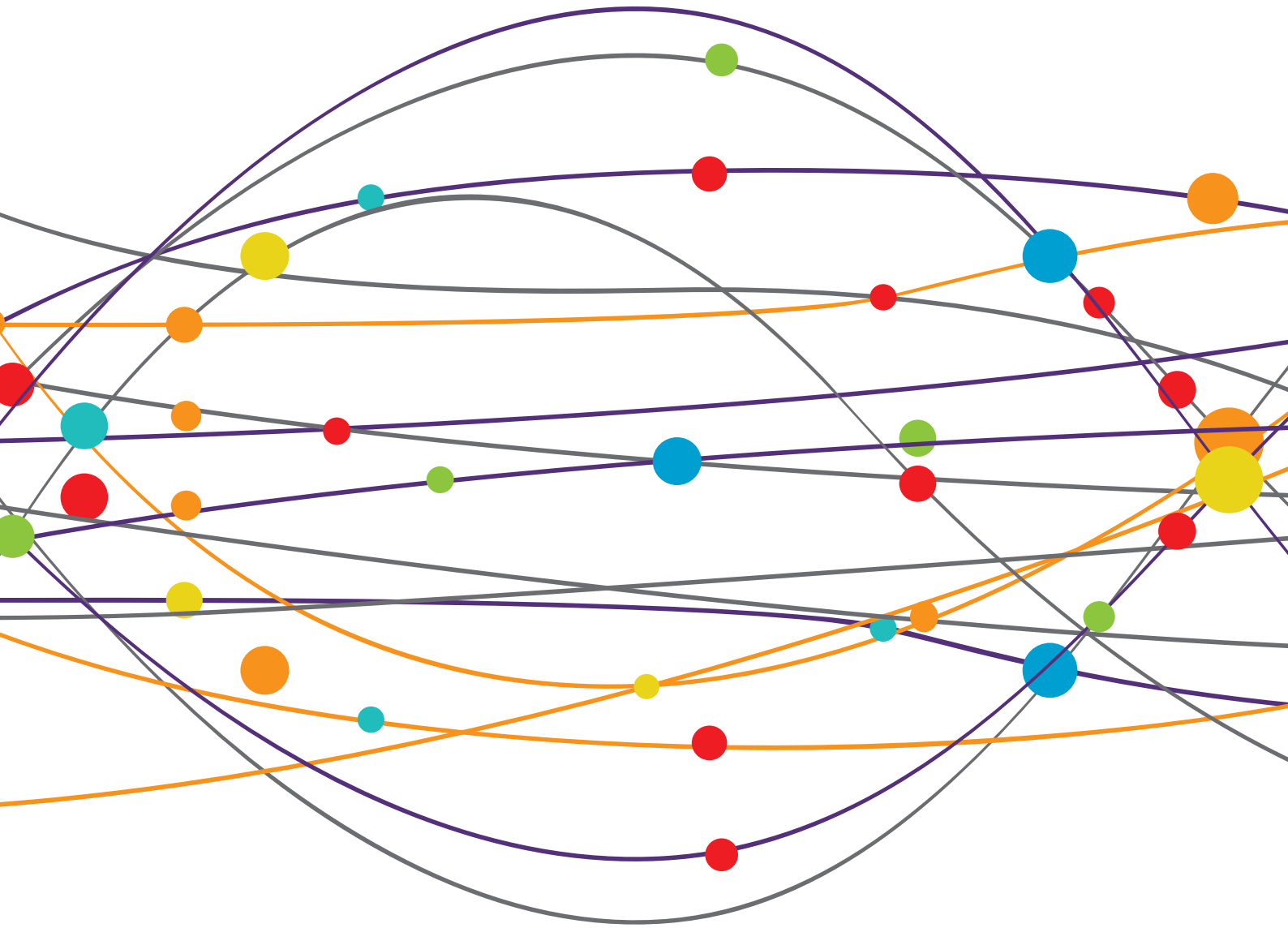
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AND ASSOCIATED DISEASES

EDITED BY: Bo Gao, Stephane Legriel, Alexander Lerner, Max Wintermark and Jeffrey Bruce Rykken

PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88966-004-9
DOI 10.3389/978-2-88966-004-9

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AND ASSOCIATED DISEASES

Topic Editors:
Bo Gao, Affiliated Hospital of Guizhou Medical University, China
Stephane Legriel, Centre Hospitalier de Versailles, France
Alexander Lerner, University of Southern California, United States
Max Wintermark, Stanford University, United States
Jeffrey Bruce Rykken, University of Minnesota Twin Cities, United States

Citation: Gao, B., Legriel, S., Lerner, A., Wintermark, M., Rykken, J. B., eds. (2020). Posterior Reversible Encephalopathy Syndrome and Associated Diseases. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88966-004-9

Table of Contents

04 ***Editorial: Posterior Reversible Encephalopathy Syndrome and Associated Diseases***
Stephane Legriel, Alexander Lerner, Max Wintermark, Jeffrey Bruce Rykken and Bo Gao

07 ***Imaging of Atypical and Complicated Posterior Reversible Encephalopathy Syndrome***
Amin F. Saad, Ruchir Chaudhari and Max Wintermark

13 ***Application of FLAIR Vascular Hyperintensity-DWI Mismatch in Ischemic Stroke Depending on Semi-Quantitative DWI-Alberta Stroke Program Early CT Score***
Lei Song, Cui Lyu, Guiquan Shen, Tingting Guo, Jiangtao Wang, Wanbi Wang, Xiaoming Qiu, Alexander Lerner, Max Wintermark and Bo Gao

23 ***Blood–Brain Barrier Disruption as a Potential Target for Therapy in Posterior Reversible Encephalopathy Syndrome: Evidence From Multimodal MRI in Rats***
Quanlai Wang, Bin Huang, Guiquan Shen, Yu Zeng, Zheng Chen, Chunqiang Lu, Alexander Lerner and Bo Gao

31 ***Delayed Posterior Reversible Leukoencephalopathy Syndrome Triggered by FLOT Chemotherapy***
Jordi Gandini, Mario Manto and Nicolas Charette

39 ***Posterior Reversible Encephalopathy Syndrome in Clinical Toxicology: A Systematic Review of Published Case Reports***
Bérenger Largeau, David Boels, Caroline Victorri-Vigneau, Clara Cohen, Charlotte Salmon Gandonnière and Stephan Ehrmann

51 ***Posterior Reversible Encephalopathy Syndrome: Clinical Features and Outcome***
Archana Hinduja

61 ***Posterior Reversible Encephalopathy Syndrome and Reversible Cerebral Vasoconstriction Syndrome: Clinical and Radiological Considerations***
Fabio Pilato, Marisa Distefano and Rosalinda Calandrelli

69 ***Advanced Imaging Techniques in Diagnosis of Posterior Reversible Encephalopathy Syndrome (PRES)***
Nasim Sheikh-Bahaei, Jay Acharya, Anandh Rajamohan and Paul E. Kim

75 ***Clinical and MRI Features of Posterior Reversible Encephalopathy Syndrome With Atypical Regions: A Descriptive Study With a Large Sample Size***
Kunhua Li, Yang Yang, Dajing Guo, Dong Sun and Chuanming Li

83 ***Posterior Reversible Encephalopathy Syndrome (PRES): Pathophysiology and Neuro-Imaging***
Redmond-Craig Anderson, Vishal Patel, Nasim Sheikh-Bahaei, Chia Shang J. Liu, Anandh G. Rajamohan, Mark S. Shiroishi, Paul E. Kim, John L. Go, Alexander Lerner and Jay Acharya

93 ***Cerebrospinal Fluid Hypovolemia and Posterior Reversible Encephalopathy Syndrome***
Yuan-yuan Zheng, Xiong-peng Weng, Fang-wang Fu, Yun-gang Cao, Yan Li, Guo-qing Zheng and Wei Chen

frontiers in Neurology

EDITORIAL
published: 24 July 2020
doi: 10.3389/fneur.2020.00667

Editorial: Posterior Reversible Encephalopathy Syndrome and Associated Diseases

Stephane Legriel[1,2], *Alexander Lerner*[3], *Max Wintermark*[4], *Jeffrey Bruce Rykken*[5] and *Bo Gao*[6]*

[1] Medico-Surgical Intensive Care Department, Centre Hospitalier de Versailles, Le Chesnay, France, [2] University Paris-Saclay, UVSQ, INSERM, CESP, Team "PsyDev", Villejuif, France, [3] Division of Neuroradiology, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States, [4] Neuroradiology Section, Department of Radiology, Stanford University School of Medicine, Stanford, CA, United States, [5] Department of Radiology, University of Minnesota, School of Medicine, Minneapolis, MN, United States, [6] Department of Radiology, Affiliated Hospital of Guizhou Medical University, Guiyang, China

Keywords: posterior reversal encephalopathy syndrome, prognosis, pathophysiology, magnetic resonance imaging, comorbidities

Editorial on the Research Topic

Posterior Reversible Encephalopathy Syndrome and Associated Diseases

OPEN ACCESS

Edited and reviewed by:
Jan Kassubek,
University of Ulm, Germany

***Correspondence:**
Bo Gao
gygb2004@163.com

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *26 May 2020*
Accepted: *03 June 2020*
Published: *24 July 2020*

Citation:
Legriel S, Lerner A, Wintermark M, Rykken JB and Gao B (2020) Editorial: Posterior Reversible Encephalopathy Syndrome and Associated Diseases. Front. Neurol. 11:667. doi: 10.3389/fneur.2020.00667

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological entity that was highlighted by Hinchey et al. (1). The typical clinical features of PRES are well-known. It associates consciousness impairment varying in severity, seizure activity, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs (2). Acute hypertension is not a pathognomonic sign, although reported associated with PRES in nearly 85% of cases (3). Cerebral MRI brain is the gold standard exam to diagnose PRES. Radiological features consist in bilateral regions of edema typically but exclusively located in the white matter and predominating in the posterior parietal and occipital lobes. Indeed, frontal lobes, temporal or posterior fossa, and cortical gray matter may also be involved (4). Rarely, PRES may imply basal ganglia or even brainstem or medullary white matter (5).

PRES can develop in association with a vast array of conditions such as exposure to toxic agents (i.e., cancer chemotherapy agents, cytotoxic agents, immunotherapy, immunosuppressive agents), acute hypertension with or without underlying acute renal insufficiency, infections, preeclampsia/eclampsia, autoimmune diseases, and other miscellaneous other conditions.

The pathophysiology of PRES is not fully understood (6). There are two main hypotheses that contradict each other. The vasogenic theory involves impaired cerebral autoregulation responsible for an increase in cerebral blood flow, whereas the cytotoxic theory involves endothelial dysfunction with cerebral hypoperfusion (7). However, over the past years, several neuropathological and histological reports have been published allowing to develop further hypotheses (8, 9). Indeed, the cytotoxic theory may itself split into 3 additional hypotheses (6). The first one is the direct cytotoxic hypothesis consisting in a direct exogenic aggression when the patients are exposed to toxics drugs. The second one is the neuropeptide hypothesis, relying on an initial inflammatory aggression

associating lymphocytes T and cytokines activation in cases of autoimmune diseases or in sepsis. The third one is the immune hypothesis implying endothelin 1, thromboxane A2, and prostacyclin release in case of acute hypertension, renal insufficiency, or even immunosuppressor use (10). Activation of vasopressin 1a receptors may be the common denominator of theses hypothetic mechanisms (11).

Outcomes PRES is considered to reversible once the cause is removed. However, severe complications have been reported such as brain ischemia, hemorrhages, or cerebral herniation. Thus, even if limited data are available on functional outcomes, permanent neurological impairment have been described in half of survivors after PRES requiring intensive care unit management (12). Death has been reported in up to 15% of patients (13). Finally, recurrences have been encountered in 7% of cases (14).

PRES must be diagnosed early and investigations must be performed to identify the causative factors (15). Symptomatic treatment should be given immediately, and the causative factors corrected without delay. ICU admission and life-supporting treatments may be required.

This Research Topic proposes a broad overview of PRES, bringing bench to bedside information on pathophysiology, epidemiological data, and review articles to better understand the ins and outs of this entity.

Wang et al. explored pathophysiology of PRES by reporting on an animal model of blood barrier disruption related to acute hypertension. Brain examination of sacrificed rats, after hypertension induction and demonstration of MRI features of PRES, demonstrated a significantly higher content of Evans blue than controls, indicating blood brain barrier disruption.

Hinduja et al. performed a huge overview of PRES, providing epidemiological information on both clinical and neurological features, diagnosis, but also neurodiagnostic tests that could comfort the diagnosis or explore its potential causes, prognosis, and finally management. Interestingly, the author reminds us the neuro-imaging definitions of mild and moderate PRES but also the particularly severe clinical presentation of malignant PRES. Importantly, the author concludes on the importance of large prospective studies to allow a better understanding of PRES.

Anderson et al. combine a general review of clinical and radiological findings of PRES, as well as they develop various pathophysiologic hypothesis.

Gandini et al. reported an interesting case report with literature review about a patient who experienced PRES delayed 2 months after receiving FLOT chemotherapy (5-fluorouracil, oxaliplatin, docetaxel, and folinic acid).

Zheng et al. analyzed 31 cases of cerebrospinal fluid hypovolemia responsible for PRES. The authors report epidural or lumbar puncture as the most common cause, but underline the possible implication of anesthetics and neurosurgical procedures.

Li et al. performed a reappraisal of clinical and MRI features of PRES in patients with atypical regions involvement such as basal ganglia, thalamus, periventricular or deep white matter, cerebellum, brainstem, midbrain, pons, medulla oblongata, and spinal cord. Interestingly, their systematic review concluded that common symptoms of PRES with atypical regions associated headaches (50.7%), altered mental status (43.7%), seizures (41.9%), visual disturbances (34.9%), nausea or vomiting (23.4%), and focal neurological deficits (18.2%). The underlying causes included hypertension, renal diseases, immunosuppressant drugs, and chemotherapy/chemoradiotherapy. Most cases were reversible within 2–3 weeks when properly treated.

Saad et al. performed a complementary review of imaging of atypical and complicated presentations of PRES. Thus, the authors discuss about atypical regional involvement in PRES and report on the various potential complications, namely: hemorrhage, transient or permanent cerebral ischemia, or vasospasm.

Pilato et al. proposed a didactic article on PRES and Reversible Cerebral Vasoconstriction Syndrome (RCVS) reviewing physiopathology, clinical, and neuroimaging features allowing diagnosis and prognosis of both these entities. The authors also emphasize the potential link between RCVS and PRES, an association reported in 10% of cases.

Largeau et al. demonstrated an interest in PRES of poisoning causes. By performing a systematic review, the authors identified 42 reported cases of various causes among alcohol acute/chronic intoxication or alcohol withdrawal, drug overdose, illicit drugs, natural toxin (snake bites, scorpion stings), and chemical substance abuse (organophosphorus).

Sheikh-Bahaei et al. focused their research in sweeping the spectrum of imaging techniques to better clarify the diagnosis and differential diagnosis of PRES, its complications, and thus its potential prognostic implications.

Song et al. provided further progress in PRES prognostication by evaluating the interest of combining diffusion-weighted imaging (DWI)-Alberta Stroke Program Early CT Score (ASPECTS) with fluid-attenuated inversion recovery (FLAIR) vascular hyperintensity (FVH)-DWI mismatch to discriminate the prognosis of cerebral infarction. The authors found that a DWI-ASPECTS score $\geq$ 8 was associated with the highest prognostic value of FVH-DWI mismatch measurement. The identification of such prognostic markers in PRES could allow to propose the evaluation of targeted therapeutic strategies.

We thank our colleagues who provided a huge effort to contribute to this very interesting Research Topic. We are also grateful to the reviewers who did not count their time allowing the production of these quality articles. We hope that this Research Topic might be a real step forward in the understanding of this intriguing and exciting syndrome.

AUTHOR CONTRIBUTIONS

SL wrote the original draft, assembled and incorporated comments from the co-authors, and crafted the final draft. All of the other co-authors contributed to manuscript review and revision.

REFERENCES

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* (1996) 334:494–500. doi: 10.1056/NEJM199602223340803
2. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol.* (2008) 29:1036–42. doi: 10.3174/ajnr.A0928
3. Legriel S, Pico F, Azoulay E. "Understanding Posterior Reversible Encephalopathy Syndrome," in *Annual Update in Intensive Care and Emergency Medicine 2011,* ed J-L Vincent (Berlin; Heidelberg: Springer) (2011). p. 631–53. doi: 10.1007/978-3-642-18081-1_56
4. Rykken JB, Mckinney AM. Posterior reversible encephalopathy syndrome. *Semin Ultrasound CT MR.* (2014) 35:118–35. doi: 10.1053/j.sult.2013.09.007
5. Gao B, Liang H, Liu FL, Lv C. Isolated pons involvement in posterior reversible encephalopathy syndrome in a patient with chronic renal insufficiency: case report and literature review. *Clin Neuroradiol.* (2012) 22:341–4. doi: 10.1007/s00062-012-0162-1
6. Gao B, Lyu C, Lerner A, Mckinney AM. Controversy of posterior reversible encephalopathy syndrome: what have we learnt in the last 20 years? *J Neurol Neurosurg Psychiatry.* (2018) 89:14–20. doi: 10.1136/jnnp-2017-316225
7. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol.* (2008) 29:1043–9. doi: 10.3174/ajnr.A0929
8. Munoz J, Kumar VA, Hamilton J, Pasche LJ, Langford LA, Taggart MW, et al. Posterior reversible encephalopathy syndrome: more than meets the eye. *J Clin Oncol.* (2013) 31:e360–3. doi: 10.1200/JCO.2012.46.6573
9. Willard N, Honce JM, Kleinschmidt-Demasters BK. PRES: review of histological features. *J Neuropathol Exp Neurol.* (2018) 77:100–18. doi: 10.1093/jnen/nlx112
10. Chen Z, Shen GQ, Lerner A, Gao B. Immune system activation in the pathogenesis of posterior reversible encephalopathy syndrome. *Brain Res Bull.* (2017) 131:93–9. doi: 10.1016/j.brainresbull.2017.03.012
11. Largeau B, Le Tilly O, Sautenet B, Salmon Gandonniere C, Barin-Le Guellec C, Ehrmann S. Arginine vasopressin and posterior reversible encephalopathy syndrome pathophysiology: the missing link? *Mol Neurobiol.* (2019) 56:6792–806. doi: 10.1007/s12035-019-1553-y
12. Legriel S, Azoulay E, Resche-Rigon M, Lemiale V, Mourvillier B, Kouatchet A, et al. Functional outcome after convulsive status epilepticus. *Crit Care Med.* (2010) 38:2295–303. doi: 10.1097/CCM.0b013e3181f859a6
13. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Arch Neurol.* (2008) 65:205–10. doi: 10.1001/archneurol.2007.46
14. Burnett MM, Hess CP, Roberts JP, Bass NM, Douglas VC, Josephson SA. Presentation of reversible posterior leukoencephalopathy syndrome in patients on calcineurin inhibitors. *Clin Neurol Neurosurg.* (2010) 112:886–91. doi: 10.1016/j.clineuro.2010.07.023
15. Chen Z, Zhang G, Lerner A, Wang AH, Gao B, Liu J. Risk factors for poor outcome in posterior reversible encephalopathy syndrome: systematic review and meta-analysis. *Quant Imaging Med Surg.* (2018) 8:421–32. doi: 10.21037/qims.2018.05.07

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 04 September 2019
doi: 10.3389/fneur.2019.00964

Imaging of Atypical and Complicated Posterior Reversible Encephalopathy Syndrome

Amin F. Saad[1]*, *Ruchir Chaudhari*[2] and *Max Wintermark*[2]

[1] Department of Radiology, Baylor University Medical Center, Dallas, TX, United States, [2] Department of Radiology, Stanford University, Stanford, CA, United States

Posterior reversible encephalopathy syndrome (PRES) is a condition clinically characterized by headache, altered mental status, seizures, and visual loss and may be associated with systemic hypertension, preeclampsia/eclampsia, chemotherapy, immunosuppressive therapies in the setting of organ transplantation, and uremic encephalopathy. While brain imaging in patients with PRES typically reveals symmetric vasogenic edema within the parietal and occipital lobes, PRES may present with atypical imaging findings such as central brainstem and deep gray involvement without subcortical edema, and even spinal cord involvement. Additionally, PRES may be complicated in some cases by the presence of cytotoxic edema and hemorrhage. This review will serve to summarize the pathophysiologic theories and controversies underlying PRES, imaging features encountered in atypical and complicated PRES, and the implications these findings may have on patient prognosis.

Keywords: PRES (posterior reversible encephalopathy syndrome), encephalopathy, hypertension, intracranial hemorrhage, pathophsiology

OPEN ACCESS

Edited by:
Jan Kassubek,
University of Ulm, Germany

Reviewed by:
Chuanming Li,
Chongqing Medical University, China
Xudong Shen,
Guizhou Medical University (GMU), China

***Correspondence:**
Amin F. Saad
asaad@americanrad.com

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *02 July 2019*
Accepted: *22 August 2019*
Published: *04 September 2019*

Citation:
Saad AF, Chaudhari R and Wintermark M (2019) Imaging of Atypical and Complicated Posterior Reversible Encephalopathy Syndrome. Front. Neurol. 10:964. doi: 10.3389/fneur.2019.00964

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a syndrome affecting the CNS with a range of clinical presentations, most often including headache, altered mental status, seizures, and visual loss. PRES was first described in 1996 by Hinchey et al. (1). A multitude of conditions may lead to the development of PRES, with most common etiologies reported including moderate to severe hypertension, preeclampsia/eclampsia, infection with sepsis and shock, autoimmune disease such as systemic lupus erythematosus, multidrug chemotherapy regimens most often in the setting of hematopoietic malignancies, and in the setting of bone marrow and stem cell transplantation (2). The typical CT and MRI imaging features encountered in the setting of PRES consist of near symmetric hemispheric vasogenic edema affecting subcortical white matter and often extending to involve overlying cortex, best demonstrated with FLAIR sequences (3). Diffusion weighted imaging (DWI) usually confirms the vasogenic nature of this edema with absence of restricted diffusion. While variations exist in the most commonly encountered patterns of edema distribution, Bartynski et al. in an analysis of a large cohort of patients, described lesion distribution patterns to include a holohemispheric watershed pattern (22.8% of 136 patients), superior frontal sulcus pattern (27.2%), and a dominant parietal-occipital pattern (22.1%), with partial or asymmetric expression of these primary patterns in 27.9% of patients. Notably, 98% of patients exhibited some degree of involvement of the parietal-occipital regions (4).

PATHOPHYSIOLOGY OF PRES

The precise pathophysiologic mechanism underlying the development of PRES remains unknown, and controversy exists regarding competing mechanistic theories. The first theory describes severe hypertension which exceeds the natural autoregulatory limits of the brain (150–160 mm Hg), with resultant injury to the capillary bed, fluid egress, and resultant vasogenic edema. This theory is supported by the common occurrence of hypertension encountered in patients with PRES (50–70%) (5), animal studies demonstrating the development of vasogenic edema and hyperperfusion with experimentally elevated blood pressure (6), and reports of hyperperfusion in patients imaged with Tc99m-HMPAO single-photon emission CT (SPECT) (7). Problems with this theory include the development of PRES in patients with normal or only mildly increased blood pressure, studies demonstrating hypoperfusion in PRES, and a lack of correlation with the degree of brain edema and the severity of hypertension (5).

A competing theory of PRES pathophysiology describes the development of vasoconstriction due to autoregulatory compensation of severe hypertension leading to reduced brain perfusion, ischemia, and the development of vasogenic edema (8). In this theory, if left untreated or severe, the resultant ischemia may go on to frank infarction, with development of diffusion restriction. This theory is supported by the development of PRES in systemic conditions characterized by endothelial injury and a typical lack of severe hypertension such as sepsis, following bone marrow transplantation, and systemic chemotherapy. Additionally, evidence of vasculopathy in the setting of PRES as demonstrated using catheter angiography with vasoconstriction and reduced perfusion supports this theory, as does the common occurrence of PRES imaging features in a watershed distribution. Finally, imaging studies using MR perfusion have demonstrated hypoperfusion in PRES (9, 10).

A third theory attempting to explain the development of PRES is immune system activation with a resultant cascade which induces endothelial dysfunction. In this theory, cytokines such as tumor necrosis factor alpha and interleukin-1 are released due to a systemic insult, which serve to induce expression of adhesion molecules which interact with circulating leukocytes and trigger the release of reactive oxygen species and proteases, leading to endothelial damage and fluid leakage (11). Additionally, these cytokines cause astrocytes to produce vascular endothelial growth factor (VEGF), which causes an increase in blood brain barrier permeability through the weakening of endothelial cell tight junctions, and has been shown to also activate the vesiculo-vacuolar organelle providing a major route for the extravasation of fluids and macromolecules (12). Marra et al. (11) note that increased circulating levels of VEGF in pre-eclamptic patients, a syndrome significantly associated with PRES, result in a 5-fold increase in vascular permeability (13). Increased levels of leukocyte adhesion molecules have also been associated with preeclampsia, allogenic bone marrow transplantation, solid organ transplantation, and infection/sepsis/shock (5). Brain biopsy in a case of PRES following cardiac transplantation showed endothelial activation, T-cell trafficking, and endothelial VEGF expression (14). In this theory, hypertension and vasoconstriction are both consequences and not primary causative factors in PRES pathogenesis (11, 15).

A recently published theory of the pathophysiology of PRES is that of arginine vasopressin (AVP) hypersecretion (16). Multiple clinical conditions associated with the development of PRES, such as eclampsia and sepsis, are associated with AVP hypersecretion. Largeau et al. thus theorize that this increase in AVP secretion or AVP receptor density results in activation of vasopressin V1a with associated cerebral vasoconstriction, endothelial dysfunction, and cerebral ischemia with resultant cytotoxic edema. This may then lead to increased endothelial permeability and subsequent vasogenic edema (16). This theory may open the possibility for pharmacologic therapies for PRES targeting the AVP axis.

ATYPICAL REGIONAL INVOLVEMENT IN PRES

While PRES most commonly manifests on imaging as subcortical/cortical edema within the cerebral hemispheres with a parietal-occipital predominance and some variable involvement of deep structures as well as the posterior fossa, it may occur in an atypical fashion (**Figure 3**) with isolated involvement of deep gray nuclei, brainstem/cerebellar hemispheres, and exceptionally the spinal cord without cerebral hemispheric involvement. These findings may lead to a diagnostic dilemma, with a delay in diagnosis and reversal of the offending condition potentially leading to a poor patient outcome. In a series of 124 patients with PRES, McKinney et al. noted 4% of patients had imaging findings of a "central variant" PRES, revealing brainstem or deep gray nuclei involvement without involvement of the cerebral hemispheres (17). In an additional series by McKinney et al. (18) consisting of 76 patients, involvement included the thalamus (30.3%), cerebellum (34.2%), brainstem (18.4%), and basal ganglia (11.8%) with unilateral involvement seen in 2.6%. Liman et al. (19) studied a cohort of 96 patients with PRES and found deep gray nuclei involvement in ∼25% of patients and infratentorial involvement (predominantly cerebellar and pontine) in more than 50% of patients. These authors found a parieto-occipital pattern in 53%, superior frontal sulcus pattern in 17%, holohemispheric watershed pattern in 17%, and a central pattern in 14%. Another cohort of 50 patients studied by Kastrup et al. (20) demonstrated basal ganglia involvement in 1.6% of patients and cerebellar involvement in 6.5%. In the few reported cases of spinal cord involvement by PRES, all patients demonstrated confluent expansile central cord T2 signal elevation spanning at least four segments, with involvement of the cervicomedullary junction (21). Five of these nine patients had supratentorial involvement, while all revealed brainstem involvement.

HEMORRHAGE IN PRES

Posterior reversible encephalopathy syndrome (PRES) may be complicated by the presence of hemorrhage (**Figures 1**–**3**), on the

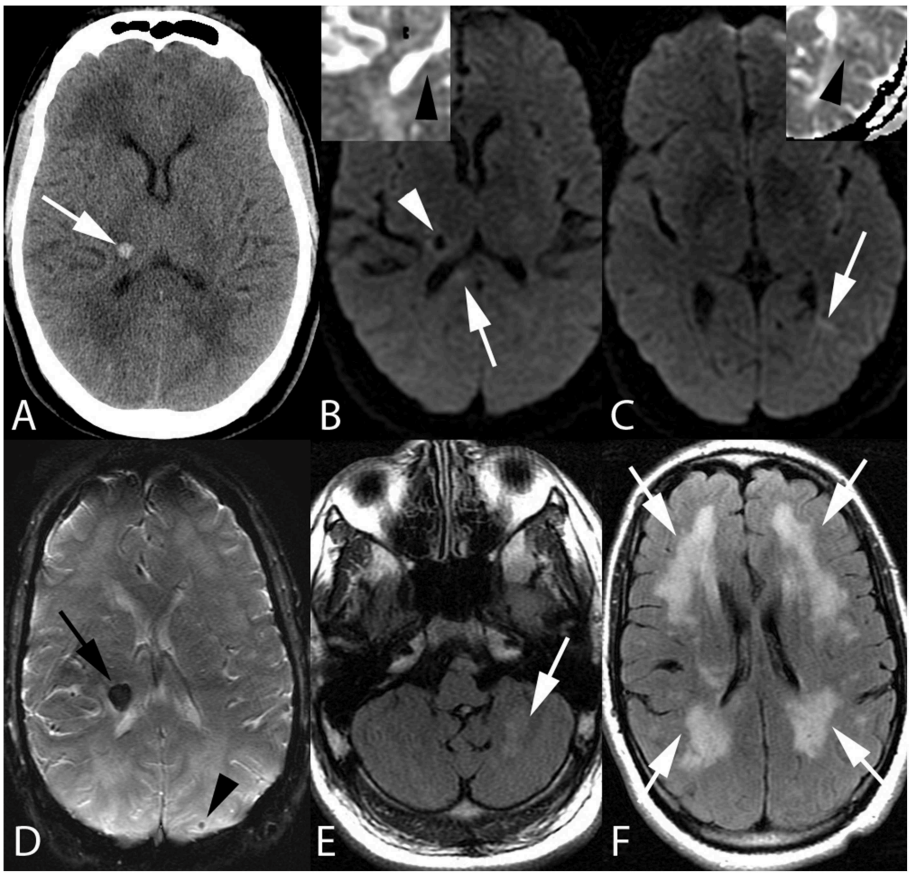


FIGURE 1 | Fifty-five-year-old man with end stage renal disease and severe hypertension. Axial CT image **(A)** reveals a focal parenchymal hemorrhage at the junction of the right thalamus and posterior limb of the right internal capsule (arrow). Axial DWI images with ADC inserts **(B,C)** show foci of diffusion restriction within the right corpus callosum splenium (arrow, **B**) and left temporo-occipital periventricular white matter (arrow, **C**). ADC maps confirm diffusion restriction (insert **B,C**, arrowheads). Again seen is right thalamocapsular hematoma (arrowhead, **B**). Axial SWI image **(D)** demonstrates blooming of right thalamocapsular hematoma (arrow) in addition to a punctate hemorrhage within left parietal subcortical white matter (arrowhead). Axial FLAIR images **(E,F)** show left cerebellar (arrow, **E**) and confluent bilateral frontoparietal (arrows, **F**) edema.

order of 15% in a series of 151 patients studies by Hefzy et al. (22) which utilized gradient echo T2* (GRE) images. In this series, focal petechial/microhemorrhages (<5 mm), sulcal subarachnoid hemorrhage, and focal hematoma formation were seen with equal frequency. Of note, hemorrhage was significantly more common in patients following bone marrow transplantation than in solid organ transplantation, potentially based on underlying coagulopathy, with similar increased incidence in those patients receiving systemic anticoagulation. No difference in hemorrhage incidence was seen in patients with normal, mildly elevated, or severely elevated blood pressure. In a series of 31 patients reported by McKinney et al. (23) utilizing susceptibility-weighted images (SWI), hemorrhage was more commonly detected (64.5% of patients). Microhemorrhages were seen in 58.1% of patients at presentation and 64.7% at follow-up, while subarachnoid hemorrhage was seen in 12.9% and parenchymal hematoma formation was seen in 6.5%. In the series reported by Liman et al. (19), microhemorrhages were seen in 14% of patients, sulcal subarachnoid hemorrhage in 4%, and parenchymal hematoma formation in 11%. Kastrup et al. (20) found microhemorrhages in 17% of the 29 patients who had T2* or SWI images available in their cohort. The overall rate of hemorrhage encountered in PRES range from 15 to 65%, with the majority likely reflecting the majority of the higher reported incidences (24). The mechanism of hemorrhage in PRES may be secondary to pial vessel rupture in the setting of severe hypertension or reperfusion injury in the setting of vasoconstriction (25).

DIFFUSION RESTRICTION IN PRES

Vasogenic edema predominates in PRES, however cases may be complicated by the development of cytotoxic edema as indicated by diffusion restriction (**Figure 1**). Some cases may show reversibility of diffusion restriction similar to findings seen in patients with transient cerebral ischemia, venous ischemia/infarction, and vasospasm following subarachnoid hemorrhage although restriction often progresses to frank infarction with encephalomalacia identified on follow-up. In a series of 76 patients reported by McKinney et al. (18), 17.3%

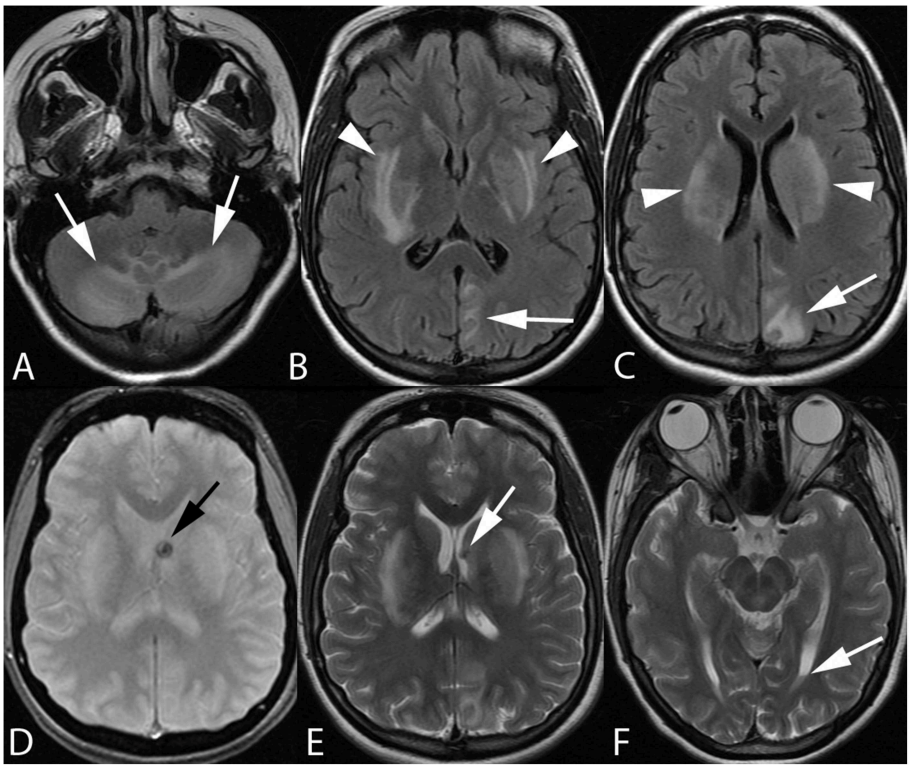


FIGURE 2 | Twenty-one-year-old pregnant woman with eclampsia. Axial FLAIR images **(A–C)** demonstrate bilateral cerebellar hemisphere and vermian (arrows, **A**), bilateral lentiform/caudate and capsular (arrowheads, **B,C**), and left parieto-occipital edema. Axial GRE **(D)** and T2-weighted **(E,F)** images reveal focal hemorrhage within the left caudothalamic groove (arrow, **D,E**) extending to the left lateral ventricular body with a small hematocrit level within the left occipital horn (arrow, **F**) from intraventricular extension of hemorrhage.

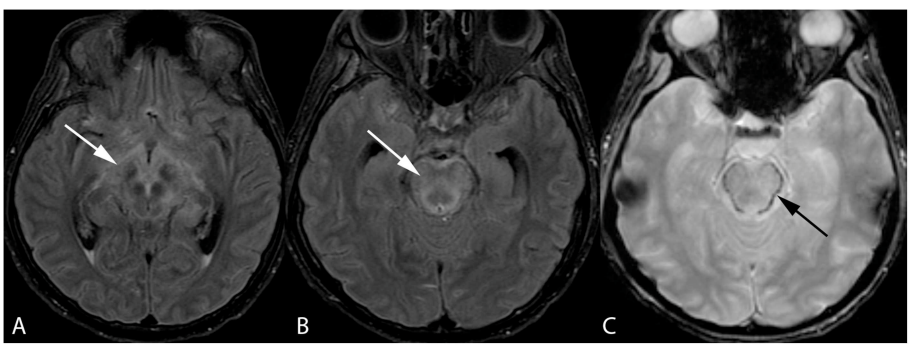


FIGURE 3 | Forty-two-year-old woman with history of bone marrow transplantation. Axial FLAIR images **(A,B)** demonstrate central variant PRES with edema involving the midbrain with extension to the hypothalamus and optic tracts (arrow, **A**) and pons (arrow, **B**). Axial GRE image **(C)** shows petechial hemorrhage at the periphery of the pons (arrow).

demonstrated areas of restricted diffusion. Covarrubias et al. (26) reported a series of 22 patients with PRES, with six patients (22%) demonstrating abnormal diffusion signal and two patients revealing progression to infarction on follow-up. In the setting of extensive vasogenic edema encountered in PRES, some areas of cytotoxic edema amidst regions of vasogenic edema may demonstrate isointense ADC signal, representing ADC pseudonormalization (24).

CONTRAST ENHANCEMENT IN PRES

Contrast enhancement has been variably reported in the setting of PRES, typically presenting as leptomeningeal or gyral cortical enhancement (24). Enhancement was seen in 37.7% of patients studied by McKinney et al. (18), who also reported the rare occurrence of deep white matter or overlying dural enhancement. Karia et al. (27) reported enhancement in 43.7% of 135

patients studied, with a leptomeningeal pattern in 17.8% and a leptomeningeal plus cortical pattern in 15.6%. These authors found no significant association between the presence or pattern of enhancement and patient outcome of MR imaging severity of PRES.

VASOSPASM IN PRES

Vasculopathic changes are commonly encountered on vessel imaging in PRES patients. Bartynski et al. (28) found evidence of diffuse vasoconstriction, focal vasculopathy, or vessel pruning in 87% of 46 patients studied with catheter and/or MR angiography (MRA). Of 11 patients with follow up MRA examinations, seven patients revealed improvement or resolution of vasculopathic changes. It is important to note the similarity of these findings with those encountered in reversible cerebral vasoconstriction syndrome (RCVS), which shares significant clinical and radiologic features with PRES (24). Additionally, 9–38% of patients with RCVS demonstrate reversible vasogenic edema (29, 30). The underlying etiologic theories of RCVS include disturbance of cerebrovascular tone and endothelial dysfunction, similar to theories of PRES pathogenesis, and the two diagnoses may reside along a spectrum of manifestations of abnormal cerebral autoregulation and/or endothelial damage (31).

ESTABLISHING PATIENT PROGNOSIS IN PRES

Although PRES is typically reversible (70–90% of cases) (24) and patient prognosis is often positive with removal of the offending condition leading to PRES, complication by hemorrhage and/or diffusion restriction often portends a poorer patient prognosis. In the series reported by Hefzy et al. (22), 23% of patients with PRES complicated by hemorrhage had a poor clinical outcome, with death of six of the seven patients. In the series by Covarrubias et al. (26), death was seen in 50% of the patients who exhibited diffusion signal changes. Additionally, brainstem involvement by PRES is associated with a poorer outcome, with two of three patients who died despite having no diffusion changes in the series by Covarrubias et al. (26) demonstrating extensive brainstem edema. In a review of PRES cases performed by Schweitzer et al. (32), 99 cases of PRES were analyzed for vasogenic edema, hemorrhage, and diffusion restriction. Areas of vasogenic edema were given discrete variables from 1 to 10 based on regional involvement, and the term "extensive vasogenic edema" was defined as involvement of five or more areas. Hemorrhage was categorized based on the presence or absence of mass effect, and diffusion restriction was confirmed with ADC maps. "Advanced radiologic PRES" was defined as at least one of the following: extensive vasogenic edema, diffusion restriction, or hemorrhage with mass effect. Patient outcomes were based on discharge disposition: home or rehabilitation vs. death or hospice, as well as modified Rankin scale (mRS) with an mRS of 3–6 considered a poor outcome. These investigators found that extensive vasogenic edema, presence of hemorrhage, and diffusion restriction (all criteria for "advanced radiologic PRES") were associated with poor clinical outcomes in terms of both hospital discharge and mRS. In this study, brainstem edema was not associated with a poor mRS at discharge.

CONCLUSION

Posterior reversible encephalopathy syndrome (PRES) is a condition commonly encountered in clinical practice, with prompt recognition and intervention to remove precipitating factors serving to optimize patient outcomes and reverse symptoms as well as imaging changes. The recognition of atypical imaging manifestation of PRES is important to avoid delays in diagnosis and treatment, as is identification of complicating factors which may adversely affect patient prognosis.

AUTHOR CONTRIBUTIONS

AS wrote the majority of the manuscript. RC wrote portions of the manuscript and supplied case material. MW provided guidance and feedback in the manuscript preparation and research on the topic.

REFERENCES

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. (1996) 334:494–500. doi: 10.1056/NEJM199602223340803
2. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol*. (2008) 29:1036–42. doi: 10.3174/ajnr.A0928
3. Casey SO, Sampaio RC, Michel E, Truwit CL. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. *AJNR Am J Neuroradiol*. (2000) 21:1199–206.
4. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol*. (2007) 28:1320–7. doi: 10.3174/ajnr.A0549
5. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol*. (2008) 29:1043–9. doi: 10.3174/ajnr.A0929
6. MacKenzie ET, Strandgaard S, Graham DI, Jones JV, Harper AM, Farrar JK. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood brain barrier. *Circ Res*. (1976) 39:33–41. doi: 10.1161/01.RES.39.1.33
7. Schwartz RB, Jones KM, Kalina P, Mantello MT, Garada B, Holman BL. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. *AJR Am J Roentgenol*. (1992) 159:379–83. doi: 10.2214/ajr.159.2.1632361
8. Toole JF. Lacunar syndromes and hypertensive encephalopathy. In: Toole JF, editor. *Cerebrovascular Disorders*. 5th ed. New York, NY: Raven (1999). p. 342–55.
9. Brubaker LM, Smith JK, Lee YZ, Lin W, Castillo M. Hemodynamic and permeability changes in posterior reversible encephalopathy syndrome measured by dynamic susceptibility perfusion-weighted MR imaging. *AJNR Am J Neuroradiol*. (2005) 26:825–30.

10. Engelter ST, Petrella JR, Alberts MJ, Provenzale JM. Assessment of cerebral microcirculation in a patient with hypertensive encephalopathy using MR perfusion imaging. *AJR Am J Roentgenol*. (1999) 173:1491–3. doi: 10.2214/ajr.173.6.10584788
11. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndromeL the endothelial hypotheses. *Med Hypotheses*. (2014) 82:619–22. doi: 10.1016/j.mehy.2014.02.022
12. Park SJ, Pai KS, Kim JH, Shin JI. Could increased vascular endothelial growth factor induced by interleukin 17 be the cause of posterior reversible encephalopathy syndrome in systemic lupus erythematosus? *J Rheumatol*. (2012) 39:870–1. doi: 10.3899/jrheum.111124
13. Bills VL, Salmon AH, Harper SJ, Overton TG, Neal CR, Jeffery B, et al. Impaired vascular permeability regulation caused by the VEGF165b splice variant in pre-eclampsia. *BJOG*. (2011) 118:1253–61. doi: 10.1111/j.1471-0528.2011.02925.x
14. Horbinski C, Bartynski WS, Carson Walter E, Hamilton RL, Tan HP, Cheng S. Reversible encephalopathy after cardiac transplantation: histologic evidence of endothelial activation, T cell specific trafficking, and vascular endothelial growth factor expression. *AJNR Am J Neuroradiol*. (2009) 30:588–90. doi: 10.3174/ajnr.A1311
15. Tetsuka S, Ogawa T. Posterior reversible encephalopathy syndrome: a review with emphasis on neuroimaging characteristics. *J Neurol Sci*. (2019) 404:72–9. doi: 10.1016/j.jns.2019.07.018
16. Largeau B, Le Tilly O, Sautenet B, Salmon Gandonniere C, Barin-Le Guellec C, Ehrmann S. Arginine vasopressin and posterior reversible encephalopathy syndrome pathophysiology: the missing link? *Mol Neurobiol*. (2019). doi: 10.1007/s12035-019-1553-y. [Epub ahead of print].
17. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical edema. *AJR Am J Roentgenol*. (2013) 201:631–8. doi: 10.2214/AJR.12.9677
18. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, et al. Posterior reversible encephalopathy syndrome; incidence of atypical regions of involvement and imaging findings. *AJR Am J Roentgenol*. (2007) 189:904–12. doi: 10.2214/AJR.07.2024
19. Liman TG, Bohner G, Heuschmann PU, Endres M, Siebert E. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the restrospective Berlin PRES study. *J Neurol*. (2012) 259:155–64. doi: 10.1007/s00415-011-6152-4
20. Kastrup O, Schlamann M, Moenninghoff C, Forsting M, Goericke S. Posterior reversible encephalopathy syndrome: the spectrum of MR imaging patterns. *Clin Neuroradiol*. (2015) 25:161–71. doi: 10.1007/s00062-014-0293-7
21. Ollivier M, Bertrand A, Clarencon F, Gerber S, Deltour S, Domont F, et al. Neuroimaging features in posterior reversible encephalopathy syndrome: a pictoral review. *J Neurol Sci*. (2017) 373:188–200. doi: 10.1016/j.jns.2016.12.007
22. Hefzy HM, Bartynski WS, Boardman JF, Lacomis D. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. *AJNR Am J Neuroradiol*. (2009) 30:1371–9. doi: 10.3174/ajnr.A1588
23. McKinney AM, Sarikaya B, Gustafson C, Truwit CL. Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging. *AJNR Am J Neuroradiol*. (2012) 33:896–903. doi: 10.3174/ajnr.A2886
24. Brady E, Parikh NS, Navi BB, Gupta A, Schweitzer AD. The imaging spectrum of posterior reversible encephalopathy syndrome: a pictoral review. *Clin Imaging*. (2018) 47:80–9. doi: 10.1016/j.clinimag.2017.08.008
25. Doss-Esper CE, Singhal AB, Smith MS, Henderson GV. Reversible posterior leukoencephalopathy, cerebral vasoconstriction, and strokes after intravenous immune globulin therapy in guillain-barre syndrome. *J Neuroimaging*. (2005) 15:188–92. doi: 10.1177/1051228404273820
26. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. *AJNR Am J Neuroradiol*. (2002) 23:1038–48.
27. Karia SJ, Rykken JB, McKinney ZJ, Zhang L, McKinney AM. Utility and significance of gadolinium-based contrast enhancement in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol*. (2016) 37:415–22. doi: 10.3174/ajnr.A4563
28. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol*. (2008) 29:447–55. doi: 10.3174/ajnr.A0839
29. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain*. (2007) 130:3091–101. doi: 10.1093/brain/awm256
30. Singhal AB, Hajj-Ali RA, Topcuoglu MA, Fok J, Bena J, Yang D, et al. Reversible cerebral vasoconstriction syndrome: analysis of 139 cases. *Arch Neurol*. (2011) 68:1005–12. doi: 10.1001/archneurol.2011.68
31. Miller TR, Shivashankar R, Mossa-Basha M, Gandhi D. Reversible cerebral vasoconstriction syndrome, part 1: epidemiology, pathogenesis, and clinical course. *AJNR Am J Neuroradiol*. (2015) 36:1392–9. doi: 10.3174/ajnr.A4214
32. Schweitzer AD, Parikh NS, Askin G, Nemade A, Lyo J, Karimi S, et al. Imaging characteristics associated with clinical outcomes in posterior reversible encephalopathy syndrome. *Neuroradiology*. (2017) 59:379–86. doi: 10.1007/s00234-017-1815-1

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past collaboration with one of the authors MW.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 September 2019
doi: 10.3389/fneur.2019.00994

Application of FLAIR Vascular Hyperintensity-DWI Mismatch in Ischemic Stroke Depending on Semi-Quantitative DWI-Alberta Stroke Program Early CT Score

Lei Song[1,2], Cui Lyu[3], Guiquan Shen[1], Tingting Guo[4], Jiangtao Wang[2], Wanbi Wang[2], Xiaoming Qiu[5], Alexander Lerner[6], Max Wintermark[7] and Bo Gao[1]**

[1] Department of Radiology, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [2] Department of Radiology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, China, [3] Healthcare Examination Center, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [4] Department of Radiology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Xiangyang, China, [5] Department of Radiology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi, China, [6] Division of Neuroradiology, Department of Radiology, Keck School of Medicine University of Southern California, Los Angeles, CA, United States, [7] Neuroradiology Section, Department of Radiology, Stanford University School of Medicine, Stanford, CA, United States

OPEN ACCESS

Edited by:
Achim Gass,
Universitätsmedizin Mannheim (UMM), Germany

Reviewed by:
Yu-Chen Chen,
Nanjing Medical University, China
Seyedmehdi Payabvash,
Yale University, United States

***Correspondence:**
Cui Lyu
ytlvcui@126.com
Bo Gao
gygb2004@163.com

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: 08 June 2019
Accepted: 02 September 2019
Published: 26 September 2019

Citation:
Song L, Lyu C, Shen G, Guo T, Wang J, Wang W, Qiu X, Lerner A, Wintermark M and Gao B (2019) Application of FLAIR Vascular Hyperintensity-DWI Mismatch in Ischemic Stroke Depending on Semi-Quantitative DWI-Alberta Stroke Program Early CT Score. Front. Neurol. 10:994. doi: 10.3389/fneur.2019.00994

Objective: Diffusion-weighted imaging (DWI)-Alberta Stroke Program Early CT Score (ASPECTS) is a simple, widely used method to estimate the size of the infarct. Our aim is to determine whether there is a relationship between DWI-ASPECTS and fluid-attenuated inversion recovery (FLAIR) vascular hyperintensity (FVH)-DWI mismatch and to better quantify FVH-DWI mismatch to assess the prognosis of cerebral infarction.

Materials and Methods: A retrospective analysis of 109 patients with MCA stenosis or occlusion with cerebral infarction was performed by dividing this cohort into FVH-DWI match group and FVH-DWI mismatch group based on FVH and DWI results. The clinical and imaging data of these two groups of patients were reviewed and analyzed to identify associations between FVH-DWI mismatch and prognosis of patients for preservation of neurological function. Correlation between DWI-ASPECTS and FVH-DWI mismatch was also performed.

Results: FVH-DWI mismatch was present in 66/109 (60.55%) patients, and FVH-DWI match was present in 43/109 (39.45%). Patients with FVH-DWI mismatch had higher DWI-ASPECTS (7.0 vs. 4.0, $P < 0.001$) and lower mRS at 3 months (3.0 vs. 4.0, $P < 0.001$) than patients without FVH-DWI mismatch. Multiple regression analysis suggested that DWI-ASPECTS (OR = 4.7, 95% CI = 2.5–9.2, $P < 0.001$) remained significantly associated with FVH-DWI mismatch. Two threshold points for DWI-ASPECTS of 3 and 8 can be used to distinguish whether there is a mismatch in FVH-DWI by smooth curve fitting.

Conclusions: The DWI-ASPECTS score was an independent predictor of FVH-DWI mismatch. At DWI-ASPECTS $\leq$ 3, the FVH-DWI mismatch offers no prognostic value; whereas, at DWI-ASPECTS $\geq$ 8, the FVH-DWI mismatch had the highest prognostic value. DWI-ASPECTS can roughly determine whether there is a FVH-DWI mismatch in order to select optimal clinical treatment and accurately assess prognosis.

Keywords: cerebral infarction, magnetic resonance imaging, ASPECTS, fluid-attenuated inversion recovery vascular hyperintensity, stroke

INTRODUCTION

Accurate assessment of the prognosis of ischemic stroke can help in selection of optimal treatment and may improve patient survival rate and reduce the rate of disability (1–3). Greater collateral circulation can reduce the infarct size, improve the patient's clinical prognosis, and further reduce the risk of recurrence (4). The latest DEFUSE 3 trial showed that large vessel occlusion thrombectomy in patients within 6–16 h after the onset of stroke resulted in lower disability and higher functional independence at 3 months, and this study have revealed that collateral circulation plays an important role in predicting outcomes (1). Multiple previous studies have explored the use of non-invasive angiography for assessment of collateral circulation after ICA occlusion. Fluid-attenuated inversion recovery vascular hyperintensity (FVH) has also been widely studied for such assessment. The current investigations of the relationship between FVH and DWI have suggest that FVH-DWI mismatch rather than FVH-DWI match can better predict prognosis (5–8). Several previous studies suggested that FVH-DWI mismatch can help assess the clinical neurological outcome, ischemic penumbra and thrombolytic therapy in patients with acute cerebral infarction (5, 7, 8). FVH-DWI mismatch has high sensitivity to PWI-DWI mismatch and can therefore be used to rapidly identify acute ischemic stroke patients with proximal vascular occlusion and reperfusion therapy (7). However, there are no unified FVH quantitative assessment methods to discriminate the relationship between FVH and DWI (7–9).

The Alberta Stroke Program Early CT Score (ASPECTS) is simple and semi-quantitative scoring systems that evaluate early ischemic changes in the middle cerebral artery territory (10). However, DWI-ASPECTS has great advantages compared to ASPECTS. This MRI based scoring system is more sensitive and consistent in detecting ischemic changes than CT and it can measure the volume of the lesions quickly and reliably. ASPECTS was used to approximately estimate the extent of hypoperfusion and the perfusion-weighted imaging (PWI)-DWI mismatch (11, 12). Above all, these prior investigations have not studied the relationship between FVH-DWI mismatch and DWI-ASPECTS. The aim of this study is to evaluate the association between FVH-DWI mismatch and DWI-ASPECTS as well as semi-quantitatively distinguish FVH-DWI mismatch and FVH-DWI match by means of DWI-ASPECTS. The hypothesis is that the association between FVH-DWI mismatch and DWI-ASPECTS would be better in acute ischemic stroke patients.

MATERIALS AND METHODS

Patients

All neurology patients who were hospitalized in the Affiliated Hospital of Guizhou Medical University from September 2015 to December 2017 were retrospectively identified and reviewed in the Medical Image Archiving and Communication System (PACS). Patients were screened according to inclusion criteria: (1) presence of M1 portion of the middle cerebral artery (MCA) stenosis; (2) MRI includes routine sequences, DWI, FLAIR sequence, and magnetic resonance angiography (MRA). Exclusion criteria: (1) peripheral vertigo, encephalitis, hysteria, brain tumors and patients with unknown diagnosis; (2) patients with severe stenosis or occlusion of the posterior circulation; (3) presence of cardiac pacemaker or metal foreign body preventing completion of the MRI examination, or resulting in severe artifacts and non-diagnostic examination; and (4) very early arterial thrombolysis or interventional treatment.

The patients enrolled in the present study were outside of the time window (>6 h) and they were reluctant to receive endovascular treatment. Total acquisition time was <10 min. All patients were admitted to the hospital to improve microcirculation, and were receiving neurotrophic drugs and other conventional concurrent care. All patients charts were reviewed for collection of demographic, clinical, and laboratory data including the following information: age, sex; smoking, alcohol, previous stroke/transient ischemic attack, coronary artery disease, arterial fibrillation; systolic blood pressure, diastolic blood pressure; blood glucose, cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, homocysteine, National Institutes of Health Stroke Scale Score (NIHSS) at admission and discharge. The patients were followed up 3 months after discharge and scored using Modified Rankin Scale (mRS).

MR Imaging Protocol

MRI examinations were performed using a Philips Achieva X-Series 3.0T superconducting MR scanner and 8-channel SENSE head coil. Axis-position scanning was performed using a single-shot echo planar imaging sequence (SS-EPI) parallel to the anterior commissure-posterior (AC-PC) plane and spanning the entire brain. All patients had cranial MR scans including transverse fast spin echo (FSE) T_2WI, transverse T_2 FLAIR, transverse SE T_1WI, cross-sectional DWI (b = 0, 1,000 s/mm^2) and 3D time-of-flight (3D TOF) MRA sequences. Specific scanning parameters as follows: (1) FSE T_2WI: TR = 3,780 ms,

TE = 104.5 ms, slice thickness = 6.0 mm, inter-slice gap = 1.8 mm, FOV = 240 × 180 mm, matrix size = 320 × 224, NEX = 1; (2) T_2 FLAIR: TR = 8,002 ms, TE = 200 ms, TI = 2,000 ms, slice thickness = 6.0 mm, inter-slice gap = 1.8 mm, FOV = 240 × 240 mm, matrix size = 256 × 192, NEX = 1; (3) T_1WI: TR = 2,459 ms, TE = 27.2 ms, TI = 760 ms, slice thickness = 6.0 mm, inter-slice gap = 6.0 mm, FOV = 240 mm × 180 mm, matrix size = 228 × 192, NEX = 2; (4) DWI: TR = 4,500 ms, TE = 81.7 ms, slice thickness with no inter-slice gap, FOV = 240 × 240 mm, matrix size = 128 × 128, NEX = 2; (5) 3D TOF MRA: TR = 24 ms, TE = 2.9 ms, slice thickness = 1 mm, inter-slice gap = 0.7 mm, FOV = 210 × 185 mm, matrix size = 288 × 192, NEX = 1.

Image Analysis

FVH was judged by the following standards (13): (1) FVH is defined as a focal, tubular or serpentine hyperintensity on the FLAIR image in the lateral fissure, sulci or near the brain surface; (2) corresponding T2WI image demonstrates flow void; (3) typical signs appear at least on one level. If the above three criteria are satisfied, the FVH sign is positive, otherwise it is considered negative. The FVH score was calculated according to the Olindo et al. (14) method, which was continuously observed from first M1-MCA appearance. The absence of FVH on one slice was rated as 0 point, and when one or more FVHs found on one slice they were rated as 1 point. FVH-DWI mismatch means the FVH signal range exceeds the DWI lesions whereas the hyperintensity area on DWI was excluded when measuring FVH (recorded only FVH outside DWI), and FVH-DWI match refers to the FVH within the hyperintensity area on DWI (recorded FVH only inside DWI) (9) (As shown in **Figures 1**, **2**).

Patients were divided into five groups based on the symptom onset to scan time gap, namely 1 day or less group, 2–4 days group, 5–9 days group, 10–13 days group, more than 14 days group (15). DWI-ASPECTS score quantifies the extent of cerebral infarction in the area of the MCA supply by dividing the area of MCA into 10 at centrum semiovale and basal ganglia area of the cerebral hemisphere. Including the caudate nucleus (C), insula (I), lentiform nucleus (L), internal capsule (IC), anterior cortex of MCA (M1), lateral cortex of MCA (M2), posterior cerebral cortex of MCA (M3), superior cortex of the anterior cerebral cortex of MCA (M4), superior cortex of the lateral cortex of MCA (M5), superior cortex of the posterior cerebral cortex of MCA (M6) (10, 12). Measurement of the degree of vascular stenosis is based on the original images of the 3D-TOF MRA and the reconstructed images. The stenosis rate of MCA is calculated according to the standard of Warfarin-Aspirin for Symptomatic Intracranial Disease study (WASID) (16), that is, the diameter stenosis rate (%) = [1-stenosis diameter/stenosis proximal normal segment diameter] × 100%. Measurement of stenosis rates are averaged three times and the most significant parts are selected for measuring tandem stenosis or multiple stenoses. The stenosis rates are divided into four levels by the above method: (1) mild stenosis, <30%; (2) moderate stenosis, 30–69%; (3) severe stenosis, 70–99%; (4) completely occluded, 100%, no signal on MRA (17).

All MRI images of patients were analyzed and measured by two senior neuroradiologists (GS and BG) with nearly 10 years of working experience without knowing the clinical details. In case of disagreement, a deputy director of neuroradiology participated in interpreting the images and helped to reach consensus. Details on the raw data are reported in Supplementary Material **Data Sheet 1**.

Statistical Analysis

All of the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). Continuous variables were presented as mean ± standard deviation (x ±s), and categorical variables expressed as a percentage or frequency. Quantitative data to meet the normal distribution and homogeneity of variance in the two groups were compared using *t*-test or analysis of variance, and the quantitative data do not satisfy the normal distribution at the same time and homogeneity of variance when comparing the two groups using the rank sum test. The group comparison of the categorical variables was compared with the Mann–Whitney and chi-square tests, and the exact probability method of Fisher was adopted when the theoretical frequency was <10. The correlation between DWI-ASPECTS and FVH-DWI mismatch/match was tested using Spearman correlation analysis. Taking the FVH-DWI mismatch/match as the dependent variable, the related independent variables were included in the Logistic regression model, and stepwise regression analysis was used to test meaningful independent prediction indicators. All the test methods were statistically significant with the difference of $P < 0.05$.

RESULTS

General Population

According to the inclusion criteria, the number of cases included in this study was 109. There were 66 males and 43 females, with an average age of 64.4 ± 13.2 years. One hundred nine patients were divided into two groups based on areas of FVH and DWI. Forty-three cases were FVH-DWI match, and 43 cases were FVH-DWI mismatch. The main baseline characteristics of clinical data and imaging data of two groups were summarized in **Table 1**.

There was no significant difference between the two groups in gender, systolic blood pressure and diastolic blood pressure, serum glucose, Cholesterol, HDL, LDL, smoking, drinking, CAD, homocysteine, stroke/TIA, stenosis rates, FVH scores, initial NIHSS scores, and discharge NIHSS scores ($P > 0.05$). The following parameters were significantly different between two study groups ($P < 0.05$): age, triglycerides, AF, symptom onset to MRI, DWI-ASPECTS, mRS score at 3 months and the number of 3-month mRS ≤ 2. In the group of FVH-DWI match, the patients were of slightly older age (67.4 ± 14.1) than in the group of FVH-DWI mismatch (62.4 ± 12.2). The levels of triglycerides in former group (1.5 ± 0.7) are lower than the latter (1.9 ± 1.0). FVH-DWI match group had the larger proportion of AF (34.9%) than FVH-DWI mismatch group (15.2%). The incidences of symptom onset to MRI in <1, 1–4, 5–9, 10–13, ≥14 days of FVH-DWI match and FVH-DWI mismatch groups were 7.0% (9.1%),

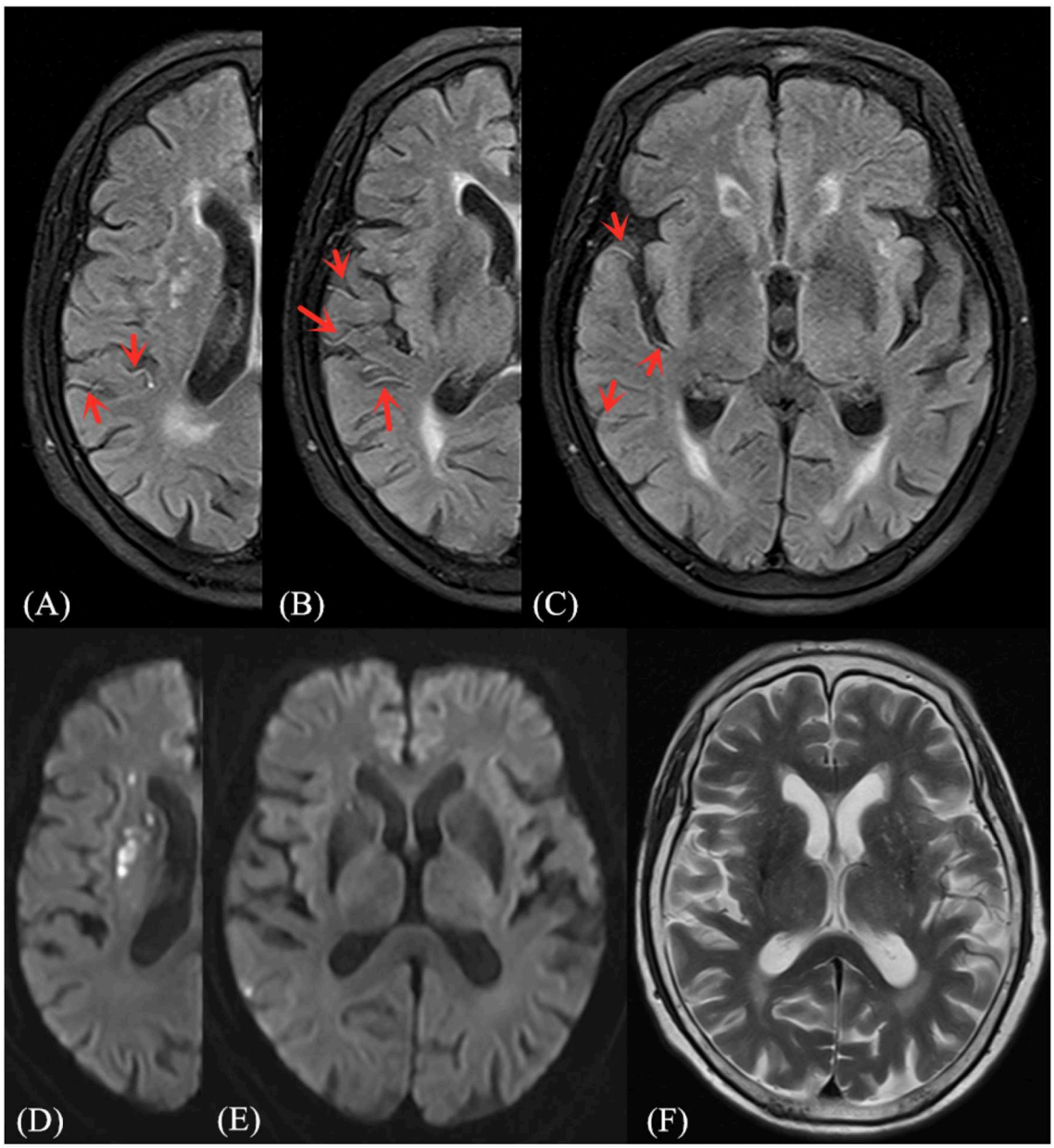


FIGURE 1 | Illustrative case of FVH-DWI mismatch. Magnetic resonance (MR) imaging of a 71-year-old man obtained 1 day after sudden onset of left hemiparesis. Prominent FVH on FLAIR **(A–C)** with small hyperintense lesions in the right MCA territory on admission DWI **(D,E)**, which is more extensive beyond the boundaries of the DWI high signal area, indicating an FVH-DWI mismatch. Prominent FVH presents flow voids on the corresponding T_2WI image **(F)**.

74.4% (43.9%), 14.0% (28.8%), 2.3% (6.1%), and 2.3% (12.1%), respectively. There was a significant difference among two groups ($P < 0.029$). Compared with the FVH-DWI match group, the DWI-ASPECTS in the FVH-DWI mismatch group was higher (7.0 vs. 4.0, $P < 0.001$), and the clinical prognosis of 3 months after discharge was better (mRS score at 3 months, 3.0 vs. 4.0, $P < 0.001$).

Univariate Analysis

Taking FVH-DWI match and FVH-DWI mismatch as a dichotomous outcome variable, age, triglycerides, AF, symptom onset to MRI, DWI-ASPECTS, mRS score at 3 months and the number of 3-month mRS ≤ 2 as dependent variables. Univariate analysis of the relationship between the dependent variables and the outcome variables was performed, results as shown in **Table 2**.

The age and symptom onset to MRI showed statistically significant difference, however the two dependent variables in univariate analysis were not associated with FVH-DWI mismatch. In addition, the DWI-ASPECTS (OR = 4.7, 95% CI = 2.5–8.7, $P < 0.001$) was strongly related to FVH-DWI mismatch. Compared with FVH-DWI match group, a high level

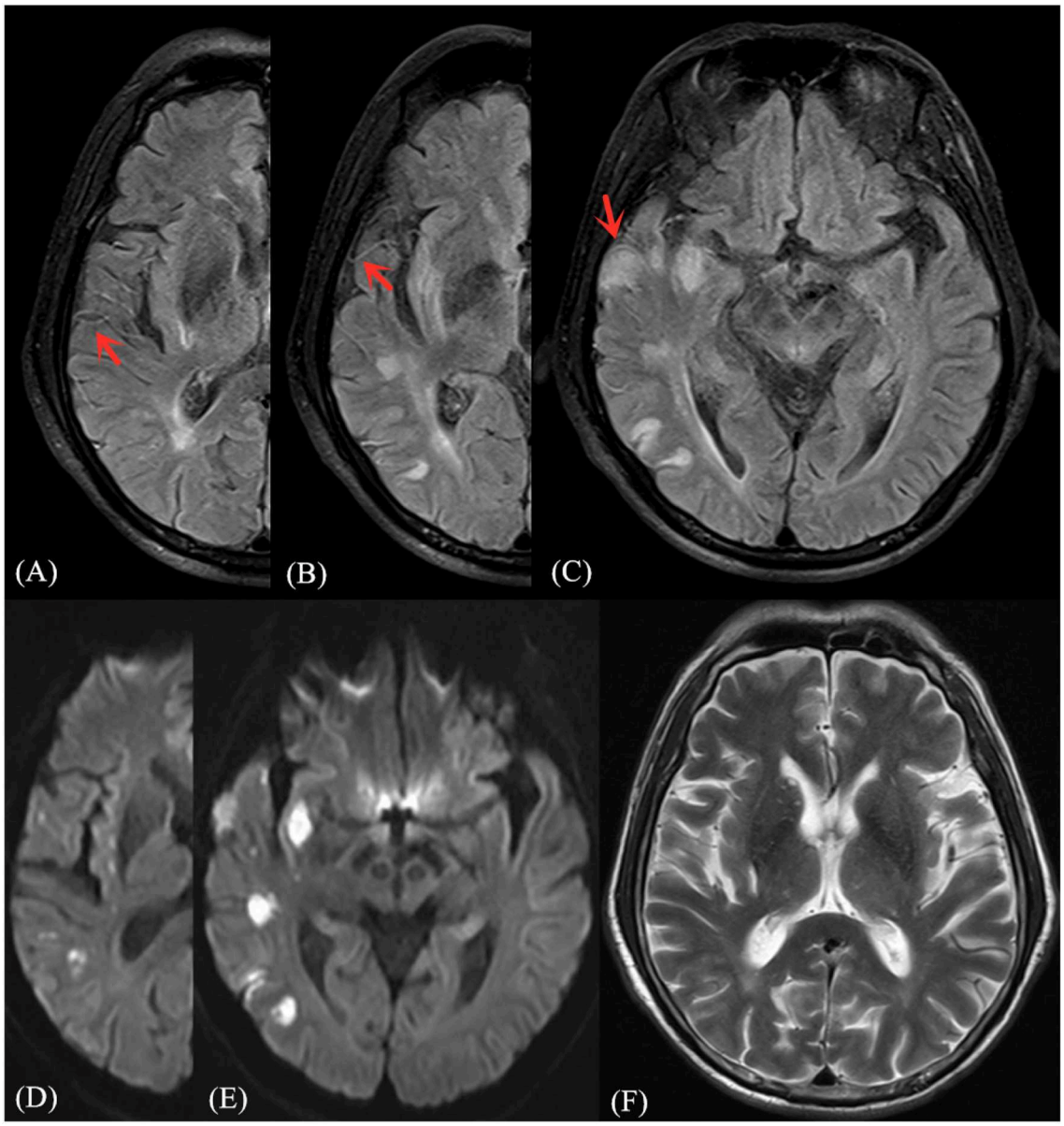


FIGURE 2 | Illustrative case of FVH-DWI match. Magnetic resonance (MR) imaging of a 68-year-old man obtained 2 days after sudden onset of left limb paralysis and speech disorder. Partial prominent FVH on FLAIR **(A–C)** is more extensive within the boundaries of the DWI **(D,E)** high signal area, indicating an FVH-DWI match. Prominent FVH presents flow voids on the corresponding T_2WI image **(F)**.

of triglycerides (OR = 1.9, 95% CI = 1.1–3.3, $P = 0.030$) was also associated with a higher risk of FVH-DWI mismatch group. Compared with patients without AF, the risk of FVH-DWI match in patients with AF increased by 70%. Additionally, the number of 3-month mRS ≤ 2 (OR = 3.1, 95% CI = 1.0–9.0, $P = 0.041$) was also relevant to FVH-DWI mismatch.

Multiple Regression Analysis

Multiple regression analysis showed that DWI-ASPECTS (OR = 4.7, 95% CI = 2.5–8.7, $P < 0.001$) was correlated to FVH-DWI mismatch without adjusting for any variables. After adjusting the variables of age and gender, DWI-ASPECTS (OR = 4.7, 95% CI = 2.5–8.6, $P < 0.001$) appeared to represent an independent predictor of FVH-DWI mismatch. Univariate analysis showed that in addition to the correlation between DWI-ASPECTS and odds ratio of FVH-DWI mismatch and FVH-DWI match, homocysteine, AF and the number of 3-month mRS ≤ 2 were also related to FVH-DWI mismatch. After the adjustment of the variables affecting the relationship between DWI-ASPECTS and FVH-DWI mismatch, multiple regression analysis suggested that DWI-ASPECTS (OR = 4.7, 95% CI = 2.5–9.2, $P < 0.001$) remained significantly associated with

FVH-DWI mismatch (**Table 3**). Furthermore, taking FVH-DWI mismatch as the dependent variable, with DWI-ASPECTS as the exposure factor, smooth curve fitting was performed after the controlling of the variables of homocysteine, AF and the number of 3-month mRS $\leq$ 2 (**Figure 3**). The curve showed two-stage change and breakpoint. When the DWI-ASPECTS value was < the point of 3, the odds ratio of FVH-DWI mismatch and FVH-DWI match was low; however if the value was more than the point of 8, the odds ratio tended to be high. Between the point of 3–8, the trend of odds ratio was gradually increasing upward.

TABLE 1 | Baseline characteristics in patients with FVH-DWI match and FVH-DWI mismatch.

Characteristics	Total (n = 109)	FVH-DWI match (n = 43)	FVH-DWI mismatch (n = 66)	P-value
Age (years)	64.4 ± 13.2	67.4 ± 14.1	62.4 ± 12.2	0.049
Male, *n* (%)	66 (60.6%)	24 (55.8%)	42 (63.6%)	0.414
Systolic BP (mm Hg)	149.1 ± 20.5	149.3 ± 24.8	149.0 ± 17.4	0.953
Diastolic BP (mm Hg)	86.9 ± 12.7	85.1 ± 15.0	88.0 ± 11.0	0.244
Serum glucose (mmol/L)	7.3 ± 3.6	6.8 ± 2.0	7.6 ± 4.3	0.215
Cholesterol (mmol/L)	4.6 ± 1.2	4.5 ± 1.0	4.7 ± 1.3	0.250
Triglycerides (mmol/L)	1.7 ± 0.9	1.5 ± 0.7	1.9 ± 1.0	0.022
HDL (mmol/L)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.971
LDL (mmol/L)	2.7 ± 1.0	2.6 ± 0.9	2.7 ± 1.1	0.464
Homocysteine (μmol/L)	17.5 ± 6.9	16.3 ± 5.9	18.3 ± 7.4	0.136
Smoking (yes), *n* (%)	45 (41.3%)	17 (39.5%)	28 (42.4%)	0.765
Drinking (yes), *n* (%)	34 (31.2%)	10 (23.3%)	24 (36.4%)	0.149
AF (yes), *n* (%)	25 (22.9%)	15 (34.9%)	10 (15.2%)	0.017
Stroke/TIA (yes), *n* (%)	20 (18.3%)	8 (18.6%)	12 (18.2%)	0.956
CAD (yes), *n* (%)	18 (16.5%)	8 (18.6%)	10 (15.2%)	0.635
Stenosis rates				0.264
<30%, *n* (%)	19 (17.4%)	5 (11.6%)	14 (21.2%)	
30∼69%, *n* (%)	7 (6.4%)	3 (7.0%)	4 (6.1%)	
70∼99%, *n* (%)	29 (26.6%)	9 (20.9%)	20 (30.3%)	
100%, *n* (%)	54 (49.5%)	26 (60.5%)	28 (42.4%)	
Symptom onset to MR (days)				0.029
<1 days, *n* (%)	9 (8.3%)	3 (7.0%)	6 (9.1%)	
1∼4 days, *n* (%)	61 (56.0%)	32 (74.4%)	29 (43.9%)	
5∼9 days, *n* (%)	25 (22.9%)	6 (14.0%)	19 (28.8%)	
10∼13 days, *n* (%)	5 (4.6%)	1 (2.3%)	4 (6.1%)	
≥14 days, *n* (%)	9 (8.3%)	1 (2.3%)	8 (12.1%)	
FVH scores	3.0 (2.0–5.0)	3.0 (2.0–4.5)	3.0 (2.0–5.0)	0.277
DWI-ASPECTS	6.0 (5.0–8.0)	4.0 (2.5–5.0)	7.0 (6.0–8.0)	<0.001
Initial NIHSS scores	18.0 (16.0–22.0)	17.0(16.0–22.0)	18.0(16.0–22.0)	0.363
Discharge NIHSS scores	16.0 (14.0–20.0)	16.0(13.0–21.0)	16.0 (15.0–19.0)	0.541
mRS score at 3 months	3.0 (3.0–4.0)	4.0 (3.0–6.0)	3.0 (2.0–4.0)	<0.001
3-month mRS ≤ 2, *n* (%)	24 (22.0%)	5 (11.6%)	19 (28.8%)	0.035

FVH-DWI match, FVH inside DWI-positive area; FVH-DWI mismatch, FVH outside DWI-positive area; HDL, high density lipoprotein; LDL, low density lipoprotein; TIA, transient ischemic attack; AF, arterial fibrillation; CAD, coronary artery disease; DWI-ASPECTS, DWI-Alberta Stroke Program Early CT Score; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; and mRS, modified Rankin Scale.

DISCUSSION

Our preliminary study has shown that in patients with MCA stroke: (1) DWI-ASPECTS was independently associated with FVH-DWI mismatch; (2) Patients with FVH-DWI mismatch compared with FVH-DWI match had a better prognosis in 3 months. The above results suggested that FVH-DWI mismatch might be used as an imaging index to assess the prognosis of cerebral infarction caused by unilateral MCA, and that DWI-ASPECTS can differentiate between FVH-DWI

TABLE 2 | Univariate analysis—variables associated with odds ratio of FVH-DWI mismatch and FVH-DWI match.

	Statistics	OR	95% CI	P-value
Age (years)	64.4 ± 13.2	1.0	(0.9, 1.0)	0.052
Triglycerides (mmol/L)	1.7 ± 0.9	1.9	(1.1, 3.3)	0.030
AF				
No	84	Reference		
Yes	25	0.3	(0.1, 0.8)	0.019
Symptom onset to MR (days)				
<1 days (%)	9	Reference		
1∼4 days (%)	61	0.5	(0.1, 2.0)	0.293
5∼9 days (%)	25	1.6	(0.3, 8.3)	0.588
10∼13 days (%)	5	2.0	(0.1, 26.7)	0.600
≥14 days (%)	9	4.0	(0.3, 48.7)	0.277
DWI-ASPECTS	5.9 ± 2.3	4.7	(2.5, 8.7)	<0.001
mRS score at 3 months	3.5 ± 1.3	0.4	(0.3, 0.6)	<0.001
3-month mRS				
>2 (%)	85	Reference		
≤2 (%)	24	3.1	(1.0, 9.0)	0.041

OR, odds ratio.

TABLE 3 | Multiple logistic regression analysis of association of DWI-ASPECTS with FVH-DWI mismatch.

Model	DWI-ASPECTS		
	OR	95% CI	P-value
Non-adjusted	4.7	(2.5, 8.7)	<0.001
Adjust I	4.7	(2.5, 8.6)	<0.001
Adjust II	4.7	(2.5, 9.2)	<0.001

Outcome variable: Odds ratio of FVH-DWI mismatch and FVH-DWI match.
Exposure variable: DWI-ASPECTS.
Non-adjusted model adjust for: none.
Adjust I model adjust for: age; gender.
Adjust II model adjust for: homocysteine; AF; the number of 3-month mRS ≤ 2.

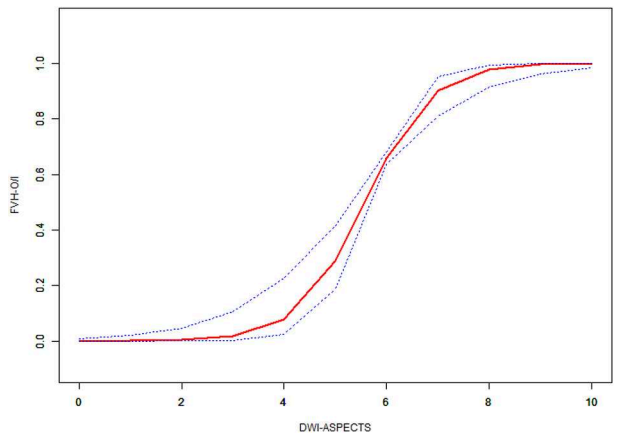


FIGURE 3 | Non-linear association of the difference between DWI-ASPECTS with odds ratio of FVH outside DWI-positive area and FVH inside DWI-positive area by smoothing curve fitting.Outcome: FVH-O/I = FVH-DWI mismatch/FVH-DWI match. Exposure: DWI-ASPECTS.

mismatch or match independently. Previous studies (5, 7–9, 18) have reported that the presence of FVH distal to a severe vascular stenosis or occlusion may reflect a reversed, slow and static flow in the leptomeningeal circulation in patients with acute ischemic stroke, which was thought to represent an imaging sign of collateral circulation and early ischemia. The investigation by Legrand et al. (7) showed that the volume of DWI lesion in the baseline FVH-DWI mismatch group was smaller than those in FVH-DWI match group in hyperacute cerebral infarction. Our study included patients who were not in the hyperacute stage, and we evaluated infarct size by using ASPECTS instead. Our results showed that DWI-ASPECTS of FVH-DWI mismatch group was higher than that of the match group which is consistent with Legrand et al. (7) study, which indirectly suggests that the prognosis of FVH-DWI mismatch group was better. Therefore, the most important finding of this study is that there is a significant correlation between ASPECTS and FVH-DWI mismatch, which represents an independent predictive metric after adjusting the relevant variables (OR: 4.7; 95% CI: 2.5–9.2; $P < 0.001$).

The innovative part of this study is that DWI-ASPECTS can quantify whether there is a FVH-DWI mismatch by smooth curve fitting. When the DWI-ASPECTS value was < the point of 3, the odds ratio of FVH-DWI mismatch and FVH-DWI match was low; however, if the value was more than the point of 8, the odds ratio of FVH-DWI mismatch and FVH-DWI match tended to be high. Between the point of 3–8, the trend of odds ratio of FVH-DWI mismatch and FVH-DWI match was gradually upward. Penumbra Pivotal Stroke Trial (19) showed that patients with ASPECTS > 7 had better clinical outcomes than ASPECTS ≤ 7, and those with ASPECTS ≤ 4 had poor clinical results. The result of this study is similar to previous related studies (20, 21). Previous studies (7, 8) revealed that FVH-DWI mismatch can predict the prognosis of acute cerebral infarction, however, there is no uniform standard on how to accurately quantify and distinguish between FVH-DWI mismatch and FVH-DWI match. DWI-ASPECTS can quickly and effectively assess the approximate volume of the lesions, and two threshold points for DWI-ASPECTS of 3 and 8 can be used to distinguish whether there is a mismatch in FVH-DWI by our study.

Prior studies confirmed that FVH is common in the early stages of acute cerebral infarction, and that with passage of time, the incidence of FVH gradually decreased (22–24). Maeda et al. (15) included 40 cases of acute and subacute MCA patients with cerebral infarction which were followed up for different time periods. They found that the positive rate of FVH in <24 h, 1–4 and 5–9 days was about 100, 40, and 18%, respectively. Our result are similar to previous study (15) apart from the numbers of acute cerebral infarction, however regression analysis showed that the incidence of FVH was not correlated in match or mismatch group. All the patients with FVH positive sign were included in this study. Therefore, the FVH sign in the two groups did not change with time. Previous studies have confirmed that FVH-DWI mismatch can be used as an indirect imaging marker to better reflect the hyperacute ischemic penumbra (5, 7, 9). At <1 day, most patients were in the hyperacute or acute early stage, and the proportion of patients in the FVH-DWI mismatch group was slightly higher than match group due to the presence of more ischemic penumbra. At 1–4 days, the collateral vessels in the infarct area were established, and FVH reflected the formation of collaterals. Therefore, the proportion of patients in the two groups should be similar in theory, however the results showed that the FVH-DWI mismatch group was significantly < the FVH-DWI match group. It was speculated that the ischemic penumbra plays a leading role (22). The ischemic penumbra gradually transformed into the infarct core region over time, thus resulting in a significant reduction in the proportion of patients in the FVH-DWI mismatch group. After 5–9, 10–13, and ≥14 days, the proportion of patients in the FVH-DWI mismatch group was > that in the FVH-DWI match group, presumably due to the stable collateral vessel formation and the role of poor ischemic penumbra in these stages (9, 23). Therefore, FVH-DWI mismatch was mainly dominated by the collateral circulation, which more reflected the better stable collateral circulation of ischemic stroke.

Similarly, past studies suggested that the incidence of FVH is positively correlated with the degree of arterial stenosis, and therefore the incidence of FVH in patients with severe stenosis or occlusion was significantly higher (25). One of the reasons for this phenomenon is that we included patients with lesions of MCA and fewer patients with acute cerebral infarction in this retrospective study and that FVH-DWI mismatch or match groups were all based on positive FVH signs. Therefore, the incidence of FVH is not time-dependent. In order to further confirm the incidence of FVH after the acute phase in this study was not associated with the onset and the degree of vascular stenosis, we quantified FVH scores (14) for FVH-DWI mismatch and match group and found no significant difference. These findings suggest that DWI-FVH mismatch can persist after the acute phase, and we speculate that the reason is that there may be a better collateral circulation. Prior similar studies revealed that distal FVH indicate a good collateral flow, smaller infarct volume, larger ischemic penumbra and

decreased neurological deficit associated with the lesion (26). However, other investigators believed that the distal FVH is not related to the severity of stroke, or that FVH indicated a lack of collateral circulation (27), which was associated with larger volume of infarction, severe neurological impairment and early deterioration of neurological function (28, 29), and increased the risk of intracranial hemorrhage (22). These different conclusions may be related to the various patient populations studied, inclusion criteria, and different FVH assessment methods. In this study, we found no significant difference between NIHSS admission and NIHSS discharge in FVH-DWI mismatch group and FVH-DWI match group. However the number of patients with mRS $\leq$ 2 in the FVH-DWI mismatch group was $>$ in the FVH-DWI match group and the ASPECTS scores were also higher. We surmised that the NIHSS score might reflect the severity of stroke, however there was a deviation in patients with coma or stroke recovery, whereas most of the patients included in this study were subacute and chronic. However, mRS is used to assess the prognosis of stroke patients and the level of functional disability in patients in rehabilitation (30), the findings of Legrand et al. (7, 9) also support this viewpoint. They found that the clinical outcome of mRS in FVH-DWI mismatch group is better than that in FVH-DWI mismatch group at 90 days after discharge, which reflect the formation of distal collateral circulation (9). An additional finding in this study was baseline data showing that patients with AF are more likely to develop in FVH-DWI match. Compared with patients without AF, the risk of FVH-DWI match in patients with AF increased by 70%, we speculate that the reason for this may be the insufficiency of collateral circulation around the infarct area or the smaller branch embolism, which is likely to cause a large area infarction, resulting in poor prognosis. Su (31) studied 144 cases of cardiogenic cerebral infarction and found that AF can further reduce cerebral perfusion blood flow and accelerate the progression of infarct, so the prognosis of patients is poor. The above studies confirmed that FVH-DWI mismatch with atrial fibrillation is a risk factor for poor prognosis. In addition, triglycerides levels were found to be higher in the FVH-DWI mismatch group than in the FVH-DWI match group. Univariate results showed that for every 1 μmol/L increase of triglycerides, the risk of FVH-DWI mismatch was increased by 90% compared with that of FVH-DWI match. The possible reason is that risk factor of triglycerides affect the formation of neovascularization and the opening of collateral circulation (32).

This study has the following limitations. First, this study is based on a single center retrospective study and the results need to be confirmed by multicenter, large sample studies. Second, the majority of MRI examinations in both groups were performed in patients with subacute or chronic symptoms and lacked acute or hyperacute MR imaging and analysis, and subjective judgment in the analysis of imaging signs may be present. Third, we only included intracranial MRA acquisition and failed to obtain extracranial carotid artery MRA, and FVH-DWI mismatch in some patients may be caused by the extracranial carotid artery pathology, which may result in bias. Additionally, it is difficult to determine the degree of vascular stenosis in cases of bilateral or multiple vessel disease. Last but not least, DWI-ASPECTS are a semi-quantitative scoring method to indirectly determine the infarct size. The main disadvantage of this technique is that smaller ischemic lesions are also involved in scoring, and this score does not completely reflect the true infarct size.

CONCLUSIONS

FVH-DWI mismatch represents the peripheral blood supply to the infarct, which may be helpful in clinical assessment of infarct size. The DWI-ASPECTS score was an independent predictor of FVH-DWI mismatch. FVH-DWI mismatch did not predict the prognostic value when DWI-ASPECTS $\leq$ 3, but FVH-DWI mismatch predicts the highest prognostic value when DWI-ASPECTS $\geq$ 8. DWI-ASPECTS can roughly determine whether there is a FVH-DWI mismatch in order to select optimal clinical treatment and accurately assess prognosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

This studies involving human participants were reviewed and approved by Ethics Committee of the Affiliated Hospital of Guizhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LS and BG: literature search, figures, study design, data collection, data analysis, data interpretation, and writing. CL: study design, data collection, and data analysis. GS, JW, and WW: data analysis. TG: study design. XQ and MW: data analysis and grammar. AL: manuscript review, revision and proofreading.

FUNDING

This study was funded by the research grant from National Natural Science Foundation of China (Grant No. 81871333) and Basic Research Program of Jiangsu Province (Grant No. BK20170704).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00994/full#supplementary-material

REFERENCES

1. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med*. (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
2. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet*. (2016) 388:1161–9. doi: 10.1016/S0140-6736(16)30968-0
3. von Gadow N, Nikoubashman O, Freiherr J, Block F, Reich A, Fesl G, et al. Endovascular stroke treatment now and then-procedural and clinical effectiveness and safety of different mechanical thrombectomy techniques over time. *Quant Imaging Med Surg*. (2017) 7:1–7. doi: 10.21037/qims.2017.02.06
4. Kao YJ, Oyarzabal EA, Zhang H, Faber JE, Shih YI. Role of genetic variation in collateral circulation in the evolution of acute stroke: a multimodal magnetic resonance imaging study. *Stroke*. (2017) 48:754–61. doi: 10.1161/STROKEAHA.116.015878
5. Mahdjoub E, Turc G, Legrand L, Benzakoun J, Edjlali M, Seners P, et al. Do fluid-attenuated inversion recovery vascular hyperintensities represent good collaterals before reperfusion therapy? *AJNR Am J Neuroradiol*. (2018) 39:77–83. doi: 10.3174/ajnr.A5431
6. Kim SE, Lee BI, Kim SE, Shin KJ, Park J, Park KM, et al. Clinical significance of fluid-attenuated inversion recovery vascular hyperintensities in borderzone infarcts. *Stroke*. (2016) 47:1548–54. doi: 10.1161/STROKEAHA.116.014262
7. Legrand L, Tisserand M, Turc G, Edjlali M, Calvet D, Trystram D, et al. Fluid-attenuated inversion recovery vascular hyperintensities–diffusion-weighted imaging mismatch identifies acute stroke patients most likely to benefit from recanalization. *Stroke*. (2016) 47:424–7. doi: 10.1161/STROKEAHA.115.010999
8. Liu D, Scalzo F, Rao NM, Hinman JD, Kim D, Ali LK, et al. Fluid-attenuated inversion recovery vascular hyperintensity topography, novel imaging marker for revascularization in middle cerebral artery occlusion. *Stroke*. (2016) 47:2763–9. doi: 10.1161/STROKEAHA.116.013953
9. Legrand L, Tisserand M, Turc G, Naggara O, Edjlali M, Mellerio C, et al. Do FLAIR vascular hyperintensities beyond the DWI lesion represent the ischemic penumbra? *AJNR Am J Neuroradiol*. (2015) 36:269–74. doi: 10.3174/ajnr.A4088
10. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme early CT score. *Lancet*. (2000) 355:1670–4. doi: 10.1016/S0140-6736(00)02237-6
11. McTaggart RA, Jovin TG, Lansberg MG, Mlynash M, Jayaraman MV, Choudhri OA, et al. Alberta stroke program early computed tomographic scoring performance in a series of patients undergoing computed tomography and MRI: reader agreement, modality agreement, and outcome prediction. *Stroke*. (2015) 46:407–12. doi: 10.1161/STROKEAHA.114.006564
12. Singer OC, Kurre W, Humpich MC, Lorenz MW, Kastrup A, Liebeskind DS, et al. Risk assessment of symptomatic intracerebral hemorrhage after thrombolysis using DWI-ASPECTS. *Stroke*. (2009) 40:2743–8. doi: 10.1161/STROKEAHA.109.550111
13. Toyoda K, Ida M, Fukuda K. Fluid-attenuated inversion recovery intraarterial signal: an early sign of hyperacute cerebral ischemia. *AJNR Am J Neuroradiol*. (2001) 22:1021–9.
14. Olindo S, Chausson N, Joux J, Saint VM, Signate A, Edimonana-Kapute M, et al. Fluid-attenuated inversion recovery vascular hyperintensity: an early predictor of clinical outcome in proximal middle cerebral artery occlusion. *Arch Neurol*. (2012) 69:1462–8. doi: 10.1001/archneurol.2012.1310
15. Maeda M, Koshimoto Y, Uematsu H, Yamada H, Kimura H, Kawamura Y, et al. Time course of arterial hyperintensity with fast fluid-attenuated inversion-recovery imaging in acute and subacute middle cerebral arterial infarction. *J Magn Reson Imaging*. (2001) 13:987–90. doi: 10.1002/jmri.1142
16. Kasner SE, Lynn MJ, Chimowitz MI, Frankel MR, Howlett-Smith H, Hertzberg VS, et al. Warfarin vs aspirin for symptomatic intracranial stenosis: subgroup analyses from WASID. *Neurology*. (2006) 67:1275–8. doi: 10.1212/01.wnl.0000238506.76873.2f
17. Moneta GL, Edwards JM, Chitwood RW, Taylor LJ, Lee RW, Cummings CA, et al. Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. *J Vasc Surg*. (1993) 17:152–7. discussion: 157–9. doi: 10.1016/0741-5214(93)90019-I
18. Ahn SH, Kim BJ, Kim YJ, Kwon SU, Kim JS, Kang DW. Fluid-attenuated inversion recovery hyperintensity is associated with hemorrhagic transformation following reperfusion therapy. *J Stroke Cerebrovasc Dis*. (2017) 26:327–33. doi: 10.1016/j.jstrokecerebrovasdis.2016.09.024
19. Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke*. (2009) 40:2761–8. doi: 10.1161/STROKEAHA.108.544957
20. Goyal M, Menon BK, Coutts SB, Hill MD, Demchuk AM. Effect of baseline CT scan appearance and time to recanalization on clinical outcomes in endovascular thrombectomy of acute ischemic strokes. *Stroke*. (2010) 42:93–7. doi: 10.1161/STROKEAHA.110.594481
21. Liebeskind DS, Jahan R, Nogueira RG, Jovin TG, Lutsep HL, Saver JL. Serial Alberta Stroke Program early CT score from baseline to 24 hours in solitaire flow restoration with the intention for Thrombectomy study: a novel surrogate end point for revascularization in acute stroke. *Stroke*. (2014) 45:723–7. doi: 10.1161/STROKEAHA.113.003914
22. Hohenhaus M, Schmidt WU, Brunecker P, Xu C, Hotter B, Rozanski M, et al. FLAIR vascular hyperintensities in acute ICA and MCA infarction: a marker for mismatch and stroke severity? *Cerebrovasc Dis*. (2012) 34:63–9. doi: 10.1159/000339012
23. Cheng B, Ebinger M, Kufner A, Kohrmann M, Wu O, Kang DW, et al. Hyperintense vessels on acute stroke fluid-attenuated inversion recovery imaging: associations with clinical and other MRI findings. *Stroke*. (2012) 43:2957–61. doi: 10.1161/STROKEAHA.112.658906
24. Ebinger M, Kufner A, Galinovic I, Brunecker P, Malzahn U, Nolte CH, et al. Fluid-attenuated inversion recovery images and stroke outcome after thrombolysis. *Stroke*. (2012) 43:539–42. doi: 10.1161/STROKEAHA.111.632026
25. Liu W, Xu G, Yue X, Wang X, Ma M, Zhang R, et al. Hyperintense vessels on FLAIR: a useful non-invasive method for assessing intracerebral collaterals. *Eur J Radiol*. (2011) 80:786–91. doi: 10.1016/j.ejrad.2010.09.043
26. Lee KY, Latour LL, Luby M, Hsia AW, Merino JG, Warach S. Distal hyperintense vessels on FLAIR: an MRI marker for collateral circulation in acute stroke? *Neurology*. (2009) 72:1134–9. doi: 10.1212/01.wnl.0000345360.80382.69
27. Kufner A, Galinovic I, Ambrosi V, Nolte CH, Endres M, Fiebach JB, et al. Hyperintense vessels on FLAIR: hemodynamic correlates and response to thrombolysis. *AJNR Am J Neuroradiol*. (2015) 36:1426–30. doi: 10.3174/ajnr.A4320
28. Nam KW, Kwon HM, Park SW, Lim JS, Han MK, Lee YS. Distal hyperintense vessel sign is associated with neurological deterioration in acute ischaemic stroke. *Eur J Neurol*. (2017) 24:617–23. doi: 10.1111/ene.13259
29. Gawlitza M, Gragert J, Quäschling U, Hoffmann KT. FLAIR-hyperintense vessel sign, diffusion-perfusion mismatch and infarct growth in acute ischemic stroke without vascular recanalisation therapy. *J Neuroradiology*. (2014) 41:227–33. doi: 10.1016/j.neurad.2013.10.004

30. Muir KW, Weir CJ, Murray GD, Povey C, Lees KR. Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke*. (1996) 27:1817–20. doi: 10.1161/01.STR.27.10.1817
31. Su YC, Lim SN, Yang FY, Lin SK. Evaluation of cerebral blood flow in acute ischemic stroke patients with atrial fibrillation: a sonographic study. *J Formos Med Assoc*. (2017) 116:287–94. doi: 10.1016/j.jfma.2016.05.009
32. Sheth SA, Liebeskind DS. Imaging evaluation of collaterals in the brain: physiology and clinical translation. *Curr Radiol Rep*. (2014) 2:29. doi: 10.1007/s40134-013-0029-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 November 2019
doi: 10.3389/fneur.2019.01211

Blood–Brain Barrier Disruption as a Potential Target for Therapy in Posterior Reversible Encephalopathy Syndrome: Evidence From Multimodal MRI in Rats

Quanlai Wang[1,2†], Bin Huang[2†], Guiquan Shen[2], Yu Zeng[2], Zheng Chen[2], Chunqiang Lu[3], Alexander Lerner[4] and Bo Gao[2]*

[1] Department of Imaging, Zhoukou Central Hospital, Zhoukou, China, [2] Department of Radiology, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [3] Jiangsu Key Laboratory of Molecular and Functional Imaging, Southeast University, Nanjing, China, [4] Division of Neuroradiology, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

OPEN ACCESS

Edited by:
Deqiang Qiu,
Emory University, United States

Reviewed by:
Gary A. Rosenberg,
University of New Mexico, United States
Shuu-Jiun Wang,
Taipei Veterans General Hospital, Taiwan

***Correspondence:**
Bo Gao
gygb2004@163.com

[†]*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *03 April 2019*
Accepted: *30 October 2019*
Published: *26 November 2019*

Citation:
Wang Q, Huang B, Shen G, Zeng Y, Chen Z, Lu C, Lerner A and Gao B (2019) Blood–Brain Barrier Disruption as a Potential Target for Therapy in Posterior Reversible Encephalopathy Syndrome: Evidence From Multimodal MRI in Rats. Front. Neurol. 10:1211. doi: 10.3389/fneur.2019.01211

Background: To explore blood–brain barrier disruption in hypertensive posterior reversible encephalopathy syndrome.

Methods: The hypertension rat models were successfully established and scanned on 7T micro-MRI. MRI parameter maps including apparent diffusion coefficient, T1 value, and perfusion metrics such as cerebral blood volume, cerebral blood flow, mean transit time and time to peak maps, were calculated.

Results: The ADC values of the experimental group were higher than those of the control group both in cortical ($P < 0.01$) and subcortical ($P < 0.05$) regions. Voxel-wise analysis of ADC maps localized vasogenic edema primarily to the posterior portion of the brain. The increase in cerebral blood volume and cerebral blood flow values were found in the cortical and subcortical regions of rats with acute hypertension. No correlation was found between perfusion metrics and mean arterial pressure. The Evans blue dye content was higher in the posterior brain region than the anterior one ($P < 0.05$).

Conclusions: Cerebral vasogenic edema resulting from acute hypertension supports the hypothesis of posterior reversible encephalopathy syndrome as the result of blood–brain barrier disruption, which maybe the potential therapeutic target for intervention.

Keywords: posterior reversible encephalopathy syndrome, acute hypertension, blood–brain barrier, MRI, rat models

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) usually occurs following a precipitous rise of blood pressure (1). Acute hypertension may lead to persistent and severe disorder of cerebral circulation with passively or forced dilation of the cerebral arterioles, resulting in cerebral hyperperfusion, brain edema, and increased intracranial pressure (2, 3). Cerebral edema primarily in bilateral occipital and parietal lobes constitutes the characteristic radiological findings in patients with PRES (4, 5). If the clinical intervention in PRES is delayed or ineffective, severe neurological complications or even death may occur (6).

The mechanism of PRES is controversial. One of the possible inciting factors is the rapid rise in blood pressure, which exceeds the upper limit of cerebral autoregulation, and results in excessive blood flow with subsequent blood–brain barrier (BBB) breakdown. The BBB is a complex multicellular structure acting as selective barrier controlling the transport of substances between intravascular and extravascular interstitial space compartments (7). BBB breakdown allows for transgression of plasma and macromolecules from the vessels into the interstitial spaces leading to vasogenic edema (8, 9). Alternatively, severe hypertension may lead to excessive reaction of the cerebrovascular autoregulation, spasm of small cerebral vessels, and decrease in perfusion, resulting in ischemia, BBB disruption, increased vascular permeability, and brain edema (10). The mechanism of cerebral edema in PRES remains to be elucidated (11). Therefore, the most important aspect of treatment in PRES is aggressive management of blood pressure. In some studies, hypertension above the autoregulatory limit has led to BBB breakdown and vasogenic edema (12). Some studies have aimed at BBB integrity through chemical and physical therapies to achieve therapeutic effects (7), and some studies have suggested that the integrity of the BBB correlates to the outcomes in this disorder (13, 14). Therefore, preservation of the integrity of BBB is important in treatment of PRES. PRES is characterized as a rapid, dynamic, and transient process of disturbance of cerebral hemodynamics. Delayed perfusion imaging or use of antihypertensive therapy during the examination may lead to inconclusive diagnostic findings and result in hemodynamic changes (15). We hypothesized that abnormalities could be detected with diffusion weighted images (DWI) and perfusion-weighted imaging (PWI) in PRES and that "normal appearing" regions would have increased water diffusion and hyperperfusion. The aim of the present study is to investigate whether cerebral edema, hemodynamic change, and BBB disruption can be detected in rat model using 7.0 T micro-MRI and to elucidate the pathophysiological mechanism of PRES.

METHODS

Animal Model Preparation and Procedures

The present study was approved by the Laboratory Animal Management Committee of Southeast University. All operations were performed according to the international guidelines concerning the care and treatment of experimental animals. A rat model of acute hypertension was established. Forty male Wistar rats weighting 250–300 g were randomly grouped into the experimental group ($n = 20$) and the control group ($n = 20$). Rats were introduced to anesthesia with 5% isoflurane, and anesthesia was maintained with intraperitoneal injection of pentobarbital (40 mg/kg, 2% in saline). A saline solution of Evans blue (EB) was injected via the tail vein. A vertical incision on both sides of inguen was performed in the rats. A femoral arterial catheter, which was connected to the pressure transducer and a physiological monitor, was inserted in one of the femoral arteries to measure the blood pressure. Femoral venous catheter was inserted for continuous injection of phenylephrine (PE) during MRI scanning. The dosage of PE was started at rate of 0.5 μl/min and increased by 0.5 μg/min. Another femoral venous catheter was also inserted in advance to inject gadolinium–diethylenetriaminepentaacetic acid (Gd-DTPA) before MRI scanning. The rats were then placed on the table of the MRI scanner and immobilized with a teeth bar and two ear bars. When the systolic blood pressure (SBP) reached 180 mmHg or mean arterial pressure reached 150 mmHg, the MRI scan would be initiated. The methods mentioned above are described by Euser et al. (16). During the preparation, temperature was maintained between 37 and 37.5°C with a self-regulating heating pad. After the MRI scan, the animal was quickly decapitated, and the brain was removed for histopathological examination. The control group was injected with saline solution instead of PE otherwise following the same procedure. We also record the duration of anesthesia of the rats; the same period of time after injection of anesthetics was ensured for all rats to be scanned by MRI.

MRI Protocols

MRI was performed on 7.0 T micro-MRI scanner (Bruker PharmaScan, Germany). Anesthesia was induced and maintained by inhalation of 1.5% isoflurane (Shandong Keyuan Pharmaceutical Co., Ltd., China). The body temperature was maintained with a feedback-controlled water bath warming system (MT1025, Bruker Biospin Inc., Germany), and the respiratory rate was monitored by a monitoring unit (Model 1025, SA Instruments Inc.). A quadrature volume resonator (inner diameter, 72 mm) was used for radio frequency transmission, and a four-element surface coil array was used for signal reception. Experiments were executed with ParaVision 5.1 software. To optimize field homogeneity, a field-map-based MAPSHIM method was used for shimming. Rapid acquisition with relaxation enhancement T2-weighted sequence was acquired in the axial plane with TR/TE, 3,000/36 ms; matrix size, 256 × 256; thickness, 1 mm; field of view (FOV), 320 mm × 320 mm; slice number, 22; average, 1. DWI were acquired with TR/TE 6,250/30 ms; matrix, 128 × 128; thickness, 1 mm; FOV, 320 × 320 mm, slice number, 22; average, 2; b values = 100, 200, 400, 600, 800, and 1,000 s/mm^2. For T2*-weighted dynamic susceptibility contrast-enhanced perfusion-weighted imaging (T2*-DSC-PWI), a GE-EPI sequence was used with TR/TE, 1,000/9 ms; FOV, 320 × 320 mm; matrix, 64 × 64; repetition, 200; and in-plane resolution of 0.5 × 0.5 mm. The intravenous bolus of gadodiamide (0.1 mmol/kg, 4 ml/s) was started after the 15th measurement was obtained. For T1 mapping, a RAREVTR sequence with six repetition times, TE of 11 ms, FOV of 320 × 320 mm, matrix of 128 × 128, thickness of 1 mm, slice number of 20, average 1 was used.

BBB Permeability

After MRI scanning, the animal was perfused with phosphate buffered saline through the ascending aorta to remove the dye from the vasculature. The whole brain was removed and divided into two halves: the posterior and anterior cerebrums sections, by making a cut in a coronal plane at the level of the optic chiasm. The tissue was homogenized in 5 ml 50% trichloroacetic acid and centrifuged (4,000g, 10 min). After centrifugation, the

supernatant was diluted three-fold with ethanol and analyzed by fluorescence spectrophotometry (620–680 nm) to determine EB content, with the data expressed as average fluorescence counts *per second* (CPS) per gram brain tissue.

Imaging Analysis and Post-processing

Before any further processing, raw ParaVision DWI and EPI datasets were converted to 32-bit NIFTI format. The NIFTI EPI datasets were then converted back to 16-bit DICOM format using a custom-made Matlab script to ensure the original raw data range. ADC maps and T1 maps were calculated with MRI analysis plugin (https://imagej.nih.gov/ij/plugins/mri-analysis.html) in Image J (Version 1.50f; National Institutes of Health, Bethesda, USA; http://rsbweb.nih.gov/ij). The PWI images in DICOM format were processed using Perfusion Mismatch Analyzer (http://asist.umin.jp/data-e.shtml) software. After creation of time intensity curve, the bolus start time and bolus end time were determined. Time concentration curves for each pixel were generated from the time intensity curves. Arterial input function pixels were automatically selected. Quantitative maps including cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP) were calculated by deconvolution the tissues curves using arterial input function. The maps of CBV, CBF, MTT, and TTP were generated automatically. Region of interest (ROI) analysis was performed in the PMA software. Two ROIs corresponding to cortex and subcortical regions were selected. The ADC maps and T1 maps were coregistered to a rat template set based on the standard rat brain atlas of Paxinos and Watson using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/). Then, spatial smoothness with an isotropic Gaussian kernel (FWHM = 2 voxels) was performed on the spatial transformed images. Two sample *t*-tests were performed on the ADC images and T1 images of the two groups. $P < 0.05$ was considered to be statistically significant. Multiple comparison correction was performed using AlphaSim method (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

Statistical Analysis

Except for voxel wise analysis, all statistical analysis was performed using SPSS software (version 18.0). All values were expressed as mean ± SD. The comparison between the groups was performed using independent sample *t*-test. Differences in tissue fluorescence between the anterior and posterior cerebrum within the same intervention group were tested with paired *t*-test. $P < 0.05$ was considered as significant.

RESULTS

Arterial Pressure

Figure 1 shows SBP and mean arterial pressure (MAP) values before and after PE injection in the experiment group and saline solution injection in the control group. The SBP and MAP in the experimental group were significantly higher than those of the controls (SBP, 182.16 ± 6.83 mmHg vs. 97.01 ± 10.65 mmHg; MAP: 162.91 ± 5.93 vs. 87.25 ± 11.37, $P < 0.05$). After a rapid rise in blood pressure, the rats were characterized by shortness of breath, rapid heartbeat, ocular proptosis, muscle contraction, salivation, and runny nose. There was no significant difference in the duration of anesthesia of the rats (time: 126 ± 6 min, $P > 0.05$).

Comparison of Changes of DWI, ADC, and T1 Values

There were no significant abnormities on both T2 images and DWI images before and after hypertension modeling. The ADC value of the experimental group was significantly higher than that of control group both in the cortex and subcortical regions (cortex: 5.1 ± 0.49 vs. 5.48 ± 0.47, $t = 3.291$, $P < 0.01$; subcortical: 5.33 ± 0.23 vs. 5.59 ± 0.32, $t = 2.186$, $P < 0.05$). Voxel wise analysis of the ADC maps showed that the vasogenic brain edema was located in the parieto-occipital cortex, subcortical nuclei, thalamus, brain stem, and cerebellum, primarily localizing to the posterior cerebral region of the rats (**Figure 2**). There was no cluster showing statistical significance in voxel wise analysis of the T1 mapping.

Comparison of PWI Parameters

Cortical and subcortical region values for CBF, CBV, and MTT parameters were calculated. The selection of ROI is shown in **Figure 3**. All rats demonstrated increased CBV (cortex: $t = 4.319$, $P < 0.01$; subcortex: $t = 6.355$, $P < 0.01$) and CBF (cortex: $t = 3.764$, $P < 0.01$; subcortex: $t = 4.33$, $P < 0.01$) values within cortex and subcortical regions (**Figure 4**). **Figure 4** shows the PWI parameter images of two rats representing the acute hypertension group and the control group, respectively. No significant difference in MTT values was detected (**Figure 5**). Furthermore, no correlation was found between CBF and MAP (cortex: $r = 0.117$, $P = 0.622$; subcortex: $r = 0.1$, $P = 0.674$); and no correlation was demonstrated between CBV and MAP (cortex: $r = 0.245$, $P = 0.297$; subcortex: $r = 0.043$, $P = 0.858$).

Blood–Brain Barrier Permeability

There was an increase in EB dye content (CPS/g) both in posterior and anterior cerebrum compared with control group (**Figures 6**, **7**). In addition, the increase in the EB dye content was significantly higher in the posterior brain region than in the anterior ($P < 0.05$), as the former was more susceptible to the formation of edema.

DISCUSSION

Several prior studies have verified the feasibility of an acute hypertension animal model (16–20). Most of the previous studies focused on pathophysiology and rarely used imaging to evaluate the distribution of acute hypertensive cerebral edema, hemodynamic changes, and BBB disruption (21). This study investigated the distribution of cerebral edema and cerebral perfusion changes non-invasively using DWI and T2*-DSC and evaluated the BBB damage qualitatively using T1 mapping. MRI findings of brain edema in PRES characteristically occur in the posterior circulation areas in the parietal–occipital lobes and cerebellum, with associated T2 hyperintensity (22). In this study, no marked signal change was observed on T2WI and DWI

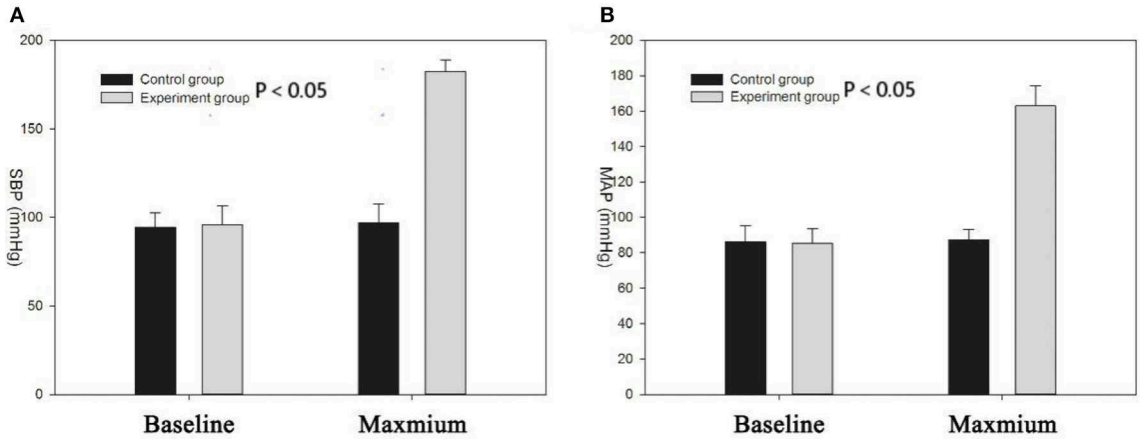


FIGURE 1 | (A) Systolic blood pressure (SBP) of experimental group increased significantly compared with the control group ($P < 0.05$); the two groups had no significant difference in baseline blood pressure; **(B)** mean arterial pressure (MAP) of experimental group increased significantly compared with the control group ($P < 0.05$).

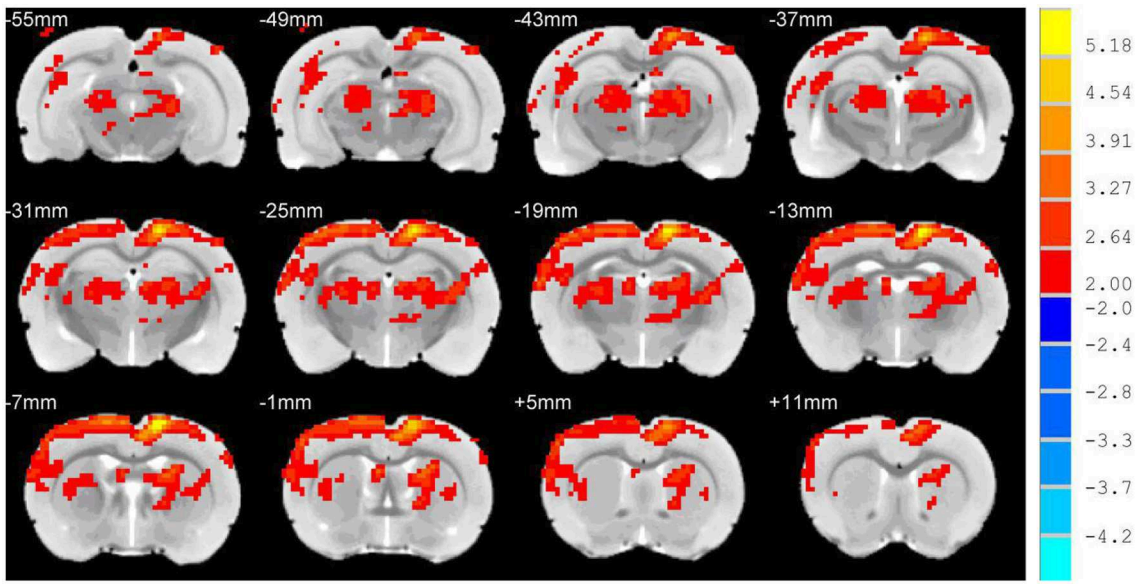


FIGURE 2 | Voxel wise analysis of the ADC maps. The red and yellow region was the region of the ADC value of the experimental group, which was significantly higher than the ADC value of the control group. The cerebral edema region was mainly seen in the posterior region of the rat brain.

images in the acute hypertension model. However, the ADC values were significantly higher than those of the control group with ROI analysis. The transport of albumin-bound EB through BBB accumulated in the extracellular spaces, which provided the evidence of BBB damage (23). If blood pressure is too high, it exceeds the brain's ability to regulate blood flow automatically. This leads to increased arterial and capillary pressure, resulting in a rupture of the BBB and leakage of fluid and proteins into the brain parenchyma, leading to vasogenic edema (24). Vasogenic edema on DWI may result in hypointensity or hyperintensity (due to T2 shine-through effect of vasogenic edema on DWI). Hypointensity on DWI is seen in some cases with diffusion facilitation with elevated ADC values, while cytotoxic edema shows hyperintensity with decreased ADC values (25). Moreover, the ADC images may demonstrate abnormalities that cannot be identified on T1WI or T2WI (25, 26).

The voxel-wise analysis of ADC images of the whole brain showed that brain edema was mainly located in the cortex of the posterior cerebrum. The preferential formation of edema in the posterior regions is due to the elevated BBB permeability. BBB permeability to EB varies regionally in response to autoregulatory breakthrough, such that increase in BBB permeability was significantly greater in the posterior regions than in the anterior regions (27, 28). The blue-stained

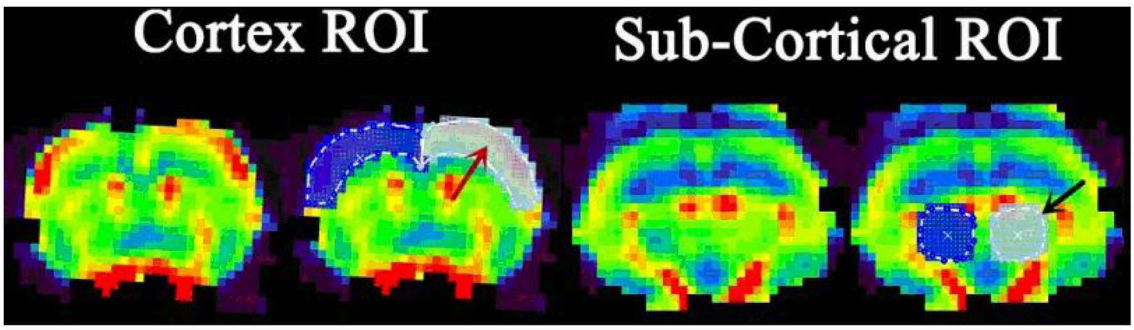


FIGURE 3 | The definition of region of interest (ROI) delineated on the perfusion image. The cortex ROI (red arrow) covers the bilateral cortex of the slice near the bregma. The subcortical ROI (black arrow) covers the bilateral thalamus, located in the slice 2 mm posterior of bregma.

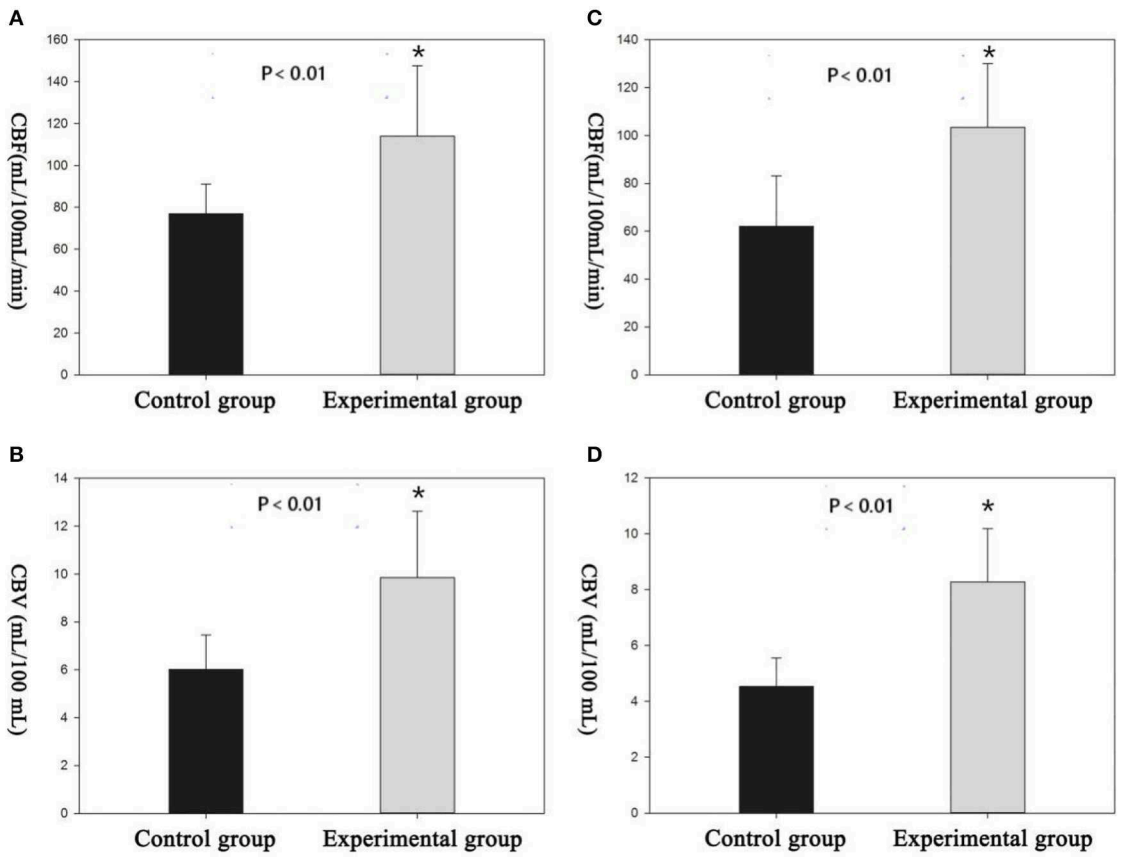


FIGURE 4 | There were significant differences in perfusion parameters between the experimental group and the control group. **(A,B)** Cortical cerebral blood flow (CBF) and cerebral blood volume (CBV) measured by region of interest (ROI). **(C,D)** Subcortical CBF and CBV measured by the ROI. *Difference is statistically significant.

area in the cerebrum, cerebellum, and other regions with EB observed staining in the experimental group were concordant with the distribution of cerebral edema on ADC maps. The anterior cerebral circulation has more autonomic receptors than the posterior circulation; consequently, cerebral autoregulation is more susceptible in the posterior vascular territory (24, 25). Such regional differences in brain regions have not been described in rats (29, 30). Furthermore, we found that these phenomena were detected in anterior cerebrum in part due to the duration of extended hypertension state over 1 h. This long-term hypertension state results in sustained hyperperfusion, which may result in decreased sympathetic nervous stimulation of the anterior circulatory vessels, causing the involvement of anterior regions in the brain. We hypothesized that these two factors

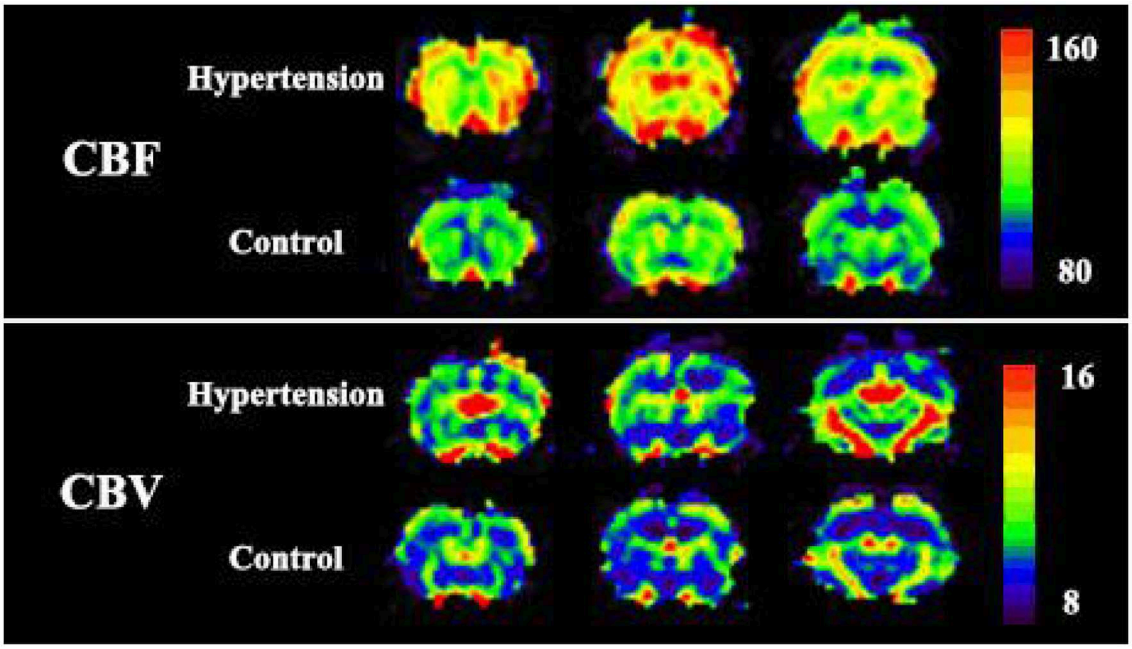


FIGURE 5 | The perfusion image of two representative rats of each groups. Cortical cerebral blood flow (CBF) and cerebral blood volume (CBV) values in the experimental group were significantly higher than the values in the control group. No apparent change in mean transit time (MTT) was observed in the whole brain of the two rats.

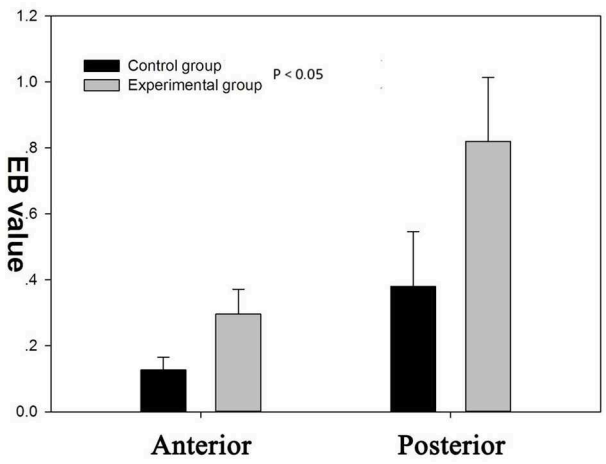


FIGURE 6 | There was a significant increase of blood–brain barrier (BBB) permeability to Evans blue (EB) in both the anterior and posterior cerebrum ($P < 0.05$). BBB permeability to EB varied regionally in response to autoregulatory breakthrough, such that the increase in BBB permeability was significantly greater in the posterior brain region than anterior.

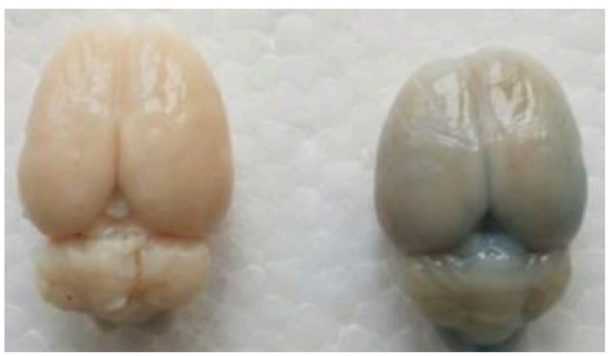


FIGURE 7 | In the experimental group, Evans blue (EB) dye content was significantly higher than control group. The presence of blue-staining areas in the brain tissue in the experimental group indicates the disruption of the blood–brain barrier.

may explain the lack of preference for regional changes in the posterior of brain in rats.

T1 mapping was used to compare abnormal enhancement area before and after injection of Gd-DTPA to determine whether the permeability of BBB has changed. Normally, Gd-DTPA cannot pass through BBB and is confined in the blood vessel. If there is Gd-DTPA enhancement in a certain region of the brain, this indicates that BBB is disrupted and that permeability is increased (31). However, no abnormal enhancement region was observed on the T1 mapping in this study. This may be due to the fact that we acquired the T1 image after a short delay, and a longer delay may be necessary to detect the signal changes caused by the slow accumulation of contrast agents in extracellular space (32).

In this short-term acute hypertension model, when compared to the control group, the values of CBF and CBV in the acute hypertension group increased significantly, and we found

a significant increase in CBF and CBV in the cortical and subcortical areas, and the increase in CBV and CBF in the cortex was greater than that of subcortical regions. This was more evident in the posterior areas of brain, indicating that the increased perfusion primarily involved the posterior regions of the brain. This suggests that hyperperfusion is the result of cerebral vascular autoregulation dysfunction, and it has also been proved in animal experiments (33). the presence of hyperperfusion in acute hypertension confirmed that vasogenic edema appears in the early stages of this disorder due to high capillary pressure and increased BBB permeability. Some PWI studies also found that patients with hypertensive encephalopathy had hyperperfusion, and the evidence was as strong (34, 35). Decreased cerebral perfusion in edema areas has also been reported (36, 37). Sundgren et al. (38) found that microvascular perfusion in region of edema was decreased, with decrease in CBF and CBV. In addition, when blood pressure was successfully controlled, the perfusion volume in the area of edema returned to normal. However, no significant change in MTT was detected either in cortex or in subcortical regions. MTT may contribute to the degree of vasoconstriction (39). Inconspicuous MTT change did not indicate the systolic or diastolic condition of vessels, which may be due to poor sensitivity of the methods, resulting in lack of detectable MTT changes (40).

In this study, we used multimodal MR imaging to study the acute hypertension model producing results which help to elucidate the pathophysiological basis of BBB damage in PRES. This study is limited by lack of longitudinal data, and there are some limitations in our study. First, we did not record the time of hypertension in animals. Second, EB dye content would be directly proportional to CBF and to the time length from EB injection to the time when the brains were harvested. However, the results of EB dye content were not corrected by CBF and the time length from EB injection to the time when the brains were harvested; we should pay attention to these factors in the future studies. Third, Gd-DTPA enhanced-T1 failed to show any difference between the control and experimental group; therefore, in this study, our animal model may not apply to all PRES due to not all PERS having or being associated with hypertension. We did not find significant abnormities on neither T2 images nor DWI images. In the future, it is necessary to build a more reasonable and applicable PRES model. Subsequent studies using longitudinal design are needed for further investigation of PRES pathophysiology.

CONCLUSION

The pattern of vasogenic cerebral edema resulting from acute hypertension in the rat model suggests that BBB disruption is an important component of PRES pathophysiology, representing a potential target for therapeutic intervention.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of international guidelines concerning the care and treatment of experimental animals, the Institutional Animal Care and Use Committee. The protocol was approved by the Institutional Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

BG, GS, and AL contributed conception and design of the study. YZ contributed data collection. QW and BH contributed data processing. CL performed the statistical analysis. QW wrote the first draft of the manuscript. BH and ZC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation of China (81471645, 81871333).

REFERENCES

1. Gao B, Lyu C, Lerner A, McKinney AM. Controversy of posterior reversible encephalopathy syndrome: what have we learnt in the last 20 years? *J Neurol Neurosurg Psychiatry*. (2018) 89:14–20. doi: 10.1136/jnnp-2017-316225
2. Mcdermott M, Miller EC, Rundek T, Hurn PD, Bushnell CD. Preeclampsia: association with posterior reversible encephalopathy syndrome and stroke. *Stroke*. (2018) 49:524–30. doi: 10.1161/STROKEAHA.117.018416
3. Mirza A. Posterior reversible encephalopathy syndrome: A variant of hypertensive encephalopathy. *J Clin Neurosci*. (2006) 13:590–5. doi: 10.1016/j.jocn.2005.03.042
4. Feske SK. Posterior reversible encephalopathy syndrome: a review. *Semin Neurol*. (2011) 31:202–15. doi: 10.1055/s-0031-1277990
5. Chen Z, Zhang G, Lerner A, Wang AH, Gao B, Liu J. Risk factors for poor outcome in posterior reversible encephalopathy syndrome: systematic review and meta-analysis. *Quant Imaging Med Surg*. (2018) 8:421. doi: 10.21037/qims.2018.05.07
6. Veglio F, Paglieri C, Rabbia F, Bisbocci D, Bergui M, Cerrato P. Hypertension and cerebrovascular damage. *Atherosclerosis*. (2009) 205:331–41. doi: 10.1016/j.atherosclerosis.2008.10.028
7. Buttler L, Jordão MT, Fragas MG, Ruggeri A, Ceroni A, Michelini LC. Maintenance of blood-brain barrier integrity in hypertension: a novel benefit of exercise training for autonomic control. *Front Physiol*. (2017) 8:1048. doi: 10.3389/fphys.2017.01048
8. Stefanie S, Celine Zoe B, Cornelia G, Holger B. Blood brain barrier breakdown as the starting point of cerebral small vessel disease? - New insights from a rat model. *Exp Transl Stroke Med*. (2013) 5:4. doi: 10.1186/2040-7378-5-4
9. Willard N, Honce JM, Kleinschmidt-Demasters BK. PRES: review of histological features. *J Neuropathol Exp Neurol*. (2018) 77:100–18. doi: 10.1093/jnen/nlx112
10. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *Am J Neuroradiol*. (2008) 29:1043–9. doi: 10.3174/ajnr.A0929

11. Marra A, Vargas M, Striano P, Guercio LD, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. *Med Hypotheses*. (2014) 82:619–22. doi: 10.1016/j.mehy.2014.02.022
12. Li Y, Jenny D, Castaldo J. Posterior reversible encephalopathy syndrome: clinicoradiological spectrum and therapeutic strategies. *Hosp Pract*. (2012) 40:202–13. doi: 10.3810/hp.2012.02.961
13. Edvardsson B. Venlafaxine as single therapy associated with hypertensive encephalopathy. *Springerplus*. (2015) 4:1–4. doi: 10.1186/s40064-015-0883-0
14. Shindo A, Maki T, Mandeville ET, Liang AC, Egawa N, Itoh K, et al. Astrocyte-derived pentraxin 3 supports blood-brain barrier integrity under acute phase of stroke. *Stroke*. (2016) 47:1094–100. doi: 10.1161/STROKEAHA.115.012133
15. Bartynski W, Boardman J. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. *Am J Neuroradiol*. (2008) 29:447–55. doi: 10.3174/ajnr.A0839
16. Euser AG, Cipolla MJ. Cerebral blood flow autoregulation and edema formation during pregnancy in anesthetized rats. *Hypertension*. (2007) 49:334–40. doi: 10.1161/01.HYP.0000255791.54655.29
17. Niklass S, Stoyanov S, Garz C, Bueche CZ, Mencl S, Reymann K, et al. Intravital imaging in spontaneously hypertensive stroke-prone rats-a pilot study. *Exp Transl Stroke Med*. (2014) 6:1. doi: 10.1186/2040-7378-6-1
18. Mencl S, Garz C, Niklass S, Braun H, Göb E, Homola G, et al. Early microvascular dysfunction in cerebral small vessel disease is not detectable on 3.0 Tesla magnetic resonance imaging: a longitudinal study in spontaneously hypertensive stroke-prone rats. *Exp Transl Stroke Med*. (2013) 5:8. doi: 10.1186/2040-7378-5-8
19. Alhilali LM, Reynolds AR, Fakhran S. A multi-disciplinary model of risk factors for fatal outcome in posterior reversible encephalopathy syndrome. *J Neurol Sci*. (2014) 347:59–65. doi: 10.1016/j.jns.2014.09.019
20. Herisson F, Zhou I, Mawet J, Du E, Barfejani AH, Qin T, et al. Posterior reversible encephalopathy syndrome in stroke-prone spontaneously hypertensive rats on high-salt diet. *J Cereb Blood Flow Metab*. (2018) 2018:0271678X1775279. doi: 10.1177/0271678X17752795
21. Isozaki M, Arai Y, Kudo T, Kiyono Y, Kobayashi M, Kubota T, et al. Clinical implication and prognosis of normal baseline cerebral blood flow with impaired vascular reserve in patients with major cerebral artery occlusive disease. *Ann Nucl Med*. (2010) 24:371–7. doi: 10.1007/s12149-010-0367-9
22. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol*. (2015) 14:914–25. doi: 10.1016/S1474-4422(15)00111-8
23. Yang Y, Kimura-Ohba S, Thompson JF, Salayandia VM, Cosse M, Raz L, et al. Vascular tight junction disruption and angiogenesis in spontaneously hypertensive rat with neuroinflammatory white matter injury. *Neurobiol Dis*. (2018) 114:S0969996118300445. doi: 10.1016/j.nbd.2018.02.012
24. Grossbach, Andrew J, Abel, Taylor J, Hodis, Brendan, et al. Hypertensive posterior reversible encephalopathy syndrome causing posterior fossa edema and hydrocephalus. *J Clin Neurosci*. (2014) 21:207–11. doi: 10.1016/j.jocn.2013.07.005
25. Marc D, Stefan L, Janine R, Sedat A, Gregor R, Arnd D. Differentiation of cytotoxic and vasogenic edema in a patient with reversible posterior leukoencephalopathy syndrome using diffusion-weighted MRI. *Diag Intervent Radiol*. (2007) 13:125–8.
26. Pande AR, Ando K, Ishikura R, Nagami Y, Takada Y, Wada A, et al. Clinicoradiological factors influencing the reversibility of posterior reversible encephalopathy syndrome: a multicenter study. *Radiat Med*. (2006) 24:659–68. doi: 10.1007/s11604-006-0086-2
27. Marrone LCP, Costa BEPD, Diogo LP, Costa JCD, Gadonski G, Laguna GDO, et al. Blood-brain barrier breakdown in reduced uterine perfusion pressure: a possible model of posterior reversible encephalopathy syndrome. *J Stroke Cerebrovasc Dis*. (2014) 23:2075–9. doi: 10.1016/j.jstrokecerebrovasdis.2014.03.012
28. Ozkan E, Gocmen R, Topcuoglu MA, Arsava EM. Blood-retina-barrier disruption accompanying blood-brain-barrier dysfunction in posterior reversible encephalopathy syndrome. *J Neurol Sci*. (2014) 346:315–7. doi: 10.1016/j.jns.2014.08.035
29. Marrone LCP, Bianca Fontana M, Julia DLPR, Giovani G, Jaderson Costa DC. Gemcitabine monotherapy associated with posterior reversible encephalopathy syndrome. *Case Rep Oncol*. (2011) 4:82–7. doi: 10.1159/000324581
30. Lamy C, Oppenheim C, Méder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. *J Neuroimaging*. (2010) 14:89–96. doi: 10.1111/j.1552-6569.2004.tb0 0223.x
31. Karia SJ, Rykken JB, Mckinney ZJ, Zhang L, Mckinney AM. Utility and significance of gadolinium-based contrast enhancement in posterior reversible encephalopathy Syndrome. *Am J Neuroradiol*. (2015) 37:415. doi: 10.3174/ajnr.A4563
32. Topakian R, Barrick TR, Howe FA, Markus HS. Blood-brain barrier permeability is increased in normal-appearing white matter in patients with lacunar stroke and leucoaraiosis. *J Neurol Neurosurg Psychiatry*. (2010) 81:192. doi: 10.1136/jnnp.2009.172072
33. Striano P, Striano S, Tortora F, Robertis ED, Servillo G. Clinical spectrum and critical care management of Posterior Reversible Encephalopathy Syndrome (PRES). *Med Sci Monit*. (2005) 11:549–53.
34. Schwartz RB. Hyperperfusion encephalopathies: hypertensive encephalopathy and related conditions. *Neurologist*. (2002) 8:22–34.35. doi: 10.1097/00127893-200201000-00003
35. Welker K, Boxerman J, Kalnin A, Kaufmann T, Shiroishi M, Wintermark M. Asfnr recommendations for clinical performance of mr dynamic susceptibility contrast perfusion imaging of the brain. *Am J Neuroradiol*. (2015) 36:E41. doi: 10.3174/ajnr.A4341
36. Edvardsson B. Hypertensive encephalopathy and cerebral infarction. *Springerplus*. (2014) 3:1–9. doi: 10.1186/2193-1801 -3-741
37. Henning EC, Steven W, Maria S. Hypertension-induced vascular remodeling contributes to reduced cerebral perfusion and the development of spontaneous stroke in aged SHRSP rats. *J Cereb Blood Flow Metab*. (2010) 30:827. doi: 10.1038/jcbfm.2009.246
38. Sundgren P, Edvardsson B, Holtås S. Serial investigation of perfusion disturbances and vasogenic oedema in hypertensive encephalopathy by diffusion and perfusion weighted imaging. *Neuroradiology*. (2002) 44:299–304. doi: 10.1007/s00234-001-0721-7
39. Weili L, Jin-Moo L, Lee YZ, Vo KD, Thomas P, Hsu CY. Temporal relationship between apparent diffusion coefficient and absolute measurements of cerebral blood flow in acute stroke patients. *Stroke*. (2003) 34:64–70. doi: 10.1161/01.STR.0000048151.28173.0D
40. Shui-Xing Z, Wen-Bo C, Chang-Hong L, Biao H. Evaluation of the applicability of Resovist in DSC-MR perfusion-weighted imaging of rat hyperacute cerebral infarction. *Turkish Neurosurgery*. (2014) 24:344–50. doi: 10.5137/1019-5149.JTN.8258-13.0

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 30 January 2020
doi: 10.3389/fneur.2019.01405

Delayed Posterior Reversible Leukoencephalopathy Syndrome Triggered by FLOT Chemotherapy

Jordi Gandini[1], *Mario Manto*[1,2*] *and Nicolas Charette*[3]

[1] *Department of Neurology, CHU-Charleroi, Charleroi, Belgium,* [2] *Service des Neurosciences, University of Mons, Mons, Belgium,* [3] *Department of Gastroenterology, CHU-Charleroi, Charleroi, Belgium*

OPEN ACCESS

Edited by:
Bo Gao,
Affiliated Hospital of Guizhou Medical University, China

Reviewed by:
Wei Chen,
Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, China
Yanwei Miao,
Dalian Medical University, China
Bérenger Largeau,
Centre Hospitalier Universitaire de Tours, France

***Correspondence:**
Mario Manto
mmanto@ulb.ac.be

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *23 August 2019*
Accepted: *23 December 2019*
Published: *30 January 2020*

Citation:
Gandini J, Manto M and Charette N (2020) Delayed Posterior Reversible Leukoencephalopathy Syndrome Triggered by FLOT Chemotherapy. Front. Neurol. 10:1405. doi: 10.3389/fneur.2019.01405

Posterior reversible encephalopathy syndrome (PRES) is a potentially severe disorder of the autoregulation of cerebral perfusion. The major clinical manifestations are headache, seizures, altered mental status, and visual loss. The typical radiological finding is vasogenic edema predominating in the white matter of occipital and parietal lobes. PRES is increasingly recognized as a clinico-radiological entity owing to improvements and fast availability of brain imaging, especially magnetic resonance imaging (MRI). We present the exceptional case of a 67-year-old female patient with a gastric adenocarcinoma at stage IIB (T3N0M0) treated by FLOT chemotherapy (5-fluorouracil, oxaliplatin, docetaxel, and folinic acid). Two months after the unique administration of FLOT regimen, she developed sudden posterior headache and visual loss. Blood pressure values were normal. Cerebral tomography showed ischemic-like occipital bilateral lesions, and angiographic sequences revealed breakdown of the blood–brain barrier (BBB). MRI revealed bilateral parieto-occipital T1 hypointensity and T2 hyperintensity, which demonstrated vasogenic edema. The rest of the parts of the lesions were T1 hyperintensity, T2 hyperintensity, and diffusion-weighted imaging (DWI) hyperintensity, which indicate cortical laminar necrosis. After injection of gadolinium, a linear enhancement of the cortex was observed. She was treated with oral nimodipine. Follow-up was characterized by permanent visual sequelae and tetraparesis. PRES represents an urgent neurological condition. Our observation highlights that PRES should be considered in patients under chemotherapy, even when their blood pressure remains within normal range. This is the first report of PRES triggered by FLOT chemotherapy and with a silent window of 2 months between chemotherapy and PRES, widening further the spectrum of chemotherapy-induced PRES. Our case highlights the potential role of FLOT regimen in the pathogenesis of PRES and the need for a novel approach in terms of prevention of this potentially fatal complication when patients receive chemotherapy.

Keywords: posterior reversible encephalopathy syndrome, reversible encephalopathy, sepsis, cancer, chemotherapy, sequelae

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological disorder of the autoregulation of cerebral perfusion, characterized by vasospasm of vertebrobasilar system (1–4). The main clinical manifestations include headache, seizures, altered mental status, and visual loss.

We report on a patient under chemotherapy who developed PRES despite normal blood pressure values and after a free interval of 2 months. We discuss our case in the light of the literature and emphasize the need to recognize this urgent neurological condition and develop novel approaches for prevention.

CASE REPORT

Chief Complaints

A 69-year-old woman was admitted to the emergency room of our hospital for sudden headache with occipital topography, associated with nape pain and visual loss.

Clinical Findings

She was under treatment by FLOT regimen (5-fluorouracil 4,200 mg, oxaliplatin 147.58 mg, docetaxel 87.5 mg, and folinic acid 350 mg) for a gastric adenocarcinoma at stage IIB (T3N0M0). The neoplasm infiltrated tunica serosa without lymph node infiltration or metastasis. The FLOT regimen was administered as a neoadjuvant treatment to prepare for the surgical procedure of removal of the lesion. She had received a unique dose of chemotherapy 2 months before admission. Chemotherapy was complicated by infectious pneumonia (*Streptococcus pneumoniae*) leading to septic shock, treated with intravenous infusion of amoxicillin/clavulanic acid, with acute renal failure requiring dialysis. For this reason, the chemotherapy was interrupted after administration. She had a personal history of arterial hypertension, vena cava and iliac deep vein thrombosis, polymyalgia rheumatica, hypercholesterolemia, chronic obstructive pulmonary disease (COPD), and blindness in the right eye. She was taking amiodarone, acetylsalicylic acid, tinzaparin, hydralazine, and lorazepam, but she was not taking any treatment for COPD.

Diagnostic Assessment

On admission, blood pressure was 136/76 mmHg, weight 58.9 kg, height 1.63 m, heart rate 92 pulse/minute, body temperature 36.0°C, and capillary blood glucose 136 mg/dl. General physical examination was unremarkable. Neurological examination showed visual loss in the left eye and weakness of the lower limbs. Blood tests showed normal values of sodium and magnesium. Lactic acid dehydrogenase (LDH) levels were within normal limits. C-reactive protein (CRP) level was slightly increased, and albumin level was slightly decreased.

Brain computed tomography (CT) showed two ischemic-like occipital lesions without hemorrhage (**Figure 1**). Angiographic sequences revealed breakdown of the blood–brain barrier (BBB) in the corresponding regions. Cerebral magnetic resonance imaging (MRI) demonstrated bilateral parieto-occipital lesions: most parts of the lesions were T1 hypointensity and T2 hyperintensity, which demonstrated vasogenic edema. The rest of the parts of the lesions were T1 hyperintensity, T2 hyperintensity, and diffusion-weighted imaging (DWI) hyperintensity, which might indicate cortical laminar necrosis. After gadolinium injection, a linear enhancement of the cortex was observed. Multiple micro-ischemic lesions were observed in the periventricular regions, indicating a background of chronic ischemic leukoencephalopathy. No lesion was demonstrated in the posterior fossa. Dynamic susceptibility contrast (DSC)-MRI was not performed. MRI angiographic sequences did not show any abnormality in the vertebrobasilar system or in Willis polygon (**Figure 2**). In particular, there was no evidence of vasospasm.

Lumbar puncture was not performed in our patient owing to absence of clinical evidence of infectious meningitis. The electroencephalography (EEG) was unremarkable. The diagnosis of PRES was made, and the patient was admitted in our cerebrovascular unit to monitor her blood pressure and cardiorespiratory function. Regarding the blood pressure monitoring, she presented one single peak of hypertension (183/91 mmHg) a few hours after admission (see **Supplementary Figure**).

Therapeutic Interventions

She was administered with oral nimodipine 360 mg/day because of the neuroprotective effect of this drug (5, 6). She left the hospital 48 h later with continuation of nimodipine at home and was followed up by ambulatory care as an outpatient.

Follow-Up and Outcome

The clinical evolution was characterized by resolution of headache 1 month after discharge. The radiological follow-up with MRI 1 month later showed ischemic-like parieto-occipital bilateral lesions (**Figure 3**). There was no rechallenge with FLOT. The patient is alive 15 months after occurrence of PRES, with permanent visual sequelae and residual paraparesis.

PATHOPHYSIOLOGY

The Theories to Explain Posterior Reversible Encephalopathy Syndrome

The pathophysiology of PRES remains controversial. At present, five theories have been proposed. First, the vasogenic theory postulates that severe hypertension causes interruption of cerebrovascular autoregulation (2, 3). Second, the endothelial theory considers that PRES is primarily due to an endothelial dysfunction caused by a systemic inflammatory state, triggered by toxics, sepsis, eclampsia, transplantation, or autoimmune disease (3). Third, the cytotoxic theory postulates that endothelial dysfunction is induced by endotoxins like chemokines or exotoxins like chemotherapeutic or immunosuppressive drugs (5). This theory can explain the occurrence of PRES during antineoplastic chemotherapy. Fourth, the immunogenic theory asserts that the first landmark of endothelial dysfunction is a T-cell-mediated inflammatory with chemokine release (5).

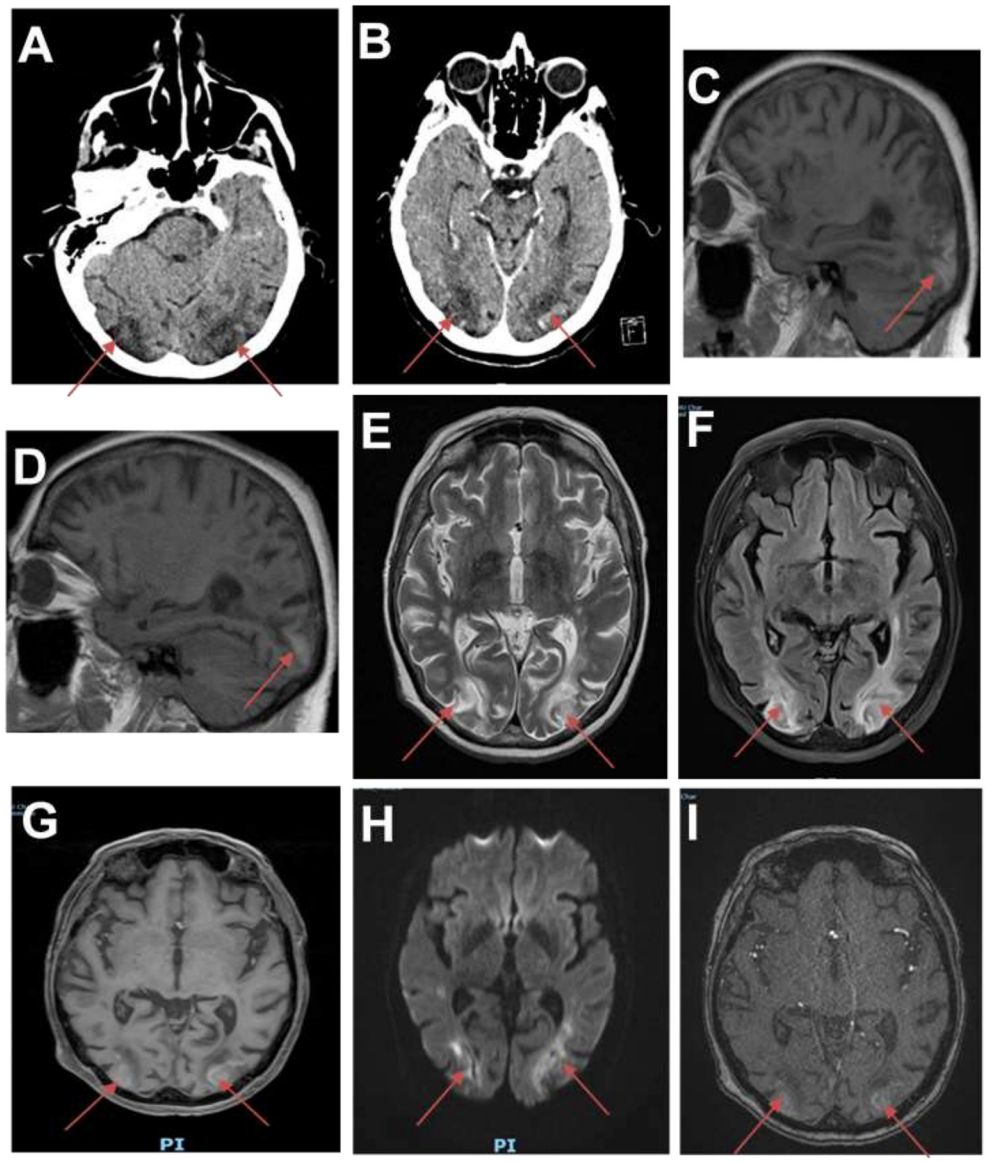


FIGURE 1 | First brain imaging. **(A)** Brain CT showing ischemic-like lesions in the occipital lobes (red arrows). **(B)** CT scan showing hypodense lesions with breakdown of the blood–brain barrier (BBB) in the occipital lobes. **(C,D)** Sagittal T1 MRI showing hyperintensities in both occipital lobes. **(E)** Brain MRI (T2-weighted images) showing hyperintense lesions in the white matter of the occipital lobes. **(F)** Fluid attenuation inversion recovery (FLAIR) images showing ischemic-like lesions in the occipital lobes. **(G)** MRI angiographic sequences showing breakdown of BBB in the occipital lobes. **(H)** Diffusion sequence showing restriction in the occipital lobes. **(I)** Magnetic resonance angiography time-of-flight (MRA TOF) sequences showing breakdown of BBB in the occipital lobes.

Given the limitations of the hypoperfusion/hyperperfusion theories above, Largeau et al. have postulated recently that PRES can be induced by hypersecretion of arginine vasopressin (AVP) or by an increase of AVP's receptor density. The authors have observed that PRES occurs in conditions with AVP hypersecretion such as sepsis or eclampsia. Activation of vasopressin V1a receptors would cause cerebral vasoconstriction, leading to endothelial dysfunction and cerebral ischemia. According to this novel theory, cytotoxic edema is induced by a transglial flux dysfunction with enhanced endothelial permeability, generating vasogenic brain edema. AVP can mediate also endothelial dysfunction through hypersecretion of vascular endothelial growth factor (VEGF) (6).

Chemotherapy and PRES: What Does Our Case Add to the Literature?

PRES occurs with certain imunosuppressive/chemotherapeutic drugs, monoclonal antibodies, and chemotherapeutic schemas (7–19). In 2016, How and colleagues reported 70 cases of PRES associated with chemotherapy. The most common chemotherapeutic agents were platinum salts (cisplatin, carboplatin, and oxaliplatin: 30 cases), daunorubicin (24 cases),

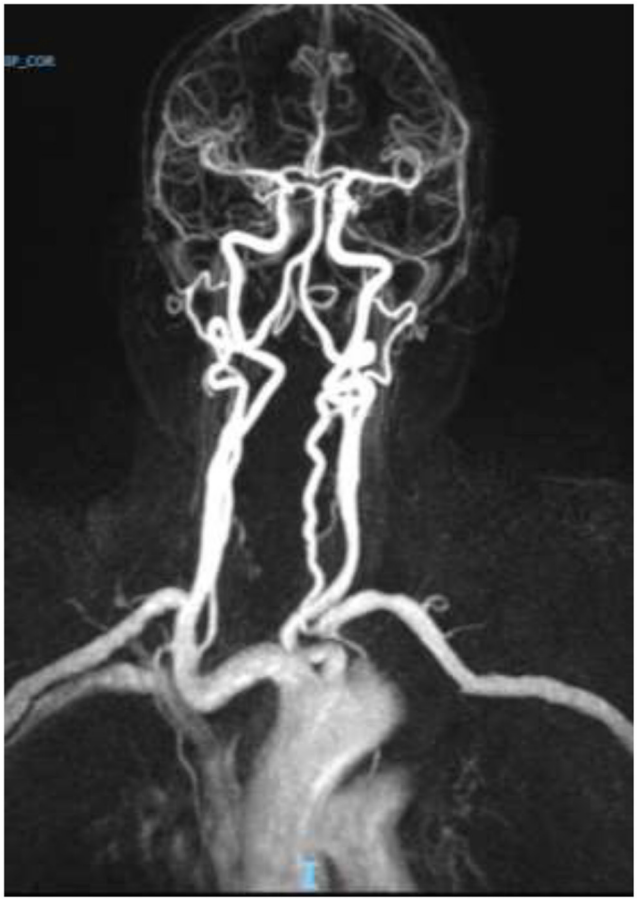


FIGURE 2 | Normal magnetic resonance (MR) angiogram. No evidence of vasospasm in the anterior of the posterior circulation.

vinca alkaloids (vincristine, vinorelbine, vinflunine, vinblastine, and vindesine: 21 cases), and 5-fluorouracil (13 cases); and only one case was associated with irinotecan (20). PRES has never been reported under chemotherapy with FLOT regimen, but one cannot exclude a key role of oxaliplatin in our patient, of course. FLOT is considered an efficient and safe neoadjuvant regimen for esophagogastric neoplasm (21, 22). Our article highlights the risk of PRES with this treatment so that oncologists can improve the monitoring of the risk factors in cancer. Our case expands the published reports on the associations of chemotherapies incriminated in PRES.

The pathophysiological relationship between chemotherapy and PRES remains to be further clarified. Several studies suggest that cytotoxic agents lead to endothelial dysfunction with production of vasoactive substances and trigger vascular leakage and edema development (23); this effect is amplified when several molecules are employed together (24). A study published by Liman and colleagues showed that patients with PRES who have received chemotherapy or immunosuppressive medication show significantly lower mean arterial pressure than did those with PRES from other etiologies (25).

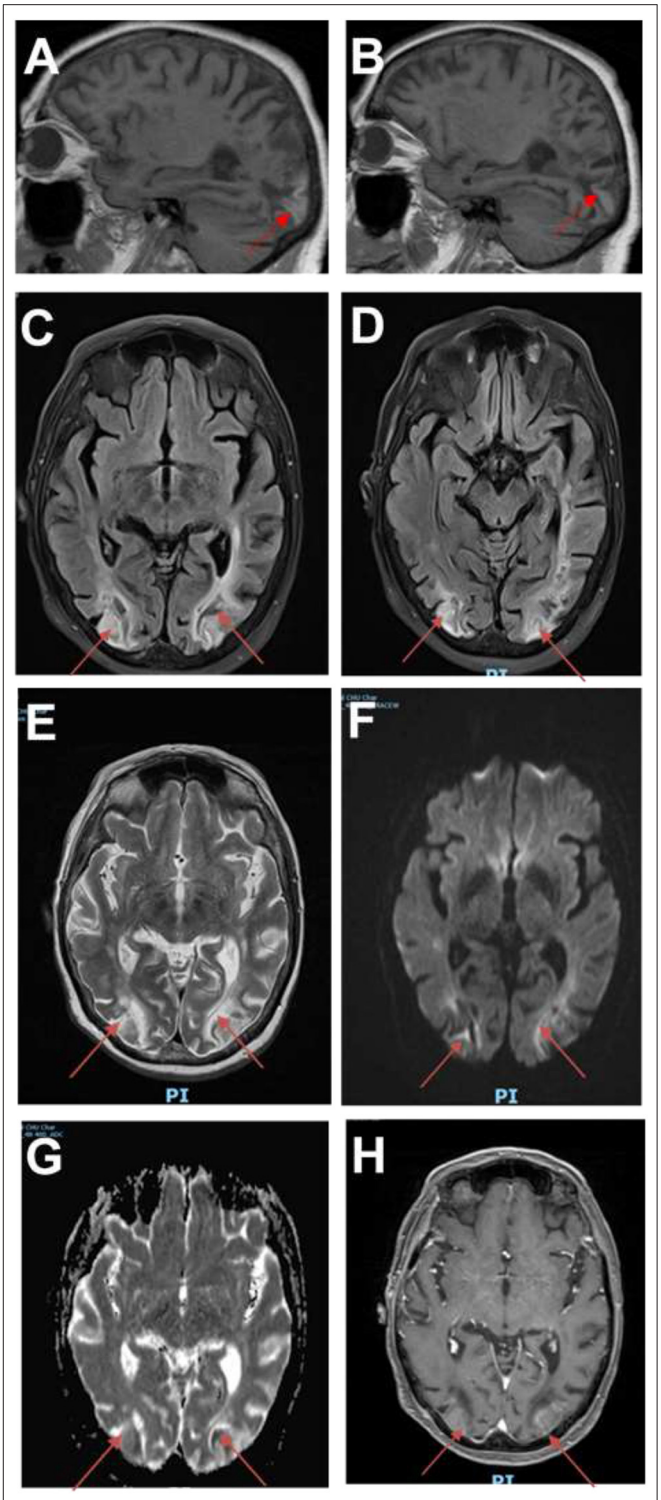


FIGURE 3 | Follow-up images. **(A,B)** Sagittal T1 MRI showing hyperintensities in both occipital lobes (red arrows). **(C,D)** MRI fluid attenuation inversion recovery (FLAIR) images showing persistent ischemic-like lesions in the occipital lobes. **(E)** T2-weighted images showing hyperintense lesions in the occipital lobes. **(F)** Diffusion images demonstrating restriction in the occipital lobes. **(G)** MRI apparent diffusion coefficient (ADC) images showing residual restriction in the occipital lobes. **(H)** MRI angiographic sequences confirming persistent breakdown of BBB in the occipital lobes.

Platinum salts are a well-known trigger of AVP hypersecretion (6), and they have a direct toxic effect on endothelial cells (26, 27).

5-Fluorouracil can cause a direct neurotoxic effect through the interruption of Krebs cycle or through thiamine deficiency (28, 29); a neurotoxic effect is reported also in case of dihydropyrimidine dehydrogenase (DPD), the initial and rate-limiting enzyme in the catabolism of fluoropyrimidines (30, 31).

Other Triggering Factors of Posterior Reversible Encephalopathy Syndrome: Relevance to Our Case

Concerning our patient, we have ruled out the other potential etiologies of PRES. She was treated with amoxicillin/clavulanic acid 2 months before admission, but only two antibiotics have been demonstrated to be associated with PRES: ciprofloxacin and linezolid (32, 33). In 2016, Van Aalst et al. described a case of PRES in a patient with an infected morphine pump (34). The patient was treated with intravenous amoxicillin/clavulanic acid, but she was withdrawn from opiates and underwent two surgical procedures to remove the infected pump. The second surgery was performed under general anesthesia; so she had at least three risk factors for PRES: infection, withdrawal (35), and general anesthesia (36). Therefore, amoxicillin/clavulanic acid cannot be considered an evident trigger factor of PRES at this stage.

Our patient suffered from polymyalgia rheumatica, but this disease is not associated with PRES (37). Furthermore, there is no evidence that PRES can be triggered by deep venous thrombosis of the leg or by vena cava thrombosis (37). Also, our patient suffered from COPD. β2-Agonists and corticosteroids employed in COPD are associated with PRES, but our patient did not take these drugs (37, 38). Amiodarone, acetylsalicylic acid, tinzaparin, hydralazine, and lorazepam are not associated with PRES (39). Septic shock and acute kidney insufficiency occurred 2 months before admission; in 2012, Kim et al. (40) described a case of PRES during a recovery from acute kidney injury (AKI), but the patient was still undergoing hemodialysis. We did not found any delayed case of PRES after AKI/dialysis.

Clinico-Radiological Criteria: Criteria and Sequelae in Our Case

The first clinical signs of PRES are unusual headache and altered mental status (4, 41, 42). Nausea, vomiting, and seizures are described in 75% of patients. The epileptic crisis is initially focal and related to the topography of the lesional charge. A secondary generalization is common. Evolution into epileptic status may occur. Visual loss is present in more than 50% of the patients, but cortical blindness is rare. Some patients present weakness and loss of coordination of limbs (43).

In 2015, three clinico-radiological criteria were suggested for the diagnosis of PRES (44): neurological symptoms of acute onset, vasogenic edema on neuroimaging, and reversibility of clinical and/or radiological findings. Our patient met the first two criteria but showed visual sequelae and permanent paraparesis.

Biological Findings

Serum findings are unspecific (38). Hypomagnesemia has been reported in the first 48 h of disease (45). Hypoalbuminemia has been observed in several patients with PRES of various etiologies (46, 47). LDH serum level has been proposed as a marker of endothelial dysfunction (48).

Radiological Findings

Although angio-CT scan demonstrates posterior leukoencephalopathy and breakdown of BBB, MRI is the gold standard for the diagnosis of PRES (4, 49–51). The most common finding is edema without infarction of the sub-cortical white matter of the temporo-parieto-occipital lobes; this sign is usually bilateral and symmetric. Calcarine fissure and the paramedian area of occipital lobes are often spared (4, 41, 49). Gray matter is involved in only 30% of patients (50, 51). The involvement of the cerebellum, basal ganglia, internal capsule, frontal lobes, and brainstem is rare (52, 53). Four patterns of junctional distribution of lesions have been described: holo-hemispheric (23%), superior frontal sulcus (27%), primary parieto-occipital (22%), and "partial or asymmetric expression of the primary patterns" (28%) (38). The early phase of PRES is characterized by vasogenic edema, and the lesions are reversible. MRI may reveal hyperintensities in T2-weighted images and in fluid attenuation inversion recovery (FLAIR) sequences and isointense or hypointense lesions in T1-weighted images, whereas the diffusion sequences do not demonstrate abnormalities. Enhancement after gadolinium injection is described only in one third of cases (4, 42, 54, 55). By contrast, in the late phase of PRES, ischemic phenomena determine cytotoxic edema, and the lesions become irreversible. At this stage, T2-weighted images and FLAIR sequences demonstrate hyperintensities with or without microhemorrhages. Diffusion sequences reveal a low diffusion coefficient, which is the expression of ischemic lesions; this is correlated with irreversibility of this damage (56, 57). MRI can provide important information about the evolution of the disease: the reduction or the resolution of the abnormalities suggest the absence of ischemic lesions. By contrast, the persistence of the radiological anomalies indicates the ischemic installed lesions, similar to our case. In this situation, the involved areas may become atrophic with time (43). Spectroscopy can detect early perturbations of cellular metabolism in PRES, such as increase of lactic acid, creatine, and choline production or decrease of *N*-acetyl-aspartate (NAA) rate (51, 58). Scintigraphy and single-photon emission CT (SPECT) show hyperperfusion in the acute phase of PRES and hypoperfusion in the late phase (7).

Differential Diagnosis

The most important differential diagnosis of PRES is ischemic stroke. In this case, the management of arterial hypertension is opposite. Several other diseases mimic the clinical presentation of PRES (59, 60).

MRI is critical for the differential diagnosis of the PRES. In particular, MRI allows a rapid diagnosis of ischemic stroke and cerebral thrombophlebitis. Black-blood angio-MRI may be helpful to make diagnosis of vasculitis: the typical pattern is characterized by thickening and enhancement of the vascular wall. A typical enhancement pattern was described for several diseases of the vessel wall (61–63). Cerebral angiography is

often non-contributory, because the abnormalities of the vessel wall in case of vasculitis can determinate an angiographic pattern indistinguishable from that of PRES. Cerebro-spinal fluid (CSF) analysis is helpful in case of infectious or inflammatory diseases of the central nervous system (CNS); in this last category, blood cultures and serologic analyses are informative (43).

Treatment

The first treatment of PRES is the control of trigger factors: suspension of immunosuppressive drugs or toxic agents, delivery in case of eclampsia, and correction of electrolytic or hemostatic disorders. The principal target of the treatment is the control of arterial hypertension; in particular, a mean arterial pressure between 105 and 125 mmHg is recommended. Cardiovascular monitoring is necessary in this early phase, and respiratory support is indicated if needed (4, 49). The antihypertensive therapy is based on three classes of molecules: calcium antagonists (nimodipine, nicardipine, and diltiazem), β-blockers (labetalol), and diuretics. The arterial dilators—sodium nitroprusside, diazoxide, and fenoldopam mesylate—are a second choice. Fenoldopam can induce a selective renal arteriolar dilatation with a beneficial effect in case of acute renal failure (64). Magnesium sulfate is proposed during pregnancy, due to a dilator effect on arterial wall, in particular in cerebral vessels (4, 43). Derived nitric oxide (NO) is not indicated, because it aggravates the cerebral edema (43). The invasive monitoring of arterial pressure is recommended in case of cardiac failure or precarious hemodynamic status (4).

The treatment of neurological complications is crucial: seizures are treated with benzodiazepines. When facing epileptic status, additional anti-epileptic drugs are required. For refractory epileptic status, deep sedation is indicated; thiopental, propofol, and midazolam are the gold standard. EEG monitoring is necessary for detection of the non-convulsive epileptic crisis and for verification of the efficiency of the therapy (4, 43).

Prognosis

If the diagnosis is made quickly and if the patient is rapidly treated, clinical resolution often occurs within 7 days (42). The radiological resolution takes from 15 days to 1 year. In case of low apparent diffusion coefficient (ADC) at first MRI, the risk of irreversible lesions is increased. The prognosis is more severe, and a lethal outcome is possible for neoplastic diseases (43). Four predictive factors of fatal outcome have been identified: altered mental state, subarachnoid hemorrhage, raised CRP level, and altered coagulation (65). PRES is often accompanied by severe complications; neurological sequelae may persist (37).

CONCLUSION

Clinical presentation of PRES is characterized by unusual headache and altered mental status, nausea, visual loss, vomiting, and seizures. Evolution to epileptic status is possible. Weakness and loss of coordination of limbs are rare. Arterial hypertension is frequent, but PRES has been reported in normotensive patients (66–69). MRI demonstrates edema without infarction of the sub-cortical white matter of bilateral temporo-parieto-occipital lobes. The involvement of the cerebellum, basal ganglia, internal capsule, frontal lobes, and brainstem is rare. Our case was unique by the silent interval between the unique dose of chemotherapy complicated by sepsis and the occurrence of the symptomatology of PRES.

Our patient presented multiple factors predisposing to breakdown of cerebrovascular regulation. We speculate that sepsis in an oncologic patient newly treated with platinum salts might have contributed to a cerebral dysregulation in the absence of arterial hypertension. However, because sepsis is a rather frequent complication in oncological immunosuppressed patients (70, 71), more studies are needed to confirm this hypothesis. The prevention of nosocomial infection, an appropriate vaccination before the administration of cytotoxic agents, and hygienic–dietary regimen could play a crucial role in the prevention of PRES in this category of patients who are especially exposed to this complication.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Written, informed consent was obtained from the patient for the publication of this case report.

AUTHOR CONTRIBUTIONS

JG wrote the draft. MM and NC corrected the draft. All the authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01405/full#supplementary-material

REFERENCES

1. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *Am J Roentgenol.* (2007) 189:904–12. doi: 10.2214/AJR.07.2024
2. Roth C, Ferbert A. The posterior reversible encephalopathy syndrome: what's certain, what's new? *Pract Neurol.* (2011) 11:36–44. doi: 10.1136/practneurol-2011-000010
3. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *ANJR Am Neuroradiol.* (2008) 29:1036–42. doi: 10.3174/ajnr.A0928

4. Servillo G, Bifulco F, De Robertis E, Piazza O, Striano P, Tortora F, et al. Posterior-reversible encephalopathy syndrome in intensive care medecine. *Intensive Care Med.* (2007) 33:230–6. doi: 10.1007/s00134-006-0459-0
5. Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. Posterior reversible encephalopathy syndrome-Insight into pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev.* (2015) 14:830–6. doi: 10.1016/j.autrev.2015.05.006
6. Largeau B, Le Tilly O, Sautenet B, Salmon Gandonnière C, Barin-Le Guellec C, Ehrmann S. Arginine vasopressin and posterior reversible encephalopathy syndrome pathophysiology: the missing link? *Mol Neurobiol.* (2019) 56:6792–806. doi: 10.1007/s12035-019-1553-y
7. Nishie M, Kurahashi K, Ogawa M, Yoshida Y, Midorikawa H. Posterior encephalopathy subsequent to cyclosporin. A presenting as irreversible abulia. *Intern Med.* (2003) 42:750–5. doi: 10.2169/internalmedicine.42.750
8. Lavigne CM, Shrier DA, Ketkar M, Powers JM. Tacrolimus leukoencephalopathy: a neuropathologic confirmation. *Neurology.* (2004) 63:1132–9. doi: 10.1212/01.WNL.0000138568.60774.E4
9. Chow S, Cheung CS, Lee DH, Howson-Jan K, Xenocostas A. Posterior reversible encephalopathy syndrome in a patient with multiple myeloma treated with thalidomide. *Leuk Lymphoma.* (2012) 53:1003–5. doi: 10.3109/10428194.2011.638070
10. Saito B, Nakamaki T, Nakashima H, Usui T, Hattori N, Kawakami K, et al. Reversible posterior leukoencephalopathy syndrome after repeat intermediate-dose cytarabin chemotherapy in a patient with acute myeloid leukemia. *Am J Hematol.* (2007) 82:304–6. doi: 10.1002/ajh.20772
11. Abali H, Eren OO, Dizdar O, Karadag O, Erman M, Yilmaz A, et al. Posterior leukoencephalopathy after combination chemotherapy in a patient with lymphoma. *Leuk Lymphoma.* (2005) 46:1825–8. doi: 10.1080/10428190500234424
12. Yasaki S, Tukamoto Y, Yuasa N, Ishikawa T, Yoshii F. Late onset leukoencephalopathy induced by long term chemotherapy with capecitabine and cyclophosphamide for liver metastasis from breast cancer. *Rinsho Shinkeigazu.* (2012) 52:251–6. doi: 10.5692/clinicalneurol.52.251
13. Sharief U, Perry DJ. Delayed reversible posterior encephalopathy syndrome following chemotherapy with oxaliplatin. *Clin Colorectal Cancer.* (2009) 8:163–5. doi: 10.3816/CCC.2009.n.026
14. Cacho-Diaz B, Lorenzana-Mendoza NA, Salmérol-Moreno K, Reyes-Soto G, Castillo-Rangel C, Corona-Cedillo R, et al. Chemotherapy-induced posterior reversible encephalopathy syndrome. *Medicine.* (2019) 98:e15691. doi: 10.1097/MD.0000000000015691
15. Abughanimeh OK, Qasrawi AH, Tahboub MY, Abu Ghanimeh MK. Posterior encephalopathy syndrome while receiving irinotecan with fluorouracil and folinic acid for metasatic gastric cancer. *BJR Case Rep.* (2017) 4:20170033. doi: 10.1259/bjrcr.20170033
16. Xie C, Vovanti TJ. Reversible posterior leukoencephalopathy syndrome following combinatorial cisplatin and pemetrexed therapy for lung cancer in a normotensive patient: a case report and litterature review. *Oncol Lett.* (2016) 11:1512–6. doi: 10.3892/ol.2015.4059
17. Katada E, Mitsui A, Sasaki S, Uematsu N, Anan C. Posterior reversible encephalopathy syndrome after a variety of combined chemotherapies containing. *Intern Med.* (2018) 57:2403–7. doi: 10.2169/internalmedicine.0284-17
18. Salmi N, Elghissassi I, Bellahammou K, Lakhdissi A, Mrabti H, Errihani H. Atypical reversible leucoencephalopathy syndrome after bevacizumab/folfox regimen for metastatic colon cancer. *Case Rep Oncol Med.* (2014) 2014:391256. doi: 10.1155/2014/391256
19. Porcello Marrone LC, Marrone BF, Pascoal TA, Schilling LP, Soder RB, Ferreira SS, et al. Posterior reversible encephalopathy syndrome associated with FOLFOX chemotherapy. *Case Rep Oncol Med.* (2013) 2013:306983. doi: 10.1155/2013/306983
20. Singer S, Grommes C, Reiner AS, Rosenblum MK, DeAngelis LM. Posterior reversible encephalopathy syndrome in patients with cancer. *Oncologist.* (2015) 20:806–11. doi: 10.1634/theoncologist.2014-0149
21. Homann N, Pauligk C, Luley K, Werner Kraus T, Bruch HP, Atmaca A, et al. Pathological complete remission in patients with oesophagogastric cancer receiving preoperative 5-fluorouracil, oxaliplatin and docetaxel. *Int J Cancer.* (2012) 130:1706–13. doi: 10.1002/ijc.26180
22. Lorenzen S, Pauligk C, Homann N, Schmalenberg H, Jäger E, Al-Batran SE. Feasibility of perioperative chemotherapy with infusional 5-FU, leucovorin, and oxaliplatin with (FLOT) or without (FLO) docetaxel in elderly patients with locally advanced esophagogastric cancer. *Br J Cancer.* (2013) 108:519–26. doi: 10.1038/bjc.2012.588
23. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. *Med Hypotheses.* (2014) 82:619–22. doi: 10.1016/j.mehy.2014.02.022
24. How J, Blattner M, Fowler S, Wang-Gillam A, Schindler SE. Chemotherapy-associated posterior reversible encephalopathy syndrome: a case report and review of the literature. *Neurologist.* (2016) 21:112–7. doi: 10.1097/NRL.0000000000000105
25. Liman TG, Bohner G, Heuschmann PU, Endres M, Siebert E. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: The retrospective Berlin PRES study. *J Neurol.* (2012) 259:155–64. doi: 10.1007/s00415-011-6152-4
26. Nguyen MT, Virk IY, Chew L, Villano JL. Extended use dexamethasone-associated posterior reversible encephalopathy syndrome with cisplatin-based chemotherapy. *J Clin Neurosci.* (2009) 16:1688–90. doi: 10.1016/j.jocn.2009.05.012
27. Schwartz RB, Bravo SM, Klufas RA, Hsu L, Barnes PD, Robson CD, et al. Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy:CT and MR findingin 16 cases. *Am J Neuroradiol.* (1995) 165:627–31. doi: 10.2214/ajr.165.3.7645483
28. Koenig H, Patel A. Biochemical basis of fluorouracil neurotoxicity. The role of krebs cycle inhibition by fluoroacetate. *Arch Neurol.* (1970) 23:155–60. doi: 10.1001/archneur.1970.00480260061008
29. Soukop M, Kalman KC. Thiamine status in cancer patients and the effect of 5-fluorouracil therapy. *Eur J Cancer.* (1978) 38:180.
30. Reerink O, Mulder NH, Szabo BG, Hospers GA. 5FUand oxaliplatin-containing chemotherapy in two dihydropyrimidine dehydrogenase-deficient patients. *Anticancer Res.* (2004) 24:1969–72.
31. Kim DW, Oh J, Cho YH, Kim SY, Yoon SY. Reversible encephalopathy following 5-?uoruracil based chemotherapy in patients with dihydropyrimidine dehydrogenase deficiency. *Asia Pac J Clin Oncol.* (2009) 5:159–64. doi: 10.1111/j.1743-7563.2009.01229.x
32. Casey SO, Sampaio RC, Michel E, Truwit CL. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. *AJNR Am J Neuroradiol.* (2000) 21:1199–206.
33. Nagel S, Köhrmann M, Huttner HB, Storch-Hagenlocher B, Schwab S. Linezolid-induced posterior reversible leukoencephalopathy syndrome. *Arch Neurol.* (2007) 64:746–8. doi: 10.1001/archneur.64.5.746
34. Van Aalst J, Teernstra OP, Weber WE, Rijkers K. An unusual case of posterior reversible encephalopathy syndrome in a patient being weaned from intrathecal morphine. *Int Med Case Rep J.* (2016) 9:117–20. doi: 10.1093/omcr/omw038
35. Ishikawa H, Natsume N, Matsui K, Tsuda H. Acute alcohol withdrawal accompanied by posterior reversible encephalopathy syndrome. *Psychiatry Clin Neurosci.* (2013) 67:189. doi: 10.1111/pcn.12033
36. Inoue S, Kawaguchi M, Furuya H. A case of posterior reversible encephalopathy syndrome after emergence from anesthesia. *J Anesth.* (2012) 26:111–4. doi: 10.1007/s00540-011-1256-7
37. Zhang S, Yuan D, Tan G. Neurological involvement in primary systemic vasculitis. *Front Neurol.* (2019) 10:430. doi: 10.3389/fneur.2019.00430
38. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol.* (2017) 264:1608–16. doi: 10.1007/s00415-016-8377-8
39. Parikh NS, Schweitzer AD, Young RJ, Giambrone AE, Lyo J, Karimi S, et al. Corticosteroid therapy and severity of vasogenic edema in posterior reversible encephalopathy syndrome. *J Neurol Sci.* (2017) 380:11–5. doi: 10.1016/j.jns.2017.06.044
40. Kim SM, Choi H, Kim Y, Shin J, Jang HR, Lee JE, et al. Posterior reversible encephalopathy syndrome during recovery from acute kidney injury after hepatitis A infection. *Case Rep Nephrol Urol.* (2012) 2:33–7. doi: 10.1159/000339253
41. Stott VL, Hurrell MA, Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. *Intern Med J.* (2005) 35:83–90. doi: 10.1111/j.1445-5994.2004.00750.x

42. Schwartz RB. Hyperpefusion encephalopathies: hypertensive encephalopathy and related conditions. *Neurologist.* (2002) 8:22–34. doi: 10.1097/00127893-200201000-00003
43. Mohebbi Amoli A, Mégarbane B, Chabriat H. La leukoencéphalopathie postérieure réversible. *Réanimation.* (2007) 16:490–7. doi: 10.1016/j.reaurg.2007.09.021
44. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc.* (2010) 85:427–32. doi: 10.4065/mcp.2009.0590
45. Chardain A, Mesnage V, Alamowitch S, Bourdain F, Crozier S, Lenglet T, et al. Posterior reversible encephalopathy syndrome (PRES) and hypomagnesemia: a frequent association? *Rev Neurol.* (2016) 172:384–8. doi: 10.1016/j.neurol.2016.06.004
46. Gao B, Yu BX, Li RS, Zhang G, Xie HZ, Liu FL, et al. Cytotoxic edema in posterior reversible encephalopathy syndrome: correlation of MRI features with serum albumine levels. *AJNR Am J Neuroradiol.* (2015) 36:1884–9. doi: 10.3174/ajnr.A4379
47. Pirker A, Kramer L, Voller B, Loader B, Auff E, Prayer D. Type of edema in posterior reversible encephalopathy syndrome depends on serum albumin levels: an MR imaging study in 28 patients. *AJNR Am J Neuroradiol.* (2011) 32:527–31. doi: 10.3174/ajnr.A2332
48. Fitzgerald RT, Wright SM, Samant RS, Kumar M, Ramakrishnaiah RH, Van Hemert R, et al. Elevation of serum lactate dehydrogenase at posterior reversible encephalopathy syndrome onset in chemotherapy-treated cancer patients. *J Clin Neurosci.* (2014) 21:1575–8. doi: 10.1016/j.jocn.2014.03.004
49. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* (1996) 334:494–500. doi: 10.1056/NEJM199602223340803
50. Mukherjee P, McKinstry RC. Reversible posterior leuckoencephalopathy syndrome: evaluation with diffusion-tensor MR imagimg. *Radiology.* (2001) 219:756–65. doi: 10.1148/radiology.219.3.r01jn48756
51. Sengar AR, Gupta RK, Dhanuka AK, Roy R, Das K. MR imaging, MR angiography, and MR spectroscopy of brain in eclampsia. *AJNR Am J Neuroradiol.* (1997) 18:1845–90.
52. Kitaguchi H, Tomimoto H, Miki Y, Yamamoto A, Terada K, Satoi H, et al. A brainstem variant of reversible posterior leukoencephalopathy syndrome. *Neuroradiology.* (2005) 47:652–6. doi: 10.1007/s00234-005-1399-z
53. Bianco F. Reversible posterior leukoencephalopathy syndrome: a changing concept. *Neuroradiology.* (2005) 47:703–4. doi: 10.1007/s00234-005-1403-7
54. Kahana A, Rowley HA, Weinstein JM. Cortical blindness: clinical and radiologic findings in reversible posterior leukoencephalopathy syndrome: case report and review of the literature. *Ophthalmology.* (2005) 112:e7–11. doi: 10.1016/j.ophtha.2004.07.036
55. Ugurel MS, Hayakawa M. Implications of postgadolinium MRI results in 13 cases with posterior reversible encephalopathy syndrome. *Eur J Radiol.* (2005) 53:441–9. doi: 10.1016/j.ejrad.2004.05.015
56. Chester EM, Agamanolis DP, Banker BQ, Victor M. Hypertensive encephalopathy: a clinicopathologic study of 20 cases. *Neurology.* (1978) 28:928–39. doi: 10.1212/WNL.28.9.928
57. Tsushima Y, Aoki J, Endo K. Brain microhemorrages detected on T2* weighted gradient-echo images. *ANJR Am J Neuroradiol.* (2003) 24:88–96.
58. Eichler FS, Wang P, Wityk RJ, Beauchamp NJ, Barker PB. Diffuse metabolic abnormalities in reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol.* (2002) 23:833–7.
59. Sasayama D, Shimojima Y, Gono T, Kaneko K, Matsuda M, Ikeda S. Henoch-Schonlein purpura nephritis complicatedby reversible posterior leukoencephalopathy syndrome. *Clin Rheumatol.* (2007) 26:1761–71. doi: 10.1007/s10067-006-0502-0
60. Yong PF, Hamour SM, Burns A. Reversible posterior leukoencephalopathy in a patient with systemic sclerosis/systemic lupus erythematosus overlap syndrome. *Nephrol Dial Transplant.* (2003) 18:2660–2. doi: 10.1093/ndt/gfg347
61. Mandell DM, Matouk CC, Farb RI, Krings T, Agid R, terBrugge K, et al. Vessel wall MRI to differentiate between reversible cerebral vasoconstriction syndrome and central nervous system vasculitis: preliminary results. *Stroke.* (2012) 43:860–2. doi: 10.1161/STROKEAHA.111.626184
62. Küker W, Gaertner S, Nagele T, Dopfer C, Schoning M, Fiehler J, et al. Vessel wall contrast enhancement: a diagnostic sign of cerebral vasculitis. *Cerebrovasc Dis.* (2008) 26: 23–9. doi: 10.1159/000135649
63. Swartz RH, Bhuta SS, Farb RI, Agid R, Willinsky RA, Terbrugge KG, et al. Intracranial arterial wall imaging using highresolution 3-tesla contrast-enhanced MRI. *Neurology.* (2009) 72:627–34. doi: 10.1212/01.wnl.0000342470.69739.b3
64. Landoni G, Biondi Zoccai GG, Tumlin JA, Bove T, De Luca M, Calabrò MG, et al. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. *Am J Kidney Dis.* (2007) 49:56–68. doi: 10.1053/j.ajkd.2006.10.013
65. Siebert E, Bohner G, Liebig T, Endres M, Liman TG. Factors associated with fatal outcome in posterior reversible encephalopathy syndrome: a retrospective analysis of the Berlin PRES study. *J Neurol.* (2017) 264:237–42. doi: 10.1007/s00415-016-8328-4
66. Ito Y, Arahata Y, Goto Y, Hirayama M, Nagamutsu M, Yasuda T, et al. Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol.* (1998) 19:415–7.
67. Dersch R, Stich O, Goller K, Meckel S, Dechent F, Doostkam S, et al. Atypical posterior reversible encephalopathy syndrome associated with chemotherapy with bevacizumab, gemcitabine and cisplatin. *J Neurol.* (2013) 260:1406–7. doi: 10.1007/s00415-013-6866-6
68. Zahir MN, Masood N, Shabbir-Moosajee M. Cisplatin-induced posterior reversible encephalopathy syndrome and successful re-treatment in a patient with non-seminomatous germ cell tumor: A case report. *J Med Case Rep.* (2012) 6:409. doi: 10.1186/1752-1947-6-409
69. Kwon EJ, Kim SW, Kim KK, Seo HS, Kim DY. A case of gemcitabine and cispaltin associated posterior reversible encephalopathy syndrome. *Cancer Res Treat.* (2009) 41:53–5. doi: 10.4143/crt.2009.41.1.53
70. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA.* (2009) 302:2323–9. doi: 10.1001/jama.2009.1754
71. Rosolem MM, Rabello LS, Lisboa T, Caruso P, Costa RT, Leal JV, et al. Critically ill patients with cancer and sepsis: clinical course and pronostic factors. *J Crit Care.* (2012) 27:301–7. doi: 10.1016/j.jcrc.2011.06.014

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 12 February 2020
doi: 10.3389/fneur.2019.01420

Posterior Reversible Encephalopathy Syndrome in Clinical Toxicology: A Systematic Review of Published Case Reports

Bérenger Largeau[1†], David Boels[2†], Caroline Victorri-Vigneau[3†], Clara Cohen[4†], Charlotte Salmon Gandonnière[5†] and Stephan Ehrmann[6†]*

[1] CHU de Nantes, Service de Pharmacologie Clinique—Centre Régional de Pharmacovigilance, Nantes, France, [2] CHU de Nantes, Service de Pharmacologie Clinique—Unité de Toxicologie Clinique et Toxicosurveillance Médicamenteuse, Nantes, France, [3] Université de Nantes, Université de Tours, INSERM, Methods in Patients-Centered Outcomes and Health Research (SPHERE)—UMR 1246, CHU de Nantes, Service de Pharmacologie Clinique—Centre d'Évaluation et d'Information sur la Pharmacodépendance et d'Addictovigilance, Nantes, France, [4] Université de Tours, CHRU de Tours, Service de Neuroradiologie Diagnostique et Interventionnelle, Tours, France, [5] CHRU de Tours, Service de Médecine Intensive Réanimation, CIC 1415, réseau CRICS-TRIGGERSEP, Tours, France, [6] Université de Tours, INSERM, Centre d'Étude des Pathologies Respiratoires (CEPR)—UMR 1100, CHRU de Tours, Service de Médecine Intensive Réanimation, CIC 1415, Réseau CRICS-TRIGGERSEP, Tours, France

OPEN ACCESS

Edited by:
Bo Gao,
Affiliated Hospital of Guizhou Medical University, China

Reviewed by:
Andrea Bink,
University Hospital Zürich, Switzerland
Mehmet Akif Topçuoglu,
Hacettepe University, Turkey

***Correspondence:**
Bérenger Largeau
berenger.largeau@etu.univ-tours.fr

†ORCID:
Bérenger Largeau
orcid.org/0000-0002-6824-7283
David Boels
orcid.org/0000-0001-5599-9593
Caroline Victorri-Vigneau
orcid.org/0000-0002-3745-2532
Clara Cohen
orcid.org/0000-0002-8200-2784
Charlotte Salmon Gandonnière
orcid.org/0000-0001-7675-9564
Stephan Ehrmann
orcid.org/0000-0001-6221-4467

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *06 July 2019*
Accepted: *30 December 2019*
Published: *12 February 2020*

Citation:
Largeau B, Boels D, Victorri-Vigneau C, Cohen C, Salmon Gandonnière C and Ehrmann S (2020) Posterior Reversible Encephalopathy Syndrome in Clinical Toxicology: A Systematic Review of Published Case Reports. Front. Neurol. 10:1420. doi: 10.3389/fneur.2019.01420

Background: Posterior reversible encephalopathy syndrome (PRES) is a rare clinical and radiological entity characterized by a typical brain edema. Although several case reports have described PRES in a context of poisoning, to our knowledge, a comprehensive assessment has not been performed. The aim of this systematic review was to raise awareness on poisoning-specific PRES features and to encourage consistent and detailed reporting of substance abuse–and drug overdose–associated PRES.

Methods: Medline/PubMed, Web of Science, and PsycINFO were screened through May 31, 2019, to systematically identify case reports and case series describing PRES associated with poisoning (i.e., alcohol, drugs, illicit drugs, natural toxins, chemical substances) in accidental context, intentional overdose, and substance abuse. The methodological quality of eligible case reports/series was assessed. Patients and exposure characteristics were recorded; relevant toxicological, radiological, and clinical data were extracted.

Results: Forty-one case reports and one case series reporting 42 unique cases were included. The median time to PRES onset from the start of exposure was 3 days (IQR 2–10). Acute high blood pressure, visual disturbance, and seizure were reported in 70, 55, and 50% of patients, respectively. The initial clinical presentation was alertness disorders in 64% of patients. Nine patients (21%) required mechanical ventilation. One-third of patients had at least one risk factor for PRES such as chronic hypertension (17%) or acute/chronic kidney failure (24%). The main imaging pattern (67%) was the combination of classical parieto-occipital edema with another anatomical region (e.g., frontal, basal ganglia, posterior fossa involvement). Vasogenic edema was found in 86% of patients. Intracranial hemorrhage occurred in 14% of patients. Both brain infarction and reversible cerebral vasoconstriction syndrome were diagnosed in 5% of patients. Three patients (12%, 3/25) had non-reversible lesions on follow-up magnetic resonance

imaging. The median time required to hospital discharge was 14 days (IQR 7–18). Mortality and neurological recurrence rate were null.

Conclusions: Comorbidities such as chronic hypertension and kidney failure were less frequent than in patients with other PRES etiologies. Imaging analysis did not highlight a specific pattern for poisoning-induced PRES. Although less described, PRES in the context of poisoning, which shares most of the clinical and radiological characteristics of other etiologies, is not to be ignored.

Keywords: leukoencephalopathy syndrome, hypertensive encephalopathy, blood–brain barrier, substance abuse, alcohol, poisoning

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a rare radiological and clinical entity characterized by a typical brain edema and various symptoms such as high blood pressure (75–80%), encephalopathy (50–80%), headache (50%), visual disturbances (33%), focal neurological deficits (10–15%), seizures (60–75%), and status epilepticus (5–15%) (1). Kidney injury is highly prevalent during PRES (up to 55%), and more than half of patients have chronic hypertension (1). PRES can occur in a number of complex clinical conditions, classically dichotomized into iatrogenic (e.g., antineoplastic therapy, calcineurin inhibitors) and PRES-associated medical conditions (e.g., eclampsia, sepsis, autoimmune disorders), requiring mechanical ventilation for 3–7 days in 35–40% of patients (2). Although there is currently no unified diagnostic algorithm, neuroimaging usually yields bilateral cortical–subcortical vasogenic edema according to three anatomic patterns: dominant parieto-occipital involvement, variant atypical PRES, and combination of different patterns. Variant atypical PRES gathers superior frontal sulcus, holohemispheric watershed, cerebellum, basal ganglia, brainstem, and spinal cord involvements (3, 4). The atypical or combined patterns are more common than the typical PRES with isolated parieto-occipital involvement.

The pathophysiology of PRES is still debated through hypoperfusion and hyperperfusion theories. Impaired cerebral autoregulation responsible for disruption of the blood–brain barrier (BBB) is one of the two main hypotheses, the other one being endothelial dysfunction (5). A recent review suggests that arginine vasopressin (AVP) axis stimulation could precipitate PRES development through an increase in AVP secretion or AVP receptor density. Activation of vasopressin V1a receptors leads to cerebral vasoconstriction, endothelial dysfunction, and subsequent brain edema (5).

Thus, PRES is a syndrome whose circumstances of occurrence and radiological features are associated with significant clinical and radiological polymorphism, making it difficult to characterize. Drug toxicity is one of the potential etiologies. Data are available in the literature regarding PRES occurring at therapeutic drug doses, but to the best of our knowledge, no review focused specifically on cases of accidental or intentional poisoning-associated PRES.

In order to investigate the occurrence of PRES in poisoned patients, the authors systematically reviewed the scientific literature of case reports and case series concerning PRES associated with poisoning (i.e., alcohol, drugs, illicit drugs, natural toxins, chemical substances) in accidental context, intentional overdose, and substance abuse. The authors did not include cases of calcineurin inhibitor overexposure, which has already been covered (6). The purpose of this study is to raise awareness of the features of PRES in poisoned patients and encourage consistent and detailed reporting of PRES in a context of overdose and substance abuse.

METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (7).

Eligibility Criteria

All language case reports and cases series were eligible if they concerned human subjects and included full-text. Records were screened if they were explicitly labeled as PRES based on head MRI (magnetic resonance imaging) or CT (computed tomography) scans. Case reports were included if PRES occurred in temporal connection with poisoning (i.e., alcohol, drugs, illicit drugs, chemical substances, natural toxins) in accidental context, intentional overdose, or substance abuse and/or a causal relationship was assumed by the authors of the report.

Data Sources, Search Strategy, and Data Extraction

A search using Medline/PubMed, Web of Science and PsycINFO was performed without any limits through May 31, 2019. The search terms in Medline were a combination of medical subject heading (MeSH) terms and keywords. The search strategy consisted of using the health multi-terminology portal HeTOP (8) for each term (i.e., text words OR MeSH OR title/abstract) with the following search algorithm: ([posterior leukoencephalopathy syndrome] AND ([poisoning] OR [overdose] OR [intoxication] OR [substance abuse] OR [solvents] OR [organophosphates] OR [licorice] OR [venoms] OR [scorpion] OR [mushroom] OR [lysergic acid] OR [cathinone] OR [cocaine] OR [amphetamine] OR [heroin] OR

[cannabis] OR [alcohol])). A manual search and screening of the bibliographies of selected articles was performed, in addition to the computerized search. The search strategy is summarized in **Supplementary Figure 1**.

Extracted data included the following clinical and toxicological considerations: age, gender, risk factors of PRES occurrence, and exposure characteristics to the causative agent. Clinical and radiological data on PRES, its time course, and outcomes were also extracted. Unreported data were considered absent. Neuroimaging results were classified according to three different patterns. Briefly, the classical PRES pattern, involving only parieto-occipital lobes; the variant, including isolated various anatomical regions (e.g., frontal, cerebellum, brainstem, basal ganglia); and finally, the combined pattern, which includes combination of various regions.

Methodological Quality Assessment

The methodological quality of case reports and cases series was assessed using the tool proposed by Murad et al. (9) modified to adapt it to the analysis of toxicological exposures associated with PRES. The selected items were based on scores used for causality assessment in drug overdose (10, 11). This new tool converges into 10 items that can be categorized into six domains: selection, ascertainment, diagnosis, causality, follow-up, and reporting (**Supplementary Table 1**). Briefly, items included time to onset of PRES, exposure characteristics (e.g., dose, drug detection, identification of species), radiological features, clinical data (e.g., symptoms, risk factors), dechallenge phenomenon, differential diagnosis, pharmacological properties of the causative agent, and clinical/radiological follow-up. The results of this modified tool have been summarized by summing the scores of the 10 binary responses into an aggregate score (**Supplementary Tables 1**, **2**).

RESULTS

Case Selection

The literature search revealed a total of 149 non-duplicate records of which 95 were excluded because they did not report poisoning-associated PRES or were not case reports or case series. Out of 54 full-texts assessed for eligibility, 13 were excluded because they did not report poisoning-associated PRES or outcomes of interest (i.e., symptoms, brain edema features, follow-up). Finally, 40 case reports and 1 case series reporting a total of 42 unique cases were included (**Supplementary Figure 1**).

Synthesized Findings

Demographic Characteristics and Clinico-Biological Findings

Demographic data, substances involved, and clinico-radiological characteristics are summarized in **Supplementary Table 3**. Out of 42 patients included, 22 were female (52%); median age was 41 years (IQR 27–55, range 3–73). Four children were included (12–15). The median time to PRES onset from the start of exposure or intoxication diagnosis was 3 days (IQR 2–10) and ranged from 2 h (13) to 4 months (16, 17). The initial clinical presentation was alertness disorders in 64% of patients (13–15, 18–40). Visual disturbances were reported in 55% of patients (23/42) (12, 13, 15, 16, 19–21, 23, 25–27, 29, 34, 35, 37, 39, 41–47) including photophobia (19, 20, 35), visual hallucination (21, 23, 26, 27), and cortical blindness (15, 16, 24, 29, 34, 37). Four patients had concurrent acute kidney failure with PRES (13, 19, 44, 48). When performed (33, 39, 43), hypomagnesemia was found in one patient (39). Cerebral spinal fluid (CSF) analysis (20, 21, 23, 24, 34, 36, 37, 45, 47, 49) showed elevated CSF protein in one patient (34). Nine patients (21%) required mechanical ventilation (14, 21, 28, 33, 38, 46–48). The median time required to hospital discharge was 14 days (IQR 7–18). Mortality and neurological recurrence rate were null.

Radiological Features

Radiological diagnosis was based on brain MRI and CT scans in 91% (38/42) and 9% (4/42) (35, 38, 40, 43), respectively. The neuroimaging findings, including anatomical pattern, diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), edema type, symmetry, and arterial characteristics, are summarized in **Supplementary Table 3**. Five patients (19, 24, 26, 34, 44) had normal initial brain CT (5/9, 56%) (19, 20, 24, 26, 34, 42, 44, 48, 50). All patients exhibited cortical and/or subcortical edema, characterized by hyperintensities in T2-weighted and/or T2 fluid-attenuated inversion recovery (FLAIR) imaging, which was consistent with PRES diagnosis in MRI. Symmetrical lesions were reported in 76% of patients (25/33) (12–15, 19, 22–25, 27, 29, 32–34, 36, 37, 39, 40, 43, 44, 46, 47, 49, 50). The combined pattern, which includes combination of various regions, was the most frequent with 67% of patients (13, 14, 17–22, 24–26, 28, 30–35, 38, 39, 41, 44, 46–49, 51). The classical PRES pattern, involving only parieto-occipital lobes, was found in 19% (8/42) of patients (12, 16, 23, 27, 37, 40, 42, 45). The variant pattern of PRES (6/42, 14%), including isolated anatomical region such as occipital (29, 36, 43, 50) and cerebellum (15, 52), occurred in 9 and 5%, respectively. In five reports, angiography (by contrast-enhanced arteriography in CT, or MRI sequences including non-contrast time-of-flight and angio-MRI or digital subtraction angiography) showed narrowing of the cerebral arteries (16, 28, 36, 37, 49). Reversible cerebral vasoconstriction syndrome (16, 49) was diagnosed in 5% of patients (2/42).

DWI was positive in 60% of patients (12/20), totally or partially in correspondence with T2/FLAIR hyperintensities, with focal or larger extent (20, 25, 26, 29, 30, 36, 37, 39, 47–49). When data related to ADC were provided, positive DWI due to vasogenic edema (i.e., no restricted ADC) (16, 17, 19, 21, 23, 25, 26, 28–31, 33, 34, 36, 45, 47–49) and cytotoxic edema (i.e., restricted ADC) (20, 24, 39, 49) were found in 86 and 19% of cases, respectively. T2* (gradient echo) or susceptibility weighted imaging revealed intracranial hemorrhage in 14% of patients (16, 20, 30, 31, 36, 43). The median time of follow-up imaging was 21 days (IQR 11–60). Out of 25 patients with follow-up imaging, 22 (88%) showed complete resolution of brain edema (12–14, 16, 21, 22, 24, 26, 29–31, 33, 38, 43–47, 50, 51).

Characteristics According to the Causative Agent

Exposure characteristics, clinico-radiological features, and follow-up data of the included cases are shown in **Table 1.**

TABLE 1 | Characteristics of the 42 included cases.

References	Substance/context	Sex/ age	Comorbidities	Time to onset	Blood pressure	Diagnosis		Follow-up	
						Symptoms	Imaging	Outcomes	Imaging
Bhagavati et al. (22) #2	Acute alcohol intoxication	M/57	Chronic alcohol abuse	2 days	131/88	Confusion	Combined and symmetrical patterns	Complete clinical resolution 2 weeks after PRES	Complete resolution after 2 weeks
Coppens et al. (23)	Acute alcohol intoxication	M/43	Chronic alcohol abuse on disulfiram	3 weeks after daily alcohol consumption	150/100	Disorientation, delirium, visual hallucination, paraparesis	Parieto-occipital and symmetrical patterns, normal diffusion on DWI	Slight improvement of lower limb paresis over several months	Almost complete resolution at day 14
Srikrishna et al. (24)	Acute alcohol intoxication	M/68	Chronic alcohol abuse on disulfiram	3 h after alcohol consumption	160/100	Vomiting, headache, confusion, cortical blindness, seizure	Combined and symmetrical patterns, positive DWI, restricted diffusion on DWI	Clinical improvement after 15 days Walk without any assistance after 21 days	Complete resolution at day 21
Kim et al. (25)	Acute alcohol intoxication	M/59	Chronic alcohol abuse	1 day	191/100	Visual disturbance, aphasia	Combined and symmetrical patterns, positive DWI	Discharge at day 14	Only slight resolution after 2 months
Ishikawa et al. (26)	Alcohol withdrawal and acute pancreatitis	F/28	Ø	2 days	112/82	Confusion, disorientation, visual hallucination, seizure	Combined pattern, positive DWI, no restricted ADC	General condition improved at day 7 Discharge at day 17	Complete resolution at day 16
Mengi et al. (27)	Alcohol withdrawal	M/53	Ø	3 days	150/90	Disorientation, visual hallucination	Parieto-occipital and symmetrical patterns	Clinical resolution at day 7	Significant regression at day 7
Gill et al. (28)	Alcohol withdrawal after admission for acute alcohol intoxication and AKI	F/58	Chronic HTN	2 days	195/108	Coma, obtundation	Combined pattern, no restricted ADC Subacute infarct in the right parietal lobe	Discharge at day 2	Resolution (date unknown)
Kimura et al. (29)	Chronic alcohol abuse	M/51	Amphetamine abuse	Not applicable	170/100	Confusion, disorientation, cortical blindness	Atypical and symmetrical patterns, positive DWI	Clinical symptoms resolved in 4 days No permanent neurological abnormalities after 1 month	Complete resolution after 1 month
Baek et al. (30)	Chronic alcohol abuse with acute pancreatitis	M/49	Ø	Concomitantly with acute pancreatitis	130/80	Confusion, disorientation	Combined pattern, positive DWI Microbleeds in cerebellum	Mental status improved after 2 days Able to walk around at day 5 Discharge at day 14	Complete resolution, except few microbleeds in cerebellum after 1 month
Magno Pereira et al. (31)	Chronic alcohol abuse	M/33	Ø	Not applicable	190/100	Headache, vomiting, confusion, seizure	Combined pattern, no restricted diffusion Subacute hemorrhage in the right frontal lobe	Discharged at day 15	Signs of hemorrhage reabsorption after 2 months
Murphy et al. (41)	Chronic alcohol abuse with acute pancreatitis	F/40	Ø	1 week after acute pancreatitis	Not available	Visual loss	Combined pattern	Visual recovery after 2 months	Lesions improved after 2 months
John et al. (32)	Severe acute alcoholic hepatitis	F/40	Hepatic encephalopathy	3 weeks after alcoholic hepatitis diagnosis	114/78	Headache, psychomotor retardation, seizure	Combined and symmetrical patterns	Not available	Not available
Fitzgerald et al. (33) #1	Lithium withdrawal after lithium intoxication with AKI	F/50	Chronic HTN	9 days after intoxication	140/80	Headache, bladder/bowel incontinence, seizure	Combined and symmetrical patterns, no restricted diffusion	Discharged at day 22	Complete resolution 5 months later

(Continued)

TABLE 1 | Continued

References	Substance/context	Sex/ age	Comorbidities	Time to onset	Blood pressure	Diagnosis		Follow-up	
						Symptoms	Imaging	Outcomes	Imaging
Fitzgerald et al. (33) - #2	Lithium withdrawal after lithium intoxication with AKI	M/61	Chronic HTN	8 days after intoxication	SBP = 170	Mental status altered	Combined and symmetrical patterns	Discharged at day 25	Not available
Loens et al. (34)	Lithium withdrawal after lithium intoxication with AKI	F/60	Chronic HTN	3 days after intoxication	MAP > 130	Somnolence, disorientation, dysarthria, cortical blindness, seizure	Combined and symmetrical patterns, no restricted diffusion on ADC	ICU for 10 days Full recovery after 22 days	Regression of the edema with residual bi-occipital lesions at day 10
Minhaj et al. (35)	Dextroamphetamine and clonidine overdose	M/17	Ø	9 h	182/111	Headache, photophobia, confusion	Combined pattern	Asymptomatic at 36 h and had no neurologic sequelae	Not available
Mann et al. (51)	Acetaminophen overdose with AKI at day 3	F/21	Ø	10 days	164/103	Seizure	Combined pattern	Discharged at day 15 Asymptomatic at day 20	Complete resolution at day 20
Kinno et al. (49)	Ephedrine overdose	M/28	Ø	3 days	Not available	Paraplegia, agraphia	Combined and symmetrical patterns, positive DWI, co-existence of restricted and no restricted ADC Brain infarction with RCVS and PRES	Not available	Residual lesions in the parietal lobe at day 27
Kawanabe et al. (36)	Phenylpropanolamine misused as eye drops for 4 days	F/57	Ø	3 days after the last dose	186/106	Headache, somnolence, seizure	Atypical and symmetrical patterns, positive DWI, no restricted ADC Intraparenchymal left occipital hemorrhage	Discharge at day 34	Nearly complete resolution after 2 months
Weidauer et al. (37) #1	Digitoxin overdose	F/73	Not available	3 days	Normal	Disorientation, vomiting, cortical blindness	Parieto-occipital and symmetrical patterns, positive DWI	Slowly improvement of visual acuity over 4 months	Not available
Akinci et al. (15)	Bismuth overdose with AKI at day 3 requiring HD	F/16	Ø	15 days	110/70	Confusion, somnolence, cortical blindness, ataxia, seizure	Atypical and symmetrical patterns	Discharged 9 days after PRES	Not available
Bazuaye-Ekwuyasi et al. (18)	Cocaine	F/41	HIV Chronic HTN ESRD	Not available	198/92	Confusion, agitation	Combined pattern	Confusion and agitation slowly resolved at day 5	Complete resolution at day 7
Dasari et al. (19)	Cocaine	F/40	Chronic HTN AKI on CKD	4 days after heavy cocaine binging	189/140	Headache, somnolence, vomiting, photophobia	Combined and symmetrical patterns, no restricted diffusion on DWI	Discharged after 2 days	Not available
Tantikittichaikul et al. (52)	Amphetamine	M/45	Not available	Not available	SBP = 250	Headache	Atypical variant and no restricted	Not available	Significant improvement of the lesions at day 3
Omer et al. (50)	Mephedrone	F/19	Alcohol abuse	2 days	SBP > 160	Seizure	Atypical and symmetrical patterns	No recurrence of seizure at day 10	Complete resolution at day 10

(Continued)

TABLE 1 | Continued

References	Substance/context	Sex/ age	Comorbidities	Time to onset	Blood pressure	Diagnosis		Follow-up	
						Symptoms	Imaging	Outcomes	Imaging
Castillo et al. (20)	Kratom	M/22	Amphetamine, marijuana abuse	"Prior to admission"	180/105	Headache, disorientation, photophobia, aphasia	Combined pattern, positive DWI, restricted diffusion Left parieto-occipital intraparenchymal bleed	Discharged after 5 days	Lesions unchanged at day 4
Legriel et al. (21)	Lysergic acid amide	M/39	Alcohol abuse	"Immediately"	185/130	Confusion, hyperreflexia, visual hallucination, seizure	Combined pattern	Discharged after 9 days in the ICU Normotensive 1 month later	Complete resolution at day 7
Delgado et al. (38)	Snake bite (*Bothrops asper*)	M/18	Ø	2 days	<140/90	Headache, respiratory distress, stuporous, seizure	Combined pattern	Discharged asymptomatic 1 month later	Completely normal at 6 months
Varalaxmi et al. (42)	Pit viper bite with AKI requiring HD at day 3	M/45	Ø	6 days	140/90	Headache, vision loss	Parieto-occipital pattern	Normal vision within 24 h	Not available
Ibrahim et al. (39)	Horned viper bite (*Cerastes cerastes*)	F/23	Ø	"Within a week"	130/80	Stuporous, vision loss	Combined pattern, positive DWI, restricted ADC	Normotensive within 1 week Persistence of vision loss 3 months later	Not available
Kaushik et al. (12)	Indian krait bite (*Bungarus caeruleus*)	M/10	Ø	15 days	"HTN"	Visual loss, seizure	Parieto-occipital and symmetrical patterns	Normal vision within 2 days Normotensive 1 month later	Complete resolution after 3 months
Marrone et al. (13)	Scorpion sting (*Tityus bahiensis*)	M/13	Ø	2 h	90/60	Vomiting, headache, visual disturbance, obnubilation, seizure	Combined and symmetrical patterns	Asymptomatic at day 5	Complete resolution at day 21
Rebahi et al. (14)	Scorpion sting (*Androctonus mauretanicus*)	F/3	Ø	2 days	170/110, then cardiogenic shock	Vomiting, impaired consciousness, seizure	Combined and symmetrical patterns	Discharge at day 18 with monoparesis and low visual acuity	Complete resolution at 6 months
Loh et al. (40)	Wasp stings complicated by AKI requiring HD	F/29	Ø	1 month	190/104	Loss of consciousness	Parieto-occipital and symmetrical patterns	Blood pressure and symptoms resolved spontaneously on the same afternoon	Not available
Du et al. (48)	Wasp stings	F/66	Not available	1 day	135/85	Headache, seizure	Combined pattern, positive DWI	Not available	Not available
Chatterjee et al. (16)	Licorice	F/49	Ø	4 months	230/130	Headache, cortical blindness, hyperreflexia, seizure	Parieto-occipital pattern Bilateral lobar hemorrhage RCVS with segmental narrowing of multiple intracranial arteries	Headache resolved at day 8 Asymptomatic at 1 month	Resolution of PRES, RCVS, and lobar hemorrhage after 3 months
Van Beers et al. (43)	Licorice	F/49	Ø	2 weeks	219/100	Headache, visual impairment	Atypical and symmetrical patterns Microbleeds in the left sylvian fissure	Quickly recovery and discharged after few days	Complete resolution at day 10
Morgan et al. (44)	Licorice	F/65	Ø	4 days after consumption	SBP > 220	Confusion, headache, loss of vision	Combined and symmetrical patterns	Discharged at day 9	Complete resolution after 2 months

(Continued)

TABLE 1 | Continued

References	Substance/context	Sex/ age	Comorbidities	Time to onset	Blood pressure	Diagnosis		Follow-up	
						Symptoms	Imaging	Outcomes	Imaging
O'Connell et al. (45)	Licorice	F/56	Chronic HTN	"Since recent months"	210/80	Headache, nausea, visual disturbance, seizure	Parieto-occipital pattern, no restricted diffusion	Not available	Complete resolution at day 21
Tassinari et al. (17)	Licorice	M/10	Ø	4 months	144/102	Headache, seizure	Combined pattern	Normotensive 1 month later	Significant regression at day 14
Zhou et al. (46)	Mushroom (*Unidentified*)	F/26	Ø	12 h	190/130	Seizure, coma	Combined and symmetrical patterns	Fully recovered within 2 days	Complete resolution (date unknown)
Phatake et al. (47)	Organophosphate	M/32	Ø	4 days	200/110	Headache, visual disturbance, seizure	Combined and symmetrical patterns, positive DWI, no restricted ADC	Improvement in vision and mental state 8 days after PRES Discharge at day 17	Complete resolution at day 24

Ø, no comorbidity related to PRES; ADC, apparent diffusion coefficient; AKI, acute kidney injury; CKD, chronic kidney disease; DBP, diastolic blood pressure; DWI, diffusion-weighted imaging; ESRD, end-stage renal disease; HTN, hypertension; HD, hemodialysis; HIV, human immunodeficiency virus; ICU, intensive care unit; MAP, mean arterial pressure; RCVS, reversible cerebral vasoconstriction syndrome; SBP, systolic blood pressure.

Alcohol

In alcohol-induced PRES, three different situations have been described: chronic alcohol intoxication (29–32, 41), acute alcohol intoxication (22–25), and alcohol withdrawal (26–28). PRES in chronic alcohol abusers occurred in conjunction with other complications of alcoholism such as acute pancreatitis (26, 30, 41) and hepatic encephalopathy due to severe acute alcoholic hepatitis (32). PRES onset occurred at the same time as acute pancreatitis (26, 30) or 1 week later (41), whereas it occurred 3 weeks after acute alcoholic hepatitis onset (32). All but four patients were hypertensive. Patients were normotensive in acute alcoholic pancreatitis (26, 30) and acute alcoholic hepatitis (32). Headache was reported in only 17% of patients (2/12) (24, 32). In three patients, PRES was complicated by intracranial hemorrhage (30, 31) or brain infarction (28).

Drug Overdose

Nine patients experienced PRES in a context of drug overdose, involving lithium (33, 34), dextroamphetamine (35), acetaminophen (51), ephedrine (49), phenylpropanolamine (36), digitoxin (37), and bismuth (15). The median time to PRES onset from the intoxication was 3 days, and two distinct situations were identified. PRES occurred during the acute phase of poisoning (35–37, 49) or at distance from intoxication (i.e., after stopping the causative drug) (15, 33, 34, 51). Three case reports indicated an association between lithium and PRES (33, 34). All these cases occurred after lithium discontinuation in patients with hypothyroidism, with chronic hypertension, and for whom intoxication was complicated by acute kidney injury (33, 34). Acute kidney injury occurred before the onset of neurological disturbances in five patients (56%) (15, 33, 34, 51). Angiography showed narrowing of the cerebral arteries in three cases (36, 37, 49). Infarction (49) and intraparenchymal hemorrhage (36) were also reported.

Illicit Drug

We collected six reports of illicit drug–induced PRES, involving cocaine (18, 19), amphetamine (52), mephedrone (50), kratom (20), and lysergic acid amide (21). Acute high blood pressure was reported in all patients (18–21, 50, 52). Patients had several risk factors for PRES such as chronic hypertension (18, 19), chronic kidney disease (18, 19), alcohol abuse (21, 50), and HIV infection (18).

Natural Toxin

In venom-induced PRES, snake bites [*Cerastes cerastes* (39), *Bothrops asper* (38), pit viper (42), *Bungarus caeruleus* (12)] were involved in four patients, scorpion stings in two cases [*Tityus bahiensis* (13), *Androctonus mauretanicus* (14)], and multiple wasp stings in two patients (40, 48). PRES was associated with mushroom (46) and licorice (16, 17, 43–45) in one and five patients, respectively. In 36% (5/14) of patients (12, 16, 17, 40, 43), the time from exposure start to PRES onset was more than 1 week. Patients required mechanical ventilation in 29% (4/14) of cases (14, 38, 46, 48); the duration of mechanical ventilation ranged from 2 (46) to 14 days (38). Acute kidney failure occurred in 36% (5/14) of patients (13, 40, 42, 44, 48), requiring

hemodialysis in two cases (40, 42). Among the five patients with licorice-associated PRES, brain hemorrhage occurred in two patients (16, 43), one of which was associated with reversible cerebral vasoconstriction syndrome (16).

Chemical Substance

Phatake et al. (47) reported a patient complaining of headache and blurred vision 4 days after coma induced by consumption of organophosphorus compounds with suicidal intention. Brain MRI showed multifocal hyperintensities mainly in subcortical areas of parietal and occipital areas with increase ADC, suggesting PRES.

DISCUSSION

Are Toxic PRES Different From Other Etiologies?

As in other etiologies, poisoning-associated PRES are very polymorphic in terms of both exposure characteristics and patient comorbidities. Regardless of the substances involved, the median of 3 days for time to onset of PRES can dichotomize the presentation of this syndrome into two distinct situations. Indeed, PRES occurring after 3 days seems to be more related to a rebound effect of intoxication or to complications related to the management of the poisoning, whereas a shorter period would support a direct link between the causative agent and PRES.

Clinical and Biological Findings

Clinically, the prevalence of symptoms usually reported in PRES patients was consistent with the published literature (1). Indeed, acute high blood pressure, visual disturbance, and seizure were reported in 70, 55, and 50% of patients, respectively. Seizure is the most common symptom found in children (53), and all children had seizures (12–15). However, comorbidities such as chronic hypertension (17%, 7/42) and acute or chronic kidney failure (24%, 10/42) were less frequently reported than in patients with other PRES etiologies, where their estimated prevalence is about 50% (1). In the literature, the frequency of isolated CSF protein elevation without pleocytosis, as a biomarker of permeability disruption of the BBB, varies from 60% (54) to 75% (55). In this review, although few cases reported CSF analysis, only one case (1/10, 10%) (34) described elevated CSF protein.

Radiological Features

All reviewed patients presented cortical and/or subcortical T2/FLAIR hyperintensities or hypodensities on CT when MRI was not performed, which was consistent with the main findings of PRES (3, 4). These hyperintensities correspond to the brain edema caused by vascular dysregulation, leading to acute vasodilatation and classically vasogenic edema, with proven pathological/imaging correlation (56). While parieto-occipital involvement (12–14, 16–18, 20–34, 36–51) was predominant (39/42, 93%), as described in the literature (57), the isolated parieto-occipital was not the main pattern in this review, supplanted by the pattern combining various anatomical regions involved. Frontal (13, 17, 18, 20, 22, 24–26, 28, 31, 33, 38, 44, 46, 48, 49, 51), temporal lobe (18, 25, 26, 30, 32, 33, 47), and cerebellum (14, 15, 18–21, 30, 35, 41, 52) involvement occurred in 41% (17/42), 17% (7/42), and 24% of patients (10/42), respectively. In this review, the prevalence of frontal and temporal involvement is lower than previously described, where it can be seen in up to 75% of cases (3). Indeed, temporal involvement was rarely reported, even though MRI images seemed to show involvement in this region. This may partially explain the difference in prevalence, especially since the whole brain MRI was not available for neuroradiological analysis.

The atypical distribution involving the thalamus (18, 19, 21, 34), basal ganglia (18, 19, 46), midbrain (18, 19), and corpus callosum (39) was less commonly reported, as described in the literature. As with other PRES etiologies, atypical imaging appearances including hemorrhage, contrast enhancement, and restricted diffusion on MRI were reported in similar proportions (58). Intracranial hemorrhage occurred in 14% of cases included (6/42) (16, 20, 30, 31, 36, 43). Among these cases, minimal occipital intraparenchymal (20, 36), microbleeds in the cerebellum (30) and sylvian fissure (43), and subarachnoid hemorrhage (31) were reported. Regarding contrast enhancement (19, 20, 22, 23, 30, 31, 38, 52), only one case described gyriform enhancement (20). In this case of PRES induced by kratom, brain MRI showed multifocal areas of abnormal T2 FLAIR; restricted diffusion in the superior parietal lobes, both occipital lobes, and both cerebellar hemispheres; and minimal hemorrhage in the left superior parietal lobe consistent with atypical PRES (20). DWI positivity (20, 25, 26, 29, 30, 36, 37, 39, 47–49) due to advanced edema was higher (12/20, 60%) than previously described in other PRES etiologies. The occurrence of cytotoxic edema (19%, 4/21) was consistent with the literature (15–30%) (3). Areas of restricted diffusion can be reversible or, conversely, progress to frank infarction (58). For instance, Kinno et al. (49) reported a case of PRES with reversible cerebral vasoconstriction syndrome due to ephedrine overdose. Initial brain MRI showed vasogenic edema in the left occipital and both parietal lobes with some hyperintense lesions on DWI with restricted diffusion on ADC maps, indicating the co-existence of cytotoxic edema. Follow-up MRI 1 month later showed residual partial hypertense areas in the superior parietal gyri bilaterally (49). Persistence of brain lesions on follow-up imaging (25, 49, 51) found in 12% of patients (3/25) is a proportion classically reported in various series of PRES.

Imaging analysis did not highlight a specific pattern for poisoning-associated PRES but reinforces the fact that PRES is neither only posterior nor always reversible.

Are Toxic PRES Different According to the Causative Agents?

Similarities

Neurological complications such as hemorrhage (16, 20, 30, 31, 36, 43), reversible cerebral vasoconstriction syndrome (16, 49), and infarction (28, 49) occurred independently of toxic etiology, i.e., kratom (20), alcohol (28, 30, 31), drug overdose (36, 49), and licorice (16, 43).

Vasoconstriction and endothelial dysfunction

Most of the pharmacological and toxicological agents involved in this review are known to induce either or both vasoconstriction and endothelial dysfunction. High alcohol concentrations have been associated with dose-related vasoconstriction and impaired dilatation of cerebral vessels (22). In addition, chronic alcoholism and long-term lithium exposure increase reactive oxygen species and nitric oxide in brain endothelial cells. This oxidative stress can induce endothelial dysregulation, leading to the BBB breakdown (27, 34). Cocaine, amphetamines, lysergic acid amide, mephedrone, kratom, and phenylpropanolamine have sympathetic and/or serotoninergic effects that cause vasoconstriction or vasculitis, leading to severe hypertension (36, 59).

In alcohol withdrawal, the hypothalamic–pituitary–adrenal system is stimulated, leading to increased levels of catecholamine and AVP, which can induce acute hypertension (27, 28). Similarly, the biologically active component of licorice, glycyrrhizic acid, inhibits 11 β-hydroxysteroid dehydrogenase, leading to hypervolemic hypertension (16). After snakebite envenomation and organophosphate severe poisoning, neurotoxins (14) and nicotinic stimulation (60), respectively, lead to autonomic dysregulation with massive release of catecholamines and angiotensin II. These effects, in combination with the presence of sympathetic denervated vasculature in the brain posterior area, may induce failure of the cerebral autoregulatory system (14). The increase in proinflammatory mediators, either exogenous, originating from the substance (e.g., venom itself), or endogenous (e.g., in acute alcoholic pancreatitis, induced by venom), can damage the BBB and is likely to cause the leakage of blood contents into the surrounding brain tissue (14, 30).

Cerebral hypoperfusion

In several reports, angiography showed multiple areas of narrowing of the intracranial arteries (16, 28, 36, 37, 49), especially in drug overdose (36, 37, 49) with sympathomimetic agents such as ephedrine (49) and phenylpropanolamine (36). Interestingly, in ephedrine overdose–induced PRES (49), although MRI revealed bilateral superior parietal lesions, single-photon emission computed tomography showed selective hypoperfusion in the left superior parietal region.

AVP axis hyperstimulation

A recent review highlighted that AVP overstimulation seems to be involved in PRES development and subsequent symptoms, in particular because of both its pathophysiological mechanism in brain edema formation and its involvement in most PRES etiologies (5). AVP hypersecretion could be the trigger of PRES through a dysregulation of ionic/water transglial flux via astrocytic ion channel dysfunction and subsequent brain edema. In the periphery, AVP receptor stimulation could be responsible for symptoms usually reported in PRES such as hyponatremia, acute hypertension, and impaired renal function (5, 61). The use of cocaine, amphetamine (62), and lysergic acid diethylamide (63) and co-administration of alcohol with disulfiram (5) are known situations to stimulate AVP neurons. Thus, these agents could be directly responsible for the pharmacological cascade described above. In several cases, patients received multiple psychotropic drugs such as quetiapine (20, 33, 34), duloxetine (33), sertraline (33), amitriptyline (33), escitalopram (51), and valproate (51); it could be argued that these drugs, known to induce AVP release (64) and cerebrovascular effects, may serve as a contributing factor in the genesis of PRES.

In hepatic encephalopathy, in addition to dysregulation of cerebral blood flow and consequent cerebral vasodilation induced by hyperammonemia (32), ammonia reaching the astrocytes is detoxified in glutamine, and its overproduction promotes, through AVP stimulation, astrocytic swelling, resulting in brain edema (65). In contrast, acute alcohol intoxication (62) and licorice (66) inhibit AVP release, and lithium inhibits renal effects of AVP (5). In PRES associated with alcohol withdrawal (26–28), licorice (44), and lithium intoxication (33, 34), the onset of neurological symptoms ranged from 2 to 9 days after intoxication; this chronology of events may suggest a rebound phenomenon on the AVP axis (5).

Specific Characteristics

Visual hallucinations have only been reported in concomitant administration of disulfiram with alcohol (22) and in alcohol withdrawal (26, 27). Visual hallucinations may be a symptom of delirium tremens but also occur in patients with PRES (2). In natural toxin–and chemical substance–associated PRES, seizure was the most frequent symptom, accounting for 67% (10/15) of cases (12–14, 16, 17, 38, 45–48). Similarly, alertness disorders were at the forefront (92%, 11/12) in alcohol-associated PRES (22–32).

Multiple risk factors in substance abuse patients

In substance abuse–related PRES, patients had several risk factors for PRES such as chronic hypertension (18, 19), chronic kidney disease (18, 19), and HIV infection (18). In these cases, the different risk factors should act synergistically on the different pathophysiological pathways leading to PRES. For instance, cocaine has the ability to synergistically increase the pathologic processes induced by HIV infection (18) including endothelial dysfunction and disruption of the BBB integrity. Interestingly, single nucleotide polymorphisms in AVP gene and AVP V1a receptor have been associated with drug abuse disorders (67), suggesting a different probability of PRES occurrence in patients with substance abuse.

In patients with multiple risk factors of PRES or in the context of multiple drug intake (20), causality assessment is difficult. In addition, combined drug intoxication also exposes to a risk of drug cocktail effect. As with drug–drug interactions, illicit drug–drug interactions can occur both at the pharmacodynamic (i.e., interactions in which drugs influence each other's effects directly) and pharmacokinetic level (i.e., modification of drug absorption, distribution, metabolism, or excretion). In pharmacodynamic illicit drug–drug interactions, the neurotoxicity and/or endothelial toxicity of both the drug and illicit drug act synergistically, which can promote the occurrence of PRES. Legriel et al. (21) reported a case of lysergic acid amide–induced PRES in a depressed patient treated with clomipramine. The analysis of urinary catecholamines and

serotonin metabolites showed a massive sympathetic storm with high urinary serotonin levels, supporting the pharmacodynamic convergence of these two adrenergic and serotoninergic agents. Castillo et al. (20) reported a case of kratom-induced PRES in a patient on fluoxetine for depression with dextroamphetamine misuse. Kratom exerts α2-adrenoreceptor agonistic effects and is known to induce high blood pressure, particularly when combined with other drugs (68). Mitragynine, the major indole-based alkaloid of kratom, is extensively metabolized by hepatic cytochrome P450 (CYP) isoform 3A4 and 2D6 (69). Amphetamine metabolism primarily involves CYP2D6 (70). Fluoxetine and its main metabolite, norfluoxetine, are well-known inhibitors of CYP2D6 and CYP3A4, respectively (71). Taken together, a probable pharmacokinetic illicit drug–drug interaction occurred between mitragynine/dextroamphetamine and fluoxetine, causing overexposure in mitragynine and dextroamphetamine. This case of kratom/amphetamine interaction shares the pharmacological characteristics of PRES induced by clonidine, another α2-adrenoreceptor agonist, and dextroamphetamine overdose described by Minhaj et al. (35).

Coagulopathy

Characteristics of PRES associated with snake bite included normal blood pressure (38, 39, 42), coagulopathy (12, 38, 39), and respiratory failure (12, 38). The mechanism of PRES associated with snake venom does not appear to be related to direct toxic effects of the venom within the central nervous system, because venom proteins do not cross the BBB. Instead, neurological manifestations are most often related to blockage of the neuromuscular transmission, causing paralysis, and abnormalities in the coagulation cascade, producing cerebrovascular events (38).

A Lack of Standardization in Reported Data on Poisoning-Induced PRES

The assessment of the methodological quality of the cases showed that the data reported are very heterogeneous, with a median overall score of 5/10 (IQR 3–6). In addition, none of the case reports met the domain selection criteria (**Supplementary Table 1**). An unclear selection approach leaves the reader with uncertainty as to whether this is the whole experience of the researchers or only the most serious case, and suggests possible selection bias. As the scientific literature on PRES is almost exclusively represented by case series and case reports, we propose a checklist with various items that should at least be reported in case reports of substance-induced PRES (**Supplementary Table 4**). Indeed, it seems essential to standardize the reporting of outcome so that studies collecting a large amount of data can be conducted.

CONCLUSIONS

PRES in a context of poisoning does not exhibit a specific imaging pattern. The predominance of various anatomical implications outside the parieto-occipital lobes in PRES, including toxic etiologies, is a key message for clinicians and radiologists. The prevalence of the neurological symptoms was also consistent with the published literature on other etiologies of PRES. In addition to toxic exposure, one-third of patients had at least one other risk factor of PRES. Chronic hypertension (17%) was less frequent than reported in other causes of PRES.

As in iatrogenic PRES, toxicology cases do not always have a temporally close relationship. PRES occurring after 3 days seems to be more related to a rebound effect of poisoning, to secondary brain damage, or to complications related to the management of the poisoning, whereas a shorter period would support a direct link between the causative agent and PRES. Poisoned patients may have a lower threshold for developing PRES. It may also be caused by the convergence of various pathophysiological processes (e.g., high blood pressure, endothelial dysfunction, AVP axis overstimulation) induced directly by the poison and/or indirectly by acting in concert with other factors such as drug–drug interaction or hypomagnesemia that ultimately causes the cerebrovascular cascade leading to PRES.

Although less described, PRES in a context of poisoning, which shares most of the clinical and radiological characteristics of other etiologies, is not to be ignored. The characterization of the pathophysiological mechanisms is essential to individualize management according to the presence of risk factors and/or specific features of PRES. Standardization of data reported in future case series of substance-induced PRES is required in order to better characterize and thus manage this syndrome.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed.

AUTHOR CONTRIBUTIONS

BL, CS, and SE conceived the idea. BL wrote the manuscript and performed the selection and summary of published literature on PRES in clinical toxicology. DB, CV-V, CS, and SE helped to design, write, and revise the paper. CC contributed in improving the article, notably enriching the analysis of neuroimaging data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01420/full#supplementary-material

REFERENCES

1. Toledano M, Fugate JE. Chapter 26 - Posterior reversible encephalopathy in the intensive care unit. In: Wijdicks EFM, Kramer AH, editors. *Handbook of Clinical Neurology Critical Care Neurology Part II*. Elsevier. (2017). p. 467–483. doi: 10.1016/B978-0-444-63599-0.00026-0
2. Legriel S, Pico F, Azoulay E. Understanding posterior reversible encephalopathy syndrome. In: Vincent, J-L, editor. *Annual Update in Intensive Care and Emergency Medicine 2011, vol. 1*. Berlin, Heidelberg: Springer Berlin Heidelberg. (2011). p. 631–53. doi: 10.1007/978-3-642-18081-1_56
3. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology,

and outstanding questions. *Lancet Neurol.* (2015) 14:914–25. doi: 10.1016/S1474-4422(15)00111-8
4. Tetsuka S, Ogawa T. Posterior reversible encephalopathy syndrome: a review with emphasis on neuroimaging characteristics. *J Neurol Sci.* (2019) 404:72–9. doi: 10.1016/j.jns.2019.07.018
5. Largeau B, Le Tilly O, Sautenet B, Salmon Gandonnière C, Barin-Le Guellec C, Ehrmann S. Arginine vasopressin and posterior reversible encephalopathy syndrome pathophysiology: the missing link? *Mol Neurobiol.* (2019) 56:6792–806. doi: 10.1007/s12035-019-1553-y
6. Song T, Rao Z, Tan Q, Qiu Y, Liu J, Huang Z, et al. Calcineurin inhibitors associated posterior reversible encephalopathy syndrome in solid organ transplantation: report of 2 cases and literature review. *Medicine.* (2016) 95:e3173. doi: 10.1097/MD.0000000000003173
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* (2009) 62:e1–34. doi: 10.1016/j.jclinepi.2009.06.006
8. Grosjean J, Merabti T, Dahamna B, Kergourlay I, Thirion B, Soualmia LF, et al. Health multi-terminology portal: a semantic added-value for patient safety. *Stud Health Technol Inform.* (2011) 166:129–38. doi: 10.3233/978-1-60750-740-6-129
9. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med.* (2018) 23:60–3. doi: 10.1136/bmjebm-2017-110853
10. Seger D, Barker K, McNaughton C. Misuse of the naranjo adverse drug reaction probability scale in toxicology. *Clin Toxicol.* (2013) 51:461–6. doi: 10.3109/15563650.2013.811588
11. Mascolo A, Scavone C, Sessa M, di Mauro G, Cimmaruta D, Orlando V, et al. Can causality assessment fulfill the new European definition of adverse drug reaction? A review of methods used in spontaneous reporting. *Pharmacol Res.* (2017) 123:122–9. doi: 10.1016/j.phrs.2017.07.005
12. Kaushik JS, Chakrabarty B, Gulati S, Patel H, Lodha R, Pai G, et al. Unusual late neurological complication in a child after an Indian krait bite. *Pediatr Neurol.* (2014) 51:130–2. doi: 10.1016/j.pediatrneurol.2014.02.014
13. Marrone LCP, Marrone BF, Neto FK, Costa FC, Thomé GG, Aramburu MB, et al. Posterior reversible encephalopathy syndrome following a scorpion sting. *J Neuroimaging.* (2013) 23:535–6. doi: 10.1111/jon.12017
14. Rebahi H, Mouaffak Y, Dilai M-O, Haimeur N, Eladib A-G, Younous S. Posterior reversible encephalopathy syndrome in a child stung by *Androctonus mauretanicus* scorpion. *J Stroke Cerebrovasc Dis.* (2015) 24:e129–32. doi: 10.1016/j.jstrokecerebrovasdis.2014.12.007
15. Akinci E, Köylü R, Yortanli M, Gümüş H, Köylü Ö, Altintepe L, et al. Acute bismuth intoxication: acute renal failure, tonsillar ulceration and posterior reversible encephalopathy syndrome. *Hong Kong J Emerg Med.* (2015) 22:121–5. doi: 10.1177/102490791502200208
16. Chatterjee N, Domoto-Reilly K, Fecci PE, Schwamm LH, Singhal AB. Licorice-associated reversible cerebral vasoconstriction with PRES. *Neurology.* (2010) 75:1939–41. doi: 10.1212/WNL.0b013e3181feb299
17. Tassinari D, Bergamaschi R, Corsini I, Landini S, Romanin B, Ballarini E, et al. Posterior reversible encephalopathy syndrome associated with licorice consumption: a case report in a 10-year-old boy. *Pediatr Neurol.* (2015) 52:457–9. doi: 10.1016/j.pediatrneurol.2014.12.001
18. Bazuaye-Ekwuyasi E, Chow RD, Schmalzle S. An atypical subacute presentation of posterior reversible encephalopathy syndrome. *J Community Hosp Intern Med Perspect.* (2017) 7:269–74. doi: 10.1080/20009666.2017.1369381
19. Dasari V, Donohoe CD. Cocaine-induced posterior reversible encephalopathy syndrome (PRES): a case report and review of the literature. *J Neuroimaging Psychiatry Neurol.* (2018). doi: 10.17756/jnpn.2018-025
20. Castillo A, Payne JD, Nugent K. Posterior reversible leukoencephalopathy syndrome after kratom ingestion. *Proc (Bayl Univ Med Cent).* (2017) 30:355–7. doi: 10.1080/08998280.2017.11929647
21. Legriel S, Bruneel F, Spreux-Varoquaux O, Birenbaum A, Chadenat ML, Mignon F, et al. Lysergic acid amide-induced posterior reversible encephalopathy syndrome with status epilepticus. *Neurocrit Care.* (2008) 9:247–52. doi: 10.1007/s12028-008-9096-5
22. Bhagavati S, Choi J. Atypical cases of posterior reversible encephalopathy syndrome. Clinical and MRI features. *Cerebrovasc Dis.* (2008) 26:564–6. doi: 10.1159/000164556
23. Coppens S, Naeije G, Mavroudakis N. Posterior reversible encephalopathy syndrome following disulfiram intoxication. *J Neurol.* (2011) 258:1548–50. doi: 10.1007/s00415-011-5945-9
24. Srikrishna Nukala SN. Posterior reversible encephalopathy syndrome (PRES) following alcohol induced disulfuram toxicity. *IOSR J Dental Med Sci.* (2013) 7:16–8. doi: 10.9790/0853-0731618
25. Kim HS, Choi JY, Seo MR. Posterior reversible encephalopathy syndrome (PRES) in a chronic alcoholic patient after having steam bath: a case report. *Brain Neurorehabil.* (2014) 7:66. doi: 10.12786/bn.2014.7.1.66
26. Ishikawa H, Natsume N, Matsui K, Tsuda H. Acute alcohol withdrawal accompanied by posterior reversible encephalopathy syndrome. *Psychiatry Clin Neurosci.* (2013) 67:189–9. doi: 10.1111/pcn.12033
27. Mengi T, Seçil Y, Çoban A, Beckmann Y. [Posterior reversible encephalopathy syndrome triggerred by alcohol withdrawal]. *Turk Psikiyatri Derg.* (2017) 28:217–20. doi: 10.5080/u18397
28. Gill D, Zayac A, Goyes Ruiz V, Sheikh N, Bhardwaj A. Alcohol withdrawal induced posterior reversible encephalopathy syndrome. *Hypertens Curr Concepts Ther.* (2017) 1. doi: 10.15761/HCCT.1000105
29. Kimura R, Yanagida M, Kugo A, Taguchi S, Matsunaga H. Posterior reversible encephalopathy syndrome in chronic alcoholism with acute psychiatric symptoms. *Gen Hosp Psychiatry.* (2010) 32:447.e3–5. doi: 10.1016/j.genhosppsych.2009.11.006
30. Baek HS, Lee S-J. A case of posterior reversible encephalopathy syndrome associated with acute pancreatitis and chronic alcoholism. *Gen Hosp Psychiatry.* (2015) 37:192.e3–5. doi: 10.1016/j.genhosppsych.2014.12.004
31. Magno Pereira V, Marote Correia L, Rodrigues T, Serrão Faria G. Acute pancreatitis and posterior reversible encephalopathy syndrome: a case report. *Acta Med Port.* (2016) 29:567–71. doi: 10.20344/amp.7368
32. John ES, Sedhom R, Dalal I, Sharma R. Posterior reversible encephalopathy syndrome in alcoholic hepatitis: hepatic encephalopathy a common theme. *World J Gastroenterol.* (2017) 23:373–6. doi: 10.3748/wjg.v23.i2.373
33. Fitzgerald RT, Fitzgerald CT, Samant RS, Kumar M, Ramakrishniah R, Van Hemert R, et al. Lithium toxicity and PRES: a novel association. *J Neuroimaging.* (2015) 25:147–9. doi: 10.1111/jon.12094
34. Loens S, Conzen J, Welte GS, Scharn N, Schrader C, Weissenborn K. Reversible posterior leukoencephalopathy syndrome after withdrawal of antipsychotic medication in the context of lithium intoxication. *Gen Hosp Psychiatry.* (2015) 37:274.e3–5. doi: 10.1016/j.genhosppsych.2015.02.011
35. Minhaj FS, Schult RF, Dvorak P, Nacca N. Amphetamine and clonidine toxicity resulting in posterior reversible encephalopathy syndrome. *Pediatr Emerg Care.* (2019) doi: 10.1097/PEC.0000000000001819. [Epub ahead of print].
36. Kawanabe T, Tanaka R, Sakaguchi Y, Akiyama O, Shimura H, Yasumoto Y, et al. Posterior reversible encephalopathy syndrome complicating intracranial hemorrhage after phenylpropanolamine exposure. *Neurol Med Chir.* (2011) 51:582–5. doi: 10.2176/nmc.51.582
37. Weidauer S, Gaa J, Sitzer M, Hefner R, Lanfermann H, Zanella FE. Posterior encephalopathy with vasospasm: MRI and angiography. *Neuroradiology.* (2003) 45:869–76. doi: 10.1007/s00234-003-1059-0
38. Delgado ME, Del Brutto OH. Reversible posterior leukoencephalopathy in a venomous snake (*Bothrops asper*) bite victim. *Am J Trop Med Hyg.* (2012) 86:496–8. doi: 10.4269/ajtmh.2012.11-0610
39. Ibrahim AM, ElSefi TT, Ghanem M, Fayed AM, Shaban NA. A horned viper bite victim with PRES. *Case Rep Neurol Med.* (2017) 2017:1835796. doi: 10.1155/2017/1835796
40. Loh HH, Tan CHH. Acute renal failure and posterior reversible encephalopathy syndrome following multiple wasp stings: a case report. *Med J Malaysia.* (2012) 67:133–5.
41. Murphy T, Al-Sharief K, Sethi V, Ranger GS. Posterior reversible encephalopathy syndrome (PRES) after acute pancreatitis. *West J Emerg Med.* (2015) 16:1173–4. doi: 10.5811/westjem.2015.8.28347
42. Varalaxmi B, Ram R, Sandeep P, Siva Kumar V. Posterior reversible encephalopathy syndrome in a patient of snake bite. *J Postgrad Med.* (2014) 60:89–90. doi: 10.4103/0022-3859.128830

43. van Beers EJ, Stam J, van den Bergh WM. Licorice consumption as a cause of posterior reversible encephalopathy syndrome: a case report. *Crit Care.* (2011) 15:R64. doi: 10.1186/cc10040
44. Morgan RD, Chou SH, Stelfox HT. Posterior reversible encephalopathy syndrome in a patient following binge liquorice ingestion. *J Neurol.* (2011) 258:1720–2. doi: 10.1007/s00415-011-5995-z
45. O'Connell K, Kinsella J, McMahon C, Holian J, O'Riordan S. Posterior reversible encephalopathy syndrome (PRES) associated with liquorice consumption. *Ir J Med Sci.* (2016) 185:945–7. doi: 10.1007/s11845-014-1214-0
46. Zhou T, Huang F, Jiang H, Yao X. Posterior reversible encephalopathy syndrome with bad imaging of cerebral venous sinus: a case report. *Commun Disord Deaf Stud Hearing Aids.* (2016) 4:4. doi: 10.4172/2375-4427.1000165
47. Phatake R, Desai S, Lodaya M, Deshpande S, Tankasali N. Posterior reversible encephalopathy syndrome in a patient of organophosphate poisoning. *Indian J Crit Care Med.* (2014) 18:250–2. doi: 10.4103/0972-5229.130580
48. Du G, Yang X, Du X. Posterior reversible encephalopathy syndrome following multiple wasp stings: a case report. *Int J Clin Exp Med.* (2017) 10:1446–8. Available online at: http://www.ijcem.com/files/ijcem0038214.pdf
49. Kinno R, Ohashi H, Mori Y, Shiromaru A, Ono K. Agraphia of the left hand with dysfunction of the left superior parietal region without callosal lesions. *eNeurologicalSci.* (2018) 10:16–8. doi: 10.1016/j.ensci.2018.01.005
50. Omer TA, Doherty C. Posterior reversible encephalopathy syndrome (PRES) complicating the "legal high" mephedrone. *BMJ Case Rep.* (2011) 2011. doi: 10.1136/bcr.02.2011.3904
51. Mann G, Gunja N. Paracetamol overdose complicated by posterior reversible encephalopathy syndrome (PRES). *Clin Toxicol.* (2019) 58:68–70. doi: 10.1080/15563650.2019.1609023
52. Tantikittichaikul S, Ruthirago D, Ali S, Claudio A, Jongyeol K. Posterior reversible encephalopathy syndrome with multiple cerebellar mass-like lesions secondary to amphetamine. *Neurology.* (2016) 86(Suppl. 16). Available online at: https://n.neurology.org/content/86/16_Supplement/P4.403
53. Chen T-H, Lin W-C, Tseng Y-H, Tseng C-M, Chang T-T, Lin T-J. Posterior reversible encephalopathy syndrome in children: case series and systematic review. *J Child Neurol.* (2013) 28:1378–86. doi: 10.1177/0883073813500714
54. Ellis CA, McClelland AC, Mohan S, Kuo E, Kasner SE, et al. Cerebrospinal fluid in posterior reversible encephalopathy syndrome: implications of elevated protein and pleocytosis. *Neurohospitalist.* (2019) 9:58–64. doi: 10.1177/1941874418802061
55. Datar S, Singh TD, Fugate JE, Mandrekar J, Rabinstein AA, et al. Albuminocytologic dissociation in posterior reversible encephalopathy syndrome. *Mayo Clin Proc.* (2015) 90:1366–71. doi: 10.1016/j.mayocp.2015.07.018
56. Sarbu N, Shih RY, Jones RV, Horkayne-Szakaly I, Oleaga L, et al. White matter diseases with radiologic-pathologic correlation. *Radiographics.* (2016) 36:1426–47. doi: 10.1148/rg.2016160031
57. Gao B, Lyu C, Lerner A, McKinney AM. Controversy of posterior reversible encephalopathy syndrome: what have we learnt in the last 20 years? *J Neurol Neurosurg Psychiatry.* (2018) 89:14–20. doi: 10.1136/jnnp-2017-316225
58. Saad AF, Chaudhari R, Wintermark M. Imaging of atypical and complicated posterior reversible encephalopathy syndrome. *Front Neurol.* (2019) 10:964. doi: 10.3389/fneur.2019.00964
59. King A, Dimovska M, Bisoski L. Sympathomimetic toxidromes and other pharmacological causes of acute hypertension. *Curr Hypertens Rep.* (2018) 20:8. doi: 10.1007/s11906-018-0807-9
60. Vale A, Lotti M. Organophosphorus and carbamate insecticide poisoning. *Handb Clin Neurol.* (2015) 131:149–68. doi: 10.1016/B978-0-444-62627-1.00010-X
61. Wong So J, Largeau B, Beau-Salinas F, Ehrmann S, Magni C, Meunier J. Pazopanib-induced posterior reversible encephalopathy syndrome with possible syndrome of inappropriate secretion of antidiuretic hormone: an incidental or pathophysiological association? *Neural Regen Res.* (2020) 15:1166–8. doi: 10.4103/1673-5374.270420
62. Godino A, Renard GM. Effects of alcohol and psychostimulants on the vasopressin system: behavioural implications. *J Neuroendocrinol.* (2018) 30:e12611. doi: 10.1111/jne.12611
63. Kies MW, Horst D, Evarts EV, Goldstein NP. Antidiuretic effect of lysergic acid diethylamide in humans. *AMA Arch Neurol Psychiatry.* (1957) 77:267–9. doi: 10.1001/archneurpsyc.1957.02330330053006
64. Shepshelovich D, Schechter A, Calvarysky B, Diker-Cohen T, Rozen-Zvi B, Gafter-Gvili A. Medication-induced SIADH: distribution and characterization according to medication class. *Br J Clin Pharmacol.* (2017) 83:1801–7. doi: 10.1111/bcp.13256
65. Park J, Masaki T, Mezaki Y, Yokoyama H, Nakamura M, Maehashi H, et al. Alpha-1 antichymotrypsin is involved in astrocyte injury in concert with arginine-vasopressin during the development of acute hepatic encephalopathy. *PLoS ONE.* (2017) 12:e0189346. doi: 10.1371/journal.pone.0189346
66. Schambelan M. Licorice ingestion and blood pressure regulating hormones. *Steroids.* (1994) 59:127–30. doi: 10.1016/0039-128X(94)90089-2
67. Randesi M, Levran O, Correa da Rosa J, Hankins J, Rule J, Kreek MJ, et al. Association of variants of arginine vasopressin and arginine vasopressin receptor 1A with severe acetaminophen liver injury. *Cell Mol Gastroenterol Hepatol.* (2017) 3:500–5. doi: 10.1016/j.jcmgh.2017.01.008
68. Michael White C. Pharmacologic and clinical assessment of kratom. *Am J Health Syst Pharm.* (2018) 75:261–7. doi: 10.2146/ajhp161035
69. Kamble SH, Sharma A, King TI, León F, McCurdy CR, Avery BA. Metabolite profiling and identification of enzymes responsible for the metabolism of mitragynine, the major alkaloid of Mitragyna speciosa (kratom). *Xenobiotica.* (2018) 49:1279–88. doi: 10.1080/00498254.2018.1552819
70. Krishnan S, Moncrief S. An evaluation of the cytochrome p450 inhibition potential of lisdexamfetamine in human liver microsomes. *Drug Metab Dispos.* (2007) 35:180–4. doi: 10.1124/dmd.106.011973
71. Mandrioli R, Forti GC, Raggi MA. Fluoxetine metabolism and pharmacological interactions: the role of cytochrome p450. *Curr Drug Metab.* (2006) 7:127–33. doi: 10.2174/138920006775541561

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 14 February 2020
doi: 10.3389/fneur.2020.00071

Posterior Reversible Encephalopathy Syndrome: Clinical Features and Outcome

*Archana Hinduja**

Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, OH, United States

Background: Posterior reversible encephalopathy syndrome (PRES) is an acute neurotoxic syndrome that is characterized by a spectrum neurological and radiological feature from various risk factors. Common neurological symptoms includes headache, impairment in level of consciousness, seizures, visual disturbances, and focal neurological deficits. Common triggering factors include blood pressure fluctuations, renal failure, eclampsia, exposure to immunosuppressive or cytotoxic agents and autoimmune disorders. The classic radiographic findings include bilateral subcortical vasogenic edema predominantly affecting the parieto-occipital regions but atypical features include involvement of other regions, cortical involvement, restricted diffusion, hemorrhage, contrast enhancement. This review is aimed to summarize the updated knowledge on the typical and atypical clinical and imaging features, prognostic markers and identify gaps in literature for future research.

Methods: Systematic literature review using PUBMED search from 1990 to 2019 was performed using terms PRES was performed.

Results: While clinical and radiographic reversibility is common, long-standing morbidity and mortality can occur in severe forms. In patients with malignant forms of PRES, aggressive care has markedly reduced mortality and improved functional outcomes. Although seizures were common, epilepsy is rare. Various factors that have been associated with poor outcome include altered sensorium, hypertensive etiology, hyperglycemia, longer time to control the causative factor, elevated C reactive protein, coagulopathy, extensive cerebral edema, and hemorrhage on imaging.

Conclusion: Large prospective studies that accurately predict factors that are associated with poor outcomes, determine the pathophysiology, and targeted therapy are required.

Keywords: posterior reversal encephalopathy syndrome, outcome, prognosis, seizures, management

OPEN ACCESS

Edited by:
Bo Gao,
Affiliated Hospital of Guizhou Medical University, China

Reviewed by:
Fabio Pilato,
Agostino Gemelli University Polyclinic, Italy
Mario U. Manto,
University of Mons, Belgium

***Correspondence:**
Archana Hinduja
archanahinduja@yahoo.com

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *01 November 2019*
Accepted: *21 January 2020*
Published: *14 February 2020*

Citation:
Hinduja A (2020) Posterior Reversible Encephalopathy Syndrome: Clinical Features and Outcome. Front. Neurol. 11:71. doi: 10.3389/fneur.2020.00071

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a well-recognized entity characterized by a combination of clinical and neuroimaging findings. It was initially described by Hinchey in 1996 and subsequently has subsequently gained increasing attention (1). Key elements that are essential in its diagnosis include a combination of clinical features, radiological findings in the presence

of various risk factors. Various neurological symptoms includes headache, impairment in level of consciousness, seizures, visual abnormalities, nausea, vomiting, and focal neurological deficits (1). On neuroimaging, it is characterized by vasogenic edema involving the cortical/subcortical regions which is bilateral affecting the parietal and occipital regions, followed in frequency by involvement of other regions (1–5). Its recognition has improved markedly over the last few decades with increased availability of magnetic resonance imaging (MRI) (6).

Common triggering factors of PRES include blood pressure fluctuations, preeclampsia/eclampsia, renal failure, cytotoxic agents, and autoimmune conditions (7, 8). Recently, several etiologies and atypical features have being increasingly recognized. Early recognition is crucial, as timely management of its precipitating factor is required to achieve reversibility (7). In severe cases, aggressive supportive care in the intensive care unit (ICU) is required. Despite a common myth of its benign course and reversibility in terms of both clinically and radiological aspects, permanent brain damage, severe functional impairments, and mortality have been reported (7, 9, 10). The aim of this review is to provide an updated knowledge of the clinical features and functional outcome in patients with PRES.

MATERIALS AND METHODS

Systematic literature review using PUBMED search from 1990 to 2019 was performed using terms posterior reversible encephalopathy syndrome, hypertensive encephalopathy, reversible posterior cerebral edema syndrome, clinical features, imaging, prognosis, seizures, epilepsy, pathophysiology, outcome. Articles in english, cases, case series, retrospective studies, meta-analysis, reviews, book chapters related to PRES were included. Articles were selected primarily based on the relevance to the topic and the information it provided. Articles related to both adults and pediatric PRES were included. Articles that provided duplicate information were deleted. Majority of studies were single center retrospective reports ranging from small to large sample sizes. However, there is paucity of data on its true incidence and prevalence in large patient populations.

Epidemiology

Following its initial description in 1996, its recognition from other etiologies has increased exponentially over the last decade. These reports are in the form of case reports, case series, and large retrospective studies from large institutions. It has been reported in all age groups starting from infancy to older adults, but most frequently affects the young or middle-aged adults (7, 11). It appears to have a female predominance, even after exclusion of patients with eclampsia (6, 8, 12). While the incidence of PRES in the general population is unknown, its incidence in a selected cohort of patients is available. The incidence of PRES in pediatric population is 0.04% (13) and in pediatric intensive care unit is 0.4% (14). Among adults, it has been reported in 2.7–25% of patients following bone marrow transplantation (15–17), 0.4% following solid organ transplantation (18), 0.84% of patients with end stage renal disease is 0.84% (19) and 0.69% of patients with systemic lupus erythematosus (20).

Pathophysiology

Several theories have been proposed in the pathogenesis of PRES (8, 21). They all lead to activation and injury of the endothelium, activation of the immune system and release of cytokines (22). The leading theory, is the "vasogenic theory," that postulated that rapidly developing hypertension with failure of cerebral autoregulation causing breakdown of blood brain barrier and secondary vasogenic edema. When the rise in blood pressure is rapid and severe, the auto regulatory response is insufficient resulting in hyperperfusion, and extravasation of plasma and macromolecules. The relative lack of sympathetic innervation in the posterior circulation is the likely mechanism for the preferential involvement of the posterior part of the brain from PRES. The hypertension hyperperfusion theory is supported by the fact that prompt treatment of hypertension leads to rapid clinical and radiological improvement (8). In a retrospective study that compared the involvement of posterior circulation exclusively by PRES from anterior circulation involvement by PRES (either exclusive or in addition to the posterior circulation) the mean blood pressure was higher in the latter group ($p < 0.01$), which supports the vasogenic theory (23). The density of the autonomic nervous system is higher in the anterior circulation providing better control of autoregulation, but an abrupt massive rise in blood pressures can make the anterior circulation susceptible. However, this theory does not explain the mechanism in patients with borderline hypertension and normotensives. The "neuropeptide" theory has postulated that release of potent vasoconstrictors, such as endothelin-1, prostacyclin, and thromboxane A2 causes vasospasm, ischemia and cerebral edema (24). To support this, both invasive and non-invasive studies have demonstrated irregularities of the cerebral vasculature and hypoperfusion on perfusion studies (25). PRES has been observed in patients with normal blood pressure, patients in the upper limit of autoregulation or did not have blood pressure fluctuations and patients with hypotension (8, 26). To support this, endothelial dysfunction from the cytotoxic effects from infection, sepsis, chemotherapeutic agents, and immunogenic effects from autoimmune disorders, immune suppressive agents have been proposed. The "cytotoxic theory" suggests that the primary insult is from endogenous stimulants or exogenous toxins like chemotherapy or immunosuppressive agents and the "immunogenic theory" has postulated that T-cell activation and cytokine release causes endothelial dysfunction and deranged autoregulatory response (21, 27). Recently, activation of arginine vasopressin (AVP) axis by increase in AVP secretion or AVP receptor density has been postulated in the development of PRES (28). Activation of cerebral AVP receptors (V1aR) leads to cerebral vasoconstriction, endothelial dysfunction and cerebral ischemia and activation of the peripheral (renal) receptors (V2R) may potentially lead to the development of hypertension, renal impairment and is responsible for the symptoms and complications of PRES. In susceptible patients, pronounced fluctuations in blood pressure rather than the absolute increase in blood pressure and

TABLE 1 | Risk factors associated with posterior reversible encephalopathy syndrome.

Preeclampsia, Eclampsia	
Blood pressure fluctuations	Hypertension, dysautonomia e.g., guillian barre syndrome, post carotid endarterectomy with reperfusion syndrome, induced hypertension—treatment of vasospasm in subarachnoid hemorrhage, drug withdrawal—clonidine, triamterene, prazosin, stimulant drugs—phenylpropanolamine, ephedrine, pseudoephedrine, amphetamine, cocaine
Infection	Sepsis, shock
Renal diseases	Hemolytic uremic syndrome, acute glomerulonephritis, acute and chronic renal failure, parenchymal diseases, renal artery stenosis
Immunosuppressive drugs, chemotherapeutic agents	Cyclosporin A, tacrolimus/FK-506, methotrexate, sirolimus, interferon alpha, intravenous immunoglobulin, cisplatin, vincristine, cytarabine, gemcitabine, oxaliplatin, ipilimumab, bortezomib, thalidomide, apatinib, rituximab, erythropoietin, interleukin, antiretroviral therapy in HIV- indinavir, ivabradine, granulocytic stimulating factor, tyrosine kinase inhibitors—pazopanib, sorafenib, sunitinib, high dose steroids (methylprednisolone), post solid organ, or bone marrow transplantation, tumor lysis syndrome
Autoimmune disorders	Systemic lupus erythematosus, sjogren's disease, vasculitis, scleroderma, cryoglobulinemia, polyarteritis nodosa, wegner's granulomatosis, behcet's disease, hashimoto's thyroiditis, primary sclerosing cholangitis
Hematological disorders	Thrombotic thrombocytopenic purpura, henoch-schonlein purpura, leukemia and lymphomas, sickle cell anemia, hemolytic uremic syndrome
Endocrine disorders	Pheochromocytoma, primary aldosteronism
Electrolyte disturbances	Hypercalcemia, hypomagnesemia
Others	Acute porphyria, blood transfusion, lithium

hypotension from sepsis may precede the occurrence of PRES. In certain cases, several factors might be coexistent. For example in patients with renal failure, it is unclear if renal dysfunction is an independent factor or the comorbid hypertension, autoimmune disease, or other systemic conditions are the culprit. Despite the heterogeneity in its etiologies and proposed mechanisms, PRES is a downstream effect that is characterized by a combination of clinical and radiological features. It is important to differentiate these features from other alternative conditions.

Risk Factors

PRES was initially observed in patients with hypertension and subsequently recognized in the normotensive and septic patients. Common risk factors associated with PRES include abrupt elevations of blood pressure, impaired renal function, preeclampsia/eclampsia, autoimmune diseases, infection, transplantation, and chemotherapeutic agents. The extensive list of risk factors associated with PRES is described in **Table 1**.

Clinical Features

The symptoms of PRES are often non-specific and manifest acutely or subacutely over several hours or days (7). However, continued progression over several weeks is uncommon. Most of the literature related to PRES comes from retrospective observational studies and the frequency of these symptoms is dependent on the sample size evaluated and the precipitating factors. The symptoms are highly non-specific, with encephalopathy and seizures being the most common symptoms followed by visual disturbances, headache, and focal neurological deficits (8, 29).

Common Clinical Manifestations

Encephalopathy of varying grades has been reported in 28–94% of patients with PRES (7–9). These range from mild confusion, cognitive deficits, somnolence, stupor, and coma. It is one of the major driving factors for admission to the intensive care unit due to their risk of respiratory failure from worsening mental status (30).

Seizures commonly occur early in the disease course, and are observed in 74–87% of patients (7, 8). Various types of seizures can occur in these patients. These include generalized tonic clonic (54–64%), partial seizures (3–28%), and status epilepticus (3–17%). The most common type is the generalized tonic-clonic seizures (31–34). These typically occur within the first 24–48 h of presentation (31, 32). It is not uncommon to have serial seizures during the acute phase (32). On certain occasions, status epilepticus may be the presenting symptom of PRES (35). In the majority, seizures are terminated spontaneously or from use of antiepileptic therapy. It is common to have provoked seizures from recurrent PRES or other provoking factors around the acute phase (31). Despite a high frequency of seizures during the acute phase, the long-term risk of unprovoked seizures is infrequent and epilepsy is rare (31). PRES related epilepsy has been reported in 1–3.9% of patients (31, 36). Patients with widespread involvement from PRES on imaging are more likely to have a single seizure upon presentation but this does not translate to worse outcomes (32). Several studies have revealed lack of correlation between the imaging findings, grade of PRES, the number of lobes affected from PRES, cortical involvement and presence of hemorrhage with predilection of seizures (33, 34). There is lack of correlation between various EEG patterns and MRI findings (32, 33). Recurrent seizures have been observed in patients with atypical PRES (37). MRI in patients with long-term PRES related epilepsy might be normal, have atrophic changes or hippocampal sclerosis (33, 34, 36). Although half of the patients have persistent abnormalities on follow up imaging, recurrent seizures, and epilepsy is rare (34). The occurrence of seizures during the acute phase has not been associated with increased length of hospital stay, morbidity, mortality, or nursing home placement upon discharge (31, 32, 34). It is possible that the occurrence of seizures might have played a role in the prompt identification of this diagnosis that translated to aggressive care and improved outcomes.

Headache has been reported in 50% of patients (9). It is usually dull, diffuse, and gradual in onset. A thunderclap headache in the context of PRES should prompt us to evaluate associated

for reversible cerebral vasoconstriction syndrome (RCVS) by additional imaging studies. PRES is reported in 9% of RCVS cases and conversely RCVS angiographic changes have been described in PRES (38, 39).

Varying degrees of visual symptoms have been reported in 39% of patients (7, 9). These include decreased visual acuity, diplopia, visual field deficits, cortical blindness, color vision abnormality, and visual hallucinations. Fundoscopic examination is often unremarkable but papilledema with flame shaped retinal hemorrhages and exudates have been observed in the setting of hypertension.

Focal neurological deficits like aphasia, hemiparesis have been observed in 19% of patients (9).

Uncommon Clinical Manifestations

In rare occasions, myelopathic symptoms and signs from spinal cord involvement have been demonstrated (40). Other uncommon presentations include abulia, agitation, delusions, ophisthotonus, optic ataxia, ocular apraxia, and simultagnosia (41–44).

Neurodiagnostics

Serology

Various serological abnormalities have been observed in patients with PRES. Patients with PRES from deranged electrolytes like hypomagnesemia, hypercalcemia, and renal failure have abnormal electrolytes and renal function tests, respectively. In patients with PRES from underlying malignancy and preeclampsia, elevated lactate dehydrogenase levels (LDH) have been reported, which supports endothelial dysfunction as the possible mechanism (45). Elevated serum LDH levels have correlated with larger and more diffuse lesions on imaging ($p < 0.01$) (46). Elevated C reactive protein (CRP) levels have been associated with increased mortality in PRES patients (47). Low serum albumin levels have been observed in 70% of patients (48, 49). Serum albumin levels may contribute to the development of edema, but its correlation with the type of edema has been inconsistent across various studies (48, 49).

Cerebrospinal Fluid

Cerebrospinal fluid (CSF) protein levels are elevated in 70% of patients (50, 51). A direct correlation between elevated protein levels with the extent and topographical distribution of cerebral edema was observed (50, 51). However, CSF pleocytosis is rare and its presence is a marker of infarction or hemorrhage (50, 51).

Electroencephalogram

Data on various electroencephalographic (EEG) patterns primarily comes from several retrospective studies. In these patients, EEG was obtained based on the clinical judgment of the treating physician at variable time frames from symptom onset. Common indications of EEG in these studies were seizures and varying degrees of encephalopathy for exclusion of non-convulsive status epilepticus (52). EEG can help identify patients with ictal or epileptiform activity. Various EEG patterns have been observed in patients with and without seizures related to PRES (31, 33, 34). The most common pattern in a patient with PRES related seizure was generalized slowing followed by focal slowing, epileptiform discharges, periodic lateralized epileptiform discharges, and normal patterns. There is great variability between EEG findings and the development of epilepsy (31, 33, 36). Focal findings on EEG are commonly observed in patients with focal seizures (32). In a prospective study, non-convulsive seizures were associated with the presence of periodic discharges ($p = 0.0002$) (53). Both non-convulsive seizures and periodic discharges are usually either lateralized or bilateral independent and predominant in the posterior head regions. However, there was lack of correlation between non-convulsive seizures and periodic discharges with the clinical presentation. Restricted diffusion involving the cortex on MRI was frequent in patients with periodic discharges and non-convulsive seizures group ($p < 0.001$). A high likelihood of poor outcome in patients with non-convulsive seizures and periodic discharges has been observed ($p < 0.04$). A brief overview of various EEG patterns observed in patients with PRES is described in **Table 2**.

TABLE 2 | EEG findings in patients with PRES.

EEG in patients with seizures at presentations
Generalized slowing with or without focal slowing
Generalized slowing with additional EEG abnormalities—Epileptiform discharges, Electrographic seizures, Periodic lateralized epileptiform discharges
Focal slowing with or without epileptiform discharge
Periodic lateralized epileptiform discharges
Electrographic status epilepticus
Normal
EEG in patients without seizures at presentation
Generalized slowing with or without additional focal slowing
Periodic lateralized epileptiform discharges
Focal sharp waves
Normal
EEG prior to discontinuation of antiepileptic drugs
Normal
Generalized slowing
Focal slowing

Neuroimaging

Brain imaging is the cornerstone in confirming a diagnosis of PRES. Although vasogenic edema can be visualized on non-contrast computed tomography (CT) in some patients, brain MRI, especially the T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences are much more sensitive (6). Currently there is no gold standard diagnostic test. When compared to T2 weighted images, FLAIR helps in detecting cortical and a subcortical lesion related to PRES and is an important sequence in establishing its diagnosis (54). Diffusion weighted imaging combined with apparent diffusion coefficient (ADC) mapping sequences are helpful in differentiating cytotoxic from vasogenic edema and thus may aid in the differentiating PRES form ischemic lesions (55, 56).

The classic imaging patterns usually reveals vasogenic edema that involves the parieto-occipital regions, bilateral, subcortical,

TABLE 3 | Imaging findings in patients with PRES.

Common features
Vasogenic cerebral edema
Parieto-occipital pattern
Holohemispherical watershed distribution
Frontal and temporal lobe involvement
Subcortical white matter
Bilateral, frequently symmetric pattern
Hyperintense T2 weighted and FLAIR sequences
Isointense, hypointense, or hyperintense lesions on DWI
Increased ADC values reflective of vasogenic cerebral edema
Uncommon
Brainstem (Central) variant
Unilateral PRES
Contrast enhancement
Microhemorrhages
Intracerebral hemorrhages
Sulcal SAH
Decreased ADC values indicative of ischemia
Grades of cerebral edema
Mild
Moderate
Severe

and symmetrical in appearance. Various patterns have been described in literature (**Table 3**). These include: parietooccipital pattern, holohemispherical watershed pattern, and superior frontal sulcus pattern (6, 57). Occasionally, the edema may have a central-variant (brainstem) pattern that affects the brainstem, basal ganglia, posterior limb of internal capsule, cerebellum, periventricular regions, and lacks cortical and subcortical involvement (58). Cerebral edema in these patients has been classified into different grades as mild, moderate, and severe (59). Mild PRES was defined as cortical or subcortical white matter edema without hemorrhage, mass effect, herniation, and minimal involvement of one of the group—cerebellum, brain stem, or basal ganglia. Moderate PRES was defined as confluent edema extending from cortex to deep white matter without extension to the ventricular margin or mild involvement of two of the group—cerebellum, brainstem, or basal ganglia. Mild mass effect but no herniation or midline shift, presence of parenchymal hemorrhage was classified as moderate. Severe PRES was defined as confluent edema extending from the cortex to the ventricle, edema, or hemorrhage causing midline shift or herniation or involvement of three of the group—cerebellum, brainstem, or basal ganglia. Patients with worsening degree of cerebral edema have worse outcomes (60). Atypical findings include unilateral involvement, restricted diffusion, intracerebral hemorrhage, microhemorrhages, and contrast enhancement (59). Lesions may be asymmetric in about 50% of cases and unilateral in rare occasions (8, 61). Small areas of restricted diffusion compared to the large areas of vasogenic edema are seen in 30% of patients (12). The presence of restricted diffusion may be associated with incomplete recovery (62). Varying degrees of PRES related hemorrhage have been observed in 10–30% of cases (12, 63). These range from minute focal hemorrhage (<5 mm), sulcal SAH, focal hematoma and microhemorrhages on susceptibility-weighted imaging (SWI) (63). The greatest frequency of hemorrhage was seen in patients after allo-BMT and in patients with coagulopathy (12, 63). The correlation between hemorrhage and the severity of edema has been inconsistent across studies (12, 59). Susceptibility weighted imaging sequence helps in differentiating frank hemorrhage from microhemorrhage that has been observed in certain cases of PRES, however its clinical relevance in patients with PRES is unknown (64). About 40% of patients have contrast enhancement on T1-weighted imaging, the most common being leptomeningeal and leptomemnigeal plus cortical (59, 60). There was no correlation between contrast enhancement with age, imaging severity, and outcome (60). On cerebral angiography or MR angiography studies, moderate to severe vessel irregularity suggestive of vasoconstriction and vasodilation is seen in more than 80% of patients (25). On follow up there is reversal of spasm in the majority with residual spasm in a few patients (65). Magnetic venograms are normal in these patients. On MR spectroscopy, the N-acetylaspartamine (NAA)/creatine (Cr), and NAA/choline-containing compounds (Cho) were significantly lower than healthy controls at initial presentation and on 2 weeks follow up and may assist in differentiating cerebral edema from ischemia (65, 66). MR Perfusion and single-photon emission CT (SPECT), technetium Tc99m-hexamethylpropyleneamine oxime (Tc99m-HM-PAO) have demonstrated decreased cerebral blood flow from hypoperfusion in the majority (67). However, in certain cases, hyperperfusion may be observed early in the disease course (67).

Diagnosis

The spectrum of clinical features, vasogenic cerebral edema and various risk factors are crucial in making a diagnosis of PRES (8). It has a fairly rapid onset and may have a stuttering course. More than 90% of patients have typical radiological and clinical features (27). In a retrospective study, seizures, encephalopathy, visual disturbances, hypertension, renal failure, chemotherapy were the best clinical predictors of PRES, while headache, immunosuppression, and autoimmune disorders were not useful in making a clinical diagnosis of PRES (68). Brain imaging in the context of clinical features to exclude other diagnostic condition is crucial in making an accurate diagnosis. About 95% of patients have cortical-subcortical appearance of vasogenic edema, irrespective of small foci of cytotoxic edema on diffusion weighted imaging, contrast enhancing foci or microhemorrhages (6, 8, 59). More than 95% have involvement of the parieto-occipital region and high precentral/posterior frontal region that is disproportionate to the rest of the brain (59, 67). Recently the PRES early warning scoring (PEWS) scale which consisted of (1) risk factors, (2) clinical features and (3) EEG features has improved the prediction of PRES early in suspected cases, with a high index of suspicion in patients with a score of 10 points or higher (65, 69).

Differential Diagnosis

Differentiating atypical features of PRES like central PRES, hemorrhagic PRES from other causes like toxic leucoencephalopathy, meningoencephalitis, central/extra

pontine myelinolysis, lupus cerebritis, malignancy, hypoxic ischemic encephalopathy requires a thorough review of risk factors, additional testing and follow up imaging (58, 70). In acute ischemic stroke, decreased ADC points toward cytotoxic edema from stroke than PRES. In central/extra pontine myelinolysis the ADC is raised and the rapid correction of electrolyte abnormalities should assist in making its diagnosis. Besides, there is enhancement in the subacute phase on follow up post contrast MRI. Differentiating tumor from PRES is based on time frame of symptom involvement and lack of resolution on follow up imaging. Gliomatosis cerebri is isointense or hypointense on T1-weighted image and hyperintense on T2-weighted image and on MR spectroscopy there is elevated choline/NAA peak. Hypoxic ischemic encephalopathy can be differentiated by the history, gyriform pattern of restricted diffusion predominantly involving the cortex and lack of resolution on follow up imaging. Infectious encephalitis especially rhombencephalitis may be made by clinical history and clinical examination. Reversible cerebral vasoconstriction syndrome may be differentiated by classic thunderclap headache in the presence of known triggers and vasoconstriction of the vessels. In certain cases, this may coexist with PRES. Acute hepatic encephalopathy is differentiated by the history of chronic liver disease, hyperintensity on FLAIR with possibly restricted diffusion in both thalami, posterior limb of internal capsule and periventricular white matter.

Management

Management is primarily supportive and guided by expert consensus. Prompt recognition is the key as timely removal of the precipitating factor is important to achieve favorable outcomes (1, 7). Currently there are no randomized trials on various interventions have been conducted in these patients. About 70% of patients require ICU care for aggressive management of their symptoms (30). Common indications for transfer to the ICU include encephalopathy, seizures, and status epilepticus (30). The following steps should be performed (1, 52):

1. Removal or reduction of the triggering factor (withdrawal of cancer chemotherapy or immunosuppressive agents). In patients with PRES related to cancer chemotherapy or immunosuppressive agents, long term management of immunosuppressive agents and chemotherapy remains a challenging issue and should be individualized.
2. Supportive care with hydration, correction of electrolyte disturbances.
3. Monitoring of airway and ventilation. Intubation may be required in patients with altered mental status.
4. In pregnant women, prompt delivery should be considered.
5. In patients with renal failure, prompt dialysis should be performed.
6. In patients with acute hypertension, gradual reduction of blood pressure should be performed (no more than 20–25% in the first few hours) to avoid the risk of cerebral, coronary, and renal ischemia (71). The goal is to maintain mean arterial pressure between 105 and 125 mm Hg. Intravenous agents are preferred to avoid fluctuations of blood pressure and the choice of agents is left to the discretion of the physician. Continuous infusions are frequently required to avoid fluctuations of blood pressure and achieve the goal blood pressure. First line agents include nicardipine, labetalol, nimodipine, and second line agents include sodium nitroprusside, hydralazine, and diazoxide. Avoid angiotensin converting enzyme inhibitors in pregnant women. Fenoldopam mesylate, a selective dopamine 1 agonist that produces renal vasodilation may improve the renal oxygen supply/demand ratio and prevent renal failure. In patients subarachnoid hemorrhage with PRES from induced hypertension for vasospasm gradual reduction of blood pressure is crucial for neurological improvement (61).

Treatment of status epilepticus

1. Intravenous anticonvulsants (first line with diazepam, second line with forphenytoin, phenobarbital.
2. In refractory cases propofol, pentobarbital, midazolam may be used.
3. Continuous EEG monitoring may be considered.
4. In pregnant women, magnesium sulfate is indicated to prevent seizures. It has cerebral vasodilatory effects and reduces blood vessel permeability.

Although seizures are common long-term data on risk of recurrent seizures and epilepsy is limited due to lack of large population based studies. Currently, there are no standard guidelines for management of PRES related seizures and treatment with antiepileptic agents must be made based on individual basis. Antiepileptic drugs are frequently prescribed to patients with seizures. As epilepsy is rare long-term antiepileptic medications are not warranted in majority of these patients. There is often a dilemma on the optimal duration of antiepileptics. The most common antiepileptics that have been used during hospitalization include benzodiazepines, levetiracetam and phenytoin and upon discharge levetiracetam and phenytoin, with majority of them on a single agent. Since seizures are uncommon out of the acute phase, antiepileptic agents may be quickly tapered. In a single center study, the median duration of antiepileptic agents was 3 months (IQR 2–7 months). The overall prognosis of both generalized and focal seizures in PRES is benign. Besides, not all patients with seizures have been treated with antiepileptic agents and none of these patients developed recurrent seizures (31, 32). It is unclear if antiepileptic agents play a role on the risk of subsequent seizures and epilepsy in these patients. If antiepileptic agents are started, discontinuation following resolution of PRES should be considered, once there is adequate control of risk factors, and absence of factors that might substantially lower the seizure threshold.

Complications

Recurrent PRES

Recurrent PRES has been observed in 4% of patients in retrospective studies (72). It is not uncommon for patients to have recurrent episodes of PRES from recurrence of risk factors like sickle cell crisis, autoimmune conditions, hypertensive crisis, renal failure, and multiorgan failure.

Malignant PRES

The term malignant PRES has been defined based on clinical criteria (Glasgow Coma Score <8 and clinical decline despite standard medical management for elevated intracranial pressure) and radiological criteria (edema with mass effect, intracerebral hemorrhage exerting mass effect, effacement of basal cisterns, transtentorial, tonsillar, or uncal herniation) (73).

Management of malignant PRES requires aggressive supportive care. In a case series, besides routine care like mechanical ventilation, transfusion of blood products for reversal of coagulopathy, steroids for autoimmune disorders, intracranial pressure monitoring is required in patients with GCS of ≤8 (73). Various interventions that have been undertaken in patients with raised ICP include osmotherapy, draining of cerebrospinal fluid by external ventricular drain, craniectomy and evacuation of hematoma. Due to aggressive care, no fatalities were observed in patients with severe or hemorrhagic PRES variants compared to historic reports of 16–29% (63, 74). All patients achieved favorable functional outcomes based on the mRS (modified Rankin Score of 1–2) on long term follow up (73).

In patients with acute obstructive hydrocephalus, an external ventricular drain placement may be required for management (75).

Prognosis

Although PRES was initially described as a benign entity that was reversible with a good outcome, mortality has been observed in 19% of patients and functional impairments of varying degree have been reported in 44% of patients (9, 10). Certain deficits that require long-term care include epilepsy and motor deficits.

PRES is an acute neurotoxic syndrome and the prognosis is highly dependent on the etiological factor. Studies have reported that patients with preeclampsia-eclampsia have less severe cerebral edema, hemorrhage, contrast enhancement with a tendency for complete resolution on imaging and good functional outcome (10, 29). A recent systemic review and meta-analysis which included 448 PRES patients showed good outcomes in patients with PRES related to pre-eclampsia/eclampsia ($p < 0.00001$) (76). Other factors that have been associated with poor outcome include severe encephalopathy, hypertensive etiology, hyperglycemia, neoplastic etiology, longer time to control the causative factor, the presence of multiple comorbidities, elevated CRP, low CSF glucose, and coagulopathy (9, 10, 47, 77). Residual structural lesions have been observed in 40% of cases on follow up imaging (12). Various imaging features that are associated with poor outcome include corpus callosum involvement, extensive cerebral edema or worsening imaging severity, hemorrhage, subarachnoid hemorrhage, and restrictive diffusion on imaging (47, 60, 76–78). The type, location and severity of hemorrhage that is associated with poor outcome are inconsistent across various studies (47, 76, 79). While small hemorrhages do not have an impact on outcome, multiple or massive hemorrhages might be associated with poor outcome. Several studies have demonstrated correlation between the degree of hypertension with clinical outcome and severity of edema on imaging. Interestingly, while the severity of edema on MRI correlated with clinical outcomes, the presence or patterns of gadolinium based contrast enhancement did not correlate with functional outcomes (60). To summarize, although there are several associations, identifying a single predictor of outcome has been challenging in these patients.

FUTURE DIRECTIONS

Recent data from animal studies have demonstrated blood brain barrier disruption as a possible mechanism for development of vasogenic cerebral edema from acute hypertension and thus may be a target of future intervention (80). Besides, based on the recent AVP theory, suppression of AVP the use of vaptans might play a role in the treatment of PRES. Currently, there is paucity of data on its clinical implications in PRES.

CONCLUSION

Currently, the available data on outcomes are from single institutions with paucity of data from long-term epidemiological studies. Its heterogeneous nature limits its ability to generalize. PRES has a favorable prognosis in general, but fatalities can occur. A standardized algorithm that incorporates the clinical, etiological, serological markers, imaging features with various comorbidities and will assist in future studies. Various pathophysiological mechanisms need to be explored at bench side to determine reliable laboratory and imaging markers and therapeutic interventions in order to improve functional outcomes are warranted.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* (1996) 334:494–500. doi: 10.1056/NEJM199602223340803
2. Schwartz RB, Jones KM, Kalina P, Bajakian RL, Mantello MT, Garada B, et al. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. *AJR Am J Roentgenol.* (1992) 159:379–83. doi: 10.2214/ajr.159.2.1632361
3. Schwartz RB, Bravo SM, Klufas RA, Hsu L, Barnes PD, Robson CD, et al. Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy: CT and MR findings in 16 cases. *AJR Am J Roentgenol.* (1995) 165:627–31. doi: 10.2214/ajr.165.3.7645483
4. Bartynski WS, Grabb BC, Zeigler Z, Lin L, Andrews DF. Watershed imaging features and clinical vascular injury in cyclosporin A neurotoxicity. *J*

Comput Assist Tomogr. (1997) 21:872–80. doi: 10.1097/00004728-199711000-00005
5. Bartynski WS, Zeigler Z, Spearman MP, Lin L, Shadduck RK, Lister J. Etiology of cortical and white matter lesions in cyclosporin-A and FK-506 neurotoxicity. *AJNR Am J Neuroradiol.* (2001) 22:1901–14.
6. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol.* (2007) 28:1320–7. doi: 10.3174/ajnr.A0549
7. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Arch Neurol.* (2008) 65:205–10. doi: 10.1001/archneurol.2007.46
8. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc.* (2010) 85:427–32. doi: 10.4065/mcp.2009.0590
9. Legriel S, Schraub O, Azoulay E, Hantson P, Magalhaes E, Coquet I, et al. Determinants of recovery from severe posterior reversible encephalopathy syndrome. *PLoS ONE.* (2012) 7:e44534. doi: 10.1371/journal.pone.0044534
10. Alhilali LM, Reynolds AR, Fakhran S. A multi-disciplinary model of risk factors for fatal outcome in posterior reversible encephalopathy syndrome. *J Neurol Sci.* (2014) 347:59–65. doi: 10.1016/j.jns.2014.09.019
11. Kummer S, Schaper J, Mayatepek E, Tibussek D. Posterior reversible encephalopathy syndrome in early infancy. *Klin Padiatr.* (2010) 222:269–70. doi: 10.1055/s-0030-1249031
12. Liman TG, Bohner G, Heuschmann PU, Endres M, Siebert E. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the retrospective Berlin PRES study. *J Neurol.* (2012) 259:155–64. doi: 10.1007/s00415-011-6152-4
13. Thavamani A, Umapathi KK, Puliyel M, Super D, Allareddy V, Ghori A. Epidemiology, comorbidities, and outcomes of posterior reversible encephalopathy syndrome in children in the United States. *Pediatr Neurol.* (2019) 103:21–6. doi: 10.1016/j.pediatrneurol.2019.07.007
14. Raj S, Overby P, Erdfarb A, Ushay HM. Posterior reversible encephalopathy syndrome: incidence and associated factors in a pediatric critical care population. *Pediatr Neurol.* (2013) 49:335–9. doi: 10.1016/j.pediatrneurol.2013.06.007
15. Reece DE, Frei-Lahr DA, Shepherd JD, Dorovini-Zis K, Gascoyne RD, Graeb DA, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. *Bone Marrow Transplant.* (1991) 8:393–401.
16. Bartynski WS, Zeigler ZR, Shadduck RK, Lister J. Pretransplantation conditioning influence on the occurrence of cyclosporine or FK-506 neurotoxicity in allogeneic bone marrow transplantation. *AJNR Am J Neuroradiol.* (2004) 25:261–9.
17. Bartynski WS, Zeigler ZR, Shadduck RK, Lister J. Variable incidence of cyclosporine and FK-506 neurotoxicity in hematopoeitic malignancies and marrow conditions after allogeneic bone marrow transplantation. *Neurocrit Care.* (2005) 3:33–45. doi: 10.1385/NCC:3:1:033
18. Bartynski WS, Tan HP, Boardman JF, Shapiro R, Marsh JW. Posterior reversible encephalopathy syndrome after solid organ transplantation. *AJNR Am J Neuroradiol.* (2008) 29:924–30. doi: 10.3174/ajnr.A0960
19. Canney M, Kelly D, Clarkson M. Posterior reversible encephalopathy syndrome in end-stage kidney disease: not strictly posterior or reversible. *Am J Nephrol.* (2015) 41:177–82. doi: 10.1159/000381316
20. Lai CC, Chen WS, Chang YS, Wang SH, Huang CJ, Guo WY, et al. Clinical features and outcomes of posterior reversible encephalopathy syndrome in patients with systemic lupus erythematosus. *Arthritis Care Res.* (2013) 65:1766–74. doi: 10.1002/acr.22047
21. Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. Posterior reversible encephalopathy syndrome–Insight into pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev.* (2015) 14:830–6. doi: 10.1016/j.autrev.2015.05.006
22. Chen Z, Shen GQ, Lerner A, Gao B. Immune system activation in the pathogenesis of posterior reversible encephalopathy syndrome. *Brain Res Bull.* (2017) 131:93–9. doi: 10.1016/j.brainresbull.2017.03.012
23. Marrone LCP, Martins WA, Borges MT, Rossi BC, Brunelli JPF, Vedana VM, et al. Posterior reversible encephalopathy syndrome: clinical differences in patients with exclusive involvement of posterior circulation compared to anterior or global involvement. *J Stroke Cerebrovasc Dis.* (2016) 25:1776–80. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.042
24. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol.* (2008) 29:1043–9. doi: 10.3174/ajnr.A0929
25. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol.* (2008) 29:447–55. doi: 10.3174/ajnr.A0839
26. Rabinstein AA, Mandrekar J, Merrell R, Kozak OS, Durosaro O, Fugate JE. Blood pressure fluctuations in posterior reversible encephalopathy syndrome. *J Stroke Cerebrovasc Dis.* (2012) 21:254–8. doi: 10.1016/j.jstrokecerebrovasdis.2011.03.011
27. Gao B, Lyu C, Lerner A, McKinney AM. Controversy of posterior reversible encephalopathy syndrome: what have we learnt in the last 20 years? *J Neurol Neurosurg Psychiatry.* (2018) 89:14–20. doi: 10.1136/jnnp-2017-316225
28. Largeau B, Le Tilly O, Sautenet B, Salmon Gandonniere C, Barin-Le Guellec C, Ehrmann S. Arginine vasopressin and posterior reversible encephalopathy syndrome pathophysiology: the missing link? *Mol Neurobiol.* (2019) 56:6792–806. doi: 10.1007/s12035-019-1553-y
29. Liman TG, Bohner G, Heuschmann PU, Scheel M, Endres M, Siebert E. Clinical and radiological differences in posterior reversible encephalopathy syndrome between patients with preeclampsia-eclampsia and other predisposing diseases. *Eur J Neurol.* (2012) 19:935–43. doi: 10.1111/j.1468-1331.2011.03629.x
30. Hinduja A, Habetz K, Raina SK, Fitzgerald RT. Predictors of intensive care unit utilization in patients with posterior reversible encephalopathy syndrome. *Acta Neurol Belg.* (2017) 117:201–6. doi: 10.1007/s13760-016-0703-5
31. Datar S, Singh T, Rabinstein AA, Fugate JE, Hocker S. Long-term risk of seizures and epilepsy in patients with posterior reversible encephalopathy syndrome. *Epilepsia.* (2015) 56:564–8. doi: 10.1111/epi.12933
32. Kastrup O, Gerwig M, Frings M, Diener HC. Posterior reversible encephalopathy syndrome (PRES): electroencephalographic findings and seizure patterns. *J Neurol.* (2012) 259:1383–9. doi: 10.1007/s00415-011-6362-9
33. Sha Z, Moran BP, McKinney AM IV, Henry TR. Seizure outcomes of posterior reversible encephalopathy syndrome and correlations with electroencephalographic changes. *Epilepsy Behav.* (2015) 48:70–4. doi: 10.1016/j.yebeh.2015.05.027
34. Hinduja A, Habetz K, Raina SK, Fitzgerald RT, Sahaya K. Predictors of seizures in patients with posterior reversible encephalopathy syndrome. *Epilepsy Behav.* (2016) 61:97–101. doi: 10.1016/j.yebeh.2016.05.001
35. Kozak OS, Wijdicks EF, Manno EM, Miley JT, Rabinstein AA. Status epilepticus as initial manifestation of posterior reversible encephalopathy syndrome. *Neurology.* (2007) 69:894–7. doi: 10.1212/01.wnl.0000269780.45472.16
36. Heo K, Cho KH, Lee MK, Chung SJ, Cho YJ, Lee BI. Development of epilepsy after posterior reversible encephalopathy syndrome. *Seizure.* (2016) 34:90–4. doi: 10.1016/j.seizure.2015.12.005
37. Kamiya-Matsuoka C, Tummala S. Electrographic patterns in patients with posterior reversible encephalopathy syndrome and seizures. *J Neurol Sci.* (2017) 375:294–8. doi: 10.1016/j.jns.2017.02.017
38. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain.* (2007) 130:3091–101. doi: 10.1093/brain/awm256
39. Ducros A, Fiedler U, Porcher R, Boukobza M, Stapf C, Bousser MG. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. *Stroke.* (2010) 41:2505–11. doi: 10.1161/STROKEAHA.109.572313
40. de Havenon A, Joos Z, Longenecker L, Shah L, Ansari S, Digre K. Posterior reversible encephalopathy syndrome with spinal cord involvement. *Neurology.* (2014) 83:2002–6. doi: 10.1212/WNL.0000000000001026

41. Nishie M, Kurahashi K, Ogawa M, Yoshida Y, Midorikawa H. Posterior encephalopathy subsequent to cyclosporin A presenting as irreversible abulia. *Intern Med.* (2003) 42:750–5. doi: 10.2169/internalmedicine.42.750
42. Kumar N, Singh R, Sharma N, Jain A. Atypical presentation of posterior reversible encephalopathy syndrome: two cases. *J Anaesthesiol Clin Pharmacol.* (2018) 34:120–2. doi: 10.4103/0970-9185.173351
43. Brown CH, Feng AJ, Cruz E. Ocular dysfunctions presenting in tacrolimus-induced posterior reversible encephalopathy syndrome: a case presentation. *PMR.* (2018) 10:105–11. doi: 10.1016/j.pmrj.2017.07.079
44. Tsai SJ, Yeh CB, Wang CW, Mao WC, Yeh TC, Tai YM, et al. Delusional infestation in a patient with posterior reversible encephalopathy syndrome. *Aust N Z J Psychiatry.* (2016) 50:1212–3. doi: 10.1177/0004867416656259
45. Fitzgerald RT, Wright SM, Samant RS, Kumar M, Ramakrishnaiah RH, Van Hemert R, et al. Elevation of serum lactate dehydrogenase at posterior reversible encephalopathy syndrome onset in chemotherapy-treated cancer patients. *J Clin Neurosci.* (2014) 21:1575–8. doi: 10.1016/j.jocn.2014.03.004
46. Gao B, Liu FL, Zhao B. Association of degree and type of edema in posterior reversible encephalopathy syndrome with serum lactate dehydrogenase level: initial experience. *Eur J Radiol.* (2012) 81:2844–7. doi: 10.1016/j.ejrad.2011.12.010
47. Siebert E, Bohner G, Liebig T, Endres M, Liman TG. Factors associated with fatal outcome in posterior reversible encephalopathy syndrome: a retrospective analysis of the Berlin PRES study. *J Neurol.* (2017) 264:237–42. doi: 10.1007/s00415-016-8328-4
48. Pirker A, Kramer L, Voller B, Loader B, Auff E, Prayer D. Type of edema in posterior reversible encephalopathy syndrome depends on serum albumin levels: an MR imaging study in 28 patients. *AJNR Am J Neuroradiol.* (2011) 32:527–31. doi: 10.3174/ajnr.A2332
49. Gao B, Yu BX, Li RS, Zhang G, Xie HZ, Liu FL, et al. Cytotoxic edema in posterior reversible encephalopathy syndrome: correlation of MRI features with serum albumin levels. *AJNR Am J Neuroradiol.* (2015) 36:1884–9. doi: 10.3174/ajnr.A4379
50. Ellis CA, McClelland AC, Mohan S, Kuo E, Kasner SE, Zhang C, et al. Cerebrospinal fluid in posterior reversible encephalopathy syndrome: implications of elevated protein and pleocytosis. *Neurohospitalist.* (2019) 9:58–64. doi: 10.1177/1941874418802061
51. Datar S, Singh TD, Fugate JE, Mandrekar J, Rabinstein AA, Hocker S. Albuminocytologic dissociation in posterior reversible encephalopathy syndrome. *Mayo Clin Proc.* (2015) 90:1366–71. doi: 10.1016/j.mayocp.2015.07.018
52. Servillo G, Bifulco F, De Robertis E, Piazza O, Striano P, Tortora F, et al. Posterior reversible encephalopathy syndrome in intensive care medicine. *Intensive Care Med.* (2007) 33:230–6. doi: 10.1007/s00134-006-0459-0
53. Bastide L, Legros B, Rampal N, Gilmore EJ, Hirsch LJ, Gaspard N. Clinical correlates of periodic discharges and nonconvulsive seizures in posterior reversible encephalopathy syndrome (PRES). *Neurocrit Care.* (2018) 29:481–90. doi: 10.1007/s12028-018-0548-2
54. Casey SO, Sampaio RC, Michel E, Truwit CL. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. *AJNR Am J Neuroradiol.* (2000) 21:1199–206.
55. Provenzale JM, Petrella JR, Cruz LC Jr, Wong JC, Engelter S, Barboriak DP. Quantitative assessment of diffusion abnormalities in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol.* (2001) 22:1455–61.
56. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. *AJNR Am J Neuroradiol.* (2002) 23:1038–48.
57. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol.* (2017) 264:1608–16. doi: 10.1007/s00415-016-8377-8
58. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical cerebral edema. *AJR Am J Roentgenol.* (2013) 201:631–8. doi: 10.2214/AJR.12.9677
59. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *AJR Am J Roentgenol.* (2007) 189:904–12. doi: 10.2214/AJR.07.2024
60. Karia SJ, Rykken JB, McKinney ZJ, Zhang L, McKinney AM. Utility and significance of gadolinium-based contrast enhancement in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol.* (2016) 37:415–22. doi: 10.3174/ajnr.A4563
61. Dhar R, Dacey R, Human T, Zipfel G. Unilateral posterior reversible encephalopathy syndrome with hypertensive therapy of contralateral vasospasm: case report. *Neurosurgery.* (2011) 69:E1176–81; E81. doi: 10.1227/NEU.0b013e318223b995
62. Moon SN, Jeon SJ, Choi SS, Song CJ, Chung GH, Yu IK, et al. Can clinical and MRI findings predict the prognosis of variant and classical type of posterior reversible encephalopathy syndrome (PRES)? *Acta Radiol.* (2013) 54:1182–90. doi: 10.1177/0284185113491252
63. Hefzy HM, Bartynski WS, Boardman JF, Lacomis D. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. *AJNR Am J Neuroradiol.* (2009) 30:1371–9. doi: 10.3174/ajnr.A1588
64. McKinney AM, Sarikaya B, Gustafson C, Truwit CL. Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging. *AJNR Am J Neuroradiol.* (2012) 33:896–903. doi: 10.3174/ajnr.A2886
65. Sengar AR, Gupta RK, Dhanuka AK, Roy R, Das K. MR imaging, MR angiography, and MR spectroscopy of the brain in eclampsia. *AJNR Am J Neuroradiol.* (1997) 18:1485–90.
66. Eichler FS, Wang P, Wityk RJ, Beauchamp NJ Jr, Barker PB. Diffuse metabolic abnormalities in reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol.* (2002) 23:833–7.
67. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol.* (2008) 29:1036–42. doi: 10.3174/ajnr.A0928
68. Faille LD, Fieuws S, Van Paesschen W. Clinical predictors and differential diagnosis of posterior reversible encephalopathy syndrome. *Acta Neurol Belg.* (2017) 117:469–75. doi: 10.1007/s13760-017-0750-6
69. Zou LP, Liu LY, Li H, Wang YY, Liu Y, Chen J, et al. Establishment and utility assessment of posterior reversible encephalopathy syndrome early warning scoring (PEWS) scale establishment and utility assessment of PEWS scale. *BMC Neurol.* (2019) 19:30. doi: 10.1186/s12883-019-1247-0
70. Rykken JB, McKinney AM. Posterior reversible encephalopathy syndrome. *Semin Ultrasound CT MR.* (2014) 35:118–35. doi: 10.1053/j.sult.2013.09.007
71. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens.* (2018) 36:1953–2041. doi: 10.1097/HJH.0000000000001940
72. Sweany JM, Bartynski WS, Boardman JF. "Recurrent" posterior reversible encephalopathy syndrome: report of 3 cases–PRES can strike twice! *J Comput Assist Tomogr.* (2007) 31:148–56. doi: 10.1097/01.rct.0000233127.21303.b9
73. Akins PT, Axelrod Y, Silverthorn JW, Guppy K, Banerjee A, Hawk MW. Management and outcomes of malignant posterior reversible encephalopathy syndrome. *Clin Neurol Neurosurg.* (2014) 125:52–7. doi: 10.1016/j.clineuro.2014.06.034
74. Aranas RM, Prabhakaran S, Lee VH. Posterior reversible encephalopathy syndrome associated with hemorrhage. *Neurocrit Care.* (2009) 10:306–12. doi: 10.1007/s12028-009-9200-5
75. Catherine C, Yanta C, Saand AR, Pilato M, Chou SH. Pearls & Oy-sters: the dangers of PRES: an atypical case with life-threatening presentation. *Neurology.* (2019) 92:e282–5. doi: 10.1212/WNL.0000000000006775
76. Chen Z, Zhang G, Lerner A, Wang AH, Gao B, Liu J. Risk factors for poor outcome in posterior reversible encephalopathy syndrome: systematic review and meta-analysis. *Quant Imaging Med Surg.* (2018) 8:421–32. doi: 10.21037/qims.2018.05.07
77. Liman TG, Bohner G, Endres M, Siebert E. Discharge status and in-hospital mortality in posterior reversible encephalopathy syndrome. *Acta Neurol Scand.* (2014) 130:34–9. doi: 10.1111/ane.12213
78. Schweitzer AD, Parikh NS, Askin G, Nemade A, Lyo J, Karimi S, et al. Imaging characteristics associated with clinical outcomes in

posterior reversible encephalopathy syndrome. *Neuroradiology*. (2017) 59:379–86. doi: 10.1007/s00234-017-1815-1

79. Hinduja A, Habetz K, Raina S, Ramakrishnaiah R, Fitzgerald RT. Predictors of poor outcome in patients with posterior reversible encephalopathy syndrome. *Int J Neurosci*. (2017) 127:135–44. doi: 10.3109/00207454.2016.1152966
80. Wang Q, Huang B, Shen G, Zeng Y, Chen Z, Lu C, et al. Blood-brain barrier disruption as a potential target for therapy in posterior reversible encephalopathy syndrome: evidence from multimodal MRI in rats. *Front Neurol*. (2019) 10:1211. doi: 10.3389/fneur.2019.01211

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 14 February 2020
doi: 10.3389/fneur.2020.00034

Posterior Reversible Encephalopathy Syndrome and Reversible Cerebral Vasoconstriction Syndrome: Clinical and Radiological Considerations

Fabio Pilato [1,2†], Marisa Distefano [3] and Rosalinda Calandrelli [1,4]*

[1] Fondazione Policlinico Universitario A. Gemelli – IRCCS, Rome, Italy, [2] UOC Neurologia, Dipartimento di Scienze dell'invecchiamento, Neurologiche, Ortopediche e Della Testa-Collo, Rome, Italy, [3] UOC Neurologia e UTN, Ospedale Belcolle, Viterbo, Italy, [4] UOC Radiologia e Neuroradiologia, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Rome, Italy

OPEN ACCESS

Edited by:
Bo Gao,
Affiliated Hospital of Guizhou Medical University, China

Reviewed by:
Bruno J. Weder,
University of Bern, Switzerland
Chuanming Li,
Chongqing Medical University, China

***Correspondence:**
Fabio Pilato
fabio.pilato@policlinicogemelli.it

†ORCID:
Fabio Pilato
orcid.org/0000-0002-7248-3916

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *16 October 2019*
Accepted: *10 January 2020*
Published: *14 February 2020*

Citation:
Pilato F, Distefano M and Calandrelli R (2020) Posterior Reversible Encephalopathy Syndrome and Reversible Cerebral Vasoconstriction Syndrome: Clinical and Radiological Considerations. Front. Neurol. 11:34. doi: 10.3389/fneur.2020.00034

Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) are relatively uncommon neurological disorders, but their detection has been increasing mainly due to clinical awareness and spreading of magnetic resonance imaging (MRI). Because these syndromes share some common clinical and radiologic features and occasionally occur in the same patient, misdiagnosis may occur. PRES is characterized by varied neurological symptoms including headache, impaired visual acuity or visual field deficit, confusion, disorders of consciousness, seizures, and motor deficits often associated to peculiar neuroradiological pattern even if uncommon localization and ischemic or hemorrhagic lesions were described. RCVS is a group of diseases typically associated with severe headaches and reversible segmental vasoconstriction of cerebral arteries, often complicated by ischemic or hemorrhagic stroke. Pathophysiological basis of PRES and RCVS are still debated but, because they share some risk factors and clinical features, a possible common origin has been supposed. Clinical course is usually self-limiting, but prognosis may fluctuate from complete recovery to death due to complications of ischemic stroke or intracranial hemorrhage. Neuroradiological techniques such as digital angiography and MRI are helpful in the diagnostic pathway and a possible prognostic role of MRI has been suggested. This review will serve to summarize clinical, neuroradiological features and controversies underlying both syndromes that may mislead the diagnostic pathway and their possible relationship with pathophysiology, clinical course, and prognosis.

Keywords: reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, RCVS, PRES, call-fleming syndrome, reversible posterior leukoencephalopathy syndrome, magnetic resonance imaging

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES), although relatively uncommon neurological disorders, have become increasingly recognized, mainly due to the spreading of brain magnetic resonance (MRI) and clinical awareness.

PRES, also called reversible posterior leukoencephalopathy syndrome, hyper-perfusion encephalopathy, or brain capillary leak syndrome, is an acute or subacute neurological disorder; even if each label describes a particular feature of the syndrome, none of them is completely satisfactory. Since the first systematic description by Hinchey et al. (1), risk factors of PRES including immunosuppression, malignancy, pre-eclampsia, renal failure, autoimmune disorders, sepsis, hypertension, transplantation, and chemotherapeutic medications remained unchanged even if it may occur also in healthy subjects.

RCVS, previously named isolated benign cerebral vasculitis, Call or Call-Fleming syndrome, and migrainous vasospasm are a group of syndromes characterized by severe headaches, typically associated with reversible segmental constriction of cerebral arteries, and it may be complicated by ischemic or hemorrhagic stroke (2). RCVS is the most important cause of thunderclap headache (3), commonly reversible, but several neurological complications including seizure, ischemic infarcts, and hemorrhage may happen.

PATHOPHYSIOLOGICAL BASIS

Several pathophysiological mechanisms have been proposed for both syndromes but pathogenesis remains unclear (1, 2). The role of disordered cerebral vascularization, autoregulation, and endothelial function has been supposed but, due to their heterogeneous manifestations and pleiomorphic nature of the lesions, probably more than one mechanism is involved in etiology and they may vary in different clinical settings (1, 4).

In both syndromes, a blood flow dysregulation has been suggested to have a causative role but other mechanisms as immune system dysregulation or endothelium dysfunction may play a role in pathogenesis or in clinical course (1, 5). However, the occurrence of both syndromes in the same patients (6–10) makes conceivable a common origin or a common pathophysiological pattern making differential diagnosis difficult (11, 12), even if a possible overlap syndrome could not be completely ruled out (13).

PRES

Pathophysiology of PRES remains controversial but the mechanism of a rapid increase in blood pressure is supposed to be central. Blood flow autoregulation indicates the capability of a tissue or a vascular bed to maintain a constant perfusion despite changes in systemic blood pressure (14, 15). Hypertension and associated conditions have often been indicated as key factors for the development of PRES and emergent pressure treatment was associated with symptoms relief in hours or days (16–18); however, also normo- or hypotensive patients with PRES have been described (19). Blood pressure rise and acute changing of blood pressure are commonly encountered in PRES; whether their role is causative or a secondary effect of the syndrome is still debated (4, 17, 20).

Some studies reported a possible immunological activation more than an effect of systemic hypertension (17, 21). Impaired cerebral autoregulation causing an increase in cerebral blood flow and endothelial dysfunction with cerebral hypoperfusion were indicated as possible mechanisms (4). Endothelial dysfunction may be the most relevant mechanism in preeclampsia or cytotoxic therapy (4, 20). Cytokines, lactate serum dehydrogenase (LDH), and vascular endothelial growth factor (VEGF) have been supposed to regulate vascular permeability (22) and endothelial dysfunction was reported in chronic renal failure, hemolytic uremic syndrome, and lupus nephritis (1, 5).

RCVS

RCVS is more common in women than in men, and it has been described in patients aged from 10 to 76 years with a peak at around 42 years (2). Incidence is uncertain, but considering rates of patient recruitment into clinical series, RCVS does not appear rare. The first single center large series was reported in 2007 (23). Recent reports have proposed an increase in incidence of RCVS, but it is unclear whether this observation reflects a true increase in the incidence or an epiphenomenon due to physician awareness and diffusion and improved imaging techniques (3). Pathophysiology of RCVS remains unknown but a possible role of a transitory cerebral vascular autoregulation dysfunction and blood–brain barrier (BBB) breakdown have been postulated (24). A transitory spontaneous or provoked central vascular discharge may cause the alteration, explaining the reversible nature of RCVS and, because cerebral blood vessels are densely innervated with sensory afferents from trigeminal nerve, these mechanisms may contribute to the severe and acute headache (25).

CLINICAL FEATURES

PRES

PRES may affect all age groups with patients ranging from 2 to 90 years (26) but commonly affects the young or middle-aged adults with a female predominance even after exclusion of patients with eclampsia (27–29). The incidence in pediatric population is low between 0.04 and 0.4% in pediatric intensive care units (30), whereas in adults, it is reported between 2 and 25% in patients after bone marrow transplantation, in about 10% of patients with autoimmune disease and in about 25% of patients with infection, sepsis, and shock. Also, end-stage renal disease may be a consistent risk factor (31–33).

PRES patients may show several neurological symptoms, commonly headache, impaired visual acuity, or visual field deficits, but confusion, focal neurological deficits, and disorders of consciousness with seizures may also occur. Clinical presentation has a great variability and course may depend on comorbidities and precipitating factors, but more than 90% of patients have typical clinical and neuroradiological features (34).

At the onset, neurological symptoms may be confusing and not specific with encephalopathy and seizures. Visual disturbance, hypertension, renal failure, and chemotherapy may be predicting factors for PRES (35) but diagnostic process may be challenging. Prognosis is generally favorable because in most patients both clinical symptoms and imaging lesions are reversible. On the other hand, long-term neurological impairments including epilepsy have been observed (16) and in-hospital death may involve one out of three patients with hemorrhagic PRES (36, 37).

PRES is usually monophasic and reversible (38) but recurrence has been reported (39).

RCVS

Clinical setting of RCVS is quite different from PRES (**Table 1**). Conditions associated with RCVS are commonly pregnancy, even without eclampsia, neurosurgical procedure, and vasoactive drug use; RCVS typically involves women between the ages of 20 and 50. Clinical course is generally self-limiting but recurrences and complications till death may occur (23, 40). Unusual, recent, severe headaches of progressive or sudden onset, associated or not with focal neurological deficits and seizures, may be initial clinical scenario. Thunderclap headache is one of the chief clinical presentations defined as "any severe headache peaking within 1 min, and 'non-thunderclap' headache any headache with a mild to severe intensity, peaking in more than 1 min" (24, 41). RCVS usually has a self-limiting course; resolution of symptoms happens by 3 weeks and resolution of vasoconstriction should occur by 3 months. A more rapidly progressive course of RCVS may lead to permanent disability or even in-hospital death in 5–10% of patients. Some factors such as glucocorticoid therapy, intra-arterial vasodilator therapy, and infarction on baseline imaging may be associated with poor outcome (42).

ROLE OF NEUROIMAGING IN DIAGNOSIS

PRES and RCVS share some clinical and pathophysiological features and neuroimaging are mandatory in differentiating these syndromes. PRES at the onset is heterogeneous because of lesions distribution and features that occasionally resemble some RCVS features, suggesting an overlapping or a common pathway in their pathophysiological mechanisms (17, 43). On the other hand, radiological features, taken together with clinical context and symptoms may help in differential diagnosis. Conversely, RCVS patients, even if they show peculiar neuroradiological features such as hemorrhage and vasoconstriction pattern, may show features commonly observed in PRES (**Table 1**) such as vasogenic edema (23).

TABLE 1 | Clinical and radiological features in PRES and RCVS patients.

	PRES	RCVS
CLINICAL FEATURES		
Associated clinical conditions	Immunosuppression, malignancy, pre-eclampsia, renal failure, dialysis, autoimmune disorders, infection, sepsis, hypertension, transplantation, chemotherapeutic medications, idiopathic	Pregnancy and puerperium, exposure to vasoactive drugs and blood products, head trauma, neurosurgical procedures, idiopathic
Headache	Moderate/severe	Thunderclap type
Seizures	Common	Uncommon
Encephalopathy	Common	Uncommon
Visual impairment	Common	Uncommon
Focal neurological deficits	Uncommon	Common in ischemic and hemorrhagic lesions
CSF analysis	Normal or near normal	Normal or near normal
RADIOLOGICAL FEATURES		
Useful MRI protocols	FLAIR, DWI, ADC, SWI, CE-MRA	FLAIR, DWI, ADC, SWI, CE-MRA
Usefulness of DSA	Rarely	Yes
Lesions distribution	Symmetric	Asymmetric
Edema distribution	*Common*: parieto-occipital pattern, holohemispheric watershed pattern, superior frontal sulcus pattern *Uncommon*: partial or asymmetric expression of above primary patterns	Uncommon: PRES-like
Ischemic lesion	Uncommon	Common
Hemorrhage lesion	*Common*: punctate type *Uncommon:* ICH, SAH	Common: SAH, ICH
Vasocostriction	Uncommon	Common: string-of-beads, distal vascular pruning
Contrast enhancement	Superficial leptomeningeal enhancement, gyral cortical enhancement	Uncommon

PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; SWI, susceptibility-weighted imaging; CE-MRA, contrast enhancement magnetic resonance angiography; DSA, digital subtraction angiography; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

PRES

In PRES, MRI shows a typical parieto-occipital pattern, but several patterns were described. Fluid-attenuated inversion recovery (FLAIR) sequences on MRI show almost symmetric hemispheric vasogenic edema involving subcortical white matter and overlying cortex, but other patterns were also found. Parietal–occipital regions may be involved in more than 90% of cases due to vascular cerebral dysregulation. Lesion distribution patterns include a holohemispheric watershed pattern, superior frontal sulcus pattern, a dominant parietal–occipital pattern, or partial or asymmetric expression of these primary patterns. These patterns may be useful to confirm the diagnosis, but notably type and severity of clinical presentation are associated neither with the pattern nor with the severity of brain edema (28).

Atypical presentations were reported in terms of regions involved (brainstem, spine, deep brain nuclei) or lesions type not related with vasogenic edema such as diffusion restriction, contrast enhancement, or hemorrhage (18, 44, 45).

MRI by FLAIR, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) are useful in differentiating types of edema in PRES. Usually, the vasogenic nature of edema is a hallmark of PRES even if small areas of cytotoxic edema may occur. Iso-intense or hyperintense signal on DWI and hyperintense signal on ADC mapping are typical appearances of vasogenic edema whereas hyperintense signal on the DWI and hypointense signal in the ADC are a hallmark of cytotoxic edema (46). Regions of reduced diffusion usually are small, punctate, or patchy and are shown within confluent lesions of vasogenic edema (**Figure 1a**); extensive regions of reduced diffusion are rarely described (43). Vasogenic edema can generally be

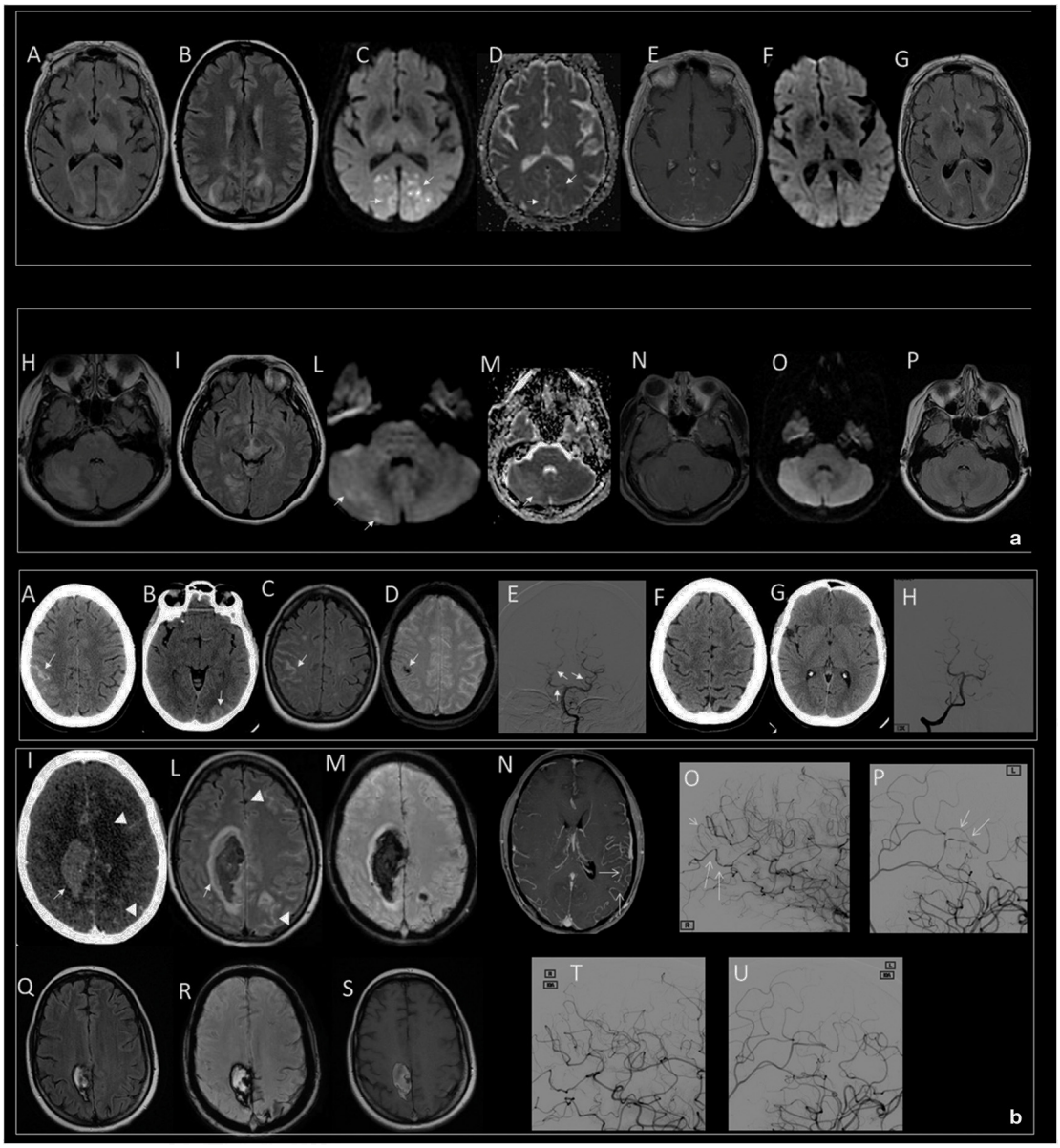


FIGURE 1 | (a) Typical dominant parietal–occipital pattern in a patient with PRES at the onset (A–E) and after 15 days (F,G). (A,B,G) FLAIR MR images; (C,F) DWI MR images; (D) ADC map; (E) T1 C+ MR image. Edema involves the parietal and occipital cortex and white matter (A,B); small, patchy, or punctate hyperintensity in DWI (white arrows in C) corresponding to hypointensity in ADC map (white arrows in D) characterize the cytotoxic edema within diffuse vasogenic edema; gyral or leptomeningeal enhancement is shown in occipital regions (E). Note resolution of the lesions 15 days after the onset (F,G). Atypical involvement of the brainstem associated to occipital pattern in a patient with PRES at the onset (H–N) and after 18 days (O,P). (H,I,P) FLAIR MR images; (L,O) DWI MR image; (M) ADC map; (N) T1 C+ MR image. Edema involves the right cerebellum, brainstem, and occipital cortex and white matter (H,I); iso-intensity with punctate foci of hyperintensity in DWI (white arrows in L) and hyperintense signal in ADC characterizes the vasogenic edema (white arrow in M), no enhancement is shown (N). Note resolution of the lesions 18 days after the onset (O,P). **(b)** Intracranial subarachnoid hemorrhage in a patient with RCVS at the onset (A–E) and after 2 months (F–H). Axial CT (A,B) shows hyperdense subarachnoid hemorrhage in the right frontal (white arrow in A) and left occipital lobes (white arrow in B); axial FLAIR MR (C) confirms subarachnoid hemorrhage as hyperintense sulci (white arrow in C); SWI MR images (D) show a component of subarachnoid hemorrhage as hypointense focus within a frontal sulcus (white arrow in D); catheter angiography of vertebro-basilar arteries demonstrate vessel irregularities with focal vasoconstriction (white arrow in E). Note resolution of SAH (F,G) and vessel irregularities (H) after 2 months. Intraparenchymal hematoma and subarachnoid hemorrhage in a patient with post-partum RCVS at the onset (I–P) and after 3 months (Q–U). Axial CT (I) shows hyperdense parenchymal hematoma in the right frontal lobe (white arrow in I) and subarachnoid hemorrhage in the left frontal lobe (white head of arrows in I); FLAIR MR (L) shows vasogenic edema marginally at the right parenchymal hematoma (white arrow in L) and left subarachnoid hemorrhage as hyperintense sulci (white head of arrows in L); SWI MR image (M) shows the hypointense signal of the parenchymal and subarachnoid hemorrhage due to acute phase of hemorrhage; contrast-enhanced MRA (CE-MRA) (N) images show vasoconstriction of some distal branches of middle cerebral arteries (with arrows in N); catheter angiography of internal carotids confirms diffuse irregularities with multifocal narrowings throughout the cerebral vasculature with a "string-of-beads" appearance (white arrows in O,P). Note reduction of ICH and SAH (Q–S) and disappearance of multifocal narrowings of distal branches of middle cerebral arteries after 3 months (T,U).

completely reversible but reduced ADC values are not a sign of irreversibility (46).

In PRES patients, on post-contrast T1WI MRI, a superficial leptomeningeal enhancement is the most common pattern but a nodular and, in about one-third of patients, a combined leptomeningeal (36, 44) and gyral cortical enhancement can be observed (47).

Several patterns of hemorrhage have been described, such as large hematomas with mass effect, subarachnoid hemorrhage (SAH) or multiple minute foci and microhemorrhages, but the most common is the punctate type (37, 47). Intracranial hemorrhage is encountered in PRES patients with an incidence of ∼15% (4). Some patients with PRES may show some RCVS-like features such as cerebral vasoconstriction (2).

RCVS

On MRI, bilateral symmetric parieto-occipital lesions, typical for PRES, are not characteristic for the RCVS. However, PRES-like reversible cerebral edema have been reported in 17–38% of patients with RCVS, suggesting common origins or mechanisms for both conditions (43, 47, 48).

The classical radiological presentation assessed by MRA or conventional angiography includes cerebral vasoconstriction, with at least two narrowings in the same artery, on two different cerebral arteries; commonly, arterial abnormalities disappear in <3 months (23). About one-third of patients develop brain hemorrhage or ischemic strokes, or reversible brain edema. SAH or intraparenchymal hemorrhage are common complications of RCVS (18, 37).

Hemorrhage is typically isolated SAH occasionally associated with superficial intracerebral hemorrhage (ICH) (**Figure 1b**). Rarely, isolated deep ICH may occur, making differential diagnosis difficult (48). Several factors have been associated with hemorrhage in RCVS such as migraine history and female gender, but despite the dramatic onset, over 90% of patients have excellent clinical outcome (42).

Catheter angiography is the gold standard for diagnosis, and MR angiography (MRA) and CT angiography (CTA) may disclose vessel irregularities with diffuse or focal vasoconstriction (**Figure 1b**), vasodilation, or a "string-of-beads" appearance; moreover, reversible distal vascular pruning may also be revealed (49).

Wall enhancement has been used in differential diagnosis between RCVS and vasculitis because it has been described as a marker of vasculitis but results of several studies are controversial and utility in differential diagnosis is debated (50, 51).

ROLE OF NEUROIMAGING IN UNDERSTANDING PATHOPHYSIOLOGY

Common features observed in PRES and RCVS make conceivable a shared pathophysiological pathway or common effects on the intracranial vascularization (12).

PRES

Systemic hypertension with tissue hyper-perfusion due to failed autoregulation was a popular theory (1, 52), even if an alternative theory of vasoconstriction, reduced perfusion, and ischemia may explain most of the lesions and edema localization in PRES (17, 20). The findings of post-contrast T1WI MRI, showing a superficial leptomeningeal enhancement in about one-third of patients (38), gyral cortical enhancement (49), and microhemorrhages detected by susceptibility-weighted imaging (SWI) seem to confirm the abovementioned mechanisms followed by the breakdown of the BBB.

RCVS

A possible pathophysiological role of BBB breakdown along with sympathetic overactivity and dysregulation of vascular tone was postulated (2, 3). A disturbance in cerebral vascular tone or in its control seems to be a critical element in RCVS. Vascular tone dysfunction may be spontaneous or caused by various exogenous or endogenous factors such as vasoactive drugs, tumors, endocrine factors, direct or neurosurgical trauma, and uncontrolled hypertension (2). Interestingly, Lee et al. confirmed BBB breakdown by contrast-enhanced fluid-attenuated inversion recovery (CE-FLAIR) on MRI performed within 7 days from clinical onset (53).

NEUROIMAGING AND TEMPORAL EVOLUTION

PRES

Time course of the lesions have not been prospectively evaluated and only few case series reported very early examinations (54). After acute phase, most PRES patients show a complete recovery and long-term prognosis is generally good but persistent neurological impairments and death may be noted in about 3–6% of patients (4). Fatalities may reach 30% of patients in hemorrhagic (18) or in malignant PRES (55). Neuroradiologic criteria for malignant PRES are edema with associated mass effect, brain hemorrhage exerting mass effect, effacement of basal cisterns, transtentorial, tonsillar, or uncal herniation (55).

RCVS

In RCVS, symptoms typically follow a self-limiting, monophasic course, with resolution by 3 weeks (56, 57) but resolution of vasoconstriction may take 3 months (2). Outcome for most patients is good; however, some patients have a delayed clinical worsening in the first few weeks often due to the development of extensive ischemic or hemorrhagic infarcts. Extensive hemorrhagic lesions need a closer attention due to a possible mass effect. A fulminant course of RCVS leading to permanent disability or death can been countered in 5–10% of patients (25). RCVS encountered in the postpartum period (58) warrants a particular care because it may have a fulminant course, with multifocal infarct or intracranial hemorrhage and extensive vasogenic edema (57, 59). Sequential examination by MRI and CT are warranted to catch initial worsening signs.

ROLE OF NEUROIMAGING IN PROGNOSIS

Prognosis is commonly good for both syndromes, but some patients may show neurological sequalae or even death (16,

57); then, neurological worsening could not indicate an alternative diagnosis. Often, in these cases, central nervous system vasculitis has been taken into account in the differential diagnostic pathway, adding further unnecessary and invasive tests or therapies (2) such as potent chemotherapeutic agents with potentially serious adverse effects (56). A previous study reported a post-angiogram worsening in RCVS (23) but a similar proportion of cases of clinical worsening within 24 h after MRA or CTA was reported (57), indicating a natural course of disease rather than a side effect of catheter angiography.

PRES

Reversibility of the lesions is a hallmark of PRES, but occasionally a mismatch between radiological reversibility and good prognosis may be noted. Most patients have a reversion of imaging abnormalities, but permanent tissue damages were also observed (16); on the other hand, some patients show radiological reversibility, but poor outcome (5), mainly due to comorbidities and complications (60). In PRES, acute hypertension is a common observation, but it is not related with either poor prognosis (54) or hemorrhage rate or type (16, 18). Unfavorable outcome is often associated with chemotherapy and sepsis, but notably, these patients have serious underlying medical conditions (16, 54).

In patients with PRES brainstem involvement, an early evidence of hemorrhage and other MR patterns as massive edema were associated with poor prognosis (54).

High DWI signal intensity and low or normal ADC mapping values are associated with cerebral infarction (54). Consequently, DWI and ADC mapping may help in predicting conversion to infarction and then tissue damage (61).

The association between contrast-enhancement (CE) pattern and prognosis in PRES is still debated (44), but recent studies reported a link among poor outcome, hemorrhage, and cytotoxic edema (54, 62). Contrast enhancement shows the breakdown or an augmented permeability of the BBB (63), but being a temporal phenomenon, it could be transitory, suggesting different stages in the integrity of the BBB (44).

RCVS

About 25% of RCVS patients develop complications, including cortical subarachnoid hemorrhage (cSAH), convulsions, and ischemic events (25) secondary to arterial vasoconstriction and cerebral edema (64). In a recent review about fatal causes of RCVS, a good prognosis was found in 78–90% of patients with RCVS, but a mortality rate of 1–5% mainly occurred in postpartum and pregnancy. Fatal course was linked also to initial focal signs on neurological examination, rapid clinical decline, or initial abnormal imaging suggestive of stroke (64).

RCVS ASSOCIATED WITH PRES

These two clinical conditions were reported in same patients (6–10) and some revisions were reported in about 10% of RCVS patients' symmetrical high-intensity lesions in posterior zones of the brain as observed in PRES patients (56, 64). These observations make conceivable a common origin or a common pathophysiological pathway but due to the lack of prospective studies, neither overlapping syndrome nor a temporal phenomenon could be ruled out (13, 65). It is probable that BBB breakdown is a dynamic process or a continuum in which either microvascular damage due to endothelium dysfunction or vascular autoregulation or both may trigger the process dependent on the patient's risk factors (toxic or pressure's changes); this cascade of events may lead to either PRES or RCVS or both.

POSSIBLE DEVELOPMENTS IN NEUROIMAGING

Possible research fields in which neuroimaging may develop could involve understanding of the pathophysiology and forecasting prognosis. In particular, the role of BBB and vascular autoregulation should be investigated. Recent researches investigated a possible role of BBB breakdown in RCVS (53). Serial MRIs in the first hours after symptoms onset may give new insight into understanding the pathophysiology of both syndromes. Moreover, early neuroradiological heraldic signs suggestive of malignant PRES or extensive ICH in RCVS are lacking. New research are mandatory in discovering these early signs that could have a significant impact in patient management. Early discovery of patients at highest risk for deterioration may be helpful to assess an appropriate triage and a consequent level of care and monitoring (57), particularly in high-risk patients such as postpartum RCVS with intracranial hemorrhage (66).

CONCLUSION

Pathophysiological mechanisms of PRES and RCVS are still unknown. Whether PRES and RCVS are independent syndromes and sometimes overlapped or part of a continuum process, these theories are still debated. However, some common characteristics make conceivable a common origin somehow linked with cerebral autoregulation, endothelial dysfunction, and BBB breakdown.

The developing and spreading of MRI and prospective neuroradiological studies at a very early time from clinical onset, linked with increased clinical awareness, may help in the diagnosis, thus enhancing recognition and avoiding unnecessary or dangerous treatments. Moreover, neuroimaging may give new insights into understanding etiologies and discovering pathophysiologic processes and, in more severe cases, it may help in personalizing treatment and thus improving outcome.

AUTHOR CONTRIBUTIONS

FP wrote the majority of the manuscript. RC wrote portions of the manuscript and supplied case material and research on the topic. MD provided feedback in the manuscript preparation and research on the topic.

REFERENCES

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* (1996) 334:494–500. doi: 10.1056/NEJM199602223340803
2. Ducros A. Reversible cerebral vasoconstriction syndrome. *Lancet Neurol.* (2012) 11:906–17. doi: 10.1016/S1474-4422(12)70135-7
3. Miller TR, Shivashankar R, Mossa-Basha M, Gandhi D. Reversible cerebral vasoconstriction syndrome, part 1: epidemiology, pathogenesis, and clinical course. *AJNR Am J Neuroradiol.* (2015) 36:1392–9. doi: 10.3174/ajnr.A4214
4. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol.* (2015) 14:914–25. doi: 10.1016/s1474-4422(15)00111-8
5. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. *AJNR Am J Neuroradiol.* (2002) 23:1038–48.
6. Feil K, Forbrig R, Thaler FS, Conrad J, Heck S, Dorn F, Pfister H-W, et al. Reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome associated with intracranial hypotension. *Neurocrit Care.* (2017) 26:103–8. doi: 10.1007/s12028-016-0320-4
7. Saito K, Shimizu Y, Higuma M, Kubodera T, Wada Y. Posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome after rapid blood transfusion. *Intern Med.* (2019) 58:2225–30. doi: 10.2169/internalmedicine.1768-18
8. Cossu G, Daniel RT, Hottinger AF, Maduri R, Messerer M. Malignant PRES and RCVS after brain surgery in the early postpartum period. *Clin Neurol Neurosurg.* (2019) 185:105489. doi: 10.1016/j.clineuro.2019.105489
9. Pop A, Carbonnel M, Wang A, Josserand J, Auliac SC, Ayoubi J-M. Posterior reversible encephalopathy syndrome associated with reversible cerebral vasoconstriction syndrome in a patient presenting with postpartum eclampsia: a case report. *J Gynecol Obstet Hum Reprod.* (2019) 48:431–4. doi: 10.1016/j.jogoh.2019.03.019
10. Ban SP, Hwang G, Kim CH, Kwon O-K. Reversible cerebral vasoconstriction syndrome combined with posterior reversible encephalopathy syndrome after heart transplantation. *J Clin Neurosci.* (2017) 42:118–21. doi: 10.1016/j.jocn.2017.03.042
11. Nabavizadeh SA, Vossough A. Reversible cerebral vasoconstriction syndrome vs posterior reversible encephalopathy syndrome. *JAMA Neurol.* (2016) 73:606. doi: 10.1001/jamaneurol.2015.5104
12. Sorensen DM. Reversible cerebral vasoconstriction syndrome. *JAMA Neurol.* (2016) 73:232–3. doi: 10.1001/jamaneurol.2015.3472
13. Ducros A, Bousser M-G. Reversible cerebral vasoconstriction syndrome. *Pract Neurol.* (2009) 9:256–67. doi: 10.1136/jnnp.2009.187856
14. Strandgaard S, Paulson OB. Cerebral autoregulation. *Stroke.* (1984) 15:413–6. doi: 10.1161/01.str.15.3.413
15. Strandgaard S, Olesen J, Skinhøj E, Lassen N. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J.* (1973) 1:507–10.
16. Siebert E, Bohner G, Liebig T, Endres M, Liman T. Factors associated with fatal outcome in posterior reversible encephalopathy syndrome: a retrospective analysis of the Berlin PRES study. *J Neurol.* (2017) 264:237–42. doi: 10.1007/s00415-016-8328-4
17. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol.* (2008) 29:1043–9. doi: 10.3174/ajnr.A0929
18. Hefzy H, Bartynski W, Boardman J, Lacomis D. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. *AJNR Am J Neuroradiol.* (2009) 30:1371–9. doi: 10.3174/ajnr.A1588
19. Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. Posterior reversible encephalopathy syndrome–Insight into pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev.* (2015) 14:830–6. doi: 10.1016/j.autrev.2015.05.006
20. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol.* (2008) 29:1036–42. doi: 10.3174/ajnr.A0928
21. Chen Z, Shen G-Q, Lerner A, Gao B. Immune system activation in the pathogenesis of posterior reversible encephalopathy syndrome. *Brain Res Bull.* (2017) 131:93–9. doi: 10.1016/j.brainresbull.2017.03.012
22. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. *Med Hypoth.* (2014) 82:619–22. doi: 10.1016/j.mehy.2014.02.022
23. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser M-G. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain.* (2007) 130:3091–101. doi: 10.1093/brain/awm256
24. Ducros A, Wolff V. The typical thunderclap headache of reversible cerebral vasoconstriction syndrome and its various triggers. *Headache.* (2016) 56:657–73. doi: 10.1111/head.12797
25. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med.* (2007) 146:34–44. doi: 10.7326/0003-4819-146-1-200701020-00007
26. Antunes N, Small TN, George D, Boulad F, Lis E. Posterior leukoencephalopathy syndrome may not be reversible. *Pediatr Neurol.* (1999) 20:241–3. doi: 10.1016/s0887-8994(98)00148-9
27. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Arch Neurol.* (2008) 65:205–10. doi: 10.1001/archneurol.2007.46
28. Bartynski W, Boardman J. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol.* (2007) 28:1320–7. doi: 10.3174/ajnr.A0549
29. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc.* (2010) 85:427–32. doi: 10.4065/mcp.2009.0590
30. Thavamani A, Umapathi KK, Puliyel M, Super D, Allareddy V, Ghori A. Epidemiology, comorbidities, and outcomes of posterior reversible encephalopathy syndrome in children in the United States. *Pediatr Neurol.* (2019) 103:21–6. doi: 10.1016/j.pediatrneurol.2019.07.007. [Epub ahead of print].
31. Reece DE, Frei-Lahr DA, Shepherd JD, Dorovini-Zis K, Gascoyne RD, Graeb DA, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. *Bone Marrow Transplant.* (1991) 8:393–401.
32. Bartynski WS, Boardman JF, Zeigler ZR, Shadduck RK, Lister J. Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. *AJNR Am J Neuroradiol.* (2006) 27:2179–90.
33. Bartynski WS, Zeigler ZR, Shadduck RK, Lister J. Variable incidence of cyclosporine and FK-506 neurotoxicity in hematopoeitic malignancies and marrow conditions after allogeneic bone marrow transplantation. *Neurocrit Care.* (2005) 3:33–45. doi: 10.1385/NCC:3:1:033
34. Gao B, Lyu C, Lerner A, McKinney AM. Controversy of posterior reversible encephalopathy syndrome: what have we learnt in the last 20 years? *J Neurol Neurosurg Psychiatry.* (2018) 89:14–20. doi: 10.1136/jnnp-2017-316225
35. Faille LD, Fieuws S, Van Paesschen W. Clinical predictors and differential diagnosis of posterior reversible encephalopathy syndrome. *Acta Neurol Belg.* (2017) 117:469–75. doi: 10.1007/s13760-017-0750-6
36. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol.* (2017) 264:1608–16. doi: 10.1007/s00415-016-8377-8
37. Sharma A, Whitesell RT, Moran KJ. Imaging pattern of intracranial hemorrhage in the setting of posterior reversible encephalopathy syndrome. *Neuroradiology*. (2010) 52:855–63. doi: 10.1007/s00234-009-0632-6
38. Jacquot C, Glastonbury CM, Tihan T. Is posterior reversible encephalopathy syndrome really reversible? Autopsy findings 4.5 years after radiographic resolution. *NP.* (2015) 34:26–33. doi: 10.5414/NP300771
39. Sweany JM, Bartynski WS, Boardman JF. "Recurrent" posterior reversible encephalopathy syndrome: report of 3 cases–PRES can strike twice! *J Comput Assist Tomogr.* (2007) 31:148–56. doi: 10.1097/01.rct.0000233127.21303.b9
40. Skiba V, Etienne M, Miller JA. Development of chronic epilepsy after recurrent episodes of posterior reversible encephalopathy syndrome associated with periodic lateralized epileptiform discharges. *Seizure.* (2010) 20:93–5. doi: 10.1016/j.seizure.2010.10.005
41. Wolff V, Ducros A. Reversible cerebral vasoconstriction syndrome without typical thunderclap headache. *Headache.* (2016) 56:674–87. doi: 10.1111/head.12794
42. Singhal AB, Topcuoglu MA. Glucocorticoid-associated worsening in reversible cerebral vasoconstriction syndrome. *Neurology.* (2017) 88:228–36. doi: 10.1212/WNL.0000000000003510

43. Brady E, Parikh NS, Navi BB, Gupta A, Schweitzer AD. The imaging spectrum of posterior reversible encephalopathy syndrome: a pictorial review. *Clin Imag.* (2018) 47:80–9. doi: 10.1016/j.clinimag.2017.08.008
44. Karia SJ, Rykken JB, McKinney ZJ, Zhang L, A.M.M Utility and significance of gadolinium-based contrast enhancement in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol.* (2016) 37:415–22. doi: 10.3174/ajnr.A4563
45. Singh RR, Ozyilmaz N, Waller S, U-King-Im J-M, Lim M, Siddiqui A, et al. A study on clinical and radiological features and outcome in patients with posterior reversible encephalopathy syndrome (PRES). *Eur J Pediatr.* (2014) 173:1225–31. doi: 10.1007/s00431-014-2301-y
46. Wagih A, Mohsen L, Rayan MM, Hasan MM, Ashraf HA-S. Posterior reversible encephalopathy syndrome (PRES): restricted diffusion does not necessarily mean irreversibility. *Pol J Radiol.* (2015) 80:210–6. doi: 10.12659/pjr.893460
47. Ollivier M, Bertrand A, Clarençon F, Gerber S, Deltour S, Domont F, et al. Neuroimaging features in posterior reversible encephalopathy syndrome: a pictorial review. *J Neurol Sci.* (2017) 373:188–200. doi: 10.1016/j.jns.2016.12.007
48. Ducros A, Fiedler U, Porcher R, Boukobza M, Stapf C, Bousser M-G. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. *Stroke.* (2010) 41:2505–11. doi: 10.1161/STROKEAHA.109.572313
49. Stevens C, Heran M. The many faces of posterior reversible encephalopathy syndrome. *Br J Radiol.* (2012) 85:1566–75. doi: 10.1259/bjr/25273221
50. Obusez EC, Hui F, Hajj-Ali RA, Cerejo R, Calabrese LH, Hammad T, et al. High-resolution MRI vessel wall imaging: spatial and temporal patterns of reversible cerebral vasoconstriction syndrome and central nervous system vasculitis. *AJNR Am J Neuroradiol.* (2014) 35:1527–32. doi: 10.3174/ajnr.A3909
51. Chen C-Y, Chen S-P, Fuh J-L, Lirng J-F, Chang F-C, Wang Y-F, et al. Vascular wall imaging in reversible cerebral vasoconstriction syndrome - a 3-T contrast-enhanced MRI study. *J Headache Pain.* (2018) 19:74. doi: 10.1186/s10194-018-0906-7
52. Lee S, Dinesh S, Thomas J. Hypertension-induced reversible posterior leukoencephalopathy syndrome causing obstructive hydrocephalus. *J Clin Neurosci.* (2008) 15:457–9. doi: 10.1016/j.jocn.2006.12.019
53. Lee MJ, Cha J, Choi HA, Woo S-Y, Kim S, Wang S-J, et al. Blood-brain barrier breakdown in reversible cerebral vasoconstriction syndrome: Implications for pathophysiology and diagnosis. *Ann Neurol.* (2017) 81:454–66. doi: 10.1002/ana.24891
54. Pilato F, Calandrelli R, Distefano M, Panfili M, Della Marca G, Colosimo C. Acute radiological pattern and outcome in posterior reversible encephalopathy syndrome patients. *Clin Neurol Neurosurg.* (2019) 185:105459. doi: 10.1016/j.clineuro.2019.105459
55. Akins PT, Axelrod Y, Silverthorn JW, Guppy K, Banerjee A, Hawk MW. Management and outcomes of malignant posterior reversible encephalopathy syndrome. *Clin Neurol Neurosurg.* (2014) 125:52–7. doi: 10.1016/j.clineuro.2014.06.034
56. Singhal AB, Topcuoglu MA, Fok JW, Kursun O, Nogueira RG, Frosch MP, et al. Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. *Ann Neurol.* (2016) 79:882–94. doi: 10.1002/ana.24652
57. Katz BS, Fugate JE, Ameriso SF, Pujol-Lereis VA, Mandrekar J, Flemming KD, et al. Clinical worsening in reversible cerebral vasoconstriction syndrome. *JAMA Neurol.* (2014) 71:68–73. doi: 10.1001/jamaneurol.2013.4639
58. Call GK, Fleming MC, Sealfon S, Levine H, Kistler JP, Fisher CM. Reversible cerebral segmental vasoconstriction. *Stroke.* (1988) 19:1159–70. doi: 10.1161/01.str.19.9.1159
59. Fugate JE, Wijdicks EFM, Parisi JE, Kallmes DF, Cloft HJ, Flemming KD, et al. Fulminant postpartum cerebral vasoconstriction syndrome. *Arch Neurol.* (2012) 69:111–7. doi: 10.1001/archneurol.2011.811
60. Kastrup O, Gerwig M, Frings M, Diener H-C. Posterior reversible encephalopathy syndrome (PRES): electroencephalographic findings and seizure patterns. *J Neurol.* (2012) 259:1383–9. doi: 10.1007/s00415-011-6362-9
61. Ay H, Buonanno FS, Schaefer PW, Le DA, Wang B, Gonzalez RG, et al. Posterior leukoencephalopathy without severe hypertension: utility of diffusion-weighted MRI. *Neurology.* (1998) 51:1369–76. doi: 10.1212/wnl.51.5.1369
62. Chen Z, Zhang G, Lerner A, Wang A-H, Gao B, Liu J. Risk factors for poor outcome in posterior reversible encephalopathy syndrome: systematic review and meta-analysis. *Quant Imaging Med Surg.* (2018) 8:421–32. doi: 10.21037/qims.2018.05.07
63. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. *Radiographics.* (2007) 27:525–51. doi: 10.1148/rg.272065155
64. Valencia-Mendoza M, Ramírez-Rodríguez N, Vargas-Avila N, Peña-Ortiz A, Corzo-Villamizar M, Serna-Ramírez L, et al. Fatal reversible cerebral vasoconstriction syndrome: A systematic review of case series and case reports. *J Clin Neurosci.* (2019) 70:183–8. doi: 10.1016/j.jocn.2019.08.014
65. Singhal AB, Bernstein RA. Postpartum angiopathy and other cerebral vasoconstriction syndromes. *Neurocrit Care.* (2005) 3:91–7. doi: 10.1385/NCC:3:1:091
66. Ursell MR, Marras CL, Farb R, Rowed DW, Black SE, Perry JR. Recurrent intracranial hemorrhage due to postpartum cerebral angiopathy: implications for management. *Stroke.* (1998) 29:1995–8. doi: 10.1161/01.str.29.9.1995

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 11 March 2020
doi: 10.3389/fneur.2020.00165

Advanced Imaging Techniques in Diagnosis of Posterior Reversible Encephalopathy Syndrome (PRES)

Nasim Sheikh-Bahaei, Jay Acharya, Anandh Rajamohan and Paul E. Kim*

Division of Neuroradiology, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

Diagnosis of Posterior Reversible Encephalopathy Syndrome (PRES) in some circumstances can be challenging and structural imaging may not be sufficient to distinguish it from other differential diagnostic considerations. Advanced imaging techniques, such as MR spectroscopy or positron emission tomography (PET) can provide additional information to determine the diagnosis. Other techniques, such as susceptibility weighted imaging (SWI) improves detection of hemorrhage which has prognostic role. CT or MR Perfusion as well as Single-Photon Emission Computed Tomography (SPECT) are more useful to understand the underlying vasculopathic changes in PRES and may answer some of the unresolved controversies in pathophysiology of this complex disease. In this review we summarized the findings of previous studies using these advanced methods and their utilities in diagnosis or prognosis of PRES.

Keywords: MR spectroscopy (MRS), CT perfusion (CTP), positron emission tomography (PET), posterior reversible encephalopathy syndrome (PRES), MR perfusion, susceptibility weight imaging

OPEN ACCESS

Edited by:
Max Wintermark,
Stanford University, United States

Reviewed by:
Ajay Gupta,
Cornell University, United States
Heng Liu,
Affiliated Hospital of Zunyi Medical College, China

****Correspondence:***
Nasim Sheikh-Bahaei
nasim.sheikh-bahaei@med.usc.edu

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *08 August 2019*
Accepted: *21 February 2020*
Published: *11 March 2020*

Citation:
Sheikh-Bahaei N, Acharya J, Rajamohan A and Kim PE (2020) Advanced Imaging Techniques in Diagnosis of Posterior Reversible Encephalopathy Syndrome (PRES). Front. Neurol. 11:165. doi: 10.3389/fneur.2020.00165

INTRODUCTION

Despite all the new developments in the field of neuroimaging, diagnosis of PRES in atypical cases remains challenging. Utilizing advanced imaging techniques can help clinicians to exclude the mimics and provide a more accurate diagnosis at the earlier stage. Some of these methods can also provide insight into the complex pathophysiology of the disease. In this article we discuss the role and findings of these advanced imaging techniques in diagnosis of PRES.

MR SPECTROSCOPY

MR spectroscopy (MRS) provides valuable information about the brain chemicals and metabolites, neuronal and glial cells activity, cell membrane integrity and composition of the cells in the region of interest. This data can be used to differentiate PRES from other diagnoses (1), predict outcome (2), or potentially enhance our understanding about the pathophysiology of the disease (3). There is lack of large comprehensive studies on MRS changes in PRES and the current data are mainly from case reports.

The main findings in most of the cases are reduction in the ratio of N-Acetylaspartate (NAA)/Creatine (Cr) (**Figure 1**) and NAA/Choline (Chol) (1–6). It has been claimed that this reduction is more due to increased Chol and Cr levels rather than a mild reduction in NAA. These alterations in the level of metabolites were seen beyond the boundary of T2/FLAIR signal changes

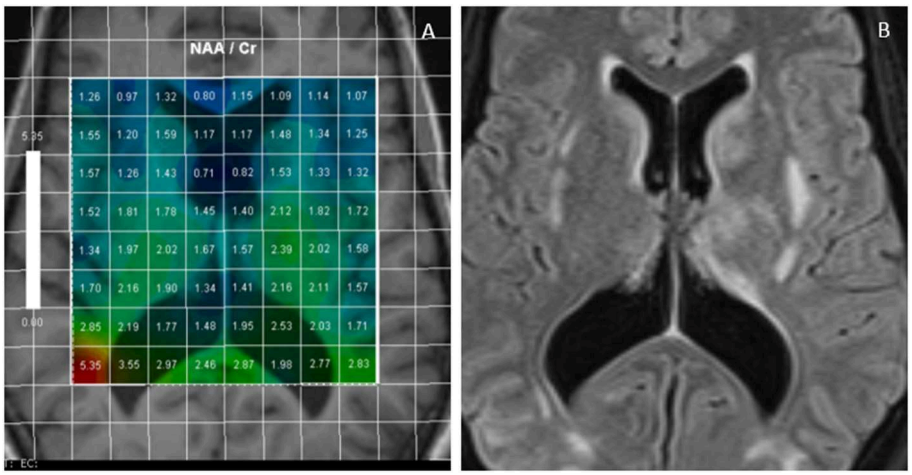


FIGURE 1 | Multivoxel MR Spectroscopy in a PRES case shows reduced NAA/Cr in many regions such as periventricular white matter and around basal ganglia **(A)**; FLAIR images of the same case demonstrates foci of white matter hyperintensities **(B)**.

and both in white and gray matters indicating the diffuse process in PRES (3). More interestingly, in some studies the level of NAA remained low and Chol high in the subacute phase of the disease (from 2 weeks to 2 months) despite normalization of the structural MRI and resolution of the clinical symptoms (1, 2, 4).

NAA is an amino acid that is mainly synthesized in the mitochondria of the neurons, axons, and dendrites. It is considered a marker of neuroaxonal viability, function, and density. Its reduction in PRES is more likely secondary to disruption of the synapses and neuroaxonal function rather than permanent loss of neurons or cell death as the changes are usually reversible with no evidence of atrophy at the later stage. Presence of vasogenic edema could also contribute to the mild reduction of NAA through dilution effect (3) with reduction of the density of neurons in each MRS voxel.

Chol is a marker of cell membrane turnover, inflammation, glial cell activation and demyelination. In PRES, increased in Chol peak is considered to be related to glial cell activation and also membrane synthesis in the subacute phase of the disease (1, 3).

There are contradictory results about the level of lactate (Lac) in PRES between different studies, as some detected increased peak of lac (2, 4) while others did not (1, 3). Know et al. presented four pediatrics cases with PRES and showed no changes in the level of NAA, Chol and Cr, but increased in Lac. Nearly all of them had complete remission in the follow up MRS exams (7). In adults and based on limited data, the peak of Lac is considered as a marker of tissue infarction rather than changes directly related to PRES (2).

Initial changes in the level of NAA, Chol, and Cr or even persistent changes in the subacute phase of PRES does not predict poor outcome but can be used to differentiate PRES from other mimicking pathologies, such as infarct, demyelination, encephalitis or tumor (8). Presence of Lac is in favor of infarct or other pathologies and could indicate permanent tissue damage. Increased ratio Chol/Cr is more favorable for tumor compared to PRES in which both Chol and Cr levels increase. Metabolic changes in demyelinating processes are usually restricted to white matter unlike PRES which are present in both gray and white matter (3).

SUSCEPTIBILITY WEIGHTED IMAGING (SWI)

Hemorrhage is identified in 15–17% of PRES cases in large cohorts using Gradient echo (GRE), FLAIR or CT (9). However, recent studies have reported higher prevalence of hemorrhage (26–64%) in PRES using SWI (10, 11). There are three main types of hemorrhage in PRES: cerebral microbleeds (CMB, <5 mm), intraparenchymal hematoma (IPH, >5 mm) and subarachnoid hemorrhage (SAH) with or without intraventricular extension. CMB has become the most common type of hemorrhage identified in recent PRES studies due to superiority of SWI in detecting CMB. This may also explain the higher prevalence of total hemorrhage in the recent data (9, 10). CMB can hardly be seen in other sequences, such as FLAIR, T1, and T2. Moreover, there are several reports confirming the advantage of SWI compared to GRE or T2* sequences in identifying CMB or small hemorrhages (12, 13).

Many studies have claimed that evidence of hemorrhage in imaging is associated with poor prognosis or fatal outcome (9, 11), while others did not show the same association (10). Hemorrhage is also associated with more severe T2/FLAIR signal changes and presence of cytotoxic edema and restriction in diffusion-weighted images (DWI) (14). Although the direct effect of CMB on prognosis of PRES is not completely understood, follow up studies (between 4 and 320 days) have shown that CMBs secondary to PRES remained unchanged even after normalization of the FLAIR signal (10), which could have long term implications.

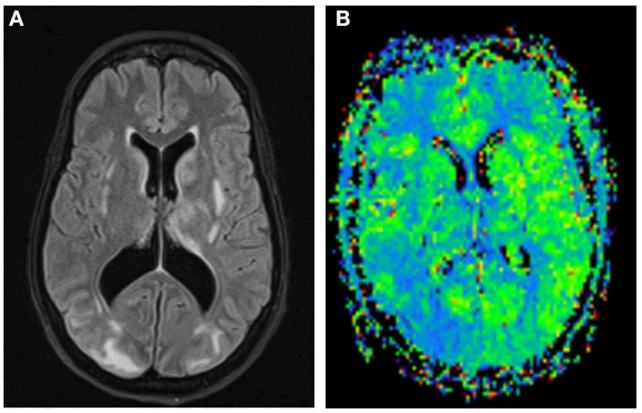


FIGURE 2 | FLAIR images of a PRES case with white matter hyperintensities more prominent in the right occipital lobe **(A)**; MR Perfusion shows reduction in MTT in the right occipital lobe suggestive of hyperperfusion **(B)**.

Moreover, there are reports of PRES development secondary to cerebral amyloid angiopathy inflammation (CAA-I) (15). Presence of multiple CMBs on SWI, particularly if they were present prior to the latest onset of PRES, can suggest CAA-I as the cause of attack.

Susceptibility weighted angiography (SWAN) has also been used in PRES showing transient reduction in the susceptibility of the venous system at the initial phase of PRES, associated with hyperperfusion which was normalized by day 40 (16).

Based on current data, performing SWI will provide additional valuable information, which can be used to predict the outcome of PRES. However, longitudinal data are required to investigate the effects of CMB secondary to PRES in long term prognosis and their potential predisposition to other neurological disorders, such as hemorrhagic stroke or Alzheimer's disease in the future.

CT AND MR PERFUSION

The results of CT perfusion studies in PRES are contradictory. Some studies have found hyperperfusion with increased cerebral blood flow (CBF), cerebral blood volume (CBV) and reduction in time to peak (TTP) and mean transit time (MTT) (17–19) (**Figure 2**). Other studies showed opposite results with vasoconstriction, reduction in CBF, near normal CBV, and increased in TTP, MTT, and time to drain (TTD) (20–22).

The reports on MR perfusion follow the same pattern with conflicting results across different studies. Although many authors reported decreased CBF, CBV, and increased MTT (23–25), there are few reports of increased perfusion in PRES cases (26–28).

There are two main theories regarding the development of vasculopathy and vasogenic edema in PRES:

(1) Severe hypertension exceeds the limit of autoregulation in vessels, leading to hyperperfusion, vascular dilatation, endothelial damage, leakage, and vasogenic edema.

(2) The earlier original theory which was based on vasospasm and hypoperfusion as a compensatory mechanism against hypertension resulting in brain ischemia and consequently vasogenic edema (29).

Collective data in recent years however, might be more suggestive of a combination pathway with vasoconstriction and vasodilatation changes both present at the same time or sequential in the course of the disease. When the systemic blood pressure rises, the neurovasculature system attempts to maintain a constant flow by autoregulation, and arterioles constrict to create compensatory resistance and avoid hyperperfusion (30, 31). It has been shown in animal models that when the blood pressure exceeds the upper limit of autoregulation, the constricted arterioles forced to dilate and there is blood brain barrier disruption and extravasation of the fluid and red blood cells into the parenchyma (32). In addition, there is evidence of endothelial injury in the small vessels leading to endothelial thickening, occlusion of the small vessels, microbleeds, and hypoperfusion.

Although the abovementioned mechanisms can explain the underlying pathophysiology of vasculopathy in hypertension induced PRES, they cannot be generalized to all PRES cases as many of them present with normal or near normal blood pressure. A growing body of evidence suggests in clinical conditions presenting with PRES, there are similar systemic processes contributing to vasculopathy including activation of immune system, increased in cytokines and interleukins, endothelial damage with increased permeability, increased leukocyte adherence, and consequently microcirculatory dysfunction, focal vasoconstriction and vasodilatation and beading of the vessels and consequently tissue damage (21, 29).

The conflicting results in perfusion studies more likely reflect the complex pathophysiology of PRES and dynamic vascular changes during the course of the disease. The initial cause of PRES might also play a role. The time of imaging in relation to the onset of symptoms and also the start of antihypertensive therapy and intensity of treatment could significantly affect the result of perfusion studies. In a report by Casey et al., they found transient hypoperfusion in a PRES case treated aggressively with antihypertensive drugs. The hypo-perfused regions returned to normal after reducing the intensity of treatment and keeping the blood pressure above a certain level (30).

Although perfusion studies may not help the diagnosis or prognosis of PRES in day to day clinical practice, they can be used for better understanding of the pathophysiology of this complex and heterogeneous condition. Further larger studies with standard techniques on more homogenous cohort are required in acute, subacute and later phases of PRES to advance our knowledge about the patterns of vasculopathy and changes of perfusion in PRES.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET)

The most common type of SPECT used in PRES is Technetium-99 m-hexamethylpropyleneamineoxime (99 mTc-HMPAO). The

TABLE 1 | Summary of imaging features using different advanced imaging techniques in PRES.

Imaging techniques	Findings
MRS	- Reduction in NAA/Cr and NAA/Chol. - Lac may or may not be present. Presence of Lac might represent infarcted tissue. - Metabolite changes are not limited to only white matter and can be even detected in regions with normal T2/FLAIR signal.
SWI	- Improves the rate of hemorrhage detection. - Pre-existing microbleeds in CAA can be a risk factor for future PRES. - Microbleeds secondary to PRES are persistent even after normalization of the FALIR signal.
Perfusion	Both - Hyperperfusion (increased CBF and CBV with reduced TTP and MTT). - Hypoperfusion (reduced CBF and CBV with increased MTT) have been reported. - The cause of PRES and administration of antihypertensive medication can influence the result of perfusion study.
PET/SPECT	- Low FDG and Met uptake in most PRES cases. - Results of HMPAO-SPECT is similar to CT/MR perfusion (both hypo- and hyperperfusion state have been reported.)

CAA, cerebral amyloid angiopathy; CBF, cerebral blood flow; CBV, cerebral blood volume; Chol, choline; Cr, creatine; HMPAO, hexamethylpropyleneamineoxime; Lac, lactate; Met, methionine; MRS, MR spectroscopy; MTT, mean transit time; NAA, N-Acetylaspartate; PET, Positron Emission Tomography; SPECT, Single-Photon Emission Computed Tomography; SWI, Susceptibility Weighed imaging; TTP, time to peak.

results of SPECT in PRES are very similar to CT and MR perfusions with conflicting reports of hypo or hyperperfusion. Some studies found hypoperfusion in watershed areas and in regions of vasogenic edema on MRI (33, 34), while other reported hyperperfusion in T2 FLAIR hyperintense regions (26–28). There are also reports of using single-photon emission CT with N-isopropyl-(123)I-p-iodoamphetamine (IMP-SPECT) during recovery stages of PRES, showing normal uptake in most cases when MRI became normal (35, 36). Although hypoperfusion in IMP-SPECT at early follow up (11 days) (34) or focal hyperperfusion in a case with persistent MRI changes after 30 days (36) were also reported. (133)Xe-SPECT has also been used to assess perfusion in PRES and showed low uptake in areas of vasogenic edema (36).

Data is limited on the utility of PET in PRES. In most of studies, the whole body PET was performed for diagnosis of the underlying cancer or to detect metastases.

The first report of using (18 F) fluorodeoxyglucose (FDG)-PET in PRES was on a young boy with systemic lupus erythematosus. They found hypometabolism in occipital-parietal region where T2 hyperintensity and hemorrhage were present (37). Rath et al. used FDG and (11 C) methionine (MET)-PET to differentiate atypical unilateral PRES from low-grade tumor, showed decreased uptake of FDG and minimal uptake of MET in the regions of MRI abnormality in PRES (38). Brain Gliomas on the other hand have high MET uptake due to increased metabolic rate and their uptake ratio is associated with the tumor viability (39). Although many studies have found hypometabolism in FDG, there is a report of increased FDG uptake in the regions of T2 FLAIR hyperintensities in a pediatric patient with Burkitt's lymphoma presented with PRES (40).

FDG-PET uptake usually has close association with the MRI changes, it becomes normal at the later stage of PRES when the FLAIR signal normalizes (41) but remains low with persistent MRI changes in more severe cases (42).

(11 C) Pittsburgh compound (PiB) and (18 F) FDG-PET were also used on a PRES case secondary to CAA-I. High amyloid uptake in PiB and focal hypometabolism in FDG was found in the regions of FLAIR/T2 hyperintensity (43).

Based on limited data available, utility of PET in PRES is mainly to distinguish it from tumor. Low FDG and MET uptake can differentiate the two that is particularly useful in cases with unilateral or marked asymmetric changes mimicking mass in the structural imaging.

DISCUSSION

When the clinical presentation of the PRES is unusual or there are atypical changes in the structural imaging, advanced imaging techniques can help in distinguishing PRES from mimics. **Table 1** summarizes the imaging features of PRES in different advanced imaging techniques.

- MRS can help differentiating PRES from low grade tumor, demyelination or other encephalitis.
- SWI is the best sequence to detect CMB and can significantly improve the rate of hemorrhage detection. The knowledge about load and number of persistent CMB after the onset of PRES would provide valuable information, which may have potential long-term implication.
- There are contradictory results about perfusion changes in PRES. These studies can be used for better understanding the disease pathophysiology rather than diagnosis of PRES. The conflicting results are most likely secondary to dynamic vascular changes during the course of the disease, complex pathophysiology with variations across different underlying causes, timing of the perfusion studies, and the use of antihypertensive treatments. To address these issues there is a need for larger cohort studies using more standard methods, alleviating some of the co-founding factors.
- MET and FDG PET can also be used to differentiate PRES from low grade glioma.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Lee SY, Kim SH, Lee SH, Baek HJ, Shon HS, Kim SS. Serial MR spectroscopy in relapsing reversible posterior leukoencephalopathy syndrome. *Neurologist*. (2009) 15:338–41. doi: 10.1097/NRL.0b013e3181914af6
2. Sengar AR, Gupta RK, Dhanuka AK, Roy R, Das K. MR imaging, MR angiography, and MR spectroscopy of the brain in eclampsia. *AJNR Am J Neuroradiol*. (1997) 18:1485–90.
3. Eichler FS, Wang P, Wityk RJ, Beauchamp NJ Jr, Barker PB. Diffuse metabolic abnormalities in reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol*. (2002) 23:833–7. Retrieved from: http://www.ajnr.org/content/23/5/833/tab-article-info
4. Ewertsen C, Kondziella D, Danielsen ER, Thomsen C. Good outcome after posterior reversible encephalopathy syndrome (PRES) despite elevated cerebral lactate: a case report. *Acta Radiol Open*. (2015) 4:2058460115578324. doi: 10.1177/2058460115578324
5. Yuan JL, Wang SK, Guo XJ, Ding LL, Gu H, Hu WL. Reduction of NAA/Cr ratio in a patient with reversible posterior leukoencephalopathy syndrome using MR spectroscopy. *Arch Med Sci Atheroscler Dis*. (2016). 1:98–100. doi: 10.5114/amsad.2016.62376
6. Ferreira TS, Reis F, Appenzeller S. Posterior reversible encephalopathy syndrome and association with systemic lupus erythematosus. *Lupus*. (2016) 25:1369–76. doi: 10.1177/0961203316643598
7. Kwon S, Koo J, Lee S. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Pediatr Neurol*. (2001) 24:361–4. doi: 10.1016/S0887-8994(01)00265-X
8. Tsutsumi M, Akimoto J, Nakajima N, Hashimoto R, Haraoka J. Two cases of posterior reversible encephalopathy syndrome resembling brainstem glioma. *Clin Neurol Neurosurg*. (2012) 114:1062–5. doi: 10.1016/j.clineuro.2012.02.027
9. Hefzy HM, Bartynski WS, Boardman JF, Lacomis D. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. *AJNR Am J Neuroradiol*. (2009) 30:1371–9. doi: 10.3174/ajnr.A1588
10. McKinney AM, Sarikaya B, Gustafson C, Truwit CL. Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging. *AJNR Am J Neuroradiol*. (2012) 33:896–903. doi: 10.3174/ajnr.A2886
11. Alhilali LM, Reynolds AR, Fakhran S. A multi-disciplinary model of risk factors for fatal outcome in posterior reversible encephalopathy syndrome. *J Neurol Sci*. (2014) 347:59–65. doi: 10.1016/j.jns.2014.09.019
12. Goos JD, van der Flier WM, Knol DL, Pouwels PJ, Scheltens P, Barkhof F, et al. Clinical relevance of improved microbleed detection by susceptibility-weighted magnetic resonance imaging. *Stroke*. (2011) 42:1894–900. doi: 10.1161/STROKEAHA.110.599837
13. Cheng AL, Batool S, McCreary CR, Lauzon ML, Frayne R, Goyal M, et al. Susceptibility-weighted imaging is more reliable than T2*-weighted gradient-recalled echo MRI for detecting microbleeds. *Stroke*. (2013) 44:2782–6. doi: 10.1161/STROKEAHA.113.002267
14. Hiremath SB, Anantrao Gautam A, Anil S, Thomas R, Benjamin G. Susceptibility-weighted angiography and diffusion-weighted imaging in posterior reversible encephalopathy syndrome–is there an association between hemorrhage, cytotoxic edema, blood pressure and imaging severity? *J Neuroradiol*. (2017) 44:319–25. doi: 10.1016/j.neurad.2017.05.002
15. Masrori P, Montagna M, De Smet E, Loos C. Posterior reversible encephalopathy syndrome caused by cerebral amyloid angiopathy-related inflammation. *Acta Neurol Belg*. (2019) 119:505–7. doi: 10.1007/s13760-019-01172-w
16. Ollivier M, Wanono E, Leclercq D, Domont F, Trunet S, Dormont D, et al. Transient reduction in venous susceptibility during posterior reversible encephalopathy syndrome. *J Neurol Sci*. (2015) 358:505–6. doi: 10.1016/j.jns.2015.09.359
17. Wartenberg KE, Parra A. CT and CT-perfusion findings of reversible leukoencephalopathy during triple-H therapy for symptomatic subarachnoid hemorrhage-related vasospasm. *J Neuroimaging*. (2006) 16:170–5. doi: 10.1111/j.1552-6569.2006.00031.x
18. Hedna VS, Stead LG, Bidari S, Patel A, Gottipati A, Favilla CG, et al., Posterior reversible encephalopathy syndrome (PRES) and CT perfusion changes. *Int J Emerg Med*. (2012) 5:12. doi: 10.1186/1865-1380-5-12
19. Oehm E, Hetzel A, Els T, Berlis A, Keck C, Will HG, et al. Cerebral hemodynamics and autoregulation in reversible posterior leukoencephalopathy syndrome caused by pre-/eclampsia. *Cerebrovasc Dis*. (2006) 22:204–8. doi: 10.1159/000093810
20. Vanacker P, Matias G, Hagmann P, Michel P. Cerebral hypoperfusion in posterior reversible encephalopathy syndrome is different from transient ischemic attack on CT perfusion. *J Neuroimaging*. (2015) 25:643–6. doi: 10.1111/jon.12158
21. Sarbu N, López-Rueda A, Chirife O, Capurro S. CT-perfusion time-maps likely disclose the earliest imaging signs of posterior reversible encephalopathy syndrome (PRES). *J Neuroradiol*. (2014) 41:147–9. doi: 10.1016/j.neurad.2013.08.003
22. Sanelli PC, Jacobs MA, Ougorets I, Mifsud MJ. Posterior reversible encephalopathy syndrome on computed tomography perfusion in a patient on "Triple H" therapy. *Neurocrit Care*. (2005) 3:46–50. doi: 10.1385/NCC:3:1:046
23. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol*. (2008) 29:447–55. doi: 10.3174/ajnr.A0839
24. Brubaker LM, Smith JK, Lee YZ, Lin W, Castillo M. Hemodynamic and permeability changes in posterior reversible encephalopathy syndrome measured by dynamic susceptibility perfusion-weighted MR imaging. *AJNR Am J Neuroradiol*. (2005) 26:825–30. Retrieved from: http://www.ajnr.org/content/26/4/825/tab-article-info
25. Engelter ST, Petrella JR, Alberts MJ, Provenzale JM. Assessment of cerebral microcirculation in a patient with hypertensive encephalopathy using MR perfusion imaging. *AJR Am J Roentgenol*. (1999) 173:1491–3. doi: 10.2214/ajr.173.6.10584788
26. Apollon KM, Robinson JN, Schwartz RB, Norwitz ER. Cortical blindness in severe preeclampsia: computed tomography, magnetic resonance imaging, and single-photon-emission computed tomography findings. *Obstet Gynecol*. (2000). 95:1017–9. doi: 10.1016/S0029-7844(00)00878-4
27. Schwartz RB, Jones KM, Kalina P, Bajakian RL, Mantello MT, Garada B, et al. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. *AJR Am J Roentgenol*. (1992) 159:379–83. doi: 10.2214/ajr.159.2.1632361
28. Schwartz RB. Hyperperfusion encephalopathies: hypertensive encephalopathy and related conditions. *Neurologist*. (2002) 8:22–34. doi: 10.1097/00127893-200201000-00003
29. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol*. (2008) 29:1043–9. doi: 10.3174/ajnr.A0929
30. Casey SO, McKinney A, Teksam M, Liu H, Truwit CL. CT perfusion imaging in the management of posterior reversible encephalopathy. *Neuroradiology*. (2004) 46:272–6. doi: 10.1007/s00234-003-1053-6
31. Auer L. The sausage-string phenomenon in acutely induced hypertension–arguments against the vasospasm theory in the pathogenesis of acute hypertensive encephalopathy. *Eur Neurol*. (1978) 17:166–73. doi: 10.1159/000114941
32. MacKenzie ET, Strandgaard S, Graham DI, Jones JV, Harper AM, Farrar JK. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood-brain barrier. *Circ Res*. (1976) 39:33–41. doi: 10.1161/01.RES.39.1.33
33. Naidu K, Moodley J, Corr P, Hoffmann M. Single photon emission and cerebral computerised tomographic scan and transcranial doppler sonographic findings in eclampsia. *Br J Obstet Gynaecol*. (1997) 104:1165–72. doi: 10.1111/j.1471-0528.1997.tb10941.x
34. Fujiwara Y, Higaki H, Yamada T, Nakata Y, Kato S, Yamamoto H, et al. Two cases of reversible posterior leukoencephalopathy syndrome, one with and the other without pre-eclampsia. *J Obstet Gynaecol Res*. (2005) 31:520–6. doi: 10.1111/j.1447-0756.2005.00345.x
35. Mima A, Matsubara T, Endo S, Murakami T, Hashimoto Y. Use of a polysulfone hemodialysis membrane may prevent recurrent posterior reversible encephalopathy syndrome in a patient undergoing hemodialysis. *Int Urol Nephrol*. (2014) 46:255–60. doi: 10.1007/s11255-013-0434-y
36. Tajima Y, Isonishi K, Kashiwaba T, Tashiro K. Two similar cases of encephalopathy, possibly a reversible posterior leukoencephalopathy syndrome: serial findings of magnetic resonance imaging, SPECT and angiography. *Intern Med*. (1999) 38:54–8. doi: 10.2169/internalmedicine.38.54

37. Pavlakis SG, Frank Y, Kalina P, Chandra M, Lu D. Occipital-parietal encephalopathy: a new name for an old syndrome. *Pediatr Neurol.* (1997) 16:145–8. doi: 10.1016/S0887-8994(96)00292-5
38. Rath JJ, Koppen H, Treurniet FE, Comans EF, Wirtz PW. Reversible posterior leucoencephalopathy syndrome mimicking low-grade glioma: differentiation by positron emission tomography. *Clin Neurol Neurosurg*. (2011) 113:785–7. doi: 10.1016/j.clineuro.2011.08.001
39. Kato T, Shinoda J, Oka N, Miwa K, Nakayama N, Yano H, et al., Analysis of 11C-methionine uptake in low-grade gliomas and correlation with proliferative activity. *AJNR Am J Neuroradiol.* (2008) 29:1867–71. doi: 10.3174/ajnr.A1242
40. Saad Aldin E, McNeely P, Menda Y. Posterior reversible encephalopathy syndrome on 18F-FDG PET/CT in a pediatric patient with Burkitt's lymphoma. *Clin Nucl Med*. (2018) 43:195–8. doi: 10.1097/RLU.0000000000001979
41. Meyer MA, Galloway G, Khan S. Transient blindness associated with reversible occipital white matter abnormalities: two patients studied by MR, CT, and 18F-FDG PET imaging. *J Neuroimaging*. (1998) 8:240–2. doi: 10.1111/jon199884240
42. Hyoung Seop Kim MD, Ja Young Choi MD, Mi Ri Seo MD. Posterior Reversible Encephalopathy Syndrome (PRES) in a chronic alcoholic patient after having steam bath: a case report. *Brain Neurorehabil.* (2014) 7:66–70. doi: 10.12786/bn.2014.7.1.66
43. Sengoku R, Matsushima S, Murakami Y, Fukuda T, Tokumaru AM, Hashimoto M, et al. ^{11}C-PiB PET imaging of encephalopathy associated with cerebral amyloid angiopathy. *Intern Med*. (2014) 53:1997–2000. doi: 10.2169/internalmedicine.53.1731

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 March 2020
doi: 10.3389/fneur.2020.00194

Clinical and MRI Features of Posterior Reversible Encephalopathy Syndrome With Atypical Regions: A Descriptive Study With a Large Sample Size

Kunhua Li[1], *Yang Yang*[2], *Dajing Guo*[1], *Dong Sun*[1] *and Chuanming Li*[1]*

[1] *Department of Radiology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China,* [2] *Department of Radiology, Chongqing Prevention and Treatment Center for Occupational Diseases, Chongqing, China*

Background: Accurate diagnosis and timely treatment for posterior reversible encephalopathy syndrome (PRES) with atypical regions are very important in clinical practice. However, until now, little has been known about the clinical and MRI manifestations of this disease. Therefore, the aim of this study is to investigate the clinical and MRI features of PRES to promote clinical management and deepen our understanding of this disease.

Materials and Methods: Data from six PRES patients with atypical regions were collected from our hospital. Data from another 550 cases were obtained by searching the PubMed, EMBASE and Web of Science databases with the keywords "posterior reversible encephalopathy syndrome" "PRES" "reversible posterior leukoencephalopathy" "RPLS" "hypertensive encephalopathy" "hyperperfusion encephalopathy" or "reversible posterior cerebral edema encephalopathy." The clinical and MRI features of these 556 cases were analyzed together.

Results: A total of 305 patients were female, and 248 were male, with a median age of 34 years. The information on sex and age of three patients was not available. The most common symptom was headache (282/556, 50.7%), followed by altered mental status (243/556, 43.7%), seizures (233/556, 41.9%), visual disturbances (194/556, 34.9%), nausea/vomiting (130/556, 23.4%), and focal neurological deficits (101/556, 18.2%). Hypertension (425/556, 76.4%), renal diseases (152/556, 27.3%), immunosuppressant drugs (79/556, 14.2%), and chemotherapy/chemoradiotherapy (59/556, 10.6%) were the major predisposing factors. The atypical regions of the lesions were the cerebellum (331/556, 59.5%), basal ganglia (135/556, 24.3%), periventricular/deep white matter (125/556, 22.5%), pons (124/556, 22.3%), brainstem (115/556, 20.7%), thalamus (114/556, 20.5%), midbrain (48/556, 8.6%), spinal cord (33/556, 5.9%), and medulla (29/556, 5.2%). Additionally, the following typical regions were observed: occipital (278/556, 50.0%), parietal (234/556, 42.1%), frontal (150/556, 27.0%), and temporal (124/556, 22.3%) lobes. The major treatments were antihypertensives (358/515, 69.5%), antiepileptics/sedation (126/515, 24.5%), discontinuation/switching agents (67/515,

OPEN ACCESS

Edited by:
Alexander Lerner, University of Southern California, United States

Reviewed by:
Bo Gao, Affiliated Hospital of Guizhou Medical University, China
Yunyun Duan, Capital Medical University, China

***Correspondence:**
Chuanming Li
lichuanming@hospital.cqmu.edu.cn

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *07 July 2019*
Accepted: *03 March 2020*
Published: *24 March 2020*

Citation:
Li K, Yang Y, Guo D, Sun D and Li C (2020) Clinical and MRI Features of Posterior Reversible Encephalopathy Syndrome With Atypical Regions: A Descriptive Study With a Large Sample Size. Front. Neurol. 11:194. doi: 10.3389/fneur.2020.00194

13.0%), and steroids (54/515, 10.5%). The median time of the clinical state improved and abnormal neuroimaging resolved is 2–3 weeks after appropriate treatment.

Conclusion: The common symptoms of PRES with atypical regions include headaches, altered mental status, seizures, visual disturbances, nausea or vomiting, and focal neurological deficits. The frequent predisposing factors include hypertension, renal diseases, immunosuppressant drugs and chemotherapy/chemoradiotherapy. MRI features are mainly characterized by vasogenic edema in central zones always accompanied by typical regions. Most cases can be reversed in 2–3 weeks when promptly recognized and properly treated.

Keywords: posterior reversible encephalopathy syndrome, clinical features, magnetic resonance imaging, atypical regions, vasogenic edema

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a reversible clinico-radiological entity associated with various conditions (e.g., renal failure, blood pressure fluctuations, cytotoxic drugs, autoimmune disorders, and pre-eclampsia or eclampsia), and the diverse clinical manifestations mainly include acute and subacute onset of headache, nausea, vomiting, seizures, altered mental status, visual disturbances, and focal neurological signs (1–4). The typical MRI feature of PRES is characterized by reversible vasogenic edema affecting the subcortical white matter of supratentorial lobes, especially in the parieto-occipital lobes (5). When promptly diagnosed and properly treated, the clinical and radiological abnormalities associated with PRES can be reversed entirely. Otherwise, some patients can progress to having hemorrhage, ischemia, massive infarction, and even death (6–8). Therefore, prompt identification of PRES is very important for the treatment and outcome of patients.

Previous studies have mostly focused on typical or classical PRES with three primary variations: a dominant parieto-occipital pattern, holohemispheric watershed pattern, and superior frontal sulcus pattern (5, 9). However, with the deepening of research on this disease in recent years, lesions have also been found to occur in atypical regions, such as the frontal lobe, thalamus, periventricular white matter, brainstem, cerebellum, and spinal cord, which are poorly understood and easily misdiagnosed (9–16). Therefore, it is very important to study the clinical and MRI features of PRES with atypical regions to improve clinical management. However, to our knowledge, most of the previous studies of PRES with atypical regions have been case reports or small case series lacking a comprehensive summary with a large sample (4, 17). Therefore, in this study, we investigate the clinical and MRI features of PRES with atypical regions in a large sample by retrospectively collecting data from patients in our hospital and from the patients reported in the literature by searching the PubMed, EMBASE, and Web of Science databases.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of our institution. The requirement for informed consent was waived.

Subjects

We retrospectively collected patient information in two ways. (1) We searched the medical records of patients admitted to our hospital with PRES between April 1, 2015, and May 31, 2019. The diagnostic criteria used for PRES were previously described (5). (2) We searched the PubMed, EMBASE and Web of Science databases for articles published until May 31, 2019, with the keywords "posterior reversible encephalopathy syndrome" "PRES" "reversible posterior leukoencephalopathy" "RPLS" "hypertensive encephalopathy" "hyperperfusion encephalopathy" or "reversible posterior cerebral edema encephalopathy" (**Table E1** in Supplementary Material). Additionally, we identified related articles through searches of the reference lists from the articles extracted from the searched files as supplements. Two authors (Kunhua Li and Yang Yang) independently reviewed the full-text articles of the relevant publications. In cases where there was ambiguity in opinions, a third author (Chuanming Li) made the final arbitration. The inclusion criteria of our study were as follows: (1) all patients underwent a minimum of fluid-attenuated inversion recovery (FLAIR), T2-weighted imaging (T2WI), and T1-weighted imaging (T1WI); (2) atypical involvements including the basal ganglia, thalamus, periventricular or deep white matter, cerebellum, brainstem, midbrain, pons, medulla oblongata, and spinal cord; and (3) only studies reported in English were included. The exclusion criteria were as follows: typical or classical PRES with three primary variations: a dominant parieto-occipital pattern, holohemispheric watershed pattern, and superior frontal sulcus pattern (9). The flowchart of the study population is shown in **Figure 1**.

Clinical Evaluation

The clinical information collected and evaluated from the patient records included age, sex, predisposing factors for the development of PRES, presenting blood pressure, related symptoms, current drugs/therapies, follow-up interval and outcome.

Imaging Evaluation

The imaging findings were evaluated on T1WI, T2WI, and FLAIR images in all cases. Diffusion-weighted imaging (DWI),

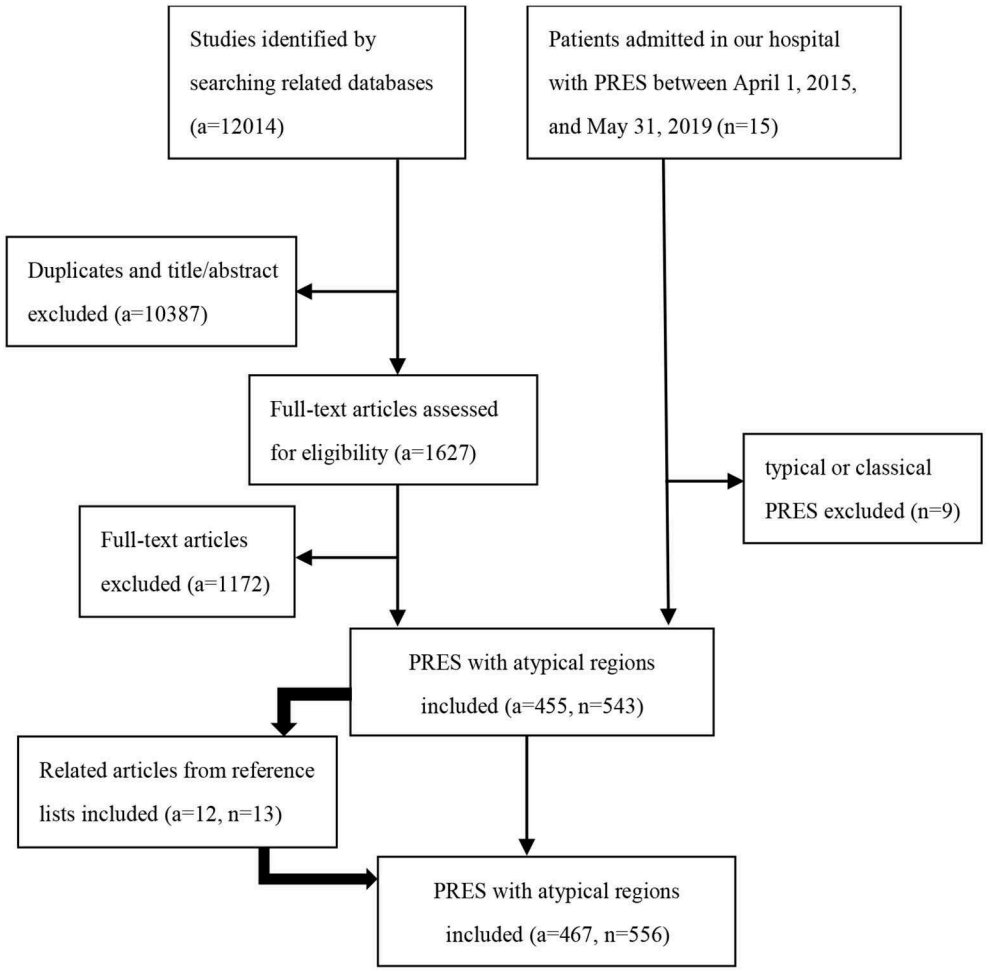


FIGURE 1 | Flowchart of the study population. a, number of articles; n, number of patients.

apparent diffusion coefficient (ADC) maps, susceptibility-weighted imaging (SWI) or T2*-weighted gradient-echo imaging (T2*WI), gadolinium-enhanced T1WI, MR angiography (MRA), MR venography (MRV), and other advanced images were evaluated if they were available. DWI and ADC maps were analyzed to determine the vasogenic or cytotoxic edema in the lesions. SWI or T2*WI was used to determine the intracranial hemorrhage and microbleeds.

Statistical Analysis

General demographic, clinical and MRI indicators were expressed as the mean ± SD (normally distributed quantitative variables), median (non-normally distributed quantitative variables), or numbers and percentages (categorical variables) for descriptive analysis.

RESULTS

In total, six patients from our hospital (the clinical and MRI features of six patients are shown in **Table 1**, and the MRI features of one patient are shown in **Figure 2**) and 550 patients from 467 articles published on PubMed, EMBASE and Web of Science met our inclusion criteria. All the articles ultimately included are shown in the **List E1** in Supplementary Material.

Clinical Features

A total of 305 patients were females, and 248 were males, with a median age of 34 years. The information regarding sex and age of three patients was not available in the descriptions in the literature. The most common symptom was headache (282/556, 50.7%), followed by altered mental status (243/556, 43.7%), seizure (233/556, 41.9%), visual disturbance (194/556, 34.9%), nausea/vomiting (130/556, 23.4%), and focal neurological deficit (104/556, 18.7%) in descending order. Other rare symptoms are shown in **Table 2**. Hypertension (425/556, 76.4%), renal diseases (152/556, 27.3%), immunosuppressant drugs (79/556, 14.2%), and chemotherapy/chemoradiotherapy (59/556, 10.6%) were the major predisposing factors. For patients with hypertension, the median systolic blood pressure was 200 mm Hg (range, 120–292 mm Hg), and the median diastolic blood pressure was

TABLE 1 | Demographic, clinical and MRI features of six patients in our hospital.

Case No.	Age (years)/sex	Symptoms	Blood pressure (mmHg)	Predisposing factors	Location	Hemorrhage	Acute infarction	Treatment
1	52/F	Headache	200/130	Hypertension	Brainstem, periventricular	–	–	Antihypertensive
2	23/F	Focal neurological deficits	163/116	Preeclampsia	Brainstem, periventricular	–	Pons (+)	Antihypertensive
3	40/M	Focal neurological deficits	189/110	Hypertension, psoriasis	Periventricular, basal ganglia, pons, cerebellum	Pons (+)	–	Antihypertensive
4	44/F	Focal neurological deficits	260/130	Hypertension, renal dysfunction, renal artery stenosis	Brainstem, periventricular	–	Cerebrum (+)	Antihypertensive
5	45/F	Insomnia	236/154	Hypertension, renal dysfunction	Periventricular, basal ganglia, pons	–	–	Antihypertensive
6	22/F	Headache, blurred vision	224/115	Hypertension	Periventricular, basal ganglia	–	–	Antihypertensive

118 mm Hg (67–220 mm Hg). The median arterial pressure (MAP) was 143 mmHg (100–237 mmHg). The demographics and clinical characteristics of PRES patients with atypical regions are summarized in **Table 2**.

Imaging Features

All patients showed hyperintensity signals on T2WI and FLAIR images. The atypical regions of the lesions were the cerebellum (331/556, 59.5%), basal ganglia (135/556, 24.3%), periventricular/deep white matter (125/556, 22.5%), pons (124/556, 22.3%), brainstem (115/556, 20.7%), thalamus (114/556, 20.5%), midbrain (48/556, 8.6%), spinal cord (33/556, 5.9%) and medulla (29/556, 5.2%). Additionally, the following typical regions were observed: occipital (278/556, 50.0%), parietal (234/556, 42.1%), frontal (150/556, 27.0%), and temporal (124/556, 22.3%). A total of 148 patients had DWI and ADC maps, and 34 (23.0%) patients showed cytotoxic edema on the background of vasogenic edema. Thirty-three (5.9%) and 35 (6.3%) patients had intracranial hemorrhage and hydrocephalus, respectively. Thirty-one patients had acute infarcts. Ninety-three patients underwent gadolinium-enhanced T1WI, and 29 (31.2%) patients showed lesion enhancements. Twenty-four (4.3%) patients in our study underwent SWI or T2*WI examination, and 79.2% (19/24) of patients were confirmed to have microbleeds based on SWI or T2*WI. The MRI characteristics of PRES with atypical regions are summarized in **Table 3**. Sixty-two patients in our study underwent MRA examination, which suggested stenosis/occlusion (8/62, 12.9%), vasospasm (6/62, 9.7%), aneurysm (3/62, 4.8%), hypoplasia (2/62, 3.2%), and dilatation (1/62, 1.6%). Fifteen patients in our study underwent MRV examination, which suggested hypoplasia (2/15, 13.3%) and thrombosis/stenosis (1/15, 6.7%). The main MRI characteristics of PRES patients with atypical regions are summarized in **Table 3**.

Treatment and Outcome

The details of the treatment were available in 515 cases. The major treatments were antihypertensives (358/515, 69.5%), antiepileptics/sedation (126/515, 24.5%), discontinuation/switching agents (67/515, 13.0%), and steroids (54/515, 10.5%). After appropriate treatments, the neurological symptoms of 244 patients resolved at follow-up [median time, 14 days (range, 0.04–540 days)]. Twenty-five patients died at follow-up; however, most of their deaths (20/25, 80.0%) were not attributable to PRES but to severe infections or malignant tumors. Moreover, the causes of the three patients' deaths were unknown. In 364 patients, data on follow-up time and MR imaging were available. Except for four patients with no significant change, the MRIs of 360 patients at follow-up showed lesion reversal [complete, 273 patients, median time, 21 days (range, 1–720 days); partial, 87 patients, median time, 18 days (0.5–300 days)].

DISCUSSION

PRES with atypical regions can be easily misdiagnosed, which can lead to a delay or wrong choice of management and subsequent irreversible injury. Thus, it is crucial for clinicians to improve their understanding of the clinical and MRI features of this disease (12, 18). To our knowledge, this is the first comprehensive study with a large sample of PRES patients with atypical regions.

Recognition of the clinical features of this disease is important for prompt diagnosis and rational management. In our study, most patients were young females, which is similar to most previous studies, but males were predominant in some other studies (12, 13). This may be due to different sample sizes and inclusion criteria. We found that the common clinical symptoms included headache, altered mental status, seizures,

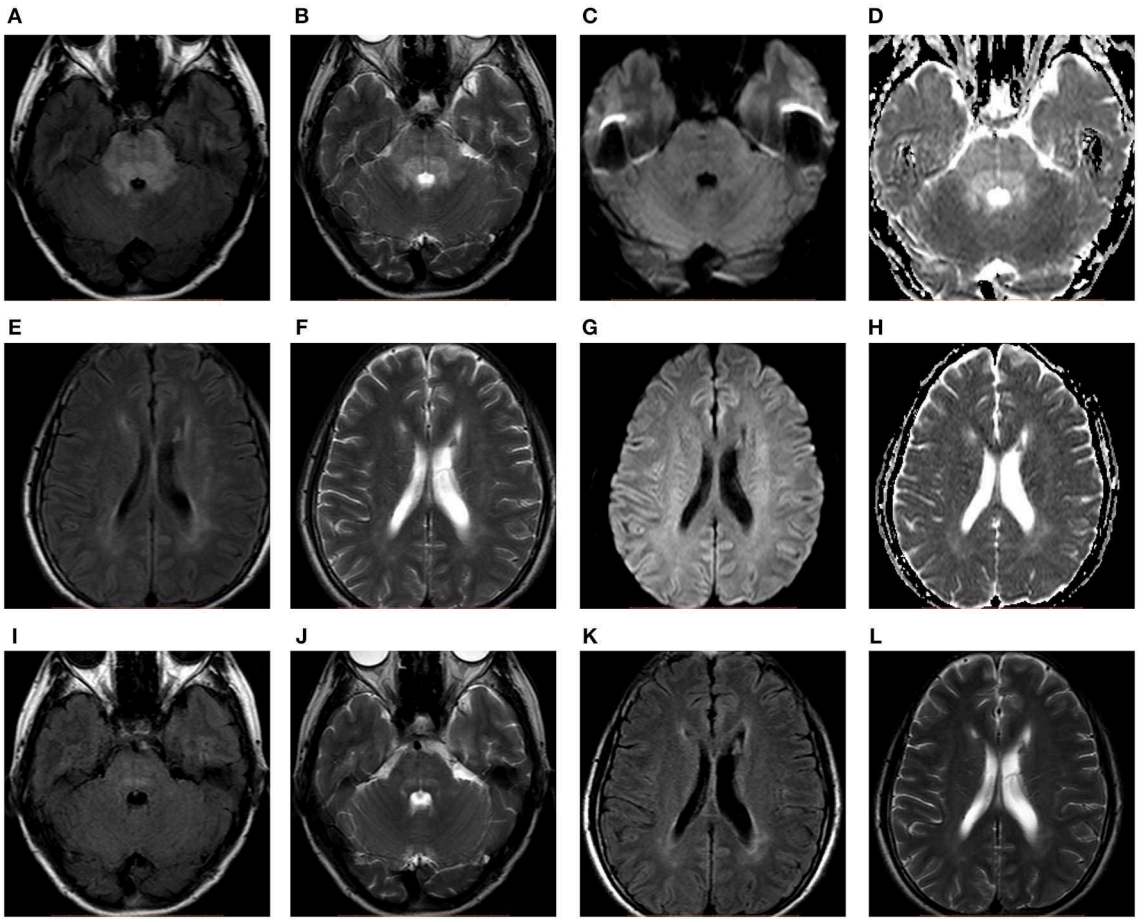


FIGURE 2 | A 52-years-old female with hypertension presented with headache. FLAIR **(A,E)**, T2WI **(B,F)**, and ADC maps **(D,H)** showed hyperintensity predominantly in the brainstem accompanied by periventricular white matter. No obvious abnormality on DWI **(C,G)**. After 11 days of follow-up, the abnormal signals **(I–L)** markedly resolved. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; T2WI, T2-weighted imaging.

visual disturbances, nausea/vomiting and focal neurological deficits. Many patients showed several different symptoms concurrently or subsequently. However, the symptoms often did not correspond to the brain lesion locations. For example, 20.7% (115/556) of patients had brainstem lesions, but most of them did not have specific brainstem signs. This may suggest that there is no obvious association between brain lesions and clinical manifestations in this disease (11, 18, 19). The frequent predisposing factors were those classically described, namely, hypertension, renal diseases, immunosuppressant drugs, and chemotherapy/chemoradiotherapy. Acute or severe hypertension occurred in 76.4% of patients in our study, which may be explained by cerebral autoregulation impairment as the primary pathogenic mechanism in PRES (4, 5, 20, 21). Previous studies have reported that the proportion of hypertension in patients with PRES ranges from 20 to 65% (4). Our results of a proportion of 76.4% are slightly higher, possibly because the central variant of PRES may be a higher incidence of hypertension (22), which had a higher incidence in our study. Nevertheless, 23.6% of patients still developed PRES without hypertension. All of them had other predisposing factors of immunosuppressant drugs, autoimmune disorders, chemotherapy or infection/sepsis/shock. These predisposing factors may induce endothelial damage or dysfunction, resulting in vasogenic edema and PRES (23–27).

In addition to the clinical features, neuroimaging, especially MRI, is essential in the evaluation and diagnosis of PRES with atypical regions (28). The lesion locations are very important in terms of the MRI features. Atypical region involvement mostly occurs in central zones (such as the basal ganglia, thalami, periventricular or deep white matter, brainstem and spinal cord). Compared with previous studies (9, 11, 16, 29), in our study, there were some similar locations but with different incidences; this may be due to the different sample sizes and populations. We focused on PRES with atypical region involvement and used a large sample. Although we excluded the three primary variations of typical PRES, we found that the occipital (278, 50.0%), parietal (234, 42.1%), and frontal (150, 27.0%) lobes were still commonly involved. This suggests that PRES with atypical region involvement is often accompanied by typical region involvement (3, 29).

TABLE 2 | Demographic and clinical characteristic of PRES patients with atypical regions.

Characteristic	*n*
DEMOGRAPHICS AND SYMPTOMS	
Sex/F	305/553 (55.2%)
Age (median, range, years)	(34, 0.08–85)
Headache	**282/556 (50.7%)**
Altered mental status	**243/556 (43.7%)**
Seizures	**233/556 (41.9%)**
Visual disturbances	**194/556 (34.9%)**
Nausea/vomiting	**130/556 (23.4%)**
Focal neurological deficits	**101/556 (18.2%)**
Dizziness	38/556 (6.8%)
Gait disturbances	27/556 (4.9%)
Fever	25/556 (4.5%)
Disorientation	23/556 (4.1%)
Ataxia	20/556 (3.6%)
Dyspnea	16/556 (2.9%)
Abdominal pain	13/556 (2.3%)
Abnormal urine	12/556 (2.2%)
Others (each symptom)[#]	≤2%
PREDISPOSING FACTOR	
Hypertension	**425/556 (76.4%)**
Renal diseases	**152/556 (27.3%)**
Immunosuppressant drugs	**79/556 (14.2%)**
Chemotherapy/chemoradiotherapy	**59/556 (10.6%)**
Autoimmune disorders	55/556 (9.9%)
Pre-eclampsia/Eclampsia	41/556 (7.4%)
Infection/sepsis/shock	32/556 (5.8%)
Steroids	24/556 (4.3%)
Metabolic disorders	15/556 (2.7%)
Miscellaneous drugs	13/556 (2.3%)
Dialysis	12/556 (2.2%)
Transfusion	11/556 (2.0%)
Endocrine disorders	7/556 (1.3%)
Surgery	6/556 (1.1%)
Others (each factor)*	≤1%
TREATMENT	
Antihypertensives	**358/515 (69.5%)**
Antiepileptics/sedation	**126/515 (24.5%)**
Discontinuation/switching agents	**67/515 (13.0%)**
Steroid	**54/515 (10.5%)**
Dehydrating/diuretics	34/515 (6.6%)
Intracranial decompression	24/515 (4.7%)
Hemodialysis	23/515 (4.5%)
Immunosuppressive therapy	20/515 (3.9%)
Anti-infective treatment	16/515 (3.1%)
Others (each treatment)[$]	≤2%

The main characteristics (>10%) are marked in bold.
Others (each symptom)[#]: involuntary movement, fatigue, behavioral changes, edema, loss of appetite, neck stiffness, diarrhea, polydipsia and weight loss, purpura, and insomnia.
Others (each factor): sickle cell disease, substance abuser, reduction in intracranial pressure, intoxication, contrast medium exposure, trauma, multiple system atrophy, embolus, hyperbaric oxygen therapy.*
Others (each treatment)[$]: plasma exchange, treatment for tumor, renal angioplasty, glyceryl trinitrate infusion, and others <1%.

Vasogenic edema, which is an essential pathological feature of PRES, is usually hypointense on T1WI, hyperintense on T2WI and FLAIR, and isointense or hyperintense on DWI and ADC maps. Hyperintensity on DWI and hypointensity on ADC maps, which are called restricted diffusion, can reflect cytotoxic edema. The presence of cytotoxic edema may suggest progression to infarction and eventual irreversible damage, which may be associated with poor outcome (30, 31). In our study, 34 (23.0%) patients showed cytotoxic edema, but only two patients had a residual infarction. This may be because most of the patients only had small areas of cytotoxic edema within the predominant backgrounds of vasogenic edema. Contrast enhancement is not necessary for the diagnosis of PRES but may be useful for the exclusion of other clinical considerations (8, 32). In this study, we found that 31.2% of patients showed lesion enhancement. The enhancement may have been induced by the breakdown of the blood-brain barrier, which is related to endothelial injury or dysfunction (33, 34). The rates of enhancement vary within the previous literature, ranging from 23.1 to 43.7% in PRES (29, 34, 35), likely related to differences in timing, magnetic field strength, and contrast agent dose/relaxivity.

In addition to the common MRI features, concomitant and coincidental events that occur on neuroimaging, mainly including hemorrhage, microbleeds and hydrocephalus, can occur in PRES. In our study, hemorrhage was found in 33 (5.9%) patients. The incidence rate was lower than that of previous SWI or T2*WI studies, where it ranges from 15 to 65% (30, 36–38). The possible reason is that SWI or T2*WI is more sensitive to hemorrhage than conventional MRI, and the previous literature has shown a higher incidence of hemorrhage with SWI or T2*WI examination. The fact that only 24 (4.3%) patients in our study with SWI or T2*WI examination supports this hypothesis. Thirty-five (6.3%) patients had obstructive hydrocephalus due to infratentorial involvement, especially of the cerebellum, which was caused by the compression of adjacent swollen brain tissue.

Once PRES has been diagnosed, the treatment, which mainly includes supportive treatment and the elimination of the cause, should be undertaken immediately to prevent poor progression. In our study, 69.5% of patients received antihypertensive treatment, and 24.5% of patients received antiepileptics/sedation. After proper and prompt treatments, the clinical state improved, and abnormal neuroimaging resolved in most patients within 2–3 weeks.

CONCLUSIONS

In conclusion, we found that PRES with atypical regions had diverse clinical and MRI features. The common symptoms of this disease include headache, altered mental status, seizure, visual disturbances, nausea or vomiting, and focal neurological deficits; the frequent predisposing factors include hypertension, renal diseases, immunosuppressant drugs, and chemotherapy/chemoradiotherapy; and the MRI features are mainly characterized by vasogenic edema in central zones (such as the basal ganglia, thalami, periventricular or deep white matter, brainstem, and spinal cord) always accompanied by

TABLE 3 | MR characteristics of PRES patients with atypical regions.

Location		MR feature	
Cerebellum	331/556 (59.5%)	T1WI(–)&T2WI(+)	556/556 (100.0%)
Occipital lobe	278/556 (50.0%)	DWI(=)&ADC(+)	47/148 (31.8%)
Parietal lobe	234/556 (42.1%)	DWI(+)&ADC(+)	43/148 (29.1%)
Frontal lobe	150/556 (27.0%)	DWI(+)&ADC(–)	31/148 (20.9%)
Basal ganglia	135/556 (24.3%)	DWI(=)&ADC(=)	20/148 (13.5%)
Periventricular/deep white matter	125/556 (22.5%)	DWI(+)&ADC(=)	5/148 (3.4%)
Temporal lobe	124/556 (22.3%)	DWI(–)&ADC(–)	3/148 (2.0%)
Pons	124/556 (22.3%)	DWI(–)&ADC(+)	2/148 (1.4%)
Brainstem	115/556 (20.7%)	DWI(–)&ADC(=)	1/148 (0.7%)
Thalamus	114/556 (20.5%)	Enhancement	29/93 (31.2%)
Midbrain	48/556 (8.6%)	Hemorrhage	33/556 (5.9%)
Spinal cord	33/556 (5.9%)	Microbleeds	19/24 (79.2%)
Medulla	29/556 (5.2%)	Hydrocephalus	35/556 (6.3%)

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; –, hypointensity; =, iso-intensity; +, hyperintensity.

abnormalities in typical regions. Most lesions are reversed in 2–3 weeks when promptly recognized and properly treated. The main limitation of this study is the possible selection bias because only publications in English were searched and included. This aspect needs to be improved in future research.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KL, YY, DG, and CL contributed the conception and design of the study. KL and YY organized the database and performed the statistical analysis. KL, YY, and DS wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

FUNDING

This work was supported by Chongqing Science and Health Joint Medical Research Project (2018ZDXM005).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00194/full#supplementary-material

REFERENCES

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* (1996) 334:494–500. doi: 10.1056/NEJM199602223340803
2. Liman TG, Bohner G, Heuschmann PU, Endres M, Siebert E. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the retrospective Berlin PRES study. *J Neurol.* (2012) 259:155–64. doi: 10.1007/s00415-011-6152-4
3. Liman TG, Siebert E, Endres M. Posterior reversible encephalopathy syndrome. *Curr Opin Neurol.* (2019) 32:25–35. doi: 10.1097/wco.0000000000000640
4. Gao B, Lyu C, Lerner A, McKinney AM. Controversy of posterior reversible encephalopathy syndrome: what have we learnt in the last 20 years? *J Neurol Neurosurg Psychiatry*. (2018) 89:14–20. doi: 10.1136/jnnp-2017-316225
5. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol.* (2015) 14:914–25. doi: 10.1016/S1474-4422(15)00111-8
6. Magsi S, Zafar A. Malignant posterior reversible encephalopathy syndrome–an exacting challenge for neurocritical care physicians. *Neurohospitalist.* (2017) 7:196–9. doi: 10.1177/1941874416688989
7. Chen S, Hu J, Xu L, Brandon D, Yu J, Zhang J. Posterior reversible encephalopathy syndrome after transplantation: a review. *Mol Neurobiol.* (2016) 53:6897–909. doi: 10.1007/s12035-015-9560-0
8. Brady E, Parikh NS, Navi BB, Gupta A, Schweitzer AD. The imaging spectrum of posterior reversible encephalopathy syndrome: a pictorial review. *Clin Imaging.* (2018) 47:80–9. doi: 10.1016/j.clinimag.2017.08.008
9. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *Am J Neuroradiol.* (2007) 28:1320–7. doi: 10.3174/ajnr.A0549
10. Shankar J, Banfield J. Posterior reversible encephalopathy syndrome: a review. *Can Assoc Radiol J.* (2017) 68:147–53. doi: 10.1016/j.carj.2016.08.005

11. Ou S, Xia L, Wang L, Xia L, Zhou Q, Pan S. Posterior reversible encephalopathy syndrome with isolated involving infratentorial structures. *Front Neurol.* (2018) 9:843. doi: 10.3389/fneur.2018.00843
12. Liu C, Cao J, Su Z, Xu S. Isolated brainstem involvement in posterior reversible encephalopathy syndrome: a case report and review of the literature. *Int J Neurosci.* (2019) 129:808–13. doi: 10.1080/00207454.2018.1561452
13. Li D, Lian L, Zhu S. Isolated cerebellar involvement in posterior reversible encephalopathy syndrome. *J Neurol Sci.* (2015) 357:101–5. doi: 10.1016/j.jns.2015.07.004
14. Chen TH, Lin WC, Kao WT, Tseng CM, Tseng YH. Posterior reversible encephalopathy syndrome with spinal cord involvement in children. *J Child Neurol.* (2017) 32:112–9. doi: 10.1177/0883073816671237
15. Wittgrove C, Kaur H, Siddiqui JH. Atypical variant of posterior reversible encephalopathy syndrome in the setting of renovascular hypertension: case report and review of literature. *Cureus.* (2018) 10:e3573. doi: 10.7759/cureus.3573
16. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical cerebral edema. *Am J Roentgenol.* (2013) 201:631–8. doi: 10.2214/AJR.12.9677
17. Ferrara M, Di Viesti P, Inchingolo V, Latino RR, Popolizio T, De Cosmo SA, et al. Isolated pons involvement in posterior reversible encephalopathy syndrome: case report and review of the literature. *eNeurologicalSci.* (2017) 6:51–4. doi: 10.1016/j.ensci.2016.11.008
18. Shen T, Chen H, Jing J, Raza HK, Zhang Z, Bao L, et al. A study on clinical characteristics and the causes of missed diagnosis of reversible posterior leukoencephalopathy syndrome in eclampsia. *Neurol Sci.* (2019) 40:1873–6. doi: 10.1007/s10072-019-03914-3
19. Srinivasan KG, Balasubramanian P, Mayilvaganan KR, Kannan UN, Bilal M. Central variant of posterior reversible encephalopathy syndrome–a rare case report. *J Clin Diagn Res.* (2017) 11:TD01–2. doi: 10.7860/JCDR/2017/23269.9682
20. Wang Q, Huang B, Shen G, Zeng Y, Chen Z, Lu C, et al. Blood-brain barrier disruption as a potential target for therapy in posterior reversible encephalopathy syndrome: evidence from multimodal MRI in rats. *Front Neurol.* (2019) 10:1211. doi: 10.3389/fneur.2019.01211
21. Allen ML, Kulik T, Keyrouz SG, Dhar R. Posterior reversible encephalopathy syndrome as a complication of induced hypertension in subarachnoid hemorrhage: a case-control study. *Neurosurgery*. (2019) 85:223–30. doi: 10.1093/neuros/nyy240
22. Moon SN, Jeon SJ, Choi SS, Song CJ, Chung GH, Yu IK, et al. Can clinical and MRI findings predict the prognosis of variant and classical type of posterior reversible encephalopathy syndrome (PRES)? *Acta Radiol.* (2013) 54:1182–90. doi: 10.1177/0284185113491252
23. Feske SK. Posterior reversible encephalopathy syndrome: a review. *Semin Neurol.* (2011) 31:202–15. doi: 10.1055/s-0031-1277990
24. Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. Posterior reversible encephalopathy syndrome–insight into pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev.* (2015) 14:830–6. doi: 10.1016/j.autrev.2015.05.006
25. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol.* (2017) 264:1608–16. doi: 10.1007/s00415-016-8377-8
26. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. *Med Hypotheses.* (2014) 82:619–22. doi: 10.1016/j.mehy.2014.02.022
27. Chen Z, Shen GQ, Lerner A, Gao B. Immune system activation in the pathogenesis of posterior reversible encephalopathy syndrome. *Brain Res Bull.* (2017) 131:93–9. doi: 10.1016/j.brainresbull.2017.03.012
28. Tetsuka S, Ogawa T. Posterior reversible encephalopathy syndrome: a review with emphasis on neuroimaging characteristics. *J Neurol Sci.* (2019) 404:72–9. doi: 10.1016/j.jns.2019.07.018
29. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *Am J Roentgenol.* (2007) 189:904–12. doi: 10.2214/AJR.07.2024
30. Schweitzer AD, Parikh NS, Askin G, Nemade A, Lyo J, Karimi S, et al. Imaging characteristics associated with clinical outcomes in posterior reversible encephalopathy syndrome. *Neuroradiology*. (2017) 59:379–86. doi: 10.1007/s00234-017-1815-1
31. Chen Z, Zhang G, Lerner A, Wang AH, Gao B, Liu J. Risk factors for poor outcome in posterior reversible encephalopathy syndrome: systematic review and meta-analysis. *Quant Imaging Med Surg.* (2018) 8:421–32. doi: 10.21037/qims.2018.05.07
32. Ollivier M, Bertrand A, Clarencon F, Gerber S, Deltour S, Domont F, et al. Neuroimaging features in posterior reversible encephalopathy syndrome: a pictorial review. *J Neurol Sci.* (2017) 373:188–200. doi: 10.1016/j.jns.2016.12.007
33. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. *Radiographics.* (2007) 27:525–51. doi: 10.1148/rg.272065155
34. Karia SJ, Rykken JB, McKinney ZJ, Zhang L, McKinney AM. Utility and significance of gadolinium-based contrast enhancement in posterior reversible encephalopathy syndrome. *Am J Neuroradiol.* (2016) 37:415–22. doi: 10.3174/ajnr.A4563
35. Kastrup O, Schlamann M, Moenninghoff C, Forsting M, Goericke S. Posterior reversible encephalopathy syndrome: the spectrum of MR imaging patterns. *Clin Neuroradiol.* (2015) 25:161–71. doi: 10.1007/s00062-014-0293-7
36. McKinney AM, Sarikaya B, Gustafson C, Truwit CL. Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging. *Am J Neuroradiol.* (2012) 33:896–903. doi: 10.3174/ajnr.A2886
37. Sharma A, Whitesell RT, Moran KJ. Imaging pattern of intracranial hemorrhage in the setting of posterior reversible encephalopathy syndrome. *Neuroradiology*. (2010) 52:855–63. doi: 10.1007/s00234-009-0632-6
38. Hefzy HM, Bartynski WS, Boardman JF, Lacomis D. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. *Am J Neuroradiol.* (2009) 30:1371–9. doi: 10.3174/ajnr.A1588

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 16 June 2020
doi: 10.3389/fneur.2020.00463

Posterior Reversible Encephalopathy Syndrome (PRES): Pathophysiology and Neuro-Imaging

*Redmond-Craig Anderson, Vishal Patel, Nasim Sheikh-Bahaei, Chia Shang J. Liu, Anandh G. Rajamohan, Mark S. Shiroishi, Paul E. Kim, John L. Go, Alexander Lerner and Jay Acharya**

Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

Posterior reversible encephalopathy syndrome (PRES) represents a unique clinical entity with non-specific clinical symptoms and unique neuroradiological findings. This syndrome may present with a broad range of clinical symptoms from headache and visual disturbances to seizure and altered mentation. Typical imaging findings include posterior-circulation predominant vasogenic edema. Although there are many well-documented diseases associated with PRES, the exact pathophysiologic mechanism has yet to be fully elucidated. Generally accepted theories revolve around disruption of the blood-brain barrier secondary to elevated intracranial pressures or endothelial injury. In this article, we will review the clinical, typical, and atypical radiological features of PRES, as well as the most common theories behind the pathophysiology of PRES. Additionally, we will discuss some of the treatment strategies for PRES related to the underlying disease state.

Keywords: PRES (posterior reversible encephalopathy syndrome), neuroimaging, neuroradiology, pathophysiology, cerebrovascular abnormalities

OPEN ACCESS

Edited by:
Jeffrey Bruce Rykken, University of Minnesota Twin Cities, United States

Reviewed by:
Carsten Lukas, Ruhr University Bochum, Germany
Wen Wang, Fourth Military Medical University, China

****Correspondence:***
Jay Acharya
jay.acharya@med.usc.edu

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *08 August 2019*
Accepted: *29 April 2020*
Published: *16 June 2020*

Citation:
Anderson R-C, Patel V, Sheikh-Bahaei N, Liu CSJ, Rajamohan AG, Shiroishi MS, Kim PE, Go JL, Lerner A and Acharya J (2020) Posterior Reversible Encephalopathy Syndrome (PRES): Pathophysiology and Neuro-Imaging. Front. Neurol. 11:463. doi: 10.3389/fneur.2020.00463

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES), first described by Hinchey et al. in 1996, represents a neurological disorder with varied clinical presentation and typical imaging findings of parieto-occipital predominant pattern of vasogenic edema (1, 2). There are numerous documented causes of PRES, with cases first described in the setting of elevated arterial pressures. Examples of clinical scenarios in which PRES may be seen include: hypertensive emergency, (pre)eclampsia, renal disease, autoimmune disorders, and cytotoxic medications, among others (3, 4) (**Table 1**). PRES can occur in any age group and has a higher occurrence rate in female patients (7, 8). Although current literature is relatively sparse compared to adult populations, particular mention should be made of PRES in the pediatric patient. Pediatric patients have a similar clinical presentation as the adult population, with hypertension, seizure, and altered mental status being common disease manifestations (9). Despite most cases of pediatric PRES being reported in oncology patients, especially the post-stem-cell transplant patients (10, 11), a study by Gupta et al. (12) found that renal disease was perhaps the most common cause of PRES in the pediatric patient. In their study, pediatric patients tended to have more atypical imaging findings (62.5%), including frontal lobe involvement (56%).

Clinical manifestations are acute to subacute and range from headache and visual disturbances to altered levels of consciousness and seizure in more severe cases (1). Treatment is generally aimed at targeting the underlying cause, with generally reversible symptoms and imaging findings in most cases (8). Although outcomes are generally favorable with proper management, poor clinical outcomes have been associated with pre-existing diabetes mellitus, and involvement of the corpus callosum; however, other reliable imaging biomarkers for prognostication are currently lacking (13). Neuroradiological imaging plays a fundamental role in the diagnosis of PRES with the typical imaging features best appreciated on magnetic resonance imaging (MRI) (2).

TABLE 1 | Major disease states associated with PRES.

Hypertensive diseases	Endothelial dysfunction
Hypertension (primary or secondary causes)	Cytotoxic substances: chemotherapy, immunosuppressants, etc. (5, 6). • Bevacizumab • Carboplatin • Cisplatin • Cyclosporin • Cytarabine • Docetaxel • Irinotecan • Methotrexate • Oxaliplatin • Paclitaxel • Prednisone • Rituximab • Vincristine
Renal disease	Infection (sepsis)
Autoimmune disorders	(Pre)eclampsia
	Autoimmune disorders

PATHOPHYSIOLOGY

The precise pathophysiologic mechanism(s) behind PRES have yet to be fully elucidated and remain controversial (3). There are currently two major proposed mechanisms for the pathophysiology of PRES (**Figure 1**). The first theory proposes increased arterial pressures as the primary factor (8). Rapid rises in blood pressures eventually overcome the autoregulatory capabilities of the cerebral vasculature causing vascular leakage and resultant vasogenic edema (14). There is eventual blood-brain barrier (BBB) dysfunction with proteins passing through the tight-junction (15). The areas supplied by the posterior circulation (vertebral arteries, basilar artery, and posterior cerebral arteries) are at exceptional risk compared to the anterior circulation (internal carotid arteries, middle cerebral arteries, and anterior cerebral arteries) due to the lack of sympathetic tone of the basilar artery vasculature (8). A related theory proposed by

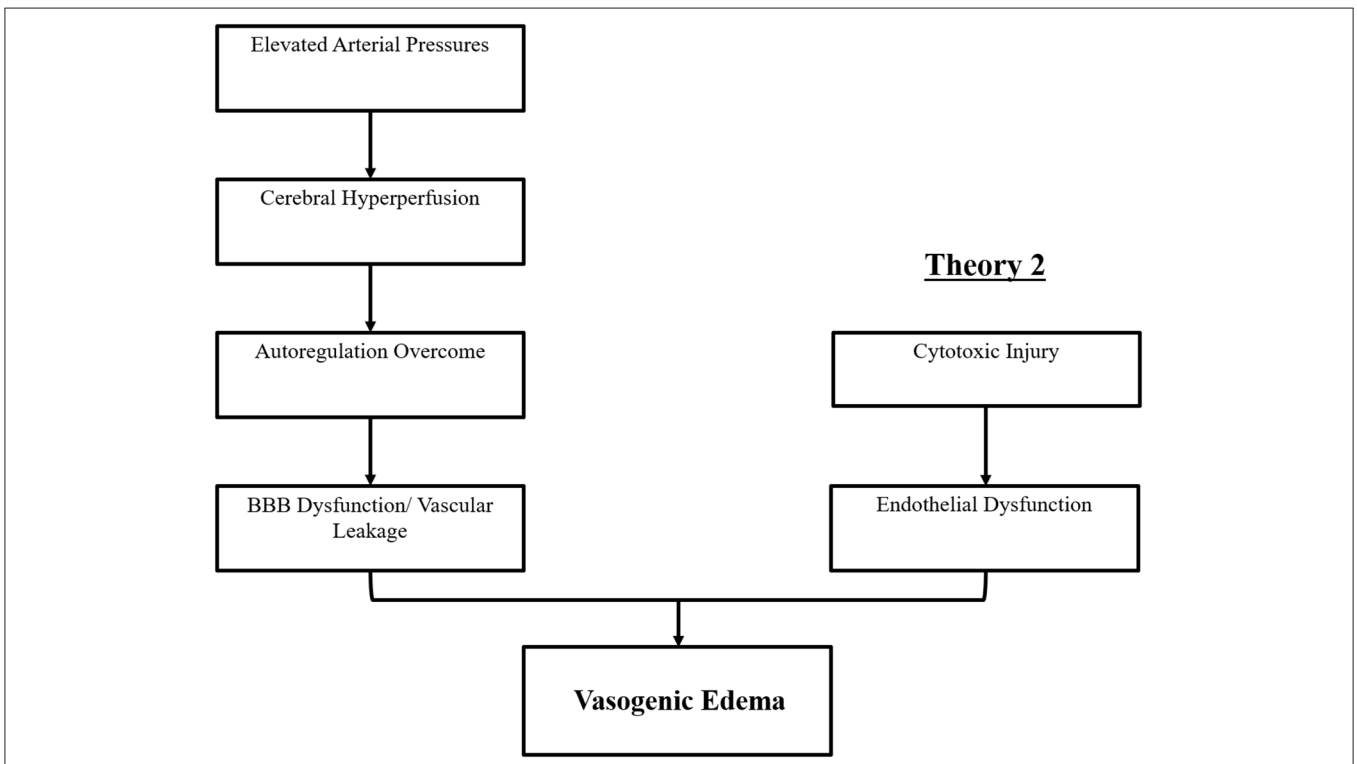


FIGURE 1 | Two major theories of the pathophysiology of PRES. Theory 1 is the hypertensive and cerebral hyperperfusion theory and Theory 2 is the endothelial dysfunction theory.

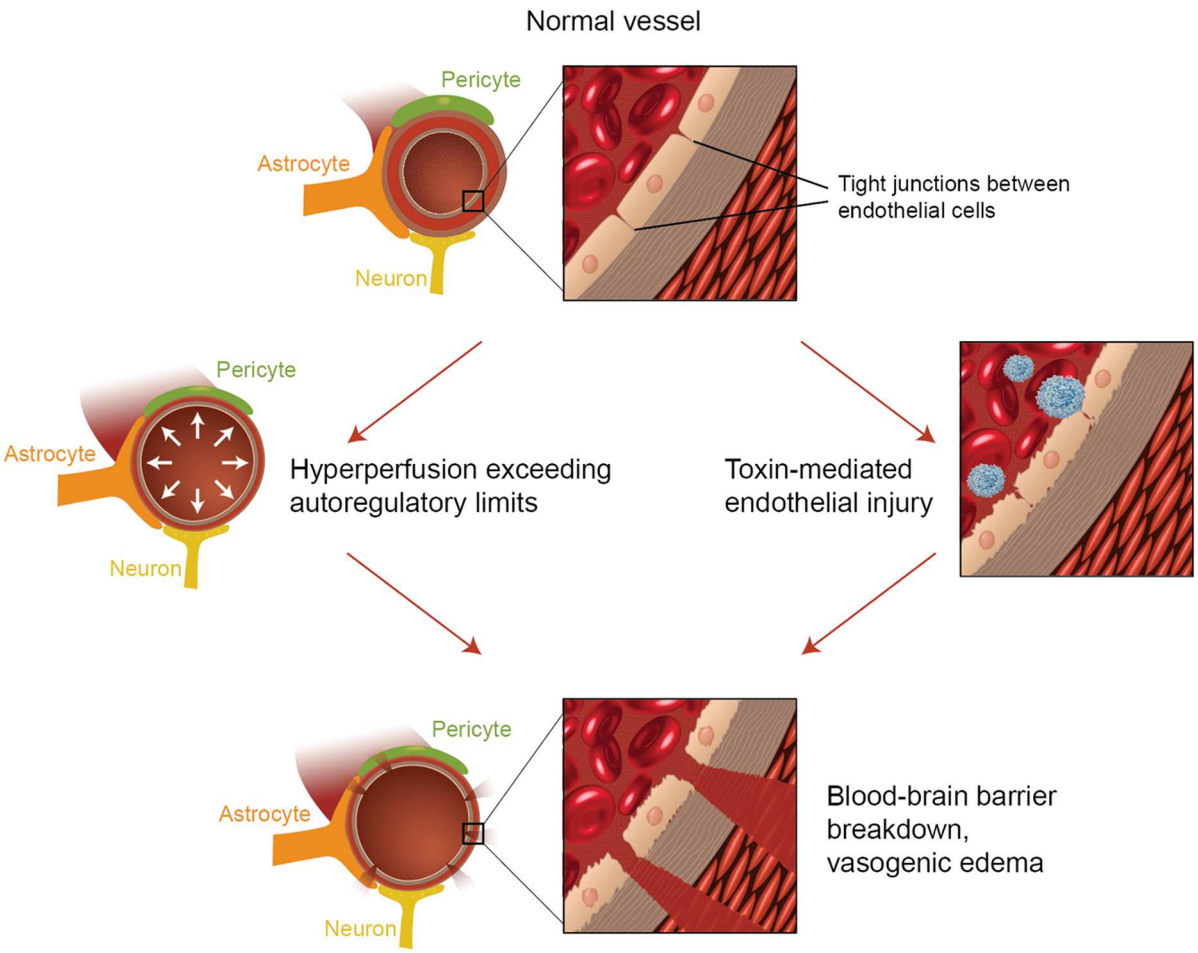


FIGURE 2 | Illustration of the two major theories of the underlying pathophysiology of PRES. Acknowledgment: Courtesy of Caroline O'Driscoll, MA (She illustrated this on her own and is an employee of our university).

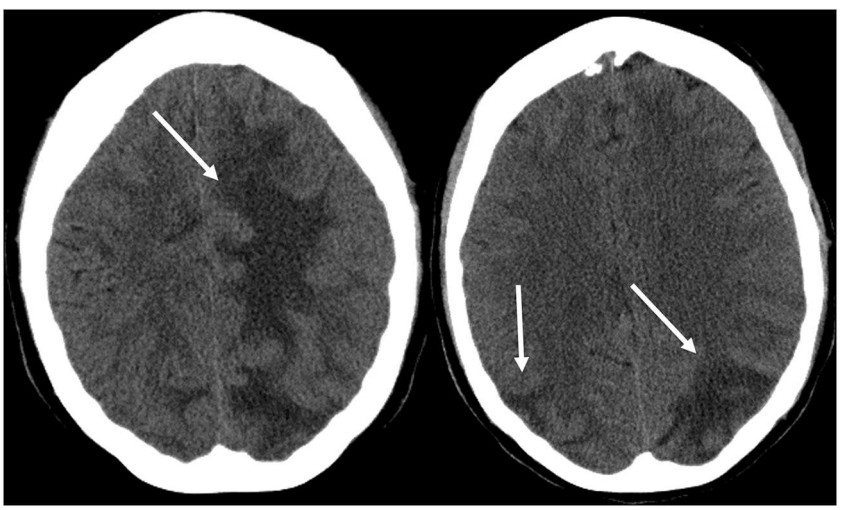


FIGURE 3 | Patient with systemic lupus erythematosus and rapidly progressive glomerulonephritis presenting with seizure. Non-contrast CT images of the head demonstrates vasogenic edema in the bilateral parietal and occipital lobes, left greater than right, as well as extension into the left frontal lobe.

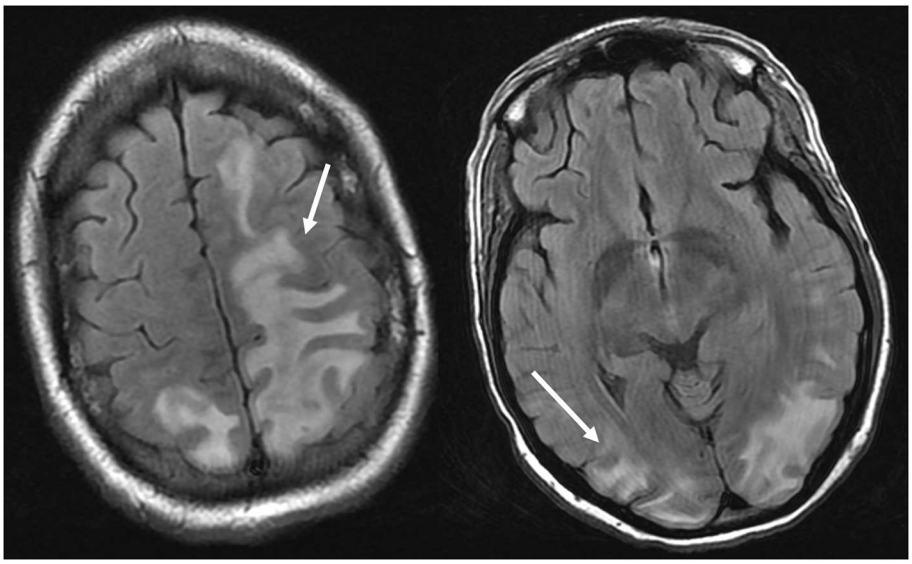


FIGURE 4 | Patient with systemic lupus erythematosus and rapidly progressive glomerulonephritis presenting with seizure. T2-FLAIR images of the head demonstrates vasogenic edema in the bilateral parietal and occipital lobes, left greater than right, as well as extension into the left frontal lobe. Note that with the vasogenic pattern of edema, there is sparing of signal abnormality in the cortex.

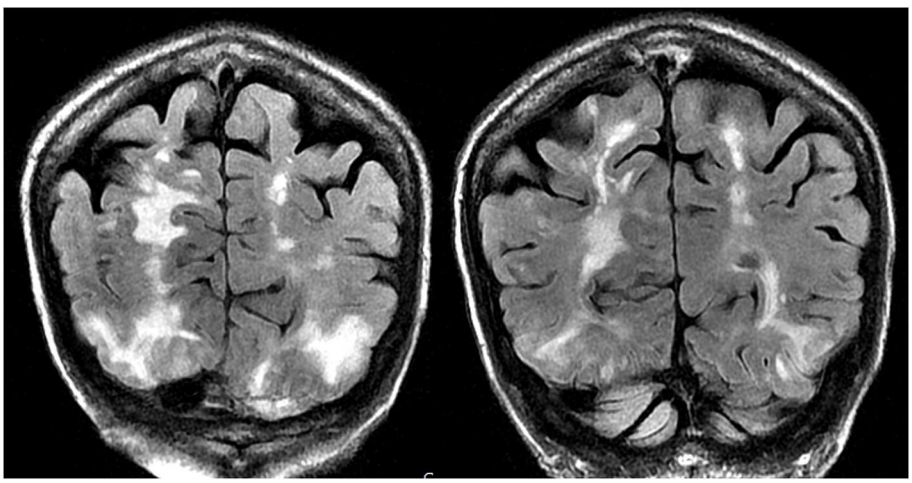


FIGURE 5 | Patient with a history of primary myelofibrosis and bone marrow transplant on Tacrolimus presenting with first time seizure. Coronal T2-FLAIR sequences demonstrate extensive signal abnormality in the bilateral occipital and parietal lobes, as is typical with PRES.

some postulates that extreme hypertension results in vasospasm and local ischemia which causes BBB breakdown and resultant vasogenic edema, as was observed in patients being treated with immunosuppressive agents cyclosporin A and FK-506 (16). The disruption in the BBB causes the typical findings of vasogenic edema vs. cytotoxic edema (which may be seen in the setting of acute infarct and represents increased intracellular water content due to loss of the usual osmotic gradient in the setting of cell death (17).

The second major theory addresses the fact that up to 30% of patients with PRES do not exhibit the elevated arterial pressures necessary to exceed the autoregulatory control of the cerebral vasculature (18, 19). This theory proposes that endothelial dysfunction is the primary culprit, which may be caused by various endogenous or exogenous toxins (20). This theory can explain the findings of PRES seen in patients receiving immunosuppressive medications and/or chemotherapy and also those patients with sepsis (21, 22). In this model, circulating toxins cause vascular injury with resultant development of vasogenic edema. The endothelial damage causes further release of vasoconstrictive and immunogenic agents, which may cause vasospasm and/or increased vascular permeability. Ultimately, endothelial dysfunction allowing for vascular leakage and vasogenic

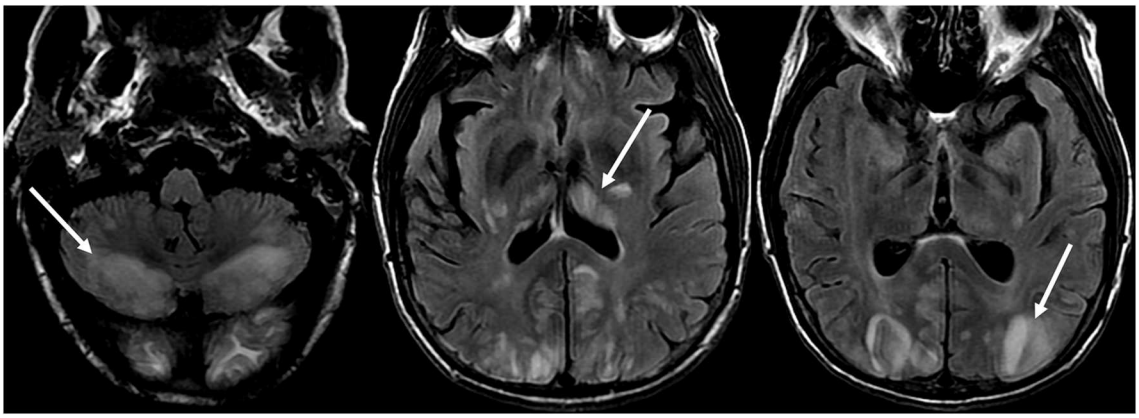


FIGURE 6 | Patient with liver transplantation 6 weeks earlier. The patient was started on Tacrolimus after liver transplantation. T2-FLAIR images of the brain demonstrate signal abnormality in the occipital lobes. There is also extensive signal abnormality seen in the bilateral cerebellar hemispheres and within the thalami. These findings quickly resolved after stopping the Tacrolimus.

edema is the driving factor behind PRES, regardless of the primary cerebral vasculature abnormality (in the case of arterial hypertension) or secondary to circulating toxins. A summary of these two theories as well as a list of previously reported chemotherapeutics and other immunosuppressants is shown in **Figure 2**.

Clinical manifestations depend on the involved region(s) of the brain; thus, the presentation may be broad. For example, primary involvement of the occipital lobes may result in visual disturbances/hallucinations. Focal neurological deficits corresponding to the location of focal lesions occurs in ∼5–15% of patients with PRES (23). Rarely, spinal cord involvement may result in clinical signs and symptoms of myelopathy or paralysis (24).

IMAGING

As its name suggests, PRES typically manifests on imaging studies as posterior-predominant white matter vasogenic edema. The parietal and occipital lobes are almost universally involved and findings are typically symmetrical and bilateral (1). Involvement of the frontal lobes, particularly adjacent to the superior frontal sulci, is also commonly seen. Vasogenic edema, although it can involve the cerebral gray matter, is often more readily appreciated in the subcortical white matter. CT examination is often the initial imaging test in setting of acute neurological symptoms and may demonstrate white matter hypoattenuation in affected regions (25) (**Figure 3**: CT of PRES). Overall, findings are best depicted by MRI which exhibits increased sensitivity and better anatomical characterization compared to CT (26). Additionally, MRI may help to distinguish other pathological states that may manifest clinically similarly to PRES. The T2-weighted and T2 FLAIR (fluid-attenuated inversion recovery) sequences, in particular, are most useful to detect vasogenic edema on MRI (**Figure 4**: MR of PRES; **Figure 5**: MR of PRES Coronal).

The differential diagnosis for PRES is broad and includes entities with similar confluent T2 white matter hyperintensity. Examples include: ischemia/infarction (particularly posterior circulation), demyelinating diseases, infectious etiologies (meningitis, encephalitis), progressive multifocal leukoencephalopathy (PML), vasculitis, and various metabolic disorders (27). A clinically related entity called reversible cerebral vasoconstriction syndrome (RCVS) is thought to be caused by alterations in cerebral vascular tone resulting in vasoconstriction. RCVS manifests as recurrent thunderclap headaches, seizure, stroke, and non-aneurysmal subarachnoid hemorrhage (28), which could be mistaken for PRES on a clinical basis. This entity typically occurs in the post-partum period or after exposure to adrenergic or serotonergic medications. RCVS can typically be diagnosed with angiographic studies demonstrating multifocal areas of narrowing involving the cerebral arteries (29). This diagnosis can be confounded with the fact that RCVS and PRES often occur concomitantly, which the neuroradiologist should be aware of to avoid misdiagnosis (30).

PRES can typically be distinguished from acute ischemia because the latter invariably demonstrates cytotoxic edema and diffusion restriction. Restricted diffusion in acute ischemia can be easily detected on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) as a hyperintense signal on DWI with corresponding decreased signal on ADC (due to the relatively decreased movement of intracellular water molecules). Vasogenic edema in the setting of PRES, on the other hand, may show hyperintense signal on DWI that is not accompanied by a corresponding decreased signal on ADC (31). Additionally, acute ischemia tends to be unilateral and within a singular vascular territory. While assessing for diffusion restriction to differentiate PRES from ischemic abnormality generally is reliable, there are rare cases of PRES that may be associated with areas of diffusion restriction superimposed upon areas of the more classically seen isolated vasogenic edema.

"Advanced" imaging techniques in PRES have recently been described as an adjunct tool in difficult or equivocal cases. These advanced imaging techniques include: CT/MR perfusion, MR Spectroscopy (MRS), Susceptibility weighted

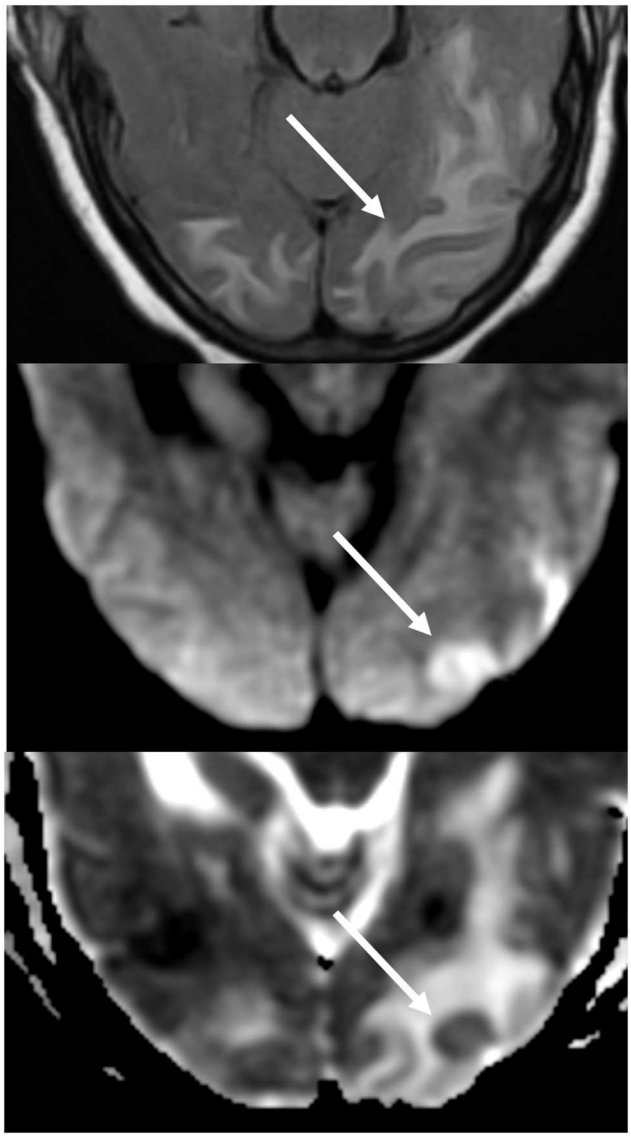


FIGURE 7 | Patient with uncontrolled hypertension presenting with alteration of mental status. T2-FLAIR (top) image demonstrates edema in the occipital lobes. DWI (middle) and ADC map (bottom) images demonstrates a small arrow of restricted diffusion, with hyperintense signal on DWI and corresponding hypointensity on the ADC map.

imaging (SWI), and nuclear medicine techniques, including single-photon emission tomography (SPECT) and positron emission tomography (PET) with varying radiotracers. Although a full discussion is beyond the scope of this review, a variety of imaging findings can be seen on these advanced techniques to help suggest a diagnosis of PRES. Hyperperfusion may be seen on CT/MR perfusion studies demonstrated by increased cerebral blood flow and blood volume with reduced time to perfusion and mean transit time (32) although cases of hypoperfusion have been reported (33). On MRS, there is generally a reduction in the N-Acetylaspartate (NAA)/Creatine (Cr) and NAA/Choline (Chol) ratio, suggestive of a disruption of normal synapses and neuroaxonal function (34). SWI can help to identify the presence of hemorrhage in PRES, with higher sensitivity than GRE imaging (35). SPECT/PET imaging typically demonstrates either hyperperfusion or hypoperfusion (similar to CT/MR perfusion studies) with low metabolism by FDG-PET (36).

Additionally, PRES can be distinguished from other conditions such as autoimmune encephalitis in the setting of acute disseminated encephalomyelitis (ADEM) by the former's diffuse bilateral but asymmetric vasogenic edema (37). PML may have a similar appearance when compared to PRES, having a parieto-occipital predominance, but may be distinguished by its more unilateral or asymmetric involvement, as well as predilection for subcortical white matter (38).

ATYPICAL IMAGING FEATURES

Atypical features of PRES include areas of contrast enhancement, hemorrhage, or diffusion restriction (39). Although the parietal and occipital lobes are generally involved, atypical areas of involvement may be seen, including: brainstem, cerebellum, corpus callosum, and other cerebral areas, with more common areas including the frontal lobes (seen in up to 68%) and inferior temporal lobes (up to 40%) (23, 40) (**Figure 6**: Cerebellum; **Figure 7**: Brainstem).

Additionally, an early finding of PRES, which may precede the typical parieto-occipital edema includes mild sulcal FLAIR hyperintensity and leptomeningeal enhancement on post-contrast T1 weighted images, as described by Nakagawa et al. (41). Benziada-Boudour et al. (42) described a concurrent development of cytotoxic edema, resulting in restricted diffusion (**Figure 8**: Diffusion Restriction). Inherent in the name of the disease process, the findings related to PRES are usually reversible, with normalization of clinical and imaging findings once the inciting issue is treated. However, in some cases, areas of restricted diffusion can ultimately result in permanent injury to the brain parenchyma (**Figure 9**: Laminar Necrosis). Hemorrhage is less commonly seen in PRES, occurring in 5–30% of cases, but should be recognized as to not mistake this finding for another pathological entity in the appropriate clinical setting of PRES (39). Imaging findings in hemorrhage may include: focal hematoma, petechial gyral hemorrhage, and/or subarachnoid hemorrhage (43) (**Figure 10**: Hemorrhage).

TREATMENT

Treatment of PRES is typically aimed at controlling the primary etiology causing PRES (44). For example, in cases of elevated arterial pressures, treatment is aimed at correcting the elevated blood pressures in a controlled environment, similar to the approach for hypertensive urgency/ emergency (45). Typically, a non-rapid reduction in blood pressure is sought to avoid the risk of causing ischemic cerebral

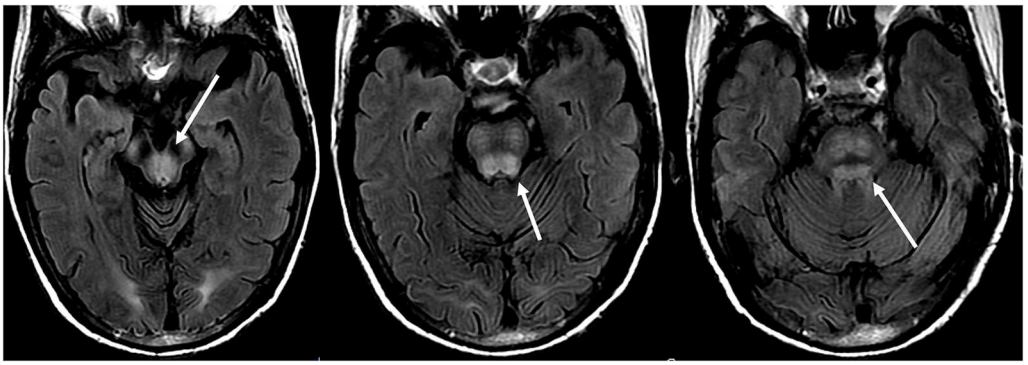


FIGURE 8 | Patient with a history of liver transplantation two weeks earlier on Tacrolimus. T2-FLAIR images show signal abnormality within the midbrain, pons, and superior cerebellar peduncles.

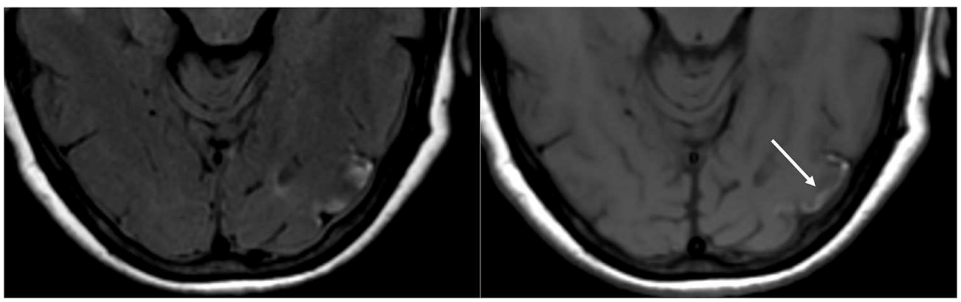


FIGURE 9 | T2-FLAIR (left) image in a patient with uncontrolled hypertension and prior imaging indicating PRES (see **Figure 6**), now controlled and 6 weeks later, demonstrates resolution of the previously seen edema. Small areas of gliosis due to injury are seen in the left temporal lobe. Axial non-contrast T1 shows curvilinear cortical laminar necrosis related to the prior injury related to PRES. While PRES generally is fully reversible, it may result in permanent injury in some situations.

disease as a result of drastic blood pressure lowering (46). Occasionally, anticonvulsant medications are used as adjunct therapy, although the optimal agent(s), timing, and length of treatment remain controversial (4) (**Figure 11**: Before and After).

In cases of (pre)eclampsia, treatment is aimed at the timely delivery of the fetus as well as blood pressure management and magnesium sulfate for seizure prophylaxis (47). In the setting of PRES induced by chemotherapeutic or other immunosuppression agents, tapering or absolute discontinuation of the drug has shown both clinical and radiological improvement (48) (**Figure 12**: Eclampsia). Hypomagnesemia is a common finding in PRES and a possible etiological factor. Hence, authors have suggested that magnesium supplementation may be a useful adjunct in PRES management (49).

CONCLUSION

PRES is a unique entity with characteristic clinical and neuroradiological findings, in addition to myriad well-documented causes. Although the precise pathophysiologic mechanism(s) behind PRES has yet to be elucidated (and indeed may be due to a combination of interrelated processes), the generally accepted mechanism is dysfunction of the blood-brain

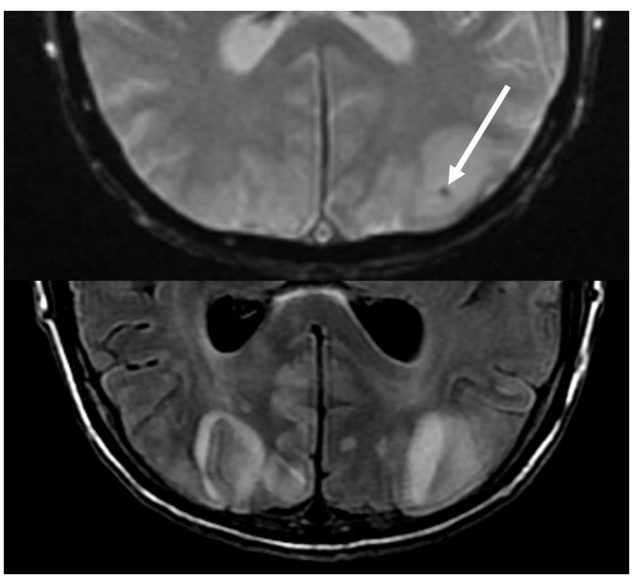


FIGURE 10 | Patient with a prior liver transplantation on Tacrolimus. T2 gradient recalled echo (top) demonstrates a focal area of hemorrhage within the vasogenic edema in the left occipital lobe. T2-FLAIR demonstrates the more typical finding related to PRES with signal abnormality in the bilateral occipital lobes.

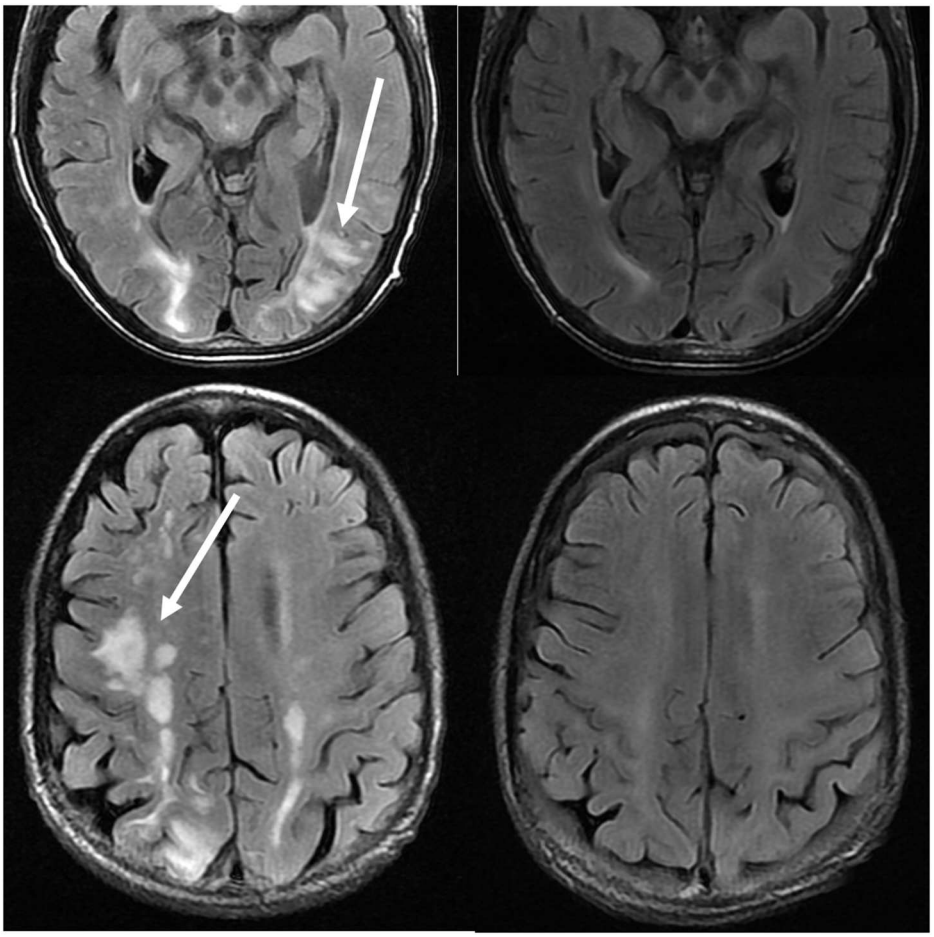


FIGURE 11 | Patient with a history of primary myelofibrosis and bone marrow transplant on Tacrolimus. Axial T2-FLAIR images demonstrate the areas of signal abnormality in the parietal and occipital lobes, and right frontal lobe (left images). The Tacrolimus was stopped and the follow up images (right images) were obtained 6 weeks after the initial images.

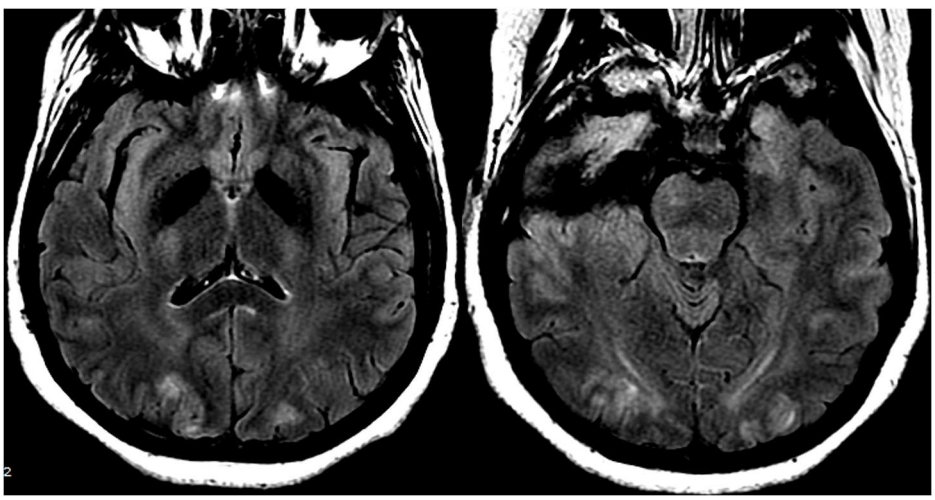


FIGURE 12 | Patient with eclampsia and presenting with seizure. Axial T2-FLAIR images demonstrate symmetric signal abnormality in the bilateral occipital lobes.

barrier resulting in vasogenic edema with posterior-circulation predominance. Imaging features are best evaluated on fluid-sensitive MR sequences which reveal parieto-occipital predominant white matter T2 hyperintensities, although many atypical imaging features can be seen and should be kept in mind when evaluating challenging cases. Various advanced imaging tools are available to help in difficult or equivocal cases. Treatment is aimed at managing the underlying cause with specific attention to blood pressure monitoring and possible seizure prophylaxis.

AUTHOR CONTRIBUTIONS

R-CA and JA: Contributions to the manuscript, figures, and tables. VP: Contributions to the manuscript and figures. NS-B, CL, AR, MS, PK, JG, and AL: Contributions to the manuscript.

REFERENCES

1. Bartynski WS. Posterior reversible encephalopathy syndrome, Part 1: fundamental imaging and clinical features. *Am J Neuroradiol.* (2008) 29:1036–42. doi: 10.3174/ajnr.A0928
2. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* (1996) 234:494–500. doi: 10.1056/NEJM199602223340803
3. Bartynski WS. Posterior reversible encephalopathy syndrome, Part 2: controversies surrounding pathophysiology of vasogenic edema. *Am J Neuroradiol.* (2008) 29:1043–9. doi: 10.3174/ajnr.A0929
4. Lamy C, Oppenheim C, Mas JL. Posterior reversible encephalopathy syndrome. *Handb Clin Neurol.* (2014) 121:1687–701. doi: 10.1016/B978-0-7020-4088-7.00109-7
5. Singer S, Grommes C, Reiner AS, Rosenblum MK, DeAngelis LM. Posterior reversible encephalopathy syndrome in patients with cancer. *Oncologist.* (2015) 20:806–11. doi: 10.1634/theoncologist.2014-0149
6. How J, Blattner M, Fowler S, Wang-Gillam A, Schindler SE. Chemotherapy-associated posterior reversible encephalopathy syndrome: a case report and review of the literature. *Neurologist.* (2016) 21:112–7. doi: 10.1097/NRL.0000000000000105
7. Habetz K, Ramakrishnaiah R, Raina SK, Fitzgerald RT, Hinduja A. Posterior reversible encephalopathy syndrome: a comparative study of pediatric versus adult patients. *Pediatr Neurol.* (2016) 65:45–51. doi: 10.1016/j.pediatrneurol.2016.09.001
8. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol.* (2015) 14:914–25. doi: 10.1016/S1474-4422(15)00111-8
9. Zama, D, Gasperini P, Berger M, Petris M, De Pasquale MD, et al. A survey on hematology-oncology pediatric AIEOP centres: the challenge of posterior reversible encephalopathy syndrome. *Eur J Haematol.* (2018) 100:75–82. doi: 10.1111/ejh.12984
10. Khan SJ, Arshad AA, Fayyaz MB, ud din Mirza I. Posterior reversible encephalopathy syndrome in pediatric cancer: clinical and radiologic findings. *J Glob Oncol.* (2018) 4:JGO.17.1-8. doi: 10.1200/JGO.17.00089
11. Kim SJ, Im SA, Lee JW, Chung NG, Cho B, et al. Predisposing factors of posterior reversible encephalopathy syndrome in acute childhood leukemia. *Pediatr Neurol.* (2012) 47:436–42. doi: 10.1016/j.pediatrneurol.2012.07.011
12. Gupta V, Bhatia V, Khandelwal N, Singh P, Singhi P. Imaging findings in pediatric posterior reversible encephalopathy syndrome (PRES): 5 years of experience from a tertiary care center in India. *J Child Neurol.* (2016) 31:1166–73. doi: 10.1177/0883073816643409
13. Hinduja A, Habetz K, Raina S, Ramakrishnaiah R, Fitzgerald RT. Predictors of poor outcome in patients with posterior reversible encephalopathy syndrome. *Int J Neurosci.* (2017) 127:134–44. doi: 10.3109/00207454.2016.1152966
14. Paulson OB, Waldemar G, Schmidt JF, Strandgaard S. Cerebral circulation under normal and pathologic conditions. *Am J Cardiol.* (1989) 63:2C−5C. doi: 10.1016/0002-9149(89)90396-2
15. MacKenzie ET, Strandgaard S, Graham DI, Jones JV, Harper AM, Farrar JK. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood brain barrier. *Circ Res.* (1976) 39:33–41. doi: 10.1161/01.RES.39.1.33
16. Bartynski WS, Zeigler Z, Spearman MP, Lin L, Shadduck RK, Lister J. Etiology of cortical and white matter lesions in Cyclosporin-A and FK-506 neurotoxicity. *Am J Neuroradiol.* (2001) 22:1901–14.
17. Dijkstra K, Hofmeijer J, van Gils SA, van Putten MJAM. A biophysical model for cytotoxic cell swelling. *J Neurosci.* (2016) 36:11881–90. doi: 10.1523/JNEUROSCI.1934-16.2016
18. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol.* (2017) 264:1608–16. doi: 10.1007/s00415-016-8377-8
19. Feske SK. Posterior reversible encephalopathy syndrome: a review. *Sem Neurol.* (2011) 31:202–15. doi: 10.1055/s-0031-1277990
20. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. *Med Hypotheses.* (2014) 82:619–22. doi: 10.1016/j.mehy.2014.02.022
21. Bartynski WS, Boardman JF, Zeigler ZR, Shadduck RK, Lister J. Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. *Am J Neuroradiol.* (2006) 27:2179–90.
22. Mayama M, Uno K, Tano S, Yoshihara M, Ukai M, Kishigami Y, et al. Incidence of posterior reversible encephalopathy syndrome in eclamptic and patients with preeclampsia with neurologic symptoms. *Am J Obstet Gynecol.* (2016) 215:239.e1–e5. doi: 10.1016/j.ajog.2016.02.039
23. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *Am J Roentgenol.* (2007) 189:904–12. doi: 10.2214/AJR.07.2024
24. de Havenon A, Joos Z, Longenecker L, Shah L, Ansari S, Digre K. Posterior reversible encephalopathy syndrome with spinal cord involvement. *Neurology.* (2014) 83:2002–6. doi: 10.1212/WNL.0000000000001026
25. Ho ML, Rojas R, Eisenberg RL. Cerebral edema. *Am J Roentgenol.* (2012) 199:W258–73. doi: 10.2214/AJR.11.8081
26. Dandoy CE, Linscott LL, Davies SM, Leach JL, Myers KC, El-Bietar J, et al. Clinical utility of computed tomography and magnetic resonance imaging for diagnosis of posterior reversible encephalopathy syndrome after stem cell transplantation in children and adolescents. *Biol Blood Marrow Transplant.* (2015) 21:2028–32. doi: 10.1016/j.bbmt.2015.07.023
27. Hugonnet E, Da Ines D, Boby H, Claise B, Petitcolin V, Lannareix V, et al. Posterior reversible encephalopathy syndrome (PRES): features on CT and MR imaging. *Diagn Interv Imaging.* (2013) 94:45–52. doi: 10.1016/j.diii.2012.02.005
28. Ducros A. Reversible cerebral vasoconstriction syndrome. *Lancet Neurol.* (2012) 11:906–17. doi: 10.1016/S1474-4422(12)70135-7
29. Miller TR, Shivashankar R, Mossa-Basha M, Gandhi D. Reversible cerebral vasoconstriction syndrome, part 1: epidemiology, pathogenesis, and clinical course. *Am J Neuroradiol.* (2015) 36:1392–9. doi: 10.3174/ajnr.A4214
30. Noda K, Fukae J, Fujishima K, Mori K, Urabe T, Hattori N, et al. Reversible cerebral vasoconstriction syndrome presenting as subarachnoid hemorrhage, reversible posterior leukoencephalopathy, and cerebral infarction. *Intern Med.* (2011) 50:1227–33. doi: 10.2169/internalmedicine.50.4812
31. Doelken M, Lanz S, Rennert J, Alibek S, Richter G, Doerfler A, et al. Differentiation of cytotoxic and vasogenic edema in a patient with reversible posterior leukoencephalopathy syndrome using diffusion-weighted MRI. *Diagn Interv Radiol.* (2007) 13:125–8.
32. Wartenberg KE, Parra A. CT and CT-perfusion findings of reversible leukoencephalopathy during triple-H therapy for symptomatic subarachnoid hemorrhage-related vasospasm. *J Neuroimaging.* (2006) 16:170–5. doi: 10.1111/j.1552-6569.2006.00031.x
33. Vanacker P, Matias G, Hagmann P, Michel P. Cerebral hypoperfusion in posterior reversible encephalopathy syndrome is different from

transient ischemic attack on CT perfusion. *J Neuroimaging.* (2015) 25:643–6. doi: 10.1111/jon.12158
34. Lee SY, Kim SH, Lee SH, Baek HJ, Shon HS, Kim SS. Serial MR spectroscopy in relapsing reversible posterior leukoencephalopathy syndrome. *Neurologist.* (2009) 15:338–41. doi: 10.1097/NRL.0b013e31819 14af6
35. McKinney AM, Sarikaya B, Gustafson C, Truwit CL. Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging. *Am J Neuroradiol.* (2012) 33:896–903. doi: 10.3174/ajnr.A2886
36. Pavlakis SG, Frank Y, Kalina P, Chandra M, Lu D. Occipital-parietal encephalopathy: a new name for an old syndrome. *Pediatr Neurol.* (1997) 16:145–8. doi: 10.1016/S0887-8994(96)00292-5
37. Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. *Neurology.* (2016) 87(9 Suppl 2):S38–45. doi: 10.1212/WNL.0000000000002825
38. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, et al. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. *Neurology.* (2013) 80:1430–8. doi: 10.1212/WNL.0b013e31828c2fa1
39. Aracki-Trenkić A, Stojanov D, Trenkić M, Radovanović Z, Ignjatović J, Ristić S, et al. Atypical presentation of posterior reversible encephalopathy syndrome: clinical and radiological characteristics in eclamptic patients. *Bosn J Basic Med Sci.* (2016) 16:180–6. doi: 10.17305/bjbms.201 6.1201
40. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *Am J Neuroradiol.* (2007) 28:1320–7. doi: 10.3174/ajnr.A0549
41. Nakagawa K, Sorond FA, Ropper AH. Ultra-early magnetic resonance imaging findings of eclampsia. *Arch Neurol.* (2008) 65:974–6. doi: 10.1001/archneur.65.7.974
42. Benziada-Boudour A, Schmitt E, Kremer S, Foscolo S, Rivière AS, Tisserand M, et al. Posterior reversible encephalopathy syndrome: a case of unusual diffusion-weighted MR images. *J Neuroradiol.* (2009) 36:102–5. doi: 10.1016/j.neurad.2008.08.003
43. Donmez FY, Basaran C, Kayahan Ulu EM, Yildirim M, Coskun M. MRI features of posterior reversible encephalopathy syndrome in 33 patients. *J Neuroimaging.* (2010) 20:22–8. doi: 10.1111/j.1552-6569.2008.00306.x
44. Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. Posterior reversible encephalopathy syndrome-Insight into pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev.* (2015) 14:830–6. doi: 10.1016/j.autrev.2015.05.006
45. Pak KJ, Hu T, Fee C, Wang R, Smith M, Bazzano LA. Acute hypertension: a systematic review and appraisal of guidelines. *Ochsner J.* (2014) 14:655–63.
46. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol.* (2010) 67:564–9. doi: 10.1001/archneurol.2010.70
47. Cozzolino M, Bianchi C, Mariani G, Marchi L, Fambrini M, Mecacci F. Therapy and differential diagnosis of posterior reversible encephalopathy syndrome (PRES) during pregnancy and postpartum. *Arch Gynecol Obstet.* (2015) 292:1217–23. doi: 10.1007/s00404-015-3800-4
48. Masetti R, Cordelli DM, Zama D, Vendemini F, Biagi C, Franzoni E, et al. PRES in children undergoing hematopoietic stem cell or solid organ transplantation. *Pediatrics.* (2015) 135:890–901. doi: 10.1542/peds.2014-2325
49. Chardain A, Mesnage V, Alamowitch S, Bourdain F, Crozier S, Lenglet T, et al. Posterior reversible encephalopathy syndrome (PRES) and hypomagnesemia: a frequent association? *Rev Neurol (Paris).* (2016) 172:384–8. doi: 10.1016/j.neurol.2016.06.004

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 23 June 2020
doi: 10.3389/fneur.2020.00591

Cerebrospinal Fluid Hypovolemia and Posterior Reversible Encephalopathy Syndrome

Yuan-yuan Zheng[1†], *Xiong-peng Weng*[1†], *Fang-wang Fu*[1†], *Yun-gang Cao*[1], *Yan Li*[1], *Guo-qing Zheng*[1] *and Wei Chen*[2*]

[1] Department of Neurology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China, [2] Department of Radiology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China

Posterior reversible encephalopathy syndrome (PRES) is a reversible neuroradiological syndrome characterized by reversible vasogenic edema. The pathophysiological mechanism is still unclear, but PRES may be triggered by various etiologies. To date, only a few PRES cases linked to cerebrospinal fluid (CSF) hypovolemia were reported. The association between PRES and CSF hypovolemia needs to be explored. We presented a case of PRES with CSF hypovolemia as a result of an inadvertent dural puncture and reviewed the literature to identify the clinical characterization and pathophysiological mechanism of PRES following CSF hypovolemia. A total of 31 cases of PRES-CSF hypovolemia was included for analysis. The median age was 33 years, with a notable female predominance (87.1%). Fifteen patients (48.4%) didn't have either a history of hypertension nor an episode of hypertension. The most common cause of CSF hypovolemia was epidural or lumbar puncture ($n = 21$), followed by CSF shunt ($n = 6$). The median interval between the procedure leading to CSF hypovolemia and PRES was 4 days. Seizure, altered mental state, and headache were the most frequent presenting symptom. The parietooccipital pattern was most frequent (71.0%). Conservative management remains the mainstay of treatment with excellent outcomes. Three patients had a second episode of PRES. CSF hypovolemia is a plausible cause of PRES via a unique pathophysiologic mechanism including arterial hyperperfusion and venous dysfunction. Patients with CSF hypovolemia is more susceptible to PRES, which is potentially life-threatening. Given that CSF hypovolemia is a common complication of anesthetic, neurological, and neurosurgical procedures, PRES should be early considered for prompt diagnosis and appropriate management.

Keywords: posterior reversible encephalopathy syndrome, cerebrospinal fluid hypovolemia, intracranial hypotension, dural puncture, epidural analgesia, cerebral hyperperfusion

OPEN ACCESS

Edited by:
Bo Gao,
Affiliated Hospital of Guizhou Medical University, China

Reviewed by:
Chenguang Zhou,
Fifth Affiliated Hospital of Zhengzhou University, China
Brian Jeremy Williams,
University of Louisville, United States

***Correspondence:**
Wei Chen
13676775267@163.com

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Applied Neuroimaging, a section of the journal Frontiers in Neurology

Received: *19 September 2019*
Accepted: *22 May 2020*
Published: *23 June 2020*

Citation:
Zheng Y, Weng X, Fu F, Cao Y, Li Y, Zheng G and Chen W (2020) Cerebrospinal Fluid Hypovolemia and Posterior Reversible Encephalopathy Syndrome. Front. Neurol. 11:591. doi: 10.3389/fneur.2020.00591

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES), initially described by Hinchey et al. in 1996 (1), refers to a reversible clinical and neuroradiological syndrome characterized by acute headache, seizures, visual disturbances, impaired consciousness, focal neurological deficits, or combinations of them (2). The typical finding in neuroimaging is reversible vasogenic edema in subcortical

white matter dominating in the bilateral posterior parieto-occipital region (2, 3). An increasing number of predisposing factors for PRES have been recognized including eclampsia, hypertensive crisis, organ transplantation, sepsis, subarachnoid hemorrhage (SAH), autoimmune disorders, renal insufficiency, and various immunosuppressive drugs (2, 4). The mechanism of PRES remains controversial. Hypertension/hyperperfusion theory and vasoconstriction/hypoperfusion theory have been commonly proposed to explain the pathophysiology of PRES (2, 5).

Cerebrospinal fluid (CSF) hypovolemia, which is used to be referred to as intracranial hypotension (IH) synonymously, is increasingly recognized as a critical but often a misdiagnosed cause of new-onset cephalalgia (6, 7). Usually, it included IH, but it was not an unequivocal definition of IH as a normal or even an increased CSF pressure was not rare in reported cases (8). It is usually triggered by dural puncture, lumbar puncture, spinal surgery, lumboperitoneal shunt, or other spontaneous reasons (6). Atypical clinical presentations including non-orthostatic headaches, visual defects, neurocognitive decline, epilepsy, and focal neurological deficits, which are similar to PRES, have already been reported. Recently, the association between PRES and CSF hypovolemia has started to emerge in the neurology (9–17), neurosurgery (18–24), and anesthesiology literature (10–13, 16, 19, 25–35). However, the association between PRES and CSF hypovolemia has not been fully elucidated.

To our knowledge, there was no systematic review exploring the pathogenesis, clinical and imaging characteristics, and management of PRES in patients with CSF hypovolemia. Herein, a case of PRES who suffered CSF hypovolemia after an inadvertent dural puncture was presented with potential evidence of hyperperfusion. Then, a systematic analysis of published literature was undertaken to reveal the possible association between PRES and CSF hypovolemia.

METHODS

The information of the patient from the department of Neurology of our hospital was collected for a preliminary analysis. The additional 30 cases (29 articles) in the PubMed and Web of Science database from inception to July 2019 using a combination with "PRES" and various terms related to CSF hypovolemia or high risks of CSF hypovolemia including "cerebrospinal fluid hypovolemia," "intracranial hypotension," "CSF leakage," "epidural puncture," "epidural anesthesia," "spinal puncture," "spinal anesthesia," "lumbar puncture," "cerebrospinal fluid shunt," "spinal surgery," and "cranial surgery." A standardized form was applied to collect clinical information from each eligible article including demographic characteristics, related medical history, the probable cause of CSF hypovolemia, clinical manifestations, magnetic resonance (MR) findings (both PRES and CSF hypovolemia), treatment, and clinical outcome. The flow diagram was shown in the **Supplementary Material**.

Written informed consent for participation, data collection, and publication was obtained from the patient. Because this is a case report and review of literature, no research legal, and ethical approval is required.

Case Presentation

A 30-year-old woman, gravida 3 para 0, without a previous history of hypertension, presented to the Department of Obstetrics at 40 weeks' gestation. Laboratory investigations at admission remained within the normal range. Epidural analgesia was planned for painless labor. An inadvertent dural puncture occurred in the first procedure. Then, no complication was found in the repeated epidural procedure. Her blood pressure remained consistently normal throughout labor, delivery, and the immediate postpartum period. Two hours after delivery, she complained of mild neck pain that resolved after receiving 2,000 ml Ringer's solution.

On postpartum day 2, she developed a moderate postural occipital headache. In the absence of other focal neurological deficits, postdural puncture headache was diagnosed. The patient was managed with non-steroidal anti-inflammatory agents, hydration, and strictly bed rest. The epidural blood patch (EBP) was recommended as the following therapeutic measure, but the patient refused. On postpartum day 3, the patient complained of progressively worsening postural headache, nausea, and photophobia. The patient had to keep a recumbent posture to relief. The blood pressure was noted elevate to an average level of 140/85 mmHg and a highest-level of 178/96 mmHg. Nifedipine was taken to control hypertension. Then, the blood pressure was under 150/90 mmHg. On the early morning of postpartum day 4, the patient became confused when she waked up and turned to a supine position with a blood pressure of 131/90 mmHg. After a few minutes, she had a generalized tonic-clonic seizure which was controlled by diazepam. After she regained consciousness, she complained of diplopia and severe headache in occipital and left frontal region. Neurological examination revealed left abducens nerve palsy, right hemianesthesia, horizontal nystagmus, right tongue paralysis, and right Babinski sign. Diazepam and magnesium sulfate were taken with a concern that the patient was developing postpartum eclampsia. Six hours later, brain magnetic resonance imaging revealed vasogenic edema in the bilateral parieto-occipital regions, basal ganglia, and brainstem (**Figures 1A–E**). Convexity SAH was identified in the left frontal lobes (**Figure 1C**). MR angiography and venography were negative for aneurysms, venous thrombosis, and cerebral vasospasm (**Figures 2A,B**). The arterial spin labeling perfusion (ASL) imaging showed hyperperfusion areas in the bilateral occipitoparietal lobe (**Figure 2F**). On susceptibility-weighted imaging (SWI), the commonly marked hypointensity of the cerebral deep venous system was absent, suggestive of blood oxygen level dependent (BOLD) effect probably induced by cerebral hyperperfusion (**Figure 2E**). In addition, brain MR showed signs of intracranial hypotension including diffuse enhancement of the dura (**Figures 2C,D**), mild enlargement of pituitary and dural sinuses (**Figure 1F**), and slightly sagging of brainstem and cerebellum (**Figure 1F**). Thus, PRES and IH was the diagnosis. Over the following hours, the patient remained normal blood pressure and seizure-free. Magnesium sulfate infusion and diazepam were stopped. The patient was treated

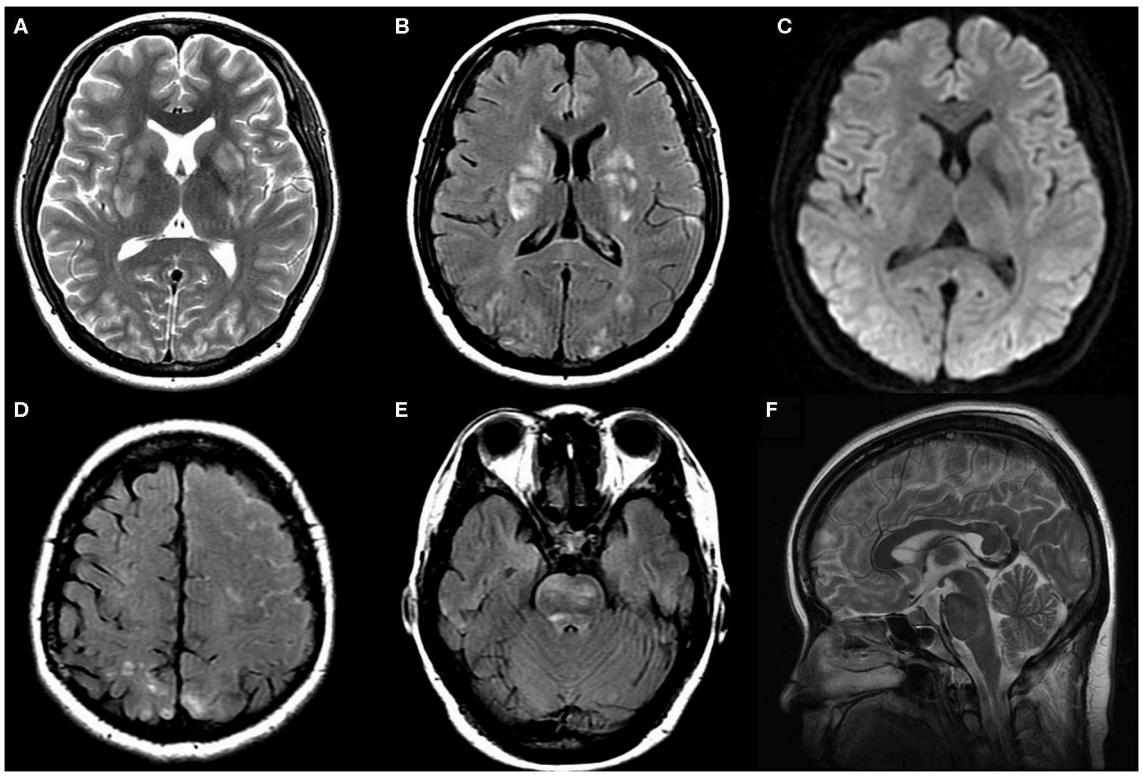


FIGURE 1 | Axial T2WI **(A)**, axial FLAIR **(B,D,E)**, axial DWI **(C)** and sagittal T2WI **(F)** images at symptom onset: T2WI, FLAIR, and DWI images demonstrated hyperintensity without diffusion restriction in bilateral parieto-occipital region, basal ganglia, and brainstem. FLAIR images demonstrated left frontoparietal sulcus subarachnoid hemorrhage. Axial T2WI images demonstrated mild enlargement of pituitary and dural sinuses.

with intravascular rehydration which was used to prevent the progression of IH and SAH-induced cerebrovascular spasm. On postpartum day 14, the patient had a full recovery without any headache and neurological deficits. Follow-up MR imaging showed the complete disappearance of vasogenic edema, venous engorgement and convexity SAH (**Figures 3A–D**), together with the normalization of the signal of the deep venous system in SWI (**Figure 3E**) and the cerebral blood flow (CBF) in the bilateral occipitoparietal lobe (**Figure 3F**).

RESULTS

In total, we collected the data on 31 patients (30 patients from literature and our patient) for descriptive analysis. The detailed data of cases were summarized in **Table 1**.

Clinical Characteristics

The clinical characteristics of patients with PRES and CSF hypovolemia were listed in **Table 2**. The median age was 33 years (range: 16–82 years). There was a female predominance (27 females, 87.1%). Thirty patients were associated with one or more known offending factors, most commonly hypertension ($n = 16$), pregnancy ($n = 14$), pre-eclampsia or eclampsia ($n = 5$), subarachnoid hemorrhage ($n = 2$). Five patients had a history of hydrocephalus or intracranial hypertension. Fifteen patients (48.4%) didn't have either a history of hypertension nor an episode of hypertension. The reduction of CSF was resulted from epidural or lumbar puncture ($n = 21$), CSF shunt ($n = 6$), spinal surgery ($n = 2$), head trauma ($n = 1$). Excluding patient 29 who had no exact date of the onset time of PRES (17), the median interval between the procedure leading to CSF reduction and the onset of PRES was 4 days, varying from 2 h to 7 weeks. Headache (71%) was the most common symptom preceding the PRES. Only one patient had a severe elevation of systolic blood pressure more than 200 mmHg. Seizure (83.9%) is the most common neurological symptom in PRES patients with CSF hypovolemia, following by headache (71.0%), altered mental state (64.5%), visual disturbances (41.9%), and hemiparesis (12.9%). Mild edema (51.6%) was most frequent, while the parieto-occipital pattern was most frequent (71.0%). In 80.6% of PRES-CSF hypovolemia patients, follow-up neuroimaging was performed. Of them, complete or nearly complete resolution of edematous lesions was noted in 80.0% of the patients, while 87.1% of the patients had a complete clinical recovery. Three of PRES-CSF hypovolemia patients had a recurrence of PRES after another experience of CSF reduction (22, 24, 36).

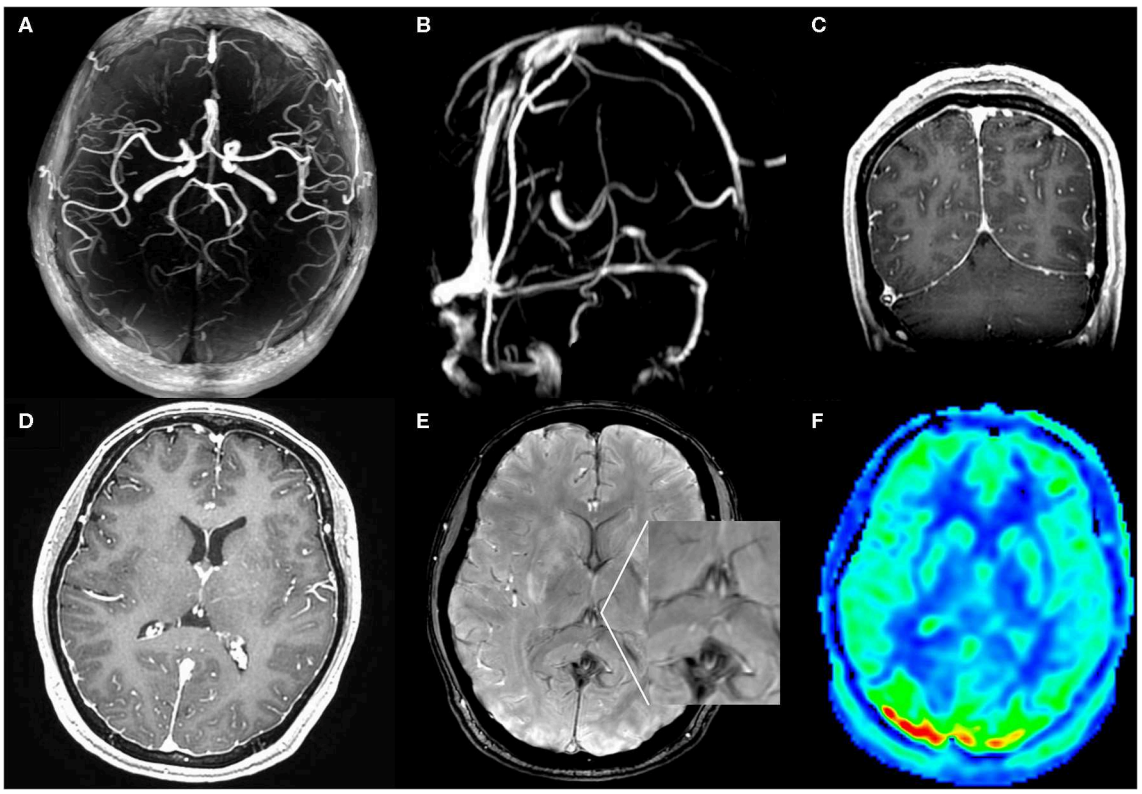


FIGURE 2 | MR angiography **(A)**, MR venography **(B)**, post contrast T1WI **(C,D)**, SWI **(E)**, and ASL **(F)** MRI images at symptom onset: MR angiography and venography were negative for aneurysms, venous thrombosis, and cerebral vasospasm. SWI images showed lack of the normal hypointensity in deep venous system. Coronal and axial T1WI images with gadolinium-enhancement showed diffuse enhancement of the dura. ASL images showed hyperperfusion areas in bilateral occipitoparietal lobe.

DISCUSSION

PRES is commonly described as a neuroradiological disease entity characterized by reversible vasogenic edema in the subcortical white matter of bilateral posterior parieto-occipital region with a rapid onset of neurological deficits including seizures, headache, visual disturbances, and altered mental state (2, 4). With the wide application of MR scans, PRES has been much more often recognized in the past decade. The precise pathophysiology underlying PRES is not entirely established. Two contradictory hypotheses are commonly cited (2, 5). The most recognized "Hypertension/hyperperfusion" theory, also called "vasogenic" theory, proposes that severe hypertension, which may overcome the limits of cerebral autoregulation, induces secondary cerebral hyperperfusion leading to an excess of cerebral blood flow, then alterations to the vascular permeability, disruptions to the blood-brain barrier, extravasations of plasma, and subsequent vasogenic edema (2, 5). This concept is primarily supported by the common presence of significant elevation of blood pressure in patients with PRES. Increased perfusion in the vasogenic edema area has been shown in case reports using ASL MRI or CT perfusion (38, 39). Nevertheless, 30–50% of patients with PRES show normal blood pressure or only slightly-to-moderate elevated blood pressure which may not exceed the auto-regulatory limits. The other theory "vasoconstriction/hypoperfusion" theory, or called "endothelial dysfunction" theory, purports that systemic toxicity induces endothelial dysfunction that leads to vascular instability, cerebral vasoconstriction, local hypoperfusion, and subsequent edema (5). This theory is supported by recent vessel imaging and perfusion imaging studies, which have demonstrated diffuse or focal cerebral vasoconstriction, and cerebral hypoperfusion in lesional areas (40). Other proposed theories, such as "cytotoxic" theory, "immunogenic" theory, "neuropeptide" theory, share a similar pathophysiologic mechanism with "vasoconstriction/hypoperfusion" theory (2).

Our case had no stigmata of pre-eclampsia or eclampsia, and the blood pressure maintained normal before and during delivery. She only showed an averaged MAP level of 105 mmHg and a peak mean artery pressure (MAP) level of 123 mmHg after delivery. Did hypertension lead to PRES? Our patient complained postural headache before the changes in blood pressure, and the development of hypertension was following the deterioration of headache. On the other hand, the patient only had a slight elevation of averaged MAP. Even the maximum blood pressure didn't exceed the upper MAP limits of autoregulation. Although puerperium might reduce the threshold of PRES, it is likely that hypertension is not pinpointed as the major cause of PRES. In

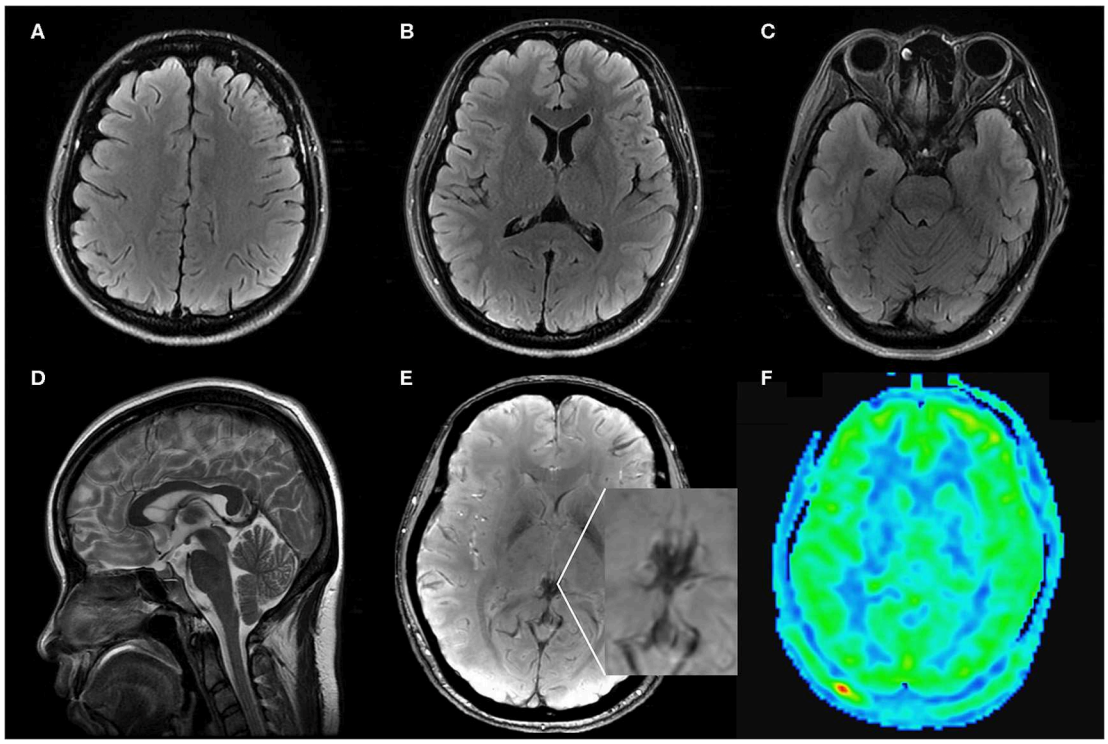


FIGURE 3 | Axial FLAIR **(A–C)**, sagittal T2WI **(D)**, SWI **(E)**, ASL **(F)** MRI images on follow up: Axial FLAIR imaging demonstrated complete regression of vasogenic edema and convexity SAH. Sagittal T2WI images showed regression of the engorgement of the pituitary and dural sinuses. SWI and ASL images showed the normalization of the signal of the deep venous system and the CBF in bilateral occipitoparietal lobe.

our review, only 16 patients had hypertension (11–14, 17, 18, 23, 25–29, 31, 32, 34, 37), while only one patient had systolic blood pressure more than 200 mmHg (18). Some patients even experienced hypotension during the development of the disease (11, 24). So, patients with CSF hypovolemia have a different pathophysiological process other than hypertension.

CSF hypovolemia is characterized by orthostatic headaches which almost relive after lying down (6). It was an unequivocal definition of IH characterized by low CSF pressure ($\leq$60 mmH_2O). However, nearly half of the IH patients showed normal CSF pressure (8). Even a few patients showed a CSF pressure of more than 200 mmH_2O (8). So, IH is a clinical syndrome resulting from CSF volume depletion. CSF hypovolemia was proposed to replace the definition of IH (7). The neuroradiological features include pachymeningeal enhancement, brain sagging, subdural fluid collections, pituitary hyperemia, and venous distension sign (41). Although the intracranial pressure was not measured in our case, CSF hypovolemia was well-established on clinical and neuroradiological evidence. Grelat et al. (36) reported a case of chronic hydrocephalus who presented PRES after a depletive lumbar puncture. Interestingly, the patient underwent another episode of PRES following emergency ventriculoperitoneal shunt placement. Similarly, Karakis et al. (22) presented a case of PRES in a patient with IH following lumbo-peritoneal shunt, who experienced PRES 1 week later in the setting of CSF hypovolemia resulting from CSF leakage in the lumbo-peritoneal shunt placement site. Both of them had no other trigger factors. So, it is not surprising that CSF hypovolemia plays a key role in the development of PRES via a different pathophysiology independent of hypertension. In our patient, the ASL imaging provided the evidence of cerebral hyperperfusion in basal ganglion and occipital regions. We speculated that CSF hypovolemia combined with a slight elevation of MAP precipitated PRES by inducing cerebral hyperperfusion. Cerebral perfusion pressure (CPP) is dependent on the relationship between MAP and intracranial pressure (ICP). Depends on the cerebral auto-regulation system, CPP varies from 60 to 80 mmHg. Either increased MAP or decreased ICP will lead to an increase in CPP. When the CPP overwhelms the limits of the cerebral auto-regulation system, cerebral hyperperfusion occurs. Therefore, on the base of CSF hypovolemia, either slightly elevated MAP or normal MAP can lead to cerebral hyperperfusion, endothelial dysfunction, and vasogenic edema (13, 15, 22). On the other hand, the cerebral auto-regulation system ensures a steady ICP in the encephalic space as long as possible. In accordance with the Monro–Kellie doctrine, cerebral blood flow and perfusion in cerebral arteries will firstly increase to maintain normal ICP when CSF leak. If the increased cerebral blood flow and perfusion failed to compensate for the loss of CSF completely, dural sinuses, and veins would engorge for increasing the cerebral blood volume which will

TABLE 1 | Characteristics and clinical manifestations of cases diagnosed with PRES and CSF hypovolemia.

No	References	Age/Sex	Related history	Highest BP (mmHg)	Cause of CSF leak	Clinical manifestation	Time of PRES	PRES patterns	Edema grading	Atypical image of PRES	Treatment for IH	Edema resolution	Relapse	Outcome
1	Moriarity et al. (18)	19/M	Hydrocephalus	200/130	Tumor resection, V-P shunt	Headache, altered mental status, GTCS, disturbed vision	2 h	Parieto-occipital	Severe	Cytotoxic edema	Conservative management	Incomplete	No	Mildly disconjugate gaze
2	Prout et al. (27)	32/F	Cesarean delivery	160/70	Spinal anesthesia	Headache, GTCS, disturbed vision	15 h	Parieto-occipital	Mild	Unilateral PRES	Conservative management	Complete	No	No residual deficit
3	Ho and Chan (25)	33/F	Cesarean delivery	140/80	Spinal anesthesia	Headache, altered mental status, disturbed vision, slurred speech, right-sided numbness	2 days	Parieto-occipital	Mild	Cytotoxic edema, diffuse arteries vasospasm	Conservative management	Incomplete	No	No residual deficit
4	Torrillo et al. (28)	32/F	Preeclampsia, cesarean delivery	160/90	Epidural anesthesia	Headache, disturbed vision, buzzing, nausea and vomiting, GTCS	4 days	Superior	Mild	Negative	Conservative management	Complete	No	No residual deficit
5	Hong et al. (26)	29/F	Cesarean delivery	170/100	Spinal anesthesia	Headache, GTCS, left side homonymous hemianopsia	4 days	Superior	Mild	Cytotoxic edema	EBPs, conservative management	Complete	No	No residual deficit
6	Ortiz et al. (9)	33/F	Multiple sclerosis	134/82	Lumbar puncture	Headache, blindness, altered mental status, GTCS	3 days	Parieto-occipital	Mild	Negative	Conservative management	Complete	No	No residual deficit
7	Pradhan et al. (30)	34/F	Renal transplant, prednisolone, daclizumab	Normal	Epidural anesthesia	Headache, GTCS	4 days	Parieto-occipital	Mild	Negative	EBPs, conservative management	Complete	No	No residual deficit
8	Eran and Barak (29)	51/F	Hypertension	144/88	Spinal anesthesia	Altered mental status	1 h	Parieto-occipital	Mild	Cortical and leptomeningeal enhancement	Conservative management	Nearly complete	No	No residual deficit
9	Pugliese et al. (10)	41/F	Cesarean delivery, preeclampsia	Normal	Epidural anesthesia	Headache, mild left motor syndrome, mild right anisocoria, altered mental status, GTCS	7 days	Holohemispheric	Medium	Pachimeningeal enhance	EBPs, conservative management	Nearly complete after 15 days	No	No residual deficit
10	Minai et al. (19)	36/F	Cesarean delivery	Normal	Epidural anesthesia	Neck pain and headache, GTCS, Babinski's sign	3 days	Parieto-occipital	Mild	Negative	Conservative management	ND	ND	No residual deficit
11	Yamada et al. (11)	59/F	Hypertension, ropivacaine	150/80	Epidural anesthesia	Headache, disturbed vision	4 days	Parieto-occipital	Mild	Diffuse arteries vasospasm	Conservative management	Complete	No	No residual deficit
12	Orehek et al. (12)	26/F	Pre-eclampsia	SBP 180	Epidural anesthesia	Headache, GCTS, altered mental status, conjugate left gaze	5 days	Holohemispheric	Medium	lAntracranial hemorrhage	Conservative management	ND	No	Mild left arm dysmetria
13	Sahin et al. (31)	31/F	Cesarean delivery	170/100	Spinal anesthesia	Headache, disturbed vision, GCTS, altered mental status	7 days	Central	Mild	Negative	Conservative management	Incomplete	No	No residual deficit
14	Doherty et al. (32)	19/F	Cesarean delivery	158/91	Epidural anesthesia	Headache, vomiting, photophobia, neck stiffness, disturbed vision, seizure	4 days	Parieto-occipital	Mild	Negative	Conservative management	Complete	No	No residual deficit
15	Grelat et al. (36)	69/F	Chronic hydrocephalus	Normal	Lumbar puncture	Right hemiplegia, altered mental status, deviation to right, disturbed vision, GTCS	12 h	Parieto-occipital	Severe	Negative	Conservative management	Incomplete	Yes	Hemiplegia, difficulties with executive functions
16	Rajan et al. (33)	38/F	Cesarean delivery	Normal	Spinal anesthesia	Headache, GTCS, altered mental status	3 days	Parieto-occipital	Medium	Negative	Conservative management	ND	No	No residual deficit

(Continued)

TABLE 1 | Continued

No	References	Age/Sex	Related history	Highest BP (mmHg)	Cause of CSF leak	Clinical manifestation	Time of PRES	PRES patterns	Edema grading	Atypical image of PRES	Treatment for IH	Edema resolution	Relapse	Outcome
17	Shah et al. (34)	62/F	Ischemic colitis, hypertension	190/80	Epidural anesthesia	Headache, disturbed vision, blurred discs, status epilepticus	3 days	Parieto-occipital	Severe	Negative	Conservative management	ND	No	Minor visual disturbances and memory problems
18	Hammad et al. (13)	72/M	Hypertension	170/100	Spinal anesthesia	Disturbed vision, altered mental status, GTCS	15 days	Parieto-occipital	Medium	Leptomeningeal enhancement	EBPs, conservative management, external lumbar drain, surgical repair	Complete	No	No residual deficit
19	Feil et al. (16)	19/F	Cesarean delivery	Normal	Epidural anesthesia	Headache, nausea, GTCS, altered mental status, gaze deviation to right	6 days	Central	Medium	Diffuse arteries vasospasm	EPBs, conservative management,	Complete	No	No residual deficit
20	Fok et al. (14)	33/F	Idiopathic intracranial hypertension	142/90	Lumboperitoneal Shunt	Orthostatic headache, GCTS	4 days	Parieto-occipital	Medium	Convexity SAH	Conservative management, removal of lumboperitoneal shunt	Complete	No	No residual deficit
21	Karakis et al. (22)	26/F	Cryptococcal meningitis, AIDS	Normal	Lumboperitoneal Shunt	Seizure, altered mental status	1 day	Parieto-occipital	Medium	Negative	Revision of lumboperitoneal shunt, conservative management,	ND	Yes	No residual deficit
22	Shields et al. (21)	47/F	Hypertension	Normal	Thoracotomy	GTCS, positional headache, altered mental status, disturbed vision	3 days	Parieto-occipital	Severe	Negative	Surgery repair	Minimal residual	No	Mildly blurred vision
23	Santillan et al. (15)	65/F	No	Normal		Headache, altered mental status, left Hoffmann sign	12 days	Parieto-occipital	Medium	Negative	Caffeine, conservative management, EBPs	Complete	No	No residual deficit
24	Sato et al. (20)	79/M	Subarachnoid hemorrhage	Normal	Ventriculo-peritoneal shunt	Headache, altered mental status, left hemiplegia	54 days	Parieto-occipital	Mild	Unilateral PRES	Conservative management	Minimal residual	No	No residual deficit
25	Niwa et al. (37)	72/M	Hypertension, subarachnoid hemorrhage	199/91	Continuous ventricular drainage	Altered mental status, GCTS	6 h	Central	Severe	Negative	Conservative management	Complete	No	No residual deficit
26		68/F	Obstructive hydrocephalus, hypertension	Normal	Cysto-peritoneal shunt placement	Altered mental status, GCTS	1 day	Parieto-occipital	Medium	Negative	Conservative management	Complete	No	No residual deficit
27	Yoon et al. (23)	16/F	Head Trauma, head surgery	SBP 160	Head trauma	GTCS	3 days	Superior	Medium	Negative	Conservative management	Complete	No	No residual deficit
28	Delgado-Lopez et al. (24)	82/F	L4, L5 laminectomy	Hypoten-sion	L4, L5 laminectomy	GTCS, altered mental status	3 days	Parieto-occipital	Medium	Negative	Conservative management	Complete	Yes	No residual deficit
29	Yilmaz et al. (17)	24/F	HELLP syndrome	150/100	Valsalva maneuver	GCTS, altered mental status	ND	Superior	Mild	Negative	Conservative management	Complete	No	No residual deficit
30	Yildiz et al. (35)	23/F	Cesarean section	Normal	Spinal anesthesia	Headache, altered mental status, GTCS	3 days	Parieto-occipital	Mild	Unilateral PRES	Conservative management	ND	No	No residual deficit
31	Present case	30/F	Pregnancy, vaginal delivery	178/96	Epidural anesthesia	Headache, nausea, photophobia, GCTS, diplopia, left abducens nerve palsy, right hemianesthesia, horizontal nystagmus, right tongue paralysis, and right Babinski sign	4 days	Central	Medium	Convexity SAH	Conservative management	Complete	No	No residual deficit

ND, not described; BP, blood pressure; SBP, systolic blood pressure; CSF, cerebrospinal fluid; GTCS, generalized tonic-clonic seizure; SAH, subarachnoid hemorrhage.

TABLE 2 | Clinical characteristics and neuroimaging manifestations of patients with PRES and CSF hypovolemia.

Characteristics	Cases, $n = 31$
Age	33 (26–62)
Gender (Female)	27 (87.1%)
Time to PRES onset (Median, range)	4 days (2 h to 7 weeks)
Clinical features	
Headache	22 (71.0%)
Seizure	26 (83.9%)
Disturbed vision	13 (41.9%)
Altered mental state	20 (64.5%)
Hemiparesis	4 (12.9%)
Brainstem symptom	3 (9.7%)
Babinski's sign	1 (3.2%)
Systolic blood pressure (mmHg)	
Normal (<140)	15 (48.4%)
Mild (140–169)	7 (22.6%)
Moderate (170–199)	7 (22.6%)
Severe > 200	1 (3.2%)
Edema grading	
Mild	16 (51.6%)
Medium	11 (35.5%)
Severe	5 (16.1%)
Distribution pattern	
Parieto-occipital	22 (71.0%)
Superior	4 (12.9%)
Central	3 (9.7%)
Holohemispheric	2 (6.5%)
Vasculopathy	3 (9.7%)
Complete restitution	20 (80%)*
Recurrence	3 (10%)*
Favorite outcome	26 (83.9%)

**The percentages for subcategories are based on the patients who have related data.*

lead to capillary and venous hypertension. As a result, fluids extravasated into the interstitial space and vasogenic edema occur. In addition, the brain sagging can result in mechanical traction on the vessels, particularly on the veins of Galen and straight sinus (10, 42). Indeed, the velocity of blood flow in the straight sinus was reported to be declined by an average of 47% in supine patients during and shortly after lumbar punctures (43). Therefore, it impairs the deep venous drainage, induces venous hypertension in the deep venous system, and leads to vasogenic edema dominating in the basal ganglia and occipital regions. To summarize, a combination of arterial hyperperfusion and venous dysfunction may be the pathophysiological link between PRES and CSF hypovolemia.

Some authors hypothesized that reversible cerebral vasoconstriction syndrome (RCVS) secondary to the mechanical stimuli of the sagging of the brain and its affiliations would trigger PRES (11, 16, 25). The pathophysiological mechanism and clinical manifestations of PRES and RCVS partially overlap (16). They share similar triggers, including postpartum, drugs, autoimmune disease, and transplantation. The activation of the adrenergic system is presumed to be key of the development of both diseases (16). In the literature, PRES was observed in nearly 9% of the RCVS patients (44). Vasoconstriction was found in up to 30% of patients with PRES (45). However, cerebral vasoconstriction was found only in three of the patients with PRES and CSF hypovolemia. What draws more attention is that the frequency of RCVS in patients with CSF hypovolemia is particularly low. In a MR-angiography study of a series of 56 patients with IH, only one patient was reported to show segmental stenosis of cerebral arteries (46). There was no evidence of RCVS in our case. As a result, we hypothesize that vasoconstriction/hypoperfusion is not the common etiology of PRES in patients with CSF hypovolemia.

In general, PRES is regarded as a benign disease with favorable outcomes (2, 47). Complete resolution of vasogenic edema and full recovery of neurological deficit were observed in 70–90% of patients. In fact, the poor prognosis was reported in nearly 26–36% cases. Meanwhile, the fatal outcome was documented in 8–17% cases (2). Early identification and rational treatments are crucial to reduce morbidity and mortality. The diagnosis of PRES was usually delayed in patients with CSF hypovolemia until the patients presented with epilepsy and encephalopathy. The most common initial clinical presentations of PRES in patients with CSF hypovolemia is headache which usually misleads to a diagnosis of postdural puncture headache, intracranial hypotension, or pain-related headache. In this regard, the symptom of headache was found to be not of value in the diagnosis of PRES in a retrospective study (48). Only the symptoms of visual disturbances, epilepsy, and encephalopathy are the reasonable predictor of PRES. So, in patients with substantial risk factors of CSF hypovolemia including dural puncture, lumbar puncture, lumboperitoneal shunt, ventriculoperitoneal shunt, and spinal surgery, PRES should be early considered when the clinical manifestations (e.g., epilepsy, visual disturbances, impaired consciousness, focal neurological deficits, resistant headache) could not be entirely explained by CSF hypovolemia, hypertension or other medical condition alone. Multi-spectral MRI sequences, including diffusion-weighted imaging (DWI) imaging, ASL imaging, SWI, and MR angiography, should be performed immediately to establish the diagnosis early, and prevent poor prognosis.

Clinical managements of PRES are based on the elimination of underlying trigger factors and immediate control of epilepsy. Due to the differences in pathogenesis, the treatment strategy for patients with CSF hypovolemia may differ from those with other etiology. Compared with other etiologies, PRES patients with CSF hypovolemia were likely to have a shorter median time from CSF loss to PRES onset, which support a direct link between the CSF hypovolemia and PRES. The time between the procedure that incited CSF loss and the ictus of the PRES syndrome may depend on the baseline ICP and the speed of the reduction of CSF volume or ICP. We found that seven patients experienced PRES within 1 day. Of them, five patients had intracranial hypertension before PRES onset; all of them had a rapid loss of CSF or a rapid reduction of ICP. One patient with chronic hydrocephalus developed PRES 2 h after a rapid CSF loss of 50 ml. The other patient developed PRES 6 h after a 2 h inadvertent overdrainage of 200 ml CSF. These two patients experienced PRES recurrence rapidly after another rapid reduction of CSF volume. On the

other hand, a marked increase in blood pressure may contribute to the development of PRES. Patients who experienced a systolic blood pressure more than 179 mmHg had a shorter interval of PRES onset. Base on the evidence from the reviewed reports, we propose the following recommendations: First, a precipitous reduction of CSF volume or ICP should be avoided. A graded reduction of ICP is strongly recommended in patients with intracranial hypertension, especially in patients with extremely high CSF pressures. Second, in patients with CSF hypovolemia, the treatment of CSF hypovolemia should be initiated at the early stage of the disease (49). CSF hypovolemia often recovered spontaneously. Conservative medical management could be processed, including strict supine positioning, ample hydration, analgesia, and non-steroidal drugs. Caffeine and steroids should be avoided due to the risks of RCVS which may induce PRES (9, 15). When the conservative measures failed to bring alleviation of the symptoms or in patients who present moderate and severe CSF hypovolemia, epidural blood patching is recommended as the mainstay of first-line treatment (49, 50). Surgical repair should be considered for patients with clearly identified leak sites and no response to non-surgical treatment and EBPs (50). Third, tight blood pressure control is recommended for patients with CSF hypovolemia due to the increased susceptibility to PRES with a slightly elevated MAP or even normal MAP (13, 15).

CONCLUSION

The present case and reviewed literature highlight the pathophysiological link between PRES and CSF hypovolemia. Both arterial hyperperfusion and venous dysfunction may contribute to the development of PRES in patients with CSF hypovolemia. PRES should be early considered in patients with a high risk of CSF hypovolemia when the clinical manifestations can not be explained by CSF hypovolemia or other conditions alone. Precipitous reduction of CSF should be avoided, while appropriate treatments of CSF hypovolemia should be initiated early. The blood pressure should be strictly controlled in patients with CSF hypovolemia to prevent the development of PRES and improve the clinical outcome.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FF designed the study. YZ and XW collected clinical data and wrote the manuscript. YC and YL searched the literature and edited the pictures. GZ revised the manuscript. All authors contributed to the manuscript revision and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00591/full#supplementary-material

REFERENCES

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* (1996) 334:494–500. doi: 10.1056/NEJM199602223340803
2. Liman TG, Siebert E, Endres M. Posterior reversible encephalopathy syndrome. *Curr Opin Neurol.* (2019) 32:25–35. doi: 10.1097/WCO.0000000000000640
3. Brady E, Parikh NS, Navi BB, Gupta A, Schweitzer AD. The imaging spectrum of posterior reversible encephalopathy syndrome: a pictorial review. *Clin Imaging.* (2018) 47:80–9. doi: 10.1016/j.clinimag.2017.08.008
4. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol.* (2015) 14:914–25. doi: 10.1016/S1474-4422(15)00111-8
5. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol.* (2008) 29:1043–9. doi: 10.3174/ajnr.A0929
6. Chung SJ, Kim JS, Lee MC. Syndrome of cerebral spinal fluid hypovolemia: clinical and imaging features and outcome. *Neurology.* (2000) 55:1321–7. doi: 10.1212/WNL.55.9.1321
7. Mokri B. Spontaneous cerebrospinal fluid leaks: from intracranial hypotension to cerebrospinal fluid hypovolemia–evolution of a concept. *Mayo Clin Proc.* (1999) 74:1113–23. doi: 10.4065/74.11.1113
8. Yao LL, Hu XY. Factors affecting cerebrospinal fluid opening pressure in patients with spontaneous intracranial hypotension. *J Zhejiang Univ Sci B.* (2017) 18:577–85. doi: 10.1631/jzus.B1600343
9. Ortiz GA, Bianchi NA, Tiede MP, Bhatia RG. Posterior reversible encephalopathy syndrome after intravenous caffeine for post-lumbar puncture headaches. *AJNR Am J Neuroradiol.* (2009) 30:586–7. doi: 10.3174/ajnr.A1321
10. Pugliese S, Finocchi V, Borgia ML, Nania C, Della Vella B, Pierallini A, et al. Intracranial hypotension and PRES: case report. *J Headache Pain.* (2010) 11:437–40. doi: 10.1007/s10194-010-0226-z
11. Yamada SM, Kitagawa R, Teramoto A. A case of reversible posterior leukoencephalopathy syndrome with acute hypotension. *Neurol Sci.* (2011) 32:165–8. doi: 10.1007/s10072-010-0417-z
12. Orehek EK, Burns JD, Koyfman F, Azocar RJ, Holsapple JW, Green DM. Postpartum trifecta: simultaneous eclamptic intracerebral hemorrhage, PRES, and herniation due to intracranial hypotension. *Neurocrit Care.* (2012) 17:434–8. doi: 10.1007/s12028-012-9742-9
13. Hammad T, DeDent A, Algahtani R, Alastal Y, Elmer L, Medhkour A, et al. Posterior reversible encephalopathy syndrome secondary to CSF leak and intracranial hypotension: a case report and literature review. *Case Rep Neurol Med.* (2015) 2015:538523. doi: 10.1155/2015/538523
14. Fok A, Chandra RV, Gutman M, Ligtermoet M, Seneviratne U, Kempster P. Posterior reversible encephalopathy syndrome and subarachnoid hemorrhage after lumboperitoneal shunt for fulminant idiopathic intracranial hypertension. *J Neuroophthalmol.* (2016) 36:164–6. doi: 10.1097/WNO.0000000000000355

15. Santillan A, Aamodt W, Bhavaraju-Sanka R. Pearls & Oy-sters: Spontaneous intracranial hypotension and posterior reversible encephalopathy syndrome. *Neurology.* (2016) 86:e55–7. doi: 10.1212/WNL.0000000000002349
16. Feil K, Forbrig R, Thaler FS, Conrad J, Heck S, Dorn F, et al. Reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome associated with intracranial hypotension. *Neurocrit Care.* (2017) 26:103–8. doi: 10.1007/s12028-016-0320-4
17. Yilmaz Z, Voyvoda N, Sirinocak PB, Terzi H. Association of hemolysis, elevated liver enzymes, low platelets syndrome with posterior reversible encephalopathy and intracranial hypotension. *Neurol India.* (2018) 66:226–7. doi: 10.4103/0028-3886.222856
18. Moriarity JL Jr, Lim M, Storm PB, Beauchamp NJ Jr, Olivi A. Reversible posterior leukoencephalopathy occurring during resection of a posterior fossa tumor: case report and review of the literature. *Neurosurgery.* (2001) 49:1237–9; discussion 9–40. doi: 10.1227/00006123-200111000-00040
19. Minai FN, Hasan SF, Sheerani M. Post-dural puncture posterior reversible encephalopathy syndrome. *J Coll Physicians Surg Pak.* (2011) 21:37–9.
20. Sato H, Koizumi T, Sato D, Endo S, Kato S. [Unilateral posterior reversible encephalopathy syndrome after ventriculo-peritoneal shunt for normal pressure hydrocephalus following subarachnoid hemorrhage: a case report]. *No Shinkei Geka.* (2016) 44:507–15. doi: 10.11477/mf.1436203320
21. Shields LB, Johnson JR, Shields CB. Posterior reversible encephalopathy syndrome following a thoracic discectomy-induced dural leak: case report. *J Neurosurg Spine.* (2016) 25:586–90. doi: 10.3171/2016.4.SPINE1623
22. Karakis I, Nuccio AH, Amadio JP, Fountain AJ Jr. The Monro-Kellie doctrine in action: posterior reversible leukoencephalopathy syndrome caused by intracranial hypotension from lumboperitoneal shunt placement. *World Neurosurg.* (2017) 98:868.e11–e5. doi: 10.1016/j.wneu.2016.12.046
23. Yoon JE, Lee CY, Kim HW. Posterior reversible encephalopathy syndrome after head trauma surgery in pediatric patient without any underlying disease. *Korean J Neurotrauma.* (2017) 13:167–70. doi: 10.13004/kjnt.2017.13.2.167
24. Delgado-Lopez PD, Garces-Perez G, Garcia-Carrasco J, Alonso-Garcia E, Gomez-Menendez AI, Martin-Alonso J. Posterior reversible encephalopathy syndrome with status epilepticus following surgery for lumbar stenosis and spondylolisthesis. *World Neurosurg.* (2018) 116:309–15. doi: 10.1016/j.wneu.2018.05.174
25. Ho CM, Chan KH. Posterior reversible encephalopathy syndrome with vasospasm in a postpartum woman after postdural puncture headache following spinal anesthesia. *Anesth Analg.* (2007) 105:770–2. doi: 10.1213/01.ane.0000278128.26896.b2
26. Hong J-Y, Jee YS, Lee IH, Shin JS, Choi HJ. Posterior reversible encephalopathy syndrome after cesarean section under spinal anesthesia -a case report. *Korean J Anesthesiol.* (2007) 52:S86. doi: 10.4097/kjae.2007.52.6.S86
27. Prout RE, Tuckey JP, Giffen NJ. Reversible posterior leucoencephalopathy syndrome in a peripartum patient. *Int J Obstet Anesth.* (2007) 16:74–6. doi: 10.1016/j.ijoa.2006.04.012
28. Torrillo TM, Bronster DJ, Beilin Y. Delayed diagnosis of posterior reversible encephalopathy syndrome (PRES) in a parturient with preeclampsia after inadvertent dural puncture. *Int J Obstet Anesth.* (2007) 16:171–4. doi: 10.1016/j.ijoa.2006.08.015
29. Eran A, Barak M. Posterior reversible encephalopathy syndrome after combined general and spinal anesthesia with intrathecal morphine. *Anesth Analg.* (2009) 108:609–12. doi: 10.1213/ane.0b013e31818f635e
30. Pradhan A, Jairam A, Kumar RS, Srivastava A, Srivastava A, Sreevastava D, et al. Posterior reversible encephalopathy syndrome posttransplantation: a case report of possible association with cerebrospinal fluid leak after epidural catheterization. *Transplant Proc.* (2009) 41:1957–60. doi: 10.1016/j.transproceed.2008.12.037
31. Sahin N, Maral J, Celik E, Solak A, Genc B, Kalaycioglu S, et al. Atypical presentation of posterior reversible encephalopathy syndrome after post-dural puncture headache. *Turk J Anesthesiol Reanim.* (2013) 41:142–5. doi: 10.5152/TJAR.2013.29
32. Doherty H, Hameed S, Ahmed I, Russell IF. Post-dural puncture headache and posterior reversible encephalopathy syndrome: a misdiagnosis or co-presentation? *Int J Obstet Anesth.* (2014) 23:279–82. doi: 10.1016/j.ijoa.2014.02.003
33. Rajan S, Puthenveettil N, Paul J, Kumar L. Posterior reversible encephalopathy syndrome following caesarean section under spinal anaesthesia. *Indian J Anaesth.* (2014) 58:762–5. doi: 10.4103/0019-5049.147179
34. Shah R, Kubisz-Pudelko A, Reid J. Posterior reversible encephalopathy syndrome following an inadvertent dural puncture during an emergency laparotomy for ischemic colitis - a case report. *Local Reg Anesth.* (2014) 7:1–4. doi: 10.2147/LRA.S57660
35. Yildiz E, Öner Ö, Çetiner M, Tokur ME, Koç A, Alan K. Posterior reversible encephalopathy syndrome after cesarean section: a case report. *Turk J Intens Care.* (2019) 17:226–30. doi: 10.4274/tybd.galenos.2019.19870
36. Grelat M, Debaux JB, Sautreaux JL. Posterior reversible encephalopathy syndrome after depletive lumbar puncture: a case report. *J Med Case Rep.* (2014) 8:261. doi: 10.1186/1752-1947-8-261
37. Niwa R, Oya S, Nakamura T, Hana T, Matsui T. Rapid intracranial pressure drop as a cause for posterior reversible encephalopathy syndrome: two case reports. *Surg Neurol Int.* (2017) 8:103. doi: 10.4103/sni.sni_55_17
38. Hedna VS, Stead LG, Bidari S, Patel A, Gottipati A, Favilla CG, et al. Posterior reversible encephalopathy syndrome (PRES) and CT perfusion changes. *Int J Emerg Med.* (2012) 5:12. doi: 10.1186/1865-1380-5-12
39. Sakashita Y, Hamada T, Machiya T, Yamada M. Acute intermittent porphyria presenting as posterior reversible encephalopathy syndrome with hyperperfusion in bilateral occipital lobes: a case report. *J Neurol Sci.* (2017) 377:47–9. doi: 10.1016/j.jns.2017.03.052
40. Brubaker LM, Smith JK, Lee YZ, Lin W, Castillo M. Hemodynamic and permeability changes in posterior reversible encephalopathy syndrome measured by dynamic susceptibility perfusion-weighted MR imaging. *AJNR Am J Neuroradiol.* (2005) 26:825–30. doi: 10.1080/02841850510021292
41. Urbach H. Intracranial hypotension: clinical presentation, imaging findings, and imaging-guided therapy. *Curr Opin Neurol.* (2014) 27:414–24. doi: 10.1097/WCO.0000000000000105
42. Savoiardo M, Minati L, Farina L, De Simone T, Aquino D, Mea E, et al. Spontaneous intracranial hypotension with deep brain swelling. *Brain J Neurol.* (2007) 130(Pt 7):1884–93. doi: 10.1093/brain/awm101
43. Canhao P, Batista P, Falcao F. Lumbar puncture and dural sinus thrombosis–a causal or casual association? *Cerebrovasc Dis.* (2005) 19:53–6. doi: 10.1159/000081912
44. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain J Neurol.* (2007) 130(Pt 12):3091–101. doi: 10.1093/brain/awm256
45. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc.* (2010) 85:427–32. doi: 10.4065/mcp.2009.0590
46. Schievink WI, Maya MM, Chow W, Louy C. Reversible cerebral vasoconstriction in spontaneous intracranial hypotension. *Headache.* (2007) 47:284–7. doi: 10.1111/j.1526-4610.2006.00696.x
47. Roth C, Ferbert A. Posterior reversible encephalopathy syndrome: long-term follow-up. *J Neurol Neurosurg Psychiatry.* (2010) 81:773–7. doi: 10.1136/jnnp.2009.189647
48. Faille LD, Fieuws S, Van Paesschen W. Clinical predictors and differential diagnosis of posterior reversible encephalopathy syndrome. *Acta Neurol Belg.* (2017) 117:469–75. doi: 10.1007/s13760-017-0750-6
49. Lin JP, Zhang SD, He FF, Liu MJ, Ma XX. The status of diagnosis and treatment to intracranial hypotension, including SIH. *J Headache Pain.* (2017) 18:4. doi: 10.1186/s10194-016-0708-8
50. Davidson B, Nassiri F, Mansouri A, Badhiwala JH, Witiw CD, Shamji MF, et al. Spontaneous intracranial hypotension: a review and introduction of an algorithm for management. *World Neurosurg.* (2017) 101:343–9. doi: 10.1016/j.wneu.2017.01.123

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership