

Posterior Reversible Encephalopathy Syndrome Caused by Induced Hypertension to Treat Cerebral Vasospasm Secondary to Aneurysmal Subarachnoid Hemorrhage

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■ **OBJECTIVE:** The aim of the present study was to describe the case of a patient who had presented to a university hospital with induced-hypertension (IH) posterior reversible encephalopathy syndrome (PRES). We also reviewed all other reports of such patients.

■ **METHODS:** We have described the clinical course of a patient who had presented to the university hospital neurosurgical department. We also performed a systematic review of studies related to the incidence of PRES caused by the use of IH in the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage.

■ **RESULTS:** The patient had presented with an acute-onset headache and found to have a subarachnoid hemorrhage due to anterior communicating artery aneurysm rupture. She underwent coiling the next day. During the subsequent days, she demonstrated fluctuating clinical examination findings, aphasia, and decreased levels of arousal. Digital subtraction angiography was performed, and the findings were concerning for mild vasospasm of the anterior and middle cerebral arteries. The systolic blood pressure goal was increased to 180–220 mm Hg for an IH trial, which had initially resulted in some transient clinical improvements in her level of arousal. However, the improvement was not sustained. During the next 36 hours, the patient worsened, and she developed left middle cerebral artery syndrome. Given the concern for a possible

ischemic event, magnetic resonance imaging was performed, which demonstrated interval development of multiple areas of cortical-based fluid-attenuated inversion recovery hyperintensity consistent with PRES. The systolic blood pressure goal was relaxed to normotension, and ~48 hours later, the patient's clinical status had significantly improved.

■ **CONCLUSION:** IH-PRES is a rare complication that should be remembered in the differential diagnosis for at-risk patients.

INTRODUCTION

Rupture of an intracranial aneurysm is the most common cause of nontraumatic subarachnoid hemorrhage (SAH), affecting ~9 in 100,000 persons in the United States annually.¹ The mortality rate of aneurysmal SAH has been estimated at 15% before hospitalization¹ and 36%–42% within 30 days from the initial onset of the SAH.² Furthermore, in addition to the increased mortality rates, ~50% of all patients with aneurysmal SAH will be left permanently disabled.² A delayed complication that will affect roughly one half of all patients with a ruptured aneurysm is SAH-associated cerebral vasospasm (CVS), with up to two thirds of patients developing moderate to severe radiographic vasospasm.³ CVS can cause transient or permanent functional neurological deficits,

Key words

- Aneurysm
- Brain diseases
- Intracranial
- Subarachnoid hemorrhage
- Vasospasm

Abbreviations and Acronyms

- ADR:** Alpha/delta ratio
CT: Computed tomography
CVS: Cerebral vasospasm
HH: Hunt and Hess
IH: Induced-hypertension
IQR: Interquartile range
MAP: Mean arterial pressure
MCA: Middle cerebral artery
mFS: Modified Fisher score

MRI: Magnetic resonance imaging

PBD: Postbleed day

PRES: Posterior reversible encephalopathy syndrome

SAH: Subarachnoid hemorrhage

SBP: Systolic blood pressure

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including hemiparesis, aphasia, and/or impaired consciousness.⁴ Although the pathophysiology of CVS has continued to unfold, a common management strategy is centered on maintaining adequate cerebral perfusion using induced-hypertension (IH) therapy.^{5,6} Although IH therapy has been reported to effectively reverse $\leq 70\%$ of neurological symptoms caused by CVS,^{7,8} an increasing blood pressure can have portending consequences, including myocardial ischemia, pulmonary edema, and, even, rupture of another unsecured aneurysm.⁹

One complication of IH therapy that has been rarely reported is posterior reversible encephalopathy syndrome (PRES). PRES is characterized radiographically by focal regions of vasogenic edema, predominantly in the parieto- or temporo-occipital lobes. Patients with PRES will present clinically with CVS-like symptoms such as headache, altered mental status, seizure, and visual disturbances, including loss of vision, or other region-specific neurological deficits such as hemiparesis and aphasia.¹⁰⁻¹² However, the radiographic and clinical findings can both be reversed by lowering the blood pressure back to homeostatic levels.¹⁰ PRES has been well-documented in patients with eclampsia, a hypertensive emergency, uremic encephalopathy, and collagen-related vascular disorders and in patients receiving immunosuppressive therapy.¹³ However, a paucity of reports have described cases of IH-PRES as a consequence of blood pressure augmentation to treat SAH-related CVS. In the present study, we have reported a case of IH-PRES secondary to blood pressure augmentation for SAH-related CVS and a review of the reported data.

LITERATURE SEARCH

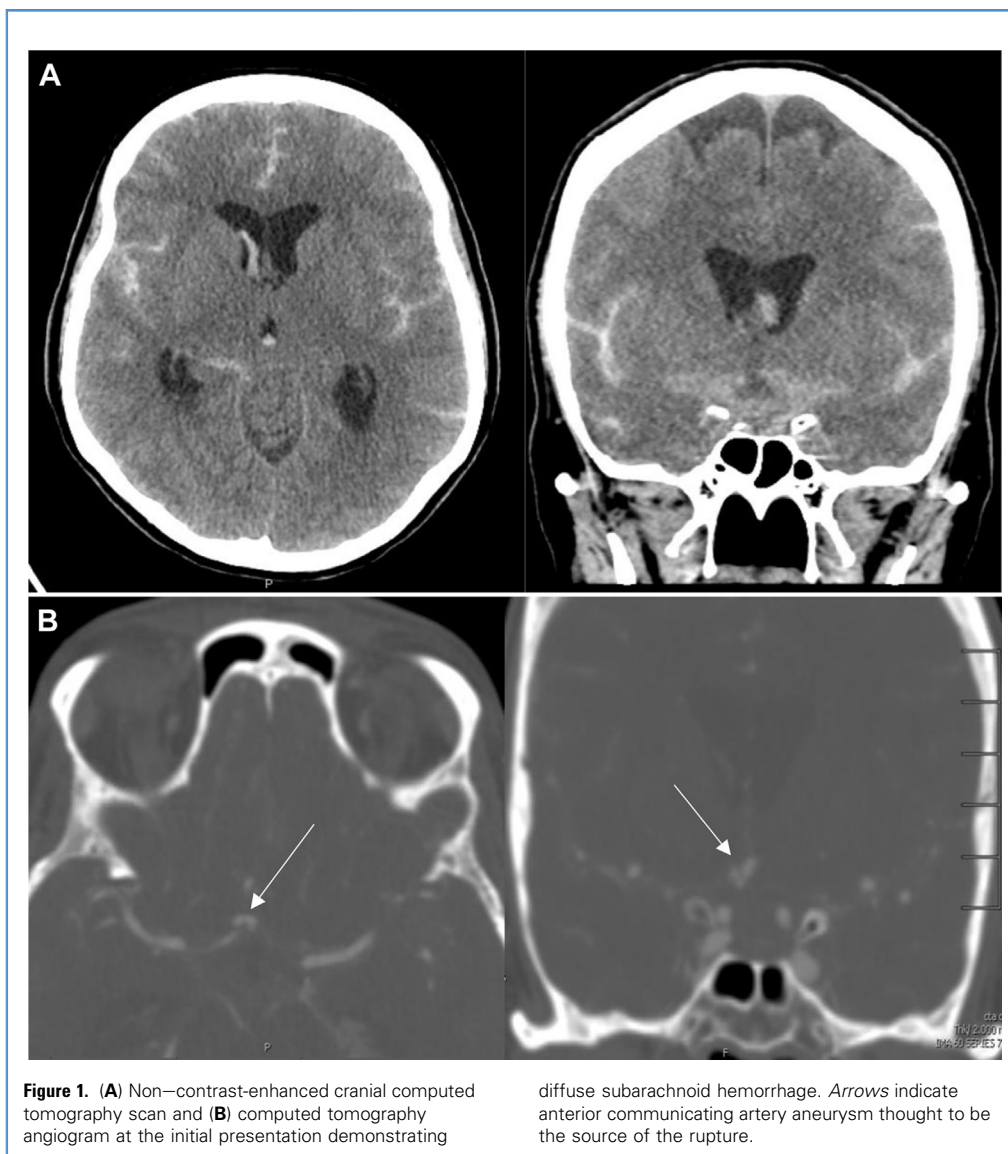
A PubMed and Google Scholar search was performed for studies related to the incidence of PRES caused by the use of IH in the treatment of CVS after aneurysmal SAH. The terms “posterior reversible encephalopathy syndrome,” “posterior reversible leukoencephalopathy,” “intracranial,” “subarachnoid,” “hemorrhage,” and “ruptured aneurysm” were searched for in combination with “induced hypertension,” “triple-H therapy,” “vasopressor,” “delayed cerebral ischemia,” and “cerebral vasospasm” to maximize the output of the related studies. Only studies that had included cases of IH-PRES after management of delayed CVS that had occurred after aneurysmal SAH were considered for review and analysis. We usually excluded reports of PRES occurring spontaneously in patients with etiologies such as eclampsia or chronic hypertension or patients undergoing immunosuppressive therapy for a variety of different conditions. Additionally, studies of those who had received IH treatment for nonaneurysmal hemorrhage were excluded from consideration. The demographic data collected included the patient’s age and sex and whether the patient had had a history of hypertension. The clinical information collected included the location and orientation of the cerebral aneurysm, Hunt and Hess (HH) grade, modified Fisher scores (mFSs), aneurysm treatment modality, interval from the initial SAH to aneurysm treatment, use of IH and incidence of PRES, vasopressor used for IH, target mean arterial pressure (MAP) for IH, duration of IH before the development of PRES, location of PRES, and symptomatic presentation of PRES.

The parametric data are presented as the mean \pm standard deviation, and nonparametric data are presented as the median and interquartile range (IQR).

CASE DESCRIPTION

A 59-year-old woman had presented to the neurosurgical department as a transfer after presenting with sudden-onset headache and progressively increasing lethargy throughout the day (HH grade III). A cranial non-contrast-enhanced computed tomography (CT) scan had revealed diffuse SAH with intraventricular extension and hydrocephalus (mFS IV), and CT angiography demonstrated an anterior communicating artery aneurysm that was concerning for rupture (**Figure 1**). She was subsequently intubated for placement of an external ventricular drain. Conventional digital subtraction angiography revealed a 4.0×2.5 -mm dysplastic anterior communicating artery that was successfully coiled on postbleed day (PBD) 2.

On PBD 3, the patient’s systolic blood pressure (SBP) had ranged from 110 to 129 mm Hg. She remained intubated but was able to open her eyes and localize symmetrically to noxious stimuli. The findings from continuous electroencephalographic monitoring were negative for seizures or epileptiform discharges but was continued for a vasospasm watch in accordance with our protocol to monitor the alpha/delta ratio (ADR; **Table 1**). On PBD 5, her clinical status had continued to fluctuate, and the findings from magnetic resonance angiography were concerning for vasospasm of the anterior and middle cerebral arteries, prompting the clinical team to narrow her SBP goal to 140–180 mm Hg. At that time, her electroencephalogram had also demonstrated asymmetry of the ADRs, suggestive of vasospasm (**Table 1**). On PBD 8, she had become significantly aphasic in the afternoon, and phenylephrine was started with an SBP goal of 180 mm Hg. Overnight to PBD 9, her examination findings had not improved. Thus, she underwent magnetic resonance imaging (MRI) and magnetic resonance angiography, which demonstrated no cerebral edema or infarction but moderate distal bilateral, middle cerebral artery (MCA) spasm, with the left greater than the right (**Figure 2**). She then underwent digital subtraction angiography. The findings were notable for proximal anterior cerebral artery (A1 segment) spasm and diffuse distal bilateral MCA vasospasm. She had a mild response to spasmolysis with verapamil injections. No angioplasty was performed given that the vasospasm had moderately narrowed the intracranial vessels and was diffuse in nature (in contrast to a single vessel that had become severely narrowed from vasospasm). It was decided to increase the SBP goal to 180–220 mm Hg, at the start of which, some transient clinical improvement was seen in her level of arousal. However, again, the improvement was not sustained. IH was continued for ~36 hours as a trial. However, sustained improvement was lacking and she had developed worsening left MCA syndrome (right arm plegia and sustained left gaze deviation in addition to her global aphasia). On PBD 10, examination of the electroencephalogram revealed no seizures or definitive epileptiform patterns. However, the ADRs demonstrated a progressive downward trend in all vascular territories with decreased variability, with the left worse than the right (**Figure 3**



and **Table 1**), which correlated with continuous left hemisphere slowing and moderate generalized slowing on the raw electroencephalogram (**Figure 3** and **Table 1**). A repeat MRI study was also performed, which demonstrated interval development of multiple areas of cortical-based fluid-attenuated inversion recovery hyperintensity involving the left parafalcine frontal and parietal cortex, bilateral parieto-occipital lobes, and bilateral thalami consistent with PRES (**Figure 4**). Additionally, no areas of restricted diffusion were found on diffusion weighted imaging to suggest the presence of acute infarction (**Figure 4**). The SBP goals were then relaxed to normotension, and she was weaned off the vasopressors over several hours. Approximately 48 hours later, the patient's clinical status had significantly improved. She had become alert and oriented to self and place, was able to briskly follow commands and move all her extremities spontaneously with improved symmetry. No

additional MRI studies were subsequently obtained because the reversibility of the patient's symptoms with IH reduction had provided sufficient evidence that the patient's symptoms had been secondary to IH-PRES.

LITERATURE REVIEW

The PubMed and Google Scholar search yielded 11 studies that had reported on 16 patients who had developed PRES after IH therapy for CVS that had occurred after aneurysmal SAH. Including our own patient, 17 patients were included in the present analysis (**Table 2**).

The cohort had a mean age of 58.65 ± 10.10 years and 12 of the 17 patients (70.6%) were women (**Figure 5A** and **B**). At hospital admission, most of the patients had presented with an HH grade of III (29.4%) or II (23.5%), with a median HH grade of

Table 1. Delayed Cerebral Ischemia Detection via Quantitative EEG During Hospitalization

Day	Epileptiform Patterns*	ADR Range†	ADR Variability‡	Focal Slow or Attenuation§	Comment
PBD 2 (baseline)				NA	NA
MCA					
Left hemisphere	None	0.47–0.91	3		
Right hemisphere	None	0.40–0.79	3		
ACA					
Left hemisphere	None	0.47–0.91	3		
Right hemisphere	None	0.40–0.79	3		
PCA					
Left hemisphere	None	0.47–0.91	3		
Right hemisphere	None	0.40–0.79	3		
PBD 3				NA	NA
MCA					
Left hemisphere	None	0.24–0.70	3		
Right hemisphere	None	0.25–0.60	3		
ACA					
Left hemisphere	Rare frontal sharp wave	0.32–0.68	3		
Right hemisphere	Rare frontal sharp wave	0.25–0.56	3		
PCA					
Left hemisphere	None	0.24–0.70	3		
Right hemisphere	None	0.25–0.60	3		
PBD 4				NA	NA
MCA	NA				
Left hemisphere		0.29–0.43	2–3		
Right hemisphere		0.28–0.48	2–3		
ACA					
Left hemisphere	Rare bifrontal sharp waves	0.28–0.37	2–3		
Right hemisphere	Rare bifrontal sharp waves	0.29–0.45	2–3		
PCA	NA				
Left hemisphere		0.27–0.47	2–3		
Right hemisphere		0.27–0.50	2–3		
PBD 5				NA	NA
MCA	NA				
Left hemisphere		0.36–0.64	2–3		
Right hemisphere		0.33–0.60	2–3		
ACA					
Left hemisphere	Occasional bifrontal sharp waves	0.27–0.51	2–3		

Continues

Table 1. Continued

Day	Epileptiform Patterns*	ADR Range†	ADR Variability‡	Focal Slow or Attenuation§	Comment
Right hemisphere	Occasional bifrontal sharp waves	0.29–0.53	2–3		
PCA	NA				
Left hemisphere		0.44–0.75	2–3		
Right hemisphere		0.35–0.65	2–3		
PBD 6				NA	NA
MCA					
Left hemisphere	Occasional left temporal sharp waves	0.8–1.2	2–3		
Right hemisphere	NA	0.8–1.0	2–3		
ACA	NA				
Left hemisphere		0.7–0.8	2–3		
Right hemisphere		0.7–0.9	2–3		
PCA	NA				
Left hemisphere		0.9–1.4	2–3		
Right hemisphere		0.9–1.3	2–3		
PBD 7					
MCA	NA				
Left hemisphere		0.8–1.0	2–3	None	Intermittent left temporal slowing and lower ADR from 3 to 8 PM only
Right hemisphere		0.9–1.1	2–3	None	NA
ACA	NA				NA
Left hemisphere		0.7–0.8	2–3	None	
Right hemisphere		0.7–0.8	2–3	None	
PCA	NA				
Left hemisphere		0.9–1.1	2–3	None	Intermittent left temporal slowing and lower ADR from 3 to 8 PM only
Right hemisphere		0.9–1.1	2–3	None	NA
PBD 8					
MCA	NA				
Left hemisphere		0.8–1.1	2–3	None	Rare to occasional left temporal slowing
Right hemisphere		0.8–1.1	2–3	None	NA

ADR, alpha/delta ratio; PBD, postbleed day; NA, not applicable; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; PRES, posterior reversible encephalopathy syndrome.

*Grading scale for epileptiform patterns: continuous, abundant, frequent, occasional, rare, or none using American Clinical Neurophysiology Society criteria; text should be changed to bold for emergence or worsening epileptiform patterns compared with baseline or previous day, with the pattern specified.

†Grading scale for ADR: ranges for the day (approximate range in which 50% of all activity occurred); text should be changed to bold if a persistent decrease from baseline or previous day has occurred (typically >0.1 or >33% change).

‡ADR variability rated as 1–4: 1, poor; 2, fair; 3, good; 4, excellent; text should be changed to bold for worsening variability compared with baseline or previous day.

§Focal slowing or attenuation: continuous, abundant, frequent, occasional, rare, or none using American Clinical Neurophysiology Society criteria; text should be changed to bold for emergence of, or worsening, slowing compared with baseline or previous day; focal delta (<4 Hz) or theta (4–7 Hz) and/or attenuation should be recorded. Continues

Table 1. Continued

Day	Epileptiform Patterns*	ADR Range†	ADR Variability‡	Focal Slow or Attenuation§	Comment
ACA	NA				NA
Left hemisphere		0.6–0.8	2–3	None	
Right hemisphere		0.6–0.8	2–3	None	
PCA	NA				
Left hemisphere		0.9–1.1	2–3	None	NA
Right hemisphere		0.9–1.1	2–3	None	Rare to occasional left temporal slowing
PBD 9					
MCA	NA				
Left hemisphere		1 to >0.5	2–3 to >2	None	Frequent becoming continuous left hemisphere slowing, temporal maximal
Right hemisphere		1 to >0.6	2–3 to >2	None	NA
ACA	NA				
Left hemisphere		1 to >0.5	2–3 to >2	None	Frequent becoming continuous left hemisphere slowing
Right hemisphere		1 to >0.6	2–3 to >2	None	NA
PCA	NA				
Left hemisphere		1 to >0.5	2–3 to >2	None	Frequent becoming continuous left hemisphere slowing, temporal maximal
Right hemisphere		1 to >0.6	2–3 to >2	None	NA
PBD 10 (PRES diagnosed)					
MCA	NA				
Left hemisphere		0.8 to >0.3	2–3 to >2	None	Frequent becoming continuous left hemisphere slowing, temporal maximal
Right hemisphere		0.8 to >0.4	2–3 to >2	None	NA
ACA	NA				
Left hemisphere		0.5 to >0.2	2–3 to >2	None	Frequent becoming continuous left hemisphere slowing
Right hemisphere		0.5 to >0.2	2–3 to >2	None	NA
PCA	NA				
Left hemisphere		0.6 to >0.4	2–3 to >2	None	Frequent becoming continuous left hemisphere slowing, temporal maximal
Right hemisphere		0.7 to >0.4	2–3 to >2	None	NA

ADR, alpha/delta ratio; PBD, postbleed day; NA, not applicable; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; PRES, posterior reversible encephalopathy syndrome.

*Grading scale for epileptiform patterns: continuous, abundant, frequent, occasional, rare, or none using American Clinical Neurophysiology Society criteria; text should be changed to bold for emergence or worsening epileptiform patterns compared with baseline or previous day, with the pattern specified.

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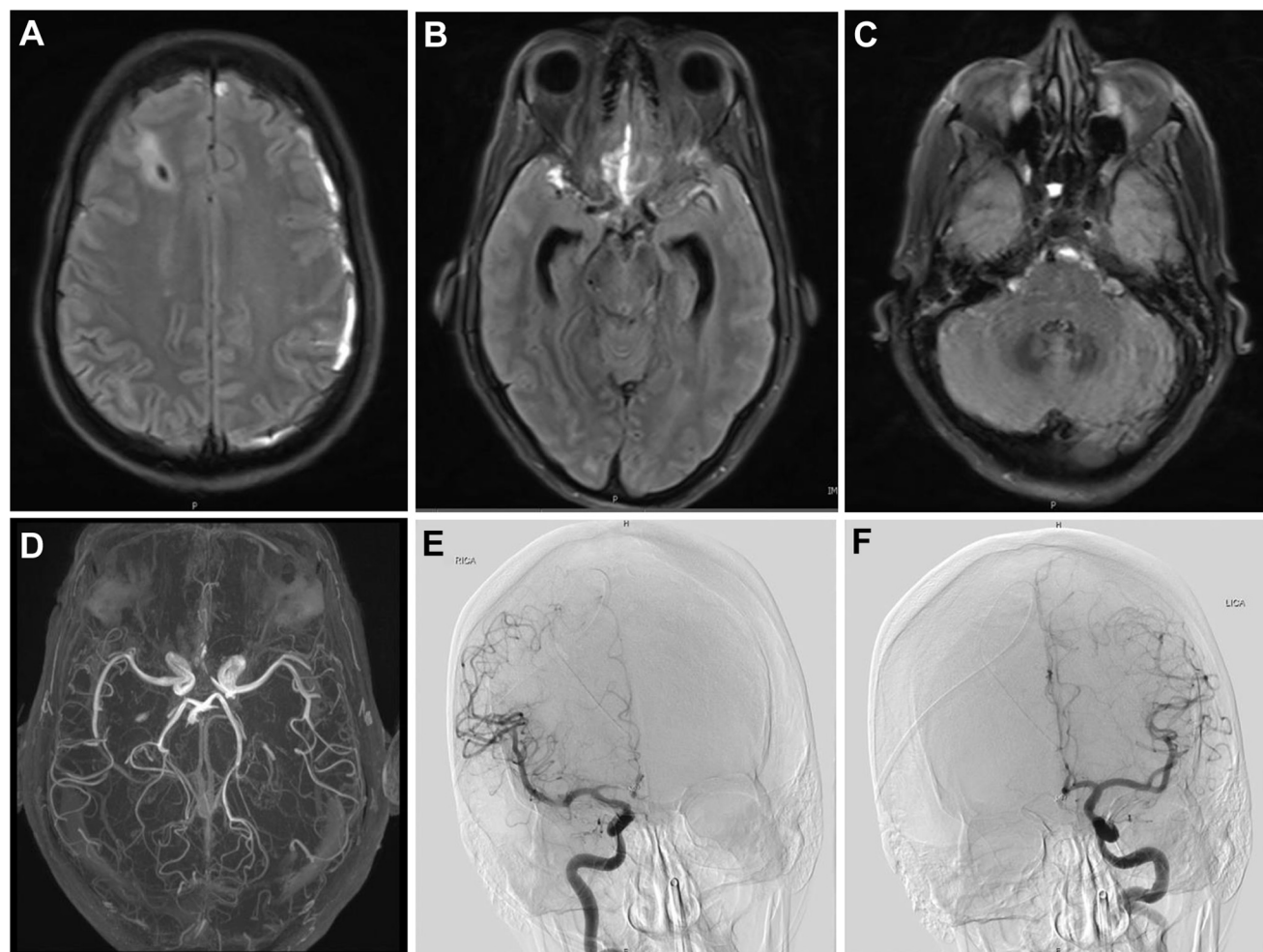


Figure 2. Imaging studies at the time of cerebral vasospasm symptoms. (A–C) Magnetic resonance imaging scans with fluid-attenuated inversion

recovery sequence. (D) Magnetic resonance angiogram. (E, F) Digital subtraction angiograms of left and right internal carotid arteries.

III (interquartile range, II–IV; **Figure 5C**). The mFSs were only available for 16 of the patients, with 15 (93.8%) presenting with an mFS of III or IV (median mFS, 4; interquartile range, III–IV; **Figure 5C**).

The location of the aneurysms were reported for 13 patients. Of these, 7 were in the anterior communicating artery, 2 were in the MCA, 2 were in the posterior cerebral artery, 1 was in the cerebellar artery, and 1 was in the internal carotid artery (**Figure 6A**). Each of the aneurysms had been neurosurgically treated, and we found that 10 of the 17 aneurysms (58.8%) had been treated by coiling and 7 by clipping (**Figure 6B**).

The location of the CVS was reported for 14 of the 17 patients, with most occurring in the MCA (35.7%) or anterior cerebral artery (35.7%) territories. The median lower and upper limits of the targeted mean arterial pressure (MAP) were 120 mm Hg (interquartile range, 110–130 mm Hg) and 132 mm Hg (interquartile range, 122.5–140 mm Hg), respectively (**Figure 7A**). The drug used for hypertensive therapy had been recorded for 14 of the 17 patients.

For most of these patients, hypertension had been induced by administration of phenylephrine ($n = 6$) or phenylephrine combined with norepinephrine ($n = 4$; **Figure 7B**). The mean interval between the initial SAH and suspected CVS was 6.17 ± 3.54 days (**Figure 7C**). PRES had developed an average of 6.0 ± 3.84 days after the target MAP range had been reached and 12.0 ± 3.11 days after aneurysmal rupture (**Figure 7C**). The locations of PRES are also listed in **Table 2**.

DISCUSSION

We have described a rare case of IH-PRES that had developed as a consequence of blood pressure augmentation to treat CVS. To the best of our knowledge, only 16 other cases have been reported to date.^{13–23}

Given the uncommon occurrence or underreporting of IH-PRES, identifying a prevalence rate would be difficult. In a prospective study that had tracked the outcomes and complications of

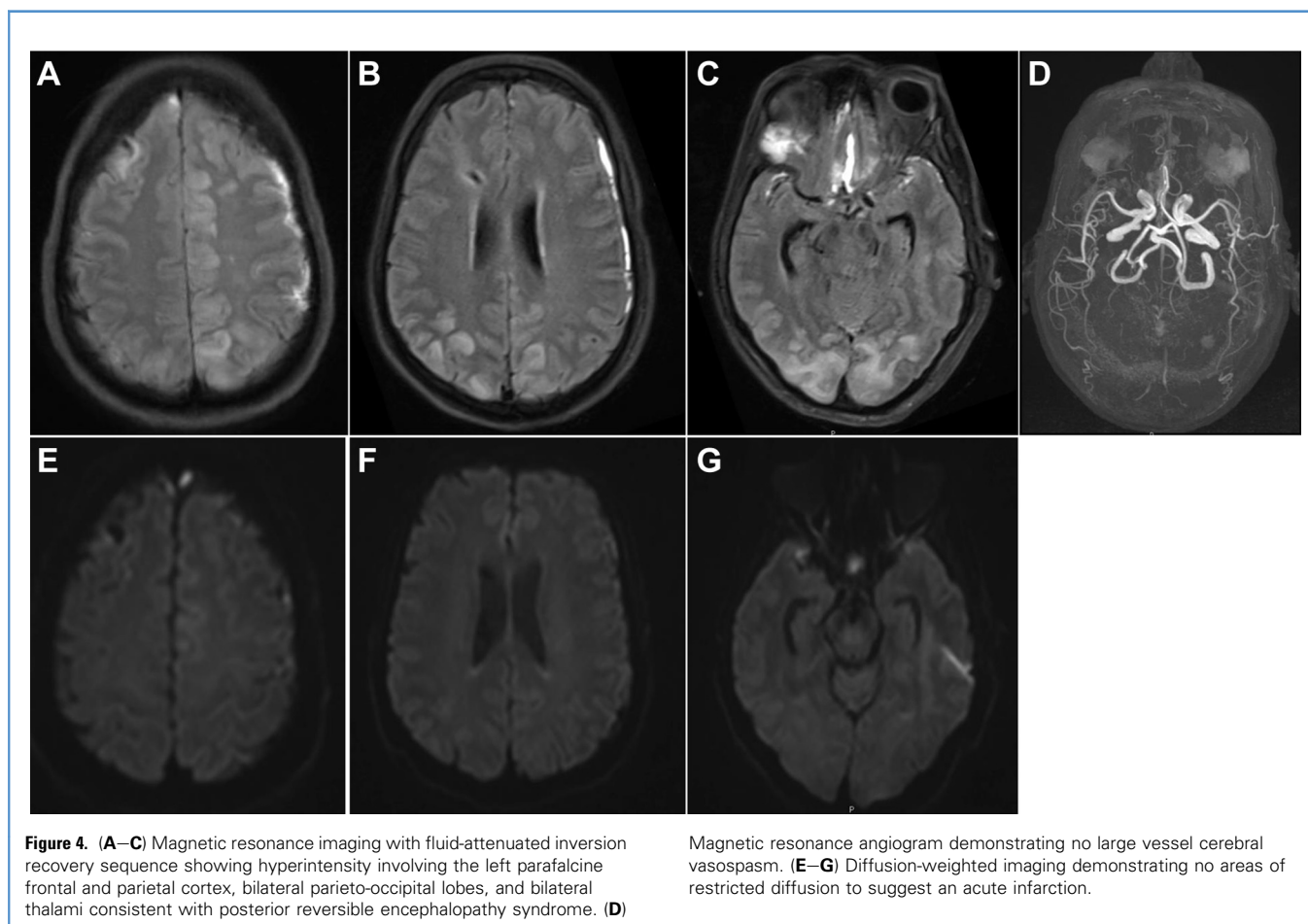
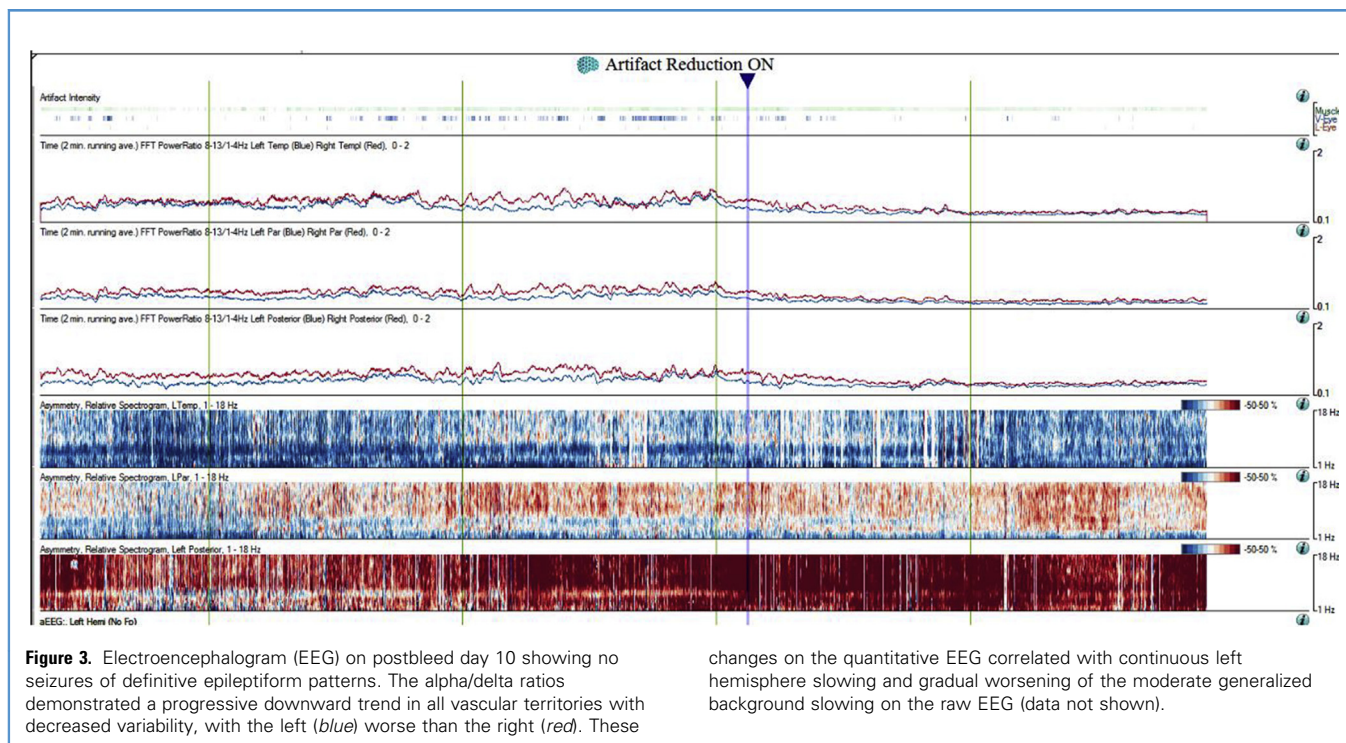


Table 2. Characteristics of Patients Presenting with Aneurysmal SAH and PRES

Investigator	Sex	Age (years)	History of HTN	Aneurysm Location (Orientation)	HH Grade	mFS	Treatment	Interval (days)		CVS Location	Target MAP (mm Hg)		Vasopressor for IH	Target MAP Duration Before PRES (days)	Interval From SAH to PRES (days)	PRES Location	PRES Clinical Presentation
								SAH to Treatment	SAH to C/F CVS		Lower Limit	Upper Limit					
Present patient	F	59	NA	ACoA	III	IV	Coiling	2	8	B distal MCA	134	139	Phenylephrine and norepinephrine	1.5	10	L parafalcine frontal and parietal cortex, B parieto-occipital, and B thalami	R MCA syndrome and aphasia
Allen et al., ¹⁴ 2019	M	56	NA	NA	V	III/IV	Coiling	NA	NA	L distal vertebral, distal basilar artery, and B PCA	130	140	Phenylephrine	6.6	NA	B parieto-occipital and thalami	Lethargy and seizure
Allen et al., ¹⁴ 2019	F	67	NA	NA	III	III/IV	Coiling	NA	NA	L distal vertebral, R vertebral	120	130	Phenylephrine and norepinephrine	1	NA	B occipital	Lethargy
Allen et al., ¹⁴ 2019	M	47	NA	NA	V	III/IV	Coiling	NA	NA	R MCA	135	155	Phenylephrine and norepinephrine	4.2	NA	R parieto-occipital	Lethargy and L HP
Allen et al., ¹⁴ 2019	F	68	NA	NA	II	III/IV	Coiling	NA	NA	B ACA, MCA, and PCA	110	125	Phenylephrine	7.2	NA	R temporal plus patchy, subcortical	Lethargy and aphasia
Muhammad et al., ¹⁵ 2016	F	67	Yes	PCoA (right)	III	III	Coiling	1	4	Multifocal	110	NA	NA	7	11	Bihemispheric supratentorial, brainstem, frontal, and cerebellum	Lethargy, seizure, and HP
Awori et al., ¹⁶ 2015	M	63	No	ACoA (left)	IV	IV	Clipping	0	13	Proximal A2 segments of ACA	110	NA	Dobutamine and norepinephrine	4	17	B temporo-occipital	Seizure and decreased level of consciousness

HTN, hypertension; HH, Hunt and Hess; mFS, modified Fisher score; SAH, subarachnoid hemorrhage; C/F: concerning for; CVS, cerebral vasospasm; MAP, mean arterial pressure; IH, induced hypertension; PRES, posterior reversible encephalopathy; F, female; NA, not available or unknown; ACoA: anterior communicating artery; B, bilateral; MCA, middle cerebral artery; L, left; R, right; M, male; PCA, posterior cerebral artery; HP, hemiparesis; ACA, anterior communicating artery; PCoA, posterior communicating artery; SCA, superior cerebellar artery; COW, circle of Willis; ICA, internal carotid artery.

*Per neuroimaging findings provided in the report.

Continues

Table 2. Continued

Investigator	Sex	Age (years)	History of HTN	Aneurysm Location (Orientation)	HH Grade	mFS	Treatment	Interval (days)		CVS Location	Target MAP (mm Hg)		Vasopressor for IH	Target MAP Duration Before PRES (days)	Interval From SAH to PRES (days)	PRES Location	PRES Clinical Presentation
								SAH to Treatment	SAH to C/F CVS		Lower Limit	Upper Limit					
Madaelil et al., ¹⁷ 2015	M	55	No	SCA	IV	IV	Coiling	0	12	Vertebral and basilar arteries	130	140	Phenylephrine	1	13	L thalamus	Seizure and declining consciousness
Dhar et al., ¹⁸ 2011	F	47	No	ACoA (right)	I	IV	Clipping	0	6	Proximal R MCA	110	120	Norepinephrine	7	13	L temporal and parieto-occipital cortex	Lethargy, confusion, left facial droop, aphasia, and HP
Giraldo et al., ¹⁹ 2011	F	62	No	ACoA	I	III*	Coiling	1	6	COW and distal branches of ACA	110	115	Phenylephrine and norepinephrine	6	12	B posterior parieto-occipital	Confusion, headache, and retro-orbital pain
Giraldo et al., ¹⁹ 2011	F	70	Yes	ACoA	III	IV	Coiling	0	NA	NA	100	120	NA	11	12	Posterior temporo-occipital with slight indication of parietal lobe involvement	Lethargy and seizure
Giraldo et al., ¹⁹ 2011	M	62	Yes	ACoA	V	IV	Clipping	1	1	NA	120	130	Phenylephrine	13	14	B temporo-occipital	Lethargy
Voetsch et al., ²⁰ 2011	F	35	NA	MCA (right)	II	III	Clipping	1	2	ICA terminus and MCA M1 and M2 branches	119	132	Phenylephrine	4	7	B occipital and cerebellum	Headache, seizure, and declining consciousness
Wartenberg et al., ¹³ 2011	F	73	Yes	ICA (left)	II	IV	Clipping	0	6	A1 portion of L ACA and M2 portion of L MCA	115	NA	Phenylephrine	7	10	B parieto-occipital lobes	Coma and decorticating posture
Jang et al., ²¹ 2010	F	65	No	PCoA	II	II	Coiling	0	6	NA	120	NA	Dopamine	1	7	B temporo-occipital, brainstem, basal ganglia, and frontal lobe	Confusion, headache, and loss of vision

Sanelli et al., ²² 2005	F	49	NA	ACoA	III	NA	Clipping	0	4	B ACA	130	140	NA	13	17	B parieto-occipital	Lethargy
Amin-Hanjani et al., ²³ 1999	F	52	No	MCA (left)	IV	III*	Clipping	0	6	NA	150	160	Dobutamine	7	13	Occipital	Lethargy

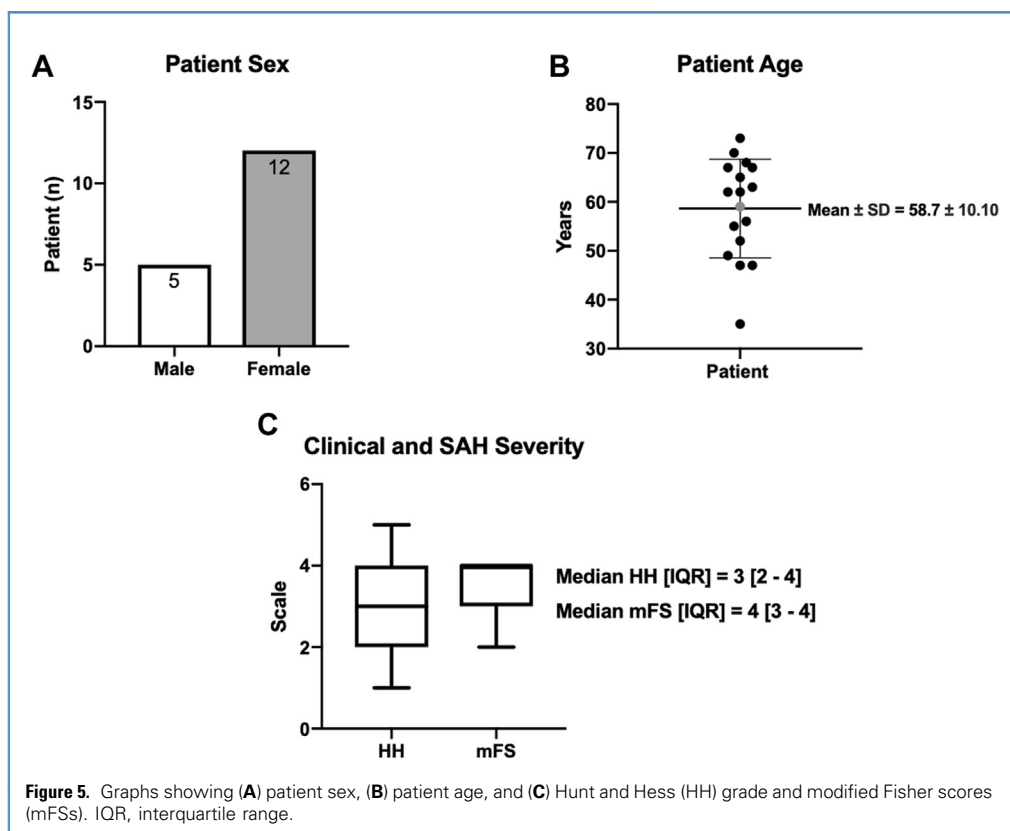
HTN, hypertension; HH, Hunt and Hess; mFS, modified Fisher score; SAH, subarachnoid hemorrhage; C/F, concerning for; CVS, cerebral vasospasm; MAP, mean arterial pressure; IH, induced hypertension; PRES, posterior reversible encephalopathy; F, female; NA, not available or unknown; ACoA, anterior communicating artery; B, bilateral; MCA, middle cerebral artery; L, left; R, right; M, male; PCA, posterior cerebral artery; HP, hemiparesis; ACA, anterior communicating artery; PCoA, posterior communicating artery; SCA, superior cerebellar artery; COW, circle of Willis; ICA, internal carotid artery.

*Per neuroimaging findings provided in the report.

IH therapy in 68 patients with SAH, of which 93% had resulted from a ruptured aneurysm, the incidence of IH-PRES was 7%.¹⁴ Our review of the reported data suggested that the development of PRES during or after IH therapy is more prevalent in women (70.6%) than in men. This difference, however, could have been confounded by the limited number of cases reported and amplified by the greater occurrence of SAH in women.¹⁵ In the study by Allen et al.,¹⁴ 70% of the 68 patients were women, increasing the possibility of observing PRES more often in women than in men. The mean age of the patients presenting with PRES did not vary from the mean age of the patients with aneurysmal SAH (age, ~52 years; range, 35–70 years), indicating that IH-PRES might not preferentially affect older or younger patients with SAH.²⁴ As more cases of IH-PRES are reported, we hope to identify and help risk-stratify patients who might develop PRES as a result of undergoing IH therapy for presumed CVS.

One commonly hypothesized risk factor for PRES has been the presence of long-term hypertension. Chronic hypertension can cause permeant endothelial damage, resulting in the loss of blood–brain barrier integrity and leaky endothelial cell junctions, which alone will increase the likelihood of spontaneous vasogenic edema.^{15,25} Therefore, IH therapy might increase the hydrostatic pressure within a blood vessel to a point that overwhelms the compromised blood–brain barrier, leading to the development of acute-onset PRES. Allen et al.¹⁴ observed that patients with PRES had a significantly greater percentage of change in the blood pressure compared with patients without PRES. Thus, increasing the MAP to 50 mm Hg above the patients' physiological levels or to an absolute range >130–140 mm Hg predicted for PRES with high sensitivity and specificity.¹⁴ Therefore, suggesting that the pathophysiology of PRES might be more closely associated with significant spikes in blood pressure could have greater implications for patients with underlying hypertension. It might be useful to increase the blood pressure in a controlled fashion rather than abruptly in patients with chronic hypertension to reduce the risk of endothelial damage and the development of PRES.

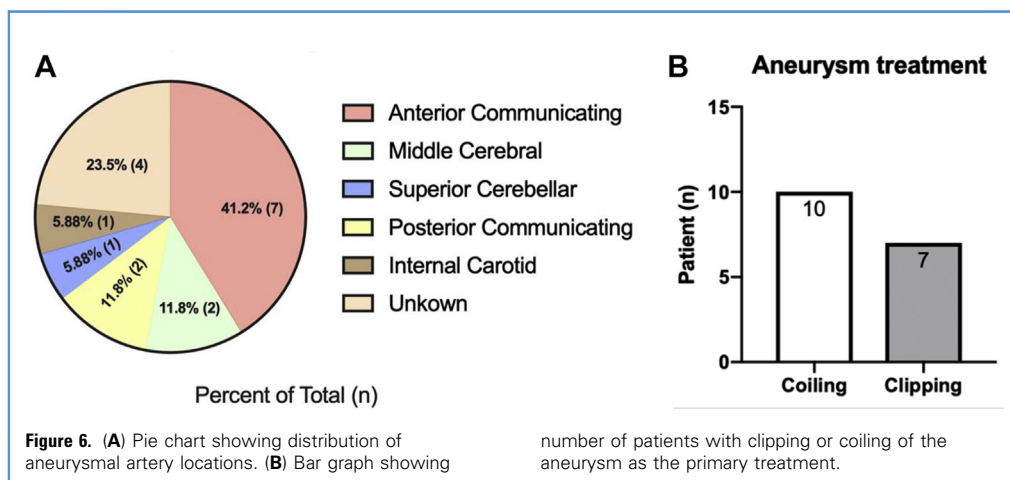
Although the mechanism of IH-PRES is not well understood, a few theories have been discussed and debated in the reported studies. The most popular theory relevant to IH-PRES has been that once the blood pressure has been increased to greater than the capacity for autoregulatory control, a resultant increase will occur in hydrostatic pressure, leading to uninhibited vasodilation and a breakdown of the vascular endothelial junctions.²⁵ This theory has been supported by the study by Allen et al.,¹⁴ which demonstrated that those who developed PRES had had a greater than average dosage of vasopressors and a significantly greater targeted MAP range than had the patients who had never developed PRES. Kontos et al.²⁶ developed a cat model generated to mimic the pathology of PRES. They showed that when the upper limits of autoregulatory control were exceeded, significant endothelial cell damage and vasogenic edema will occur.²⁶ Thus, although IH will aid in retaining the patency and perfusion of spasming vessels, it will also raise the blood pressure in unaffected vessels. This increase in the blood pressure in other vessels could lead to a pathologic increase in the hydrostatic pressures and to the vasodilation of vessels not involved in CVS, pushing fluid from inside the vessel into the

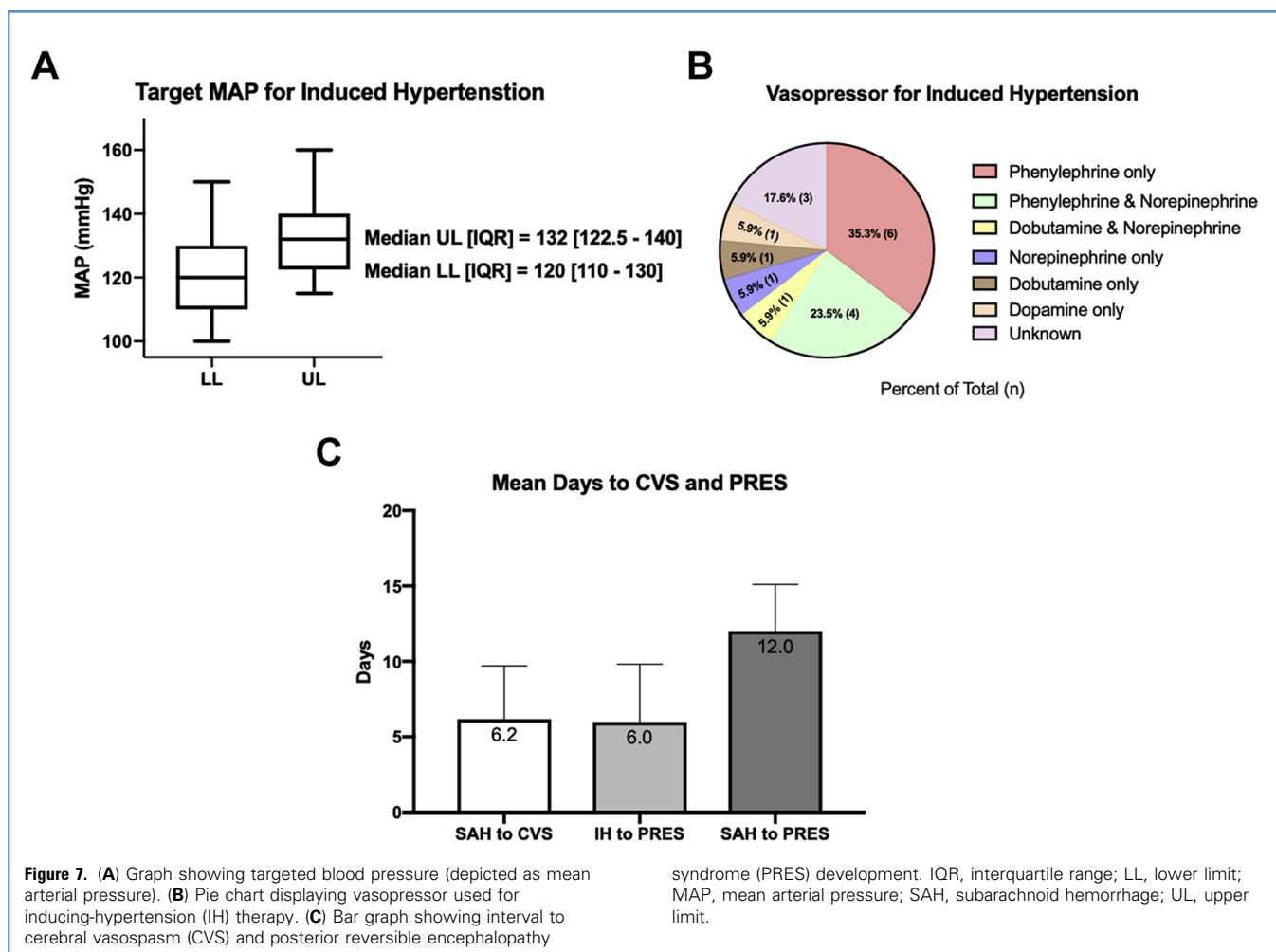


cerebral interstitial space.¹⁵ Proximal arterial CVS is thought to lower the distal perfusion pressures, decreasing susceptibility to hypertensive vascular damage.¹⁸ In the first documented case of unilateral PRES, Dhar et al.¹⁸ used this explanation to demonstrate that patients with unilateral or asymmetric CVS might be more likely to develop PRES because the percentage of unaffected vascular territory remaining susceptible to damage induced by severe increases in blood pressure would be greater. Therefore, IH augmentation in the cerebral blood flow within

the unaffected vasculature might increase the risk of PRES.¹³ Further investigation using CT perfusion imaging is necessary to better elucidate this suggested mechanism of PRES pathology.

However, the theory of blood pressure augmentation as an underlying cause of PRES has been debated. In a cohort study of 22 patients taking cyclosporine or FK-506 after an allogenic bone marrow transplant or for an aplastic marrow disorder, Bartynski et al.²⁷ showed that PRES frequently develops in normotensive or mildly hypertensive patients. In a follow-up review that had





focused on the complex nature of PRES pathogenesis in a variety of conditions, Bartynski²⁸ also contended 2 key points. First, that the blood pressure will rarely surpass the limits of autoregulatory control; and second, that the severity of radiographically observed vasogenic edema does not correlate with the severity of hypertension in patients with PRES.²⁸ Further challenging this proposed mechanism, immunosuppressive drugs have been extensively reported in the case studies and clinical trials to cause PRES by cytotoxic endothelial disruption or altered cerebral blood flow not related to hypertensive stress.^{15,25,29,30} In a case report of a 73-year-old woman undergoing IH therapy for aneurysmal SAH-related CVS, Wartenberg et al.¹³ showed an increase in cerebral flow and a decrease in the mean transit time within the vasculature of the parietal and occipital lobes using CT perfusion. They suggested that irregular cerebral blood flow was possibly the main cause of PRES and not hypertensive breakdown of the cerebrovascular junctions.¹³ Additionally, in a case report of a 52-year-old woman receiving treatment of an aneurysmal SAH, Kuroda et al.¹² noted that PRES had been present in their patient before CVS and IH therapy.

However, the patient had had a history of hypertension and had presented to the hospital with a blood pressure of 191/76 mm Hg, which might have been high enough to acutely induce PRES.¹² Among the conflicting data, it seems the most common theme pervasive throughout all various PRES etiologies is endothelial dysfunction. In a review, Chung et al.³¹ described an alternative phenomenon of spreading depolarizations in association with delayed cerebral ischemia and SAH, which might contribute to the endothelial damage via processes of inflammation and microcirculatory dysfunction. Because endothelial injury has been well documented in patients with aneurysmal SAH,³² it is likely that IH-PRES could arise secondary to SAH-related endothelial damage, which renders the affected vessels unable to compensate for high hydrostatic pressures or abnormal perfusion.

In addition to the clinical presentation, the radiographic features should be considered. PRES has most commonly been diagnostically assessed using fluid-attenuated inversion recovery or T2-weighted MRI, on which PRES lesions will appear hyperintense.²⁰ The radiographic PRES presentation resulting from

postaneurysmal SAH does not differ from that of PRES that has developed secondary to other conditions.³³ PRES was predominately observed in the white matter regions of posterior segments of the brain such as the occipital^{13,14,16,18-23} and parietal^{13,14,18,19,22} lobes and in the posterior regions of the temporal lobe.^{14,16,18,19,21} However, despite the predominately posterior presentation of PRES, most of the documented patients with aneurysmal SAH who had developed IH-PRES had initially presented with an aneurysm located in the anterior communicating artery,^{15,16,18,19,22} MCA,^{20,23} or internal carotid artery,¹³ which we also found in our patient. The use of additional imaging modalities during the presentation of PRES could provide a better understanding of the radiographic characteristics that might be an early indication of PRES.

The paucity of reports demonstrating IH-PRES in patients with aneurysmal SAH has limited the ability to completely understand the prevalence, risk factors, and pathogenesis of the complication. Continued documentation and reporting of IH-PRES could help create a risk-stratification system to determine which patients might be more susceptible to IH-PRES and potentially improve the therapeutic strategies and diagnostic and prognostic outcomes. As demonstrated from our patient and the systematic review, IH therapy caused further worsening of the clinical symptoms with the provocation of PRES rather than treatment of the CVS. The reduction in blood pressure will improve the clinical syndrome. Therefore, IH-PRES is a possible complication that healthcare

providers should remain cognizant of and attentive to when managing CVS in patients with aneurysmal SAH.

CONCLUSION

IH-PRES as a consequence of blood pressure augmentation for CVS is a rare complication that can occur. Given the potential reversibility of this clinical phenomenon by reducing the hypertensive therapy, IH-PRES should be considered in these patients with complex cases because the management directly opposes that for CVS.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Aladine A. Elsamadicy: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Project administration. **Andrew B. Koo:** Methodology, Writing - original draft, Writing - review & editing. **Benjamin C. Reeves:** Formal analysis, Data curation, Writing - review & editing. **Nanthiya Sujjantarat:** Writing - original draft, Writing - review & editing. **Wyatt B. David:** Writing - original draft, Writing - review & editing. **Ajay Malhotra:** Resources, Writing - review & editing. **Emily J. Gilmore:** Conceptualization, Methodology, Supervision, Resources, Writing - review & editing. **Charles C. Matouk:** Conceptualization, Methodology, Supervision, Resources, Writing - review & editing, Project administration. **Ryan Hebert:** Conceptualization, Methodology, Supervision, Resources, Writing - review & editing, Project administration.

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