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Features of Infratentorial-Predominant Posterior Reversible Encephalopathy Syndrome

Ryan T Fitzgerald, MD, Rohan S Samant, MD, Manoj Kumar, MD, Rudy Van Hemert, MD, and Edgardo J Angtuaco, MD

Abstract

Introduction—PRES is a neurotoxic process that typically occurs in the setting of immune dysregulation. In contrast to the characteristic pattern involving parieto-occipital and posterior frontal regions, predominant involvement of the infratentorial brain occurs in a minority of PRES patients. We examined six patients with IPPRES relative to those with typical PRES in terms of clinical factors of toxicity and outcomes. We review the current understanding of PRES pathophysiology.

Methods—An institutional database of PRES patients was created through an IRB-approved search of the electronic record from 2007-2012. MR images were reviewed and classified by two neuroradiologists. Clinical data including laboratory data, blood pressure, and discharge outcome were collected through review of existing electronic medical records. Characteristics of the two groups were compared.

Results—Six cases among 80 PRES patients displayed an atypical distribution of signal abnormality predominantly involving the infratentorial brain. In IPPRES patients, signal abnormalities within the supratentorial brain, when present, showed a predominantly central distribution rather than the typical peripheral distribution. IPPRES patients showed higher rates of extreme hypertension, renal dysfunction, abnormal serum calcium, and abnormal serum magnesium relative to typical PRES patients. Outcomes were similar between the two groups.

Discussion—In our small series, IPPRES differs from typical PRES patients not only in the distribution of imaging abnormalities but also in rates of extreme hypertension and several laboratory indices. Despite these differences, clinical outcome in the IPPRES group was similar to that of typical PRES.

Keywords

posterior reversible encephalopathy syndrome; PRES; hypertensive encephalopathy; brainstem; cerebellum

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic process resulting from endothelial dysfunction associated with various etiologies including systemic infection,

transplantation, pregnancy, autoimmune disease, and malignancy/chemotherapy. [1, 2] Typical imaging findings of PRES consist of vasogenic edema predominantly involving peripheral white matter within parieto-occipital and posterior frontal regions. [1, 3] Edema involving the brainstem, basal ganglia, and cerebellum is less commonly encountered and when present, is typically found in combination with edema involving typical locations. Prior reports of infratentorial-predominant, brainstem-predominant, or “central” PRES have ascribed this variant to extreme hypertension beyond that seen in typical PRES. [3-6] Relatively little existing literature examines the clinical aspects and potential etiologic factors responsible for this rare PRES variant. The purpose of our study was to compare PRES-contributing factors, imaging phenotype, and disease outcomes in infratentorial-predominant PRES (IPPRES) versus typical PRES in a single-institution cohort of PRES patients with the goal of better understanding the natural history and implications of this rare PRES variant.

Methods

With IRB approval, we performed a search of our electronic medical database for ICD-9 codes encompassing the diagnosis of PRES from January 2007 through October 2012 using an institutional search engine at our tertiary academic hospital. Inclusion criteria included MR imaging of the brain consistent with PRES as verified by consensus of two board-certified neuroradiologists combined with a clinical diagnosis of PRES within the electronic medical record, typically on the discharge summary. MR images were reviewed and characterized as one of two groups based on the pattern of abnormality on fluid-attenuated inversion recovery (FLAIR) imaging: 1) IPPRES (ratio of infratentorial to supratentorial FLAIR signal abnormality >1) or 2) typical PRES pattern. Collected clinical data included predisposing factors for the development of PRES, pertinent medical history, and current drugs/therapies. Admission laboratory data included serum creatinine, calcium, magnesium, and white blood cell count. First reported blood pressure at toxicity presentation was obtained from the electronic record and mean arterial pressure (MAP) was calculated $[(2 \times \text{diastolic pressure mmHg}) + \text{systolic pressure mmHg}] / 3$. Hypertension was defined according to criteria of the American Heart Association as systolic pressure ≥ 140 and/or diastolic pressure ≥ 90 . [7] Extreme hypertension was defined as systolic pressure ≥ 180 and/or diastolic pressure ≥ 110 . Outcomes were characterized using a binary classification into baseline (complete resolution of presenting symptoms and return to pre-morbid neurological status at discharge) versus non-baseline (persistent neurological dysfunction at discharge or death). Renal dysfunction was defined as serum creatinine $> 1.3 \text{ mg/dL}$; abnormal calcium includes patients with serum calcium $< 8.6 \text{ mg/dL}$ or $> 10.2 \text{ mg/dL}$; hypomagnesemia denotes serum magnesium $< 1.6 \text{ mg/dL}$; Leukocytosis was indicated by WBC automated count $> 12 \text{ K/uL}$. Values for continuous variables (Table 2) are reported as 1st quartile, median, and 3rd quartile.

Results

Initial ICD-9 code search and medical records review yielded 85 patients with a presumptive diagnosis of PRES. Five patients did not meet inclusion criteria based on MR imaging

findings inconclusive for PRES. Of the remaining 80 patients, 6 (7.5%) showed an IPPRES edema pattern on initial MR imaging.

Presenting symptoms among the brainstem-predominant group included altered mental status (2), visual disturbance (2), headache (2), altered mental status (4) and seizure (2). Table 1 lists additional demographic and clinical characteristics of the IPPRES group. With regard to blood pressure, the IPPRES group showed a higher rate of extreme hypertension (67%) compared to the group at large (40%). Renal dysfunction at presentation was observed in 5 (83%) of the IPPRES cohort compared with 36 (50%) of the typical PRES group. Abnormal serum calcium was seen in 67% of IPPRES patients versus 44% of typical PRES patients and abnormal serum magnesium was encountered in 33% of IPPRES patients compared with 11% in the typical PRES cohort. Leukocytosis was more commonly encountered in typical PRES patients (49%) versus IPPRES patients (17%).

In contrast to the usual pattern of PRES edema that shows preferential involvement of peripheral and/or sub-cortical portions of the supratentorial brain, usually the parieto-occipital and posterior frontal regions, patients with IPPRES often manifest supratentorial changes in a periventricular distribution that, in some cases, may mimic that of a demyelinating process (Figures 1 and 2). One of 6 (17%) IPPRES patients, the only patient of the group to show reduced diffusivity within the brainstem lesion (Figure 3), had a non-baseline outcome (death). Of 74 typical PRES patients, 13 (18%) had a non-baseline outcome (including 2 deaths).

Discussion

The imaging manifestations of PRES may take on a variety of patterns, however most PRES cases conform to one of three previous described patterns: dominant parietal-occipital, holohemispheric, or superior frontal sulcal. [8] Involvement of the infra-tentorial brain is encountered in a minority of patients. In prior PRES series, 32-34% of patients harbored CT or MR abnormalities within the cerebellum. [2, 8] Involvement of the brainstem is even less frequently encountered, seen in 13-18% of patients in the same series. Predominant involvement of the infratentorial structures with relative or complete sparing of supratentorial parenchyma is much more rare, although several such cases have been described in the literature. [2-5] Edema within regions characteristic of typical PRES may be minor or completely absent in those patients with IPPRES.

The pathophysiology underlying the clinical and imaging manifestations of PRES continues to be debated. The role of endothelial dysfunction leading to vasoconstriction continues to gain support over traditional theories centered upon hypertension in excess of cerebral autoregulatory control as the inciting event. Evolution of this understanding is, in part, related to work demonstrating imaging evidence of vasculopathy (both by catheter angiography and MR angiography) in the vast majority PRES patients that may normalize on follow up imaging. [9]. Further, several groups have demonstrated reduced cerebral blood flow (CBF) by DSC-MR perfusion imaging in most PRES lesions relative to normal-appearing white matter indicating a state of hypoperfusion rather than hyperperfusion. [9, 10] Endothelial dysfunction leading to vasoconstriction is thought to occur as a result of an

underlying milieu of immune activation with elicitation of vasoactive factors that have a deleterious effect on the cerebral endothelium. [6, 11] Some form of immuno-modulation is common to most, if not all, PRES-predisposing conditions. [6] Additionally, in the rare reported biopsy/autopsy cases of PRES, immune activation as manifested by endothelial activation, T-cell trafficking, and vascular endothelial growth factor expression (VEGF) has been observed. [11, 12] Thus, PRES is increasingly viewed as a state of hypoperfusion that occurs as a result of immune activation/dysfunction eventually leading to vasoconstriction within the cerebral arterial vasculature.

In our series, several clinical factors differed between those with IPPRES and the typical PRES edema pattern. Greater elevation of blood pressure in IPPRES is in agreement with prior literature. [2] Rates of renal dysfunction, abnormal serum calcium, and abnormal serum magnesium were more commonly encountered in the IPPRES cohort. Renal dysfunction is a common finding in previously published PRES cohorts and was seen in 53% of the original PRES patients described by Hinchey et al. [13] Whether alterations in renal function contribute to the development of PRES or simply reflect a concomitant effect of an underlying systemic toxicity remains unclear. Hypomagnesemia, which may occur as a result of renal wasting in the setting of altered renal endothelial dysfunction, has been implicated as a contributing factor in PRES, particularly in normotensive patients, through its role in modulation of vascular tone and reactivity. [14, 15] Additionally, hypomagnesemia may contribute to impaired vascular autoregulation through antagonism of calcium channels. [16] Further support for the role of hypomagnesemia in the development of PRES can be found in the obstetrics literature, as magnesium therapy is a mainstay of treatment in patients with eclampsia/preeclampsia, a disease process that closely parallels the pathophysiology of PRES. [14, 17]

Explanations for the distribution of brain edema in PRES remain incomplete, however many authors have cited variations in sympathetic innervation within the posterior circulation vasculature as a potential factor in the typical PRES pattern preferentially involving parieto-occipital regions. [2, 18, 19] Why the imaging phenotype of IPPRES differs from the typical pattern is unknown, but could potentially be related to individual variation in cerebrovascular sympathetic innervation, variant vascular anatomy, pre-existing vascular pathology affecting how regional vasculature responds to the systemic toxicity of PRES, as yet unidentified factors leading to IPPRES, or a combination thereof.

Outcomes were similar in both groups, with the majority of all patients recovering to baseline neurological status at the time of discharge. A single non-baseline outcome in the IPPRES group occurred in a 47 year-old male with a history of HIV who presented with sepsis, seizure, and rapid mental status decline who died on hospital day 3. (Figure 3) Rates of non-baseline outcome in this study, 17% and 18% in the IPPRES and typical PRES groups respectively, are somewhat lower than those reported elsewhere, such as the 30% rate of poor outcome reported by Hefzy et. al. and a more recent paper by Legriel et. al. describing severe functional impairment in 44% of surviving subjects and a 16% rate of death [20, 21]. The basis of a relatively lower rate of non-baseline outcome in our study is unclear but likely stems in part from the retrospective study design and potential selection biases. Given the somewhat common perception of PRES as a reversible relatively benign

entity, discharge summaries of patients who died as a result of PRES may not have included PRES in the final diagnosis, thus may not have been detected by our database search. The small number of brainstem-predominant PRES cases (6) relative to the entire cohort (80) is a major limitation of our study that limits the ability to perform a meaningful statistical analysis between these two groups. Going forward, prospective collection of additional cases and/or pooled multi-institutional analysis may facilitate improved understanding of the IPPRES phenotype.

In summary, IPPRES constitutes a small but important portion of the PRES population as this atypical imaging phenotype may potentially confound the PRES diagnosis. Central distribution of the supratentorial manifestations of IPPRES contrasts with the typical peripheral PRES edema pattern. In our study, the rate of extreme hypertension and incidence of renal dysfunction differed between the two groups however outcomes did not differ significantly between those with typical PRES and IPPRES. Further study is necessary to gain a better understanding of the pathophysiology underlying the infratentoria-predominant PRES variant.

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Abbreviations

PRES	posterior reversible encephalopathy syndrome
IPPRES	Infratentorial predominant posterior reversible encephalopathy syndrome
DSC-MR	dynamic susceptibility contrast magnetic resonance

Figure 1.

A 23 y/o female with a history of systemic lupus erythematosus (SLE) and end-stage renal disease (ESRD) presented after a seizure accompanied by headache and blurred vision. Axial FLAIR MR image (A) revealed areas of hyperintense signal in the pons and cerebellum (arrow). Imaging of the supratentorial brain (B) showed several small FLAIR-hyperintense lesions within the periventricular regions (arrow). *Patient 1 from Table 1*

Figures 2.

A 57 y/o male with a history of paraplegia and decubitus ulcer presented with clinical signs of sepsis and altered mental status. Axial MR imaging showed patchy areas of FLAIR abnormality within the cerebellum (arrow, panel A), pons (arrow, panel B) as well as several small areas of abnormal signal involving supratentorial periventricular regions (arrow, panel C). *Patient 4 from Table 1*

Figure 3.

A 47 y/o male with a history of HIV presented with fever, rapidly declining mental status, and seizure; recent medical history was also notable for leiomyosarcoma of the lower extremity. Axial FLAIR-weighted images (panels A and C) showed extensive FLAIR abnormality throughout the brainstem (arrow, panel A) extending supratentorially to involve the periventricular regions (arrow, panel C). ADC map demonstrated areas of cytotoxic (arrow, panel B) and vasogenic (arrowhead, panel B) edema. *Patient 6 from Table 1*

Table 1

Demographic/Clinical Characteristics of IPPRES Group

	Age/Sex	Predisposition	Presentation	BP	Creatinine	Ca	Mg	WBC	Outcome
1	23/F	Lupus	HA, seizure, visual changes	220/150	6.4	8.5	2.2	8.4	Baseline
2	35/F	HTN, ESRD	HA, visual changes	192/121	1.7	9.4	2.1	15.2	Baseline
3	40/F	HTN, ARF	AMS	260/206	2.1	8.1	1.4	9.8	Baseline
4	57/M	Sepsis	AMS	145/90	1.4	7.5	1.6	8.5	Baseline
5	38/M	HTN	AMS	240/130	1.9	10.5	2.4	8.8	Baseline
6	47/M	Sepsis, HIV, leiomyosarcoma	Seizure, AMS	90/51	1.0	8.6	1.4	4.9	Death

* blood pressure and laboratory values represent initial measurements on admission)

** Abbreviations: AMS=altered mental status; ARF=acute renal failure; BP=blood pressure; Ca=serum calcium; ESRD=end stage renal disease; HA=headache; HTN=hypertension; Mg= serum magnesium; WBC; white blood cell count

Table 2
Clinical Characteristics of IPPRES vs. Typical PRES Groups (continuous variables
reported as 1st quartile, median, and 3rd quartile)

	IPPRES (n=6)	Others (n=74)
Age	35.75/39.00/45.25	28.75/50.50/61.00
Sex (male)	3 (50%)	13 (18%)
Mean arterial pressure	117.2/156.0/171.5	107.5/118.5/139.8
Blood Pressure		
Extreme hypertension	4 (67%)	29 (40%)
Hypertension	1 (17%)	35 (49%)
Normotensive	1 (17%)	8 (11%)
Renal Dysfunction	5 (83%)	36 (50%)
Abnormal Calcium	4 (67%)	32 (44%)
Hypomagnesemia	2 (33%)	8 (11%)
Leukocytosis	1 (17%)	35 (49%)