Posterior Reversible Encephalopathy Syndrome Complicating Ruptured Appendicitis and Abscess Drainage in a Previously Healthy Pediatric Patient

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Abstract

Keywords

- autoregulation
- endothelium
- seizures
- sepsis
- PRES

In this study, we present the youngest reported case of posterior reversible encephalopathy syndrome (PRES) in the United States, which developed following perforated appendicitis with subsequent peritonitis and intra-abdominal abscess formation. Additionally, we discuss potential physiological factors contributing to her acute neurological deterioration and resultant cerebral vasogenic edema.

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiological diagnosis of acute neurological deterioration with vasogenic edema predominantly localized to the posterior cerebral hemispheres. Two frequently cited mechanisms of action include severe hypertension with loss of cerebral autoregulation and alteration of the blood–brain barrier secondary to endothelial dysfunction.¹ PRES is often associated with underlying conditions such as renal disease, eclampsia, autoimmune disorders, malignancy, and transplantation.² A recent study estimated an incidence of 0.4% in a pediatric intensive care unit.³ We present a previously healthy patient who developed PRES following laparotomy and appendectomy secondary to perforated appendicitis complicated by *Escherichia coli* and *Bacteroides fragilis* peritonitis with intra-abdominal abscess formation.

Case Description

The patient is a previously healthy 5-year-old female, who originally presented to a facility outside of our institution,

where she was admitted with influenza A and complaints of abdominal pain, fever, and emesis. Her symptoms continued to worsen, so computerized tomography (CT) of the abdomen was obtained revealing appendicitis. She was taken for exploratory laparotomy and found to have a perforated appendix. Postoperatively she developed signs of sepsis including fever, tachycardia, and tachypnea. She required fluid resuscitation and was subsequently transferred to our facility. Upon arrival, she was noted to have pulmonary edema and hypoxia with increasing oxygen requirements.

Despite intravenous antibiotics, correction of electrolyte abnormalities and improved clinical status, the patient remained febrile with sustained C-reactive protein elevation and increasing leukocytosis (►Fig. 1). On postoperative day (POD) 6, CT scan of the abdomen and pelvis showed multiple fluid collections concerning for abscesses. She was taken for exploratory laparotomy with abscess drainage. Peritoneal fluid cultures consistently grew *E. coli* and *B. fragilis*. Due to concerns for abdominal compartment syndrome related to severe peritonitis and plan for repeated surgical re-exploration, debridement, and peritoneal lavage, the patient remained on mechanical ventilation and abdominal wall closure was

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Fig. 1 Temperature (Tmax) and WBC count of patient. WBC, white blood cell.

delayed until POD 11. During this postoperative period, the patient maintained normal laboratory values for indices of renal function with transient minimal elevation of bilirubin and liver enzyme levels. On POD 12, the patient's sedation and analgesic infusions were stopped, allowing for successful extubation. She was found to be neurologically stable and with the help of physical therapy began ambulating.

Both her clinical and laboratory status continued to improve over the ensuing days, although she remained febrile. On POD 15 from her initial appendectomy, the patient suddenly developed dilated and sluggish pupils, eye fluttering, lip smacking, and tonic-clonic movement of the upper extremities. She required intravenous benzodiazepines and fosphenytoin to control seizure activity and

orotracheal intubation for airway protection. CT scan of the brain showed bilateral hypodensities in the parietal and occipital lobes, potentially related to subacute infarcts with surrounding edema (►**Fig. 2A**). Follow-up magnetic resonance imaging (MRI) showed T1 low-density areas in both gray and white matter of bilateral parietal and occipital lobes. There were corresponding hyperintense T2 and FLAIR (fluid-attenuated inversion recovery) signals (►**Figs. 2D, 2E**) and in these areas diffusion weighted imaging (DWI) demonstrated hyperintense signal alterations (►**Fig. 2B**). In these abnormal signals, apparent diffusion coefficient (ADC) mapping revealed increased diffusion indicating vasogenic edema (►**Fig. 2C**). In vasogenic edema, one should expect low-density signals with DWI indicating increased diffusion

Fig. 2 (A) Computerized tomography of brain without contrast. (B) Diffusion-weighted MRI of brain without contrast, apparent diffusion coefficient. (C) Diffusion-weighted MRI of brain without contrast, apparent diffusion coefficient. (D) T2-weighted MRI of brain without contrast. (E) T2 FLAIR MRI of brain without contrast. MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

that was not observed in our patient. We suspect the hyperintense signals seen in DWI were from a phenomenon known as “T2 shine-through.” It refers to high signals on DWI images that are not due to restricted diffusion, but rather to a high T2 signal that “shines through” to the DWI image. None of the hyperintense signal alterations on DWI showed decreased ADC values, as would have been expected in ischemic brain injury with cytotoxic edema. Magnetic resonance angiography and venography showed no evidence of septic emboli, aneurysms, large vessel occlusion, or venous sinus thrombosis. Review of patient’s vital signs demonstrated increased systolic, diastolic, and mean arterial pressures (MAP) preceding the acute neurological symptoms, but only moderately exceeding the 95th percentile MAP for the patient’s age and gender (►Fig. 3).

Long-term electroencephalography conducted postseizure showed no documented electrographic epileptiform activity, but did reveal generalized mild to moderate background slowing in the posterior cerebral regions bilaterally. After airway intubation and cessation of seizures with anticonvulsants the patient’s mild hypertension resolved without administration of antihypertensives. The patient returned to her baseline neurological state within 36 hours. She remained hospitalized on anticonvulsants with subsequent resolution of fever and leukocytosis, while completing intravenous antibiotics. The patient was discharged on POD 25 with a normal neurological examination. During an outpatient follow-up, 2 weeks after discharge, the patient was normotensive with normal cognitive and motor function with no interval history of new seizure activity. Unfortunately, the patient was lost to follow-up thereafter.

Discussion

The presence of vasogenic edema on brain imaging has been the hallmark of PRES since it was initially described in 1996 by Hinchey et al, but the etiology has remained both elusive

and controversial.¹ Current debate centers on 2 primary mechanisms of action: (1) severe hypertension resulting in loss of autoregulation and (2) systemic inflammation resulting in endothelial dysfunction.⁴

Hypertension with resultant loss of autoregulation remains the most popular explanation for PRES, but fails to account for 20 to 30% of patients with normal to mild elevations in blood pressure reported in most case series and as seen in our patient.⁴ In patients with systemic inflammatory response syndrome or sepsis, blood pressure elevations could stem from multiple etiologies including acute kidney injury, narcotic withdrawal, pain with inadequate analgesia, and fluid overload. However, our patient had normal serum creatinine and estimated creatinine clearance for age throughout her admission. The patient was on vancomycin and piperacillin/tazobactam. The vancomycin dose was reviewed regularly by a clinical pharmacist with monitoring of additional parameters including urine output, serum creatinine, creatinine clearance, and blood urea nitrogen/creatinine ratio. The vancomycin was significantly subtherapeutic and we were unable to achieve therapeutic levels despite escalation of the dose. The antibiotics were then switched to linezolid and subsequently to meropenem and ampicillin. Our patient was also on analgesic and sedation infusions with fentanyl and versed in the immediate postoperative period after exploratory laparotomy and delayed secondary closure of her abdomen. During this time, she had adequate renal function as indicated by urine output and creatinine clearance. A cumulative fluid balance of approximately 85 mL/kg was noted, preceding the diagnosis of PRES. This could be considered moderate volume overload, but we considered the patient to be clinically euvoletic after fluid resuscitation given her initial shock and dehydration on admission. During the hospital course, the patient’s urine output ranged from 2.1 to 6.8 mL/kg/hour, while receiving intermittent furosemide.

Although the etiology of the patient’s mild hypertension as precipitating versus consequential factor in developing

Fig. 3 Average daily MAP, systolic and diastolic arterial pressures during patient’s hospitalization. MAP, mean arterial pressure.

PRES remains unclear, sepsis undoubtedly played a key role. Our patient's persistent febrile condition and leukocytosis indicate ongoing systemic inflammation. Endothelial dysfunction in PRES is proposed to result from activation of both the endothelium and immune system. As a byproduct of the proinflammatory state, this dysfunction has been shown to inhibit vasodilation and potentially impair cerebral autoregulation through disruption of the tight junction proteins.⁵ Disruption of the tight junction integrity leads to interstitial edema, further cytokine release, and injury to astrocytes innervating the vascular smooth muscle.⁵⁻⁷

Cerebral autoregulation describes the arteriolar dilation and constriction that occurs in response to transmural pressure, chemical signals, and autonomic innervation.⁸ This process serves to maintain consistent cerebral perfusion despite fluctuations in blood pressure.⁸ The posterior parietal and occipital regions of the brain are thought to have fewer sympathetic fibers and are thus more prone to autoregulatory dysfunction and vasogenic edema.⁴ Our patient exhibited increased mean arterial pressures preceding her seizure and diagnosis of PRES, but was far from exceeding the upper limit of cerebral autoregulatory capacity (► Fig. 3). However, there is a paucity of data regarding cerebral autoregulation in pediatric patients. Most literature centers on establishing the lower limits of autoregulation in children, but a study by Vavilala et al showed that dynamic cerebral autoregulation in healthy adolescents had lower mean arterial autoregulation pressure limits than adults.⁹

The scarcity of information regarding PRES in the pediatric population is important, as prior analyses have revealed marked differences between presentation in adults and children.¹⁰ Headaches and visual disturbances are significantly less common in children, who tend to present with seizure activity.¹⁰ This has been speculated to be due in part to increased permeability of an immature blood-brain barrier and susceptibility to proinflammatory cytokines.^{10,11}

We hypothesize that sepsis-related endothelial dysfunction caused our patient to be prone to vasogenic edema. Although our patient's MAPs were not to the degree typically seen in PRES; it is possible that her auto-regulatory capabilities were less efficacious in maintaining proper vascular tone.

Conclusion

We report the youngest documented case of PRES in the United States occurring in a previously healthy 5-year-old following perforated appendicitis and sepsis complicated by *E. coli* and *B. fragilis* peritonitis with intra-abdominal abscess

formation. Although there is no specific treatment for PRES, imaging modalities, such as MRI along with an increased clinical diagnostic suspicion is mandatory for initiation of supportive therapy. We suggest PRES should be considered in the differential diagnosis of unexpected neurological deterioration or seizures in patients with sepsis and proinflammatory conditions. Whether hypertension is an etiology of, or response to, cerebral vasogenic edema in these septic patients, prevention or mitigation of PRES must include strict control of systemic blood pressure as normal autoregulatory capabilities are likely compromised.

Conflict of Interest

None declared.

References

- 1 Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;334(08):494-500
- 2 Ettinger N, Pearson M, Lamb FS, Wellons JC III. Pediatric posterior reversible encephalopathy syndrome presenting with isolated cerebellar edema and obstructive hydrocephalus. *J Neurosurg Pediatr* 2014;14(04):344-347
- 3 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(05):335-339
- 4 Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *Am J Neuroradiol* 2008;29(06):1036-1042
- 5 Bolton SJ, Anthony DC, Perry VH. Loss of the tight junction proteins occludin and zonula occludens-1 from cerebral vascular endothelium during neutrophil-induced blood-brain barrier breakdown in vivo. *Neuroscience* 1998;86(04):1245-1257
- 6 Pfister D, Siegemund M, Dell-Kuster S, et al. Cerebral perfusion in sepsis-associated delirium. *Crit Care* 2008;12(03):R63
- 7 Vallet B. Bench-to-bedside review: endothelial cell dysfunction in severe sepsis: a role in organ dysfunction? *Crit Care* 2003;7(02):130-138
- 8 Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol* 2015;14(09):914-925
- 9 Vavilala MS, Newell DW, Junger E, et al. Dynamic cerebral autoregulation in healthy adolescents. *Acta Anaesthesiol Scand* 2002;46(04):393-397
- 10 Siebert E, Bohner G, Endres M, Liman TG. Clinical and radiological spectrum of posterior reversible encephalopathy syndrome: does age make a difference?—A retrospective comparison between adult and pediatric patients *PLoS One* 2014;9(12):e115073
- 11 Zheng W. Neurotoxicology of the brain barrier system: new implications. *J Toxicol Clin Toxicol* 2001;39(07):711-719