclampsia/preeclampsia, autoimmune diseases, and thrombotic microangiopathy syndromes, have been linked to PRES.^{1,2} These varied conditions may act through multiple mechanisms—including failure of cerebral autoregulation and hyperperfusion, vascular endothelial cell dysfunction, and upregulation of inflammatory cytokines—to

produce reversible vasogenic edema.³⁻⁵ Given this diversity of potential precipitants and pathophysiological mechanisms, it is possible that PRES represents not one but rather a collection of distinct entities that all produce breakdown of the blood–brain barrier and vasogenic edema as a final common pathway.⁶

¹ Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

² Division of Neuroradiology, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

³ Department of Neurosurgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

⁴ Department of Neurology, New York University Medical Center, NY, USA

Corresponding Author:

Ramani Balu, Department of Neurology, University of Pennsylvania 3400 Spruce St, 3 West Gates building, Philadelphia, PA 19104, USA.
Email: ramani.balu@uphs.upenn.edu

Cerebrospinal fluid (CSF) sampling is often performed during the evaluation of unexplained neurologic deterioration to aid in diagnosis, identify pathogenic mechanisms, and track disease progression. Although CSF analysis is not considered necessary for the diagnostic evaluation of patients with PRES, it is often performed to exclude alternative diagnoses such as infection or malignancy. The range of CSF findings in patients who are ultimately diagnosed with PRES is relevant to clinical interpretation of these data and has only recently begun to be systematically described.^{7,8} Additionally, these early studies have consistently found that a small fraction of patients have elevated CSF white blood cells (WBCs; pleocytosis), but the clinical significance of this finding has not been previously explored.

To aid clinical interpretation of CSF results in patients who may have PRES, and to better understand the significance of pleocytosis in these patients, we performed a retrospective observational study of all patients diagnosed with PRES over a 12-year period at our institution. We examined clinical and radiographic characteristics of patients who did versus those who did not undergo CSF analysis. In those patients where CSF samples were analyzed, we identified clinical and radiologic findings that associated with CSF abnormalities and hypothesized that elevated CSF protein and pleocytosis may be associated with radiographic severity, hemorrhage, diffusion restriction, contrast enhancement, time to lumbar puncture, and presence of seizure.

Methods

This retrospective cohort study investigated patients diagnosed with PRES who were treated within our health-care system between 2003 and 2015. The study was approved with waiver of informed consent by our institutional review board.

Patient Identification

Patients with PRES were identified by searching the text of radiology reports and neurologic intensive care unit progress notes as well as *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes for the following search terms: posterior reversible encephalopathy syndrome, reversible posterior leukoencephalopathy, hypertensive encephalopathy, eclampsia, PRES, RPLS, PLE, tacrolimus toxicity, and calcineurin toxicity. We included in the analysis those who met the following criteria for PRES¹: (1) acute to subacute onset of neurologic symptoms, including headaches, confusion, seizures, and/or focal neurologic deficits; (2) radiographic evidence of vasogenic edema on magnetic resonance (MR) or computed tomography (CT) imaging; and (3) clinical and/or radiographic evidence of reversibility. Patients were excluded only if they did not meet these criteria or if available documentation was insufficient to determine that inclusion criteria were met. All uncertain cases were adjudicated by

consensus of 2 authors (C.A.E. and R.B.), both clinical neurologists.

Clinical Characteristics

Eligible patients underwent a thorough review of hospital records for extraction of clinical data. Cerebrospinal fluid studies were included only if obtained within 7 days of PRES diagnosis, defined as the date of the diagnostic magnetic resonance imaging (MRI) or CT scan. Cell counts from the tube with the lowest red blood cell (RBC) count were used to reduce the effect of traumatic punctures. In samples with elevated CSF WBC and RBC counts, the CSF WBC count was adjusted to account for the presence of blood based on the standard complete blood counts from peripheral blood on the day of the lumbar puncture, using the following formula: [corrected CSF WBC] = [measured CSF WBC] – ([CSF RBC] * [peripheral blood WBC:RBC ratio]). Pleocytosis was defined as corrected CSF WBC >5 cells/μL. Abnormal CSF protein was defined as >45 mg/dL, the upper limit of normal in our institution's laboratory. Cerebrospinal fluid protein was not corrected for presence of blood. Opening pressure was either not measured or not well documented in nearly all cases and so was not included in the analysis. Clinical conditions associated with PRES, including history of allogeneic transplantation (solid organ or hematopoietic stem cell), primary autoimmune disease, thrombotic microangiopathy syndrome, pregnancy/eclampsia, prior history of hypertension or chronic kidney disease, and sepsis, were identified for all 188 patients.

Magnetic Resonance Imaging Characteristics

Magnetic resonance images were reviewed and adjudicated by 1 board-certified neuroradiologist (S.M.) and 1 neuroradiology fellow (A.C.M.) who were blinded to clinical and CSF data. The severity of PRES was categorized based on a previously published rating scale⁹ as follows:

Mild. Cortical/subcortical white matter signal-intensity alterations without involvement of periventricular white matter and without mass effect, or involvement of none or only one of the following: cerebellum, brain stem, or basal ganglia.

Moderate. Edema involving the cortex and subcortical white matter without involvement of the periventricular white matter, with mild mass effect but without midline shift/herniation, or involvement of 2 of the following: cerebellum, brain stem, or basal ganglia.

Severe. Edema extending from the cortex to the periventricular white matter or the presence of midline shift/herniation, or involvement of all 3 of the following: cerebellum, brain stem, and basal ganglia.

In addition, radiographic findings (vasogenic edema, restricted diffusion, hemorrhage, and contrast enhancement)

Table 1. Patients Characteristics.

Patients Characteristics	All Patients	With CSF	Without CSF	P Value (Uncorrected)
No of patients	188	77	111	
Age, median (range)	50 (15-92)	54 (16-82)	48 (15-92)	.51
Female, n (%)	141 (75%)	63 (81%)	78 (70%)	.09
Precipitants of PRES, n (%)				
Hypertension	166 (89%)	69 (87%)	97 (90%)	.60
Immunosuppression ^a	66 (34%)	32 (41%)	34 (31%)	.17
Sepsis	31 (16%)	14 (18%)	17 (16%)	.70
Autoimmune disease	25 (13%)	12 (15%)	13 (12%)	.50
Pregnancy/eclampsia	32 (17%)	11 (14%)	21 (19%)	.35
Other thrombotic microangiopathy	11 (6%)	4 (5%)	7 (6%)	.70
Symptoms of PRES, n (%)				
Seizure	115 (61%)	49 (62%)	66 (61%)	.94
Encephalopathy	108 (58%)	47 (59%)	61 (56%)	.68
Headache	80 (43%)	35 (44%)	45 (42%)	.72
Vision changes	49 (26%)	17 (22%)	32 (29%)	.24
Other	25 (13%)	10 (13%)	15 (14%)	.85
Hospital LOS, days, median (range)	10 (2-135)	11 (2-70)	10 (2-135)	.67
Hospital disposition, n (%)				.87
Home	120 (64%)	51 (65%)	69 (63%)	
Facility	57 (30%)	23 (30%)	34 (30%)	
Died	9 (5%)	3 (4%)	6 (6%)	

Abbreviations: CSF, cerebrospinal fluid; LOS, length of stay; PRES, posterior reversible encephalopathy syndrome.

^aIncludes immunosuppressive and chemotherapeutic medications

were cataloged as present or absent in each of the following areas: occipital lobe, parietal lobe, frontal lobe, temporal lobe, cerebellum, brain stem, thalamus, basal ganglia, and corpus callosum. Hemorrhages were classified as subarachnoid or parenchymal, or both, based on gradient echo sequences. Parenchymal hemorrhages were further identified as microhemorrhages (identified only as punctate foci of susceptibility on gradient recall echo sequences) or frank space-occupying hematoma.

Data Analysis

Descriptive statistics were calculated for clinical, radiographic, and CSF data. Inferential statistics were performed with nonparametric tests because data were not normally distributed. Patients with and without CSF analysis were compared using χ^2 statistics to compare categorical variables and Mann-Whitney *U* tests to compare continuous variables.

To test associations between CSF protein levels and various clinical/radiographic features, we treated CSF protein as independent (exposure) variable and the following as dependent (outcome) variables: radiographic severity of PRES, presence of diffusion restriction, presence of enhancement, presence of seizure, and time from symptom onset to lumbar puncture. We used Spearman rank-order correlations for ordinal and continuous outcome variables (radiographic severity, time from symptom onset to lumbar puncture) and binary logistic regression for dichotomous outcome variables (seizure, diffusion restriction, enhancement) using rank-ordered CSF protein as exposure variable. Similar analyses

using CSF WBC were not performed because there were too few cases with elevated WBC to make meaningful statistical comparisons. All statistical tests were 2-sided, and *P* values <.05 were considered statistically significant.

Data analysis was performed with Stata 13 software (StataCorp, College Station, Texas) and with the R programming language.

Results

Screening yielded 1097 potential candidates. Of these, 560 were excluded because of insufficient data (eg, screened positive by *ICD9* code but had no neuroimaging or inpatient records). The remaining 537 underwent full chart review. Of these, 188 met inclusion criteria and were included in the study.

Clinical Characteristics

Characteristics of the 188 patients who met inclusion criteria are summarized in Table 1. Women were overrepresented among patients with PRES, likely due to its association with eclampsia and autoimmune diseases. Hypertension (blood pressure >140/90) was present in 89% at the time of presentation. The most common presenting symptoms were seizure (61%) and encephalopathy (59%). Cerebrospinal fluid was obtained in 77 (41%) patients. There were no significant differences in gender, associated precipitants, presenting symptoms, or outcome (hospital length of stay and disposition) between patients who had CSF sampled and those who did not.

Table 2. Neuroimaging Findings.

Imaging Findings	All Patients	With CSF	Without CSF	P Value (Uncorrected)
No of patients	184	75	109	
Severity of PRES, n (%)				.57
Mild	90 (49%)	34 (44%)	56 (52%)	
Moderate	41 (22%)	17 (23%)	23 (21%)	
Severe	54 (29%)	24 (32%)	30 (27%)	
Diffusion restriction present, n (%)	46 (25%)	23 (30%)	23 (21%)	.18
Subarachnoid hemorrhage, n (%)	6 (3%)	4 (5%)	2 (2%)	.21
Parenchymal hemorrhage, n (%)	42 (23%)	20 (26%)	22 (20%)	.37
Enhancement present, n (%) ^a	15 (16%)	8 (19%)	7 (14%)	.36

Abbreviations: CSF, cerebrospinal fluid; PRES, posterior reversible encephalopathy syndrome.

^aFor enhancement, percentages are from total patients who received gadolinium: All patients 93, with CSF 43, without CSF 50.

Neuroimaging Findings

Magnetic resonance imaging findings are summarized in Table 2 (n = 184; 4 patients were diagnosed with PRES based on CT scan findings and did not undergo MRI, thus were not included in this analysis). Figure 1 shows examples of the spectrum of radiographic findings across the cohort. Mild, moderate, and severe categories were well represented. Diffusion restriction and parenchymal hemorrhage (mostly microhemorrhage) were present in 25% and 23% of patients, respectively. Gadolinium enhancement was slightly less common; subarachnoid hemorrhage (SAH) was uncommon. None of these imaging characteristics was significantly different between patients with versus without CSF sampling. Involvement of each of 9 different anatomical brain regions (occipital lobe, parietal lobe, frontal lobe, temporal lobe, cerebellum, brain stem, thalamus, basal ganglia, and corpus callosum) also showed no significant differences between these 2 groups.

Cerebrospinal Fluid Findings

Cerebrospinal fluid findings in 77 patients who underwent lumbar puncture are shown in Table 3. Median time from diagnosis to lumbar puncture was 0 days (range: -6 to +6 days), and median time from symptom onset to lumbar puncture was 1 day (range: -4 to 27 days). Cerebrospinal fluid profile was abnormal in 60% of patients. The most common abnormality was elevated protein. Protein elevation was significantly associated with radiographic severity of PRES, with patients with more severe vasogenic edema having higher levels of CSF protein (Spearman $\rho = 0.32$, $P = .0058$; see Figure 2). Associations between CSF protein and each of the following variables were not statistically significant: presence of seizure ($P = .46$), time from symptom onset to lumbar

puncture ($P = .24$), MRI diffusion restriction ($P = .65$), or MRI enhancement ($P = .78$).

Pleocytosis (corrected CSF WBC > 5 cells/ μ L) was seen in 5 (7%) of 77 patients. White blood cells were neutrophil predominant in 4 cases and lymphocyte predominant in 1 case. All CSF microbiology studies were negative in these cases, including Gram stain and culture, viral polymerase chain reaction studies, and fungal cultures. Cytology was not tested in these patients. All 5 of these patients had evidence of cytotoxic edema, SAH, or both on MRI. Four of the 5 cases with pleocytosis had eclampsia. These cases represent 4 (44%) of 9 of cases with eclampsia in which CSF sampling was performed. In post hoc analyses of the complete cohort, patients with eclampsia were not significantly different from patients with PRES due to other causes with respect to their rates of diffusion restriction (31% vs 20%, $P = .37$) or SAH (6% vs 3%, $P = .29$) and had significantly fewer cases of parenchymal hemorrhage (3% vs 27%, $P = .003$ uncorrected). All 5 patients with CSF pleocytosis made full neurologic recoveries and were discharged home after hospitalizations ranging 3 to 24 days. Complete descriptions of these 5 cases are provided as supplementary material.

Discussion

In this retrospective cohort of patients with PRES, we identified elevated CSF protein without CSF pleocytosis ("albumino-cytologic dissociation") as a common finding, present in the majority of patients with PRES. This protein elevation is associated with the radiographic severity of PRES but not with the presence of seizure, MRI diffusion restriction, or enhancement. A small proportion of patients had CSF pleocytosis. All of these patients had atypical imaging features such as infarction or SAH, and eclampsia was strikingly over-represented in this group.

Until very recently, descriptions of the CSF in patients with PRES could be found only in case reports. Most of these reported normal CSF composition, but some reported elevated protein and pleocytosis which may be lymphocyte predominant or neutrophil predominant.¹⁰⁻¹² Among early cohort studies, Lee and colleagues reported that the CSF from 18 patients with PRES had a mean white cell count of 1.6/ μ L (range 0-5) and mean protein 92 mg/dL (range 10-455) but did not comment further on these data.¹³

More recently, several studies have reported the CSF profiles of cohorts of patients with PRES in more detail. Datar and colleagues reported on 73 patients, with median CSF protein 58 mg/dL (range 10-295) and median CSF WBC of 1.⁷ In this cohort, 5 (7%) of 73 had CSF pleocytosis (WBC range 7-41), but the clinical and radiographic findings of these patients were not reported. Only 1 patient in this cohort had preeclampsia/eclampsia. In another study, Neeb and colleagues reported on 87 patients, with mean CSF protein 79 $\pm$ 92 (range not reported).⁸ Pleocytosis was present in 8 (9%) of 87, with maximum CSF WBC of 41, but no further details

Figure 1. Spectrum of radiographic findings in PRES. (A) mild, (B) moderate and (C) severe vasogenic edema; (D) with diffusion restriction, (E) with intracerebral hemorrhage, and (F) with subarachnoid hemorrhage, demonstrated here by diffuse sulcal contrast enhancement. Magnetic resonance imaging sequences: (A-C) FLAIR, (D) diffusion-weighted image (E) gradient echo (F) postgadolinium FLAIR. FLAIR indicates fluid attenuated inversion recovery; PRES, posterior reversible encephalopathy syndrome.

Table 3. Cerebrospinal Fluid Findings.

CSF Findings	Value
No of patients	77
WBC per μL , median (range)	1 (0-107)
Patients with WBC >5 , n (%)	5 (7%)
neutrophil predominant	4/5 (80%)
lymphocyte predominant	1/5 (20%)
Protein, mg/dL, median (range)	53 (16-428)
Patients with protein >45 , n (%)	46 (60%)
RBC per μL , median (range)	6 (0-22 000)
Glucose, mg/dL, median (range)	68 (47-219)

Abbreviations: CSF, cerebrospinal fluid; RBC, red blood cells; WBC, white blood cells.

were reported about these patients. Only 4 patients in this cohort had preeclampsia/eclampsia. A third study, by Alhilali and colleagues, described CSF pleocytosis in 7 (36%) of 47 of their cohort.¹⁴ However, 9 of 47 in this cohort had low CSF glucose (a finding that has not been replicated in other studies), and mortality was 20%, higher than is typically associated with PRES^{3,15}. These observations raise the concern that this cohort may not be representative of other patients with PRES.

Our study confirms the findings of prior studies that CSF protein elevation is common in patients with PRES and that the degree of CSF protein elevation is associated with the radiographic severity of vasogenic edema. These findings, consistent now across several studies, offer clues to the underlying pathophysiology of this disease. In most patients, breakdown of the blood–brain barrier caused either by exceeding the brain’s capacity for cerebral autoregulation or by direct endothelial injury causes leakage of interstitial fluid, leading to vasogenic edema seen on MRI and commensurate protein elevation measured in the CSF. Interestingly, elevated CSF protein was not associated with gadolinium enhancement on MRI, another marker of blood–brain barrier breakdown. Future studies should investigate the specific types and molecular weights of CSF proteins present in these patients, which may play a role in this dissociation.

Another consistent finding across multiple studies is the presence of a small subcohort of patients with CSF pleocytosis. This finding suggests an infrequent inflammatory component that may represent an alternative pathophysiologic mechanism in this subset. In our cohort, 5 patients had CSF WBC >5 . This pleocytosis was present after correcting for the

Figure 2. Distribution of (A) CSF white blood cells and (B) CSF protein (right panel) in 77 patients with PRES. Horizontal dashed lines represent upper limit of normal for each assay. In panel B, CSF protein distribution is shown first for all cases, then grouped by radiographic severity of PRES. There is a significant association between radiographic severity and CSF protein level (Spearman $\rho = 0.32$, $P = .0058$). CSF indicates cerebrospinal fluid; PRES, posterior reversible encephalopathy syndrome.

presence of RBCs in the CSF and cannot be explained by the presence of peripheral blood contaminating the CSF from traumatic punctures or SAH. All 5 of these cases with CSF pleocytosis had atypical radiographic features, such as infarction (3 patients) or SAH (2 patients had radiographic evidence of SAH, and a third had elevated CSF RBC and xanthochromia, suggesting possible imaging-negative SAH). Cerebrospinal fluid pleocytosis can occur in SAH and, less often, in ischemic stroke.¹⁶ Therefore, it is possible that the CSF pleocytosis in these 5 patients was a direct effect of infarct or hemorrhage, unrelated to the presence of PRES per se. Cytology was not tested in these 5 cases, but the observation that all rapidly recovered clinically and radiographically without antineoplastic treatment, including steroids, argues against a neoplastic etiology.

Alternatively, it is possible that these patients represent a distinct subtype of PRES, mediated not by simple dysfunction of the blood–brain barrier but by an inflammatory process which creates a similar radiographic appearance to other types of PRES but predisposes patients to infarct and/or hemorrhage. Our sample is small, and this should be considered an intriguing hypothesis that warrants further study. Definitively confirming cerebral inflammation in patients will be challenging, because brain tissue is rarely if ever obtained in these patients. Notably, all of our cases with CSF pleocytosis were discharged home, apparently without persistent neurologic deficits. However, if CSF pleocytosis is associated with infarct and/or hemorrhage, we would predict that larger sample sizes may reveal poorer outcomes in patients with this “inflammatory subtype” of PRES.¹⁷

Of the 5 cases with CSF pleocytosis, 4 had eclampsia, raising the possibility that eclampsia may be particularly prone to pleocytosis and may be mediated by different

pathophysiologic mechanisms than PRES due to other causes. However, our sample is small, and this hypothesis is tempered by several other observations. First, we did not find increased rates of infarction or hemorrhage in patients with eclampsia compared to other causes of PRES. Second, in other studies, the number with pleocytosis exceeded the number of patients with eclampsia implying that pleocytosis can occur in patients with PRES due to causes other than eclampsia.^{7,8} Finally, eclampsia has better outcomes than PRES due to other causes,¹⁴ suggesting low predisposition to infarction or hemorrhage. The reason for the association we observed between eclampsia and CSF pleocytosis warrants further investigation.

Our study has several limitations. It was a retrospective study conducted at a tertiary care center. There may be referral bias, as more complicated patients may be overrepresented. There is selection bias, particularly regarding which patients with PRES undergo lumbar puncture. However, we did not find evidence of clinical or radiographic differences between those who do and those who do not undergo lumbar puncture. The clinical data used in the analysis were collected from written medical records, which may not capture some information (eg, a clinical symptom may have been present but not recorded in the chart) and may at times be incomplete, illegible, or otherwise limited. Similarly, CSF data was limited to the tests ordered for clinical diagnostic purposes. In the future, access to physical CSF specimens, either prospectively or via biobanking, may be useful for more standardized and/or novel testing.

In conclusion, most patients with PRES have normal CSF or mild protein elevation commensurate with the radiographic severity of vasogenic edema, which supports endothelial dysfunction and breakdown of the blood–brain barrier as part of

underlying pathophysiology. A small subset of patients with pleocytosis may represent a distinct subtype of PRES with an inflammatory mechanism and a predisposition toward infarct and/or hemorrhage.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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