SAGE Open Medical Case Reports
Volume 9: 1–4

DOI: 10.1177/2050313X211053454
journals.sagepub.com/home/sco
SAGE

Posterior reversible encephalopathy syndrome following appendicitis in a young child: A case report and review of the pediatric literature

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Abstract

Posterior reversible encephalopathy syndrome is an acute or subacute neurological disorder with variable clinical manifestations including encephalopathy, headache, seizures, visual disturbance, and focal neurologic deficits. Neuroimaging often shows frequently reversible vasogenic edema that predominantly involves the subcortical parieto-occipital lobes. Posterior reversible encephalopathy syndrome has been associated with hypertension and reported in patients with many conditions including eclampsia/pre-eclampsia and immunosuppressive therapy. Recently, posterior reversible encephalopathy syndrome is recognized to occur in association with severe infections such as complicated appendicitis. Here, we describe a case of 11-year-old male admitted for complicated appendicitis and severe sepsis. He developed seizures and had an altered mental status 10 days into his hospitalization with brain magnetic resonance imaging findings consistent with posterior reversible encephalopathy syndrome. We review the pediatric literature and discuss the pathogenesis of posterior reversible encephalopathy syndrome in association with an infection. We highlight the importance of recognizing this syndrome as a possible cause for acute neurological deterioration in children with severe infections.

Keywords

Infectious diseases, neurology

Date received: 10 June 2021; accepted: 28 September 2021

Introduction

Posterior reversible encephalopathy syndrome (PRES) is an acute or subacute neurological disorder with variable clinical manifestations including encephalopathy, headache, seizures, visual disturbance, and focal neurologic deficits.[1,2] Neuroimaging often shows frequently reversible vasogenic edema that predominantly involves the subcortical parieto-occipital lobes.[3] PRES has been associated with hypertension and reported in patients with many conditions including eclampsia/pre-eclampsia and immunosuppressive therapy. Recently, PRES is recognized to occur in association with severe infections such as complicated appendicitis.[4,5] Here, we describe a case of 11-year-old male admitted for complicated appendicitis and severe sepsis. He developed seizures and had an altered mental status 10 days into his hospitalization with brain magnetic resonance imaging (MRI) findings consistent with PRES. We review the pediatric literature and discuss the pathogenesis of PRES in association with an infection. We highlight the importance of recognizing this syndrome as a possible cause for acute neurological deterioration in children with severe infections.

Case description

A previously healthy 11-year-old male presented with fever, abdominal pain, and vomiting of 7 days duration. He had no significant medical history. His growth and development were appropriate for his age. His immunizations were complete for his age. There was no travel history. His vital signs

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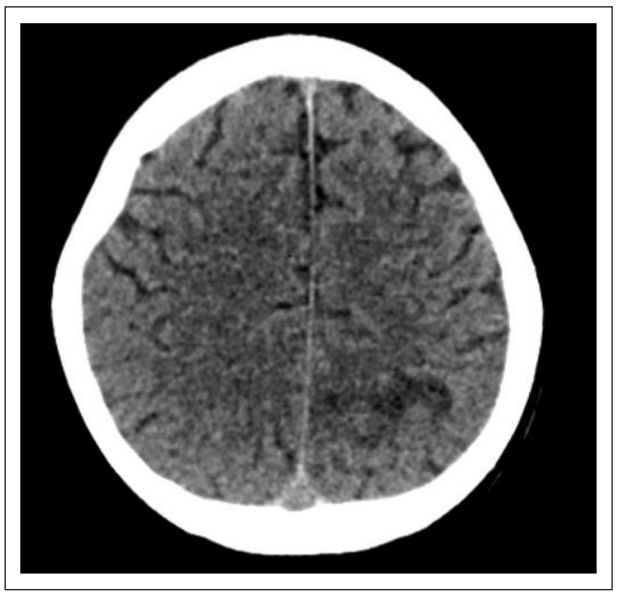

Image 1. Axial CT shows hypodensity in the left parietal region.

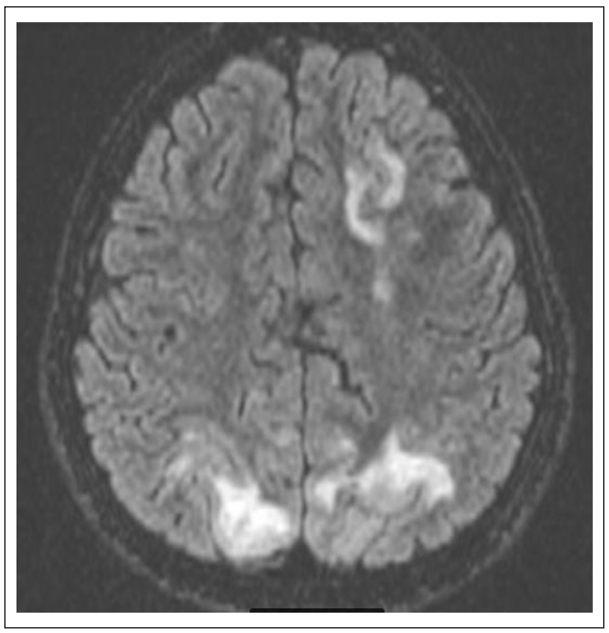

Image 2. Axial FLAIR images show abnormal hyperintense signal in the bilateral parietal and left frontal region.

were as follows: temperature of 36.8°C, respiratory rate of 32 breaths per minute, blood pressure of 108/70 mm Hg, and oxygen saturation of 100% on room air. The patient was drowsy and looked sick. His physical exam showed diffuse abdominal tenderness, distention, and rigidity. He has white blood cell count of 30,400/mm^3 with 32% bands. Computed tomography (CT) of the abdomen demonstrated perihepatic large collection consistent with abscess. He was diagnosed with complicated appendicitis. Subsequently, he was admitted to the intensive care unit (ICU) and was started on empiric broad-spectrum antibiotics. He underwent open laparotomy with appendectomy and drain placement. His intrabdominal wound culture grew polymicrobial growth of *Escherichia coli*, *Pseudomonas Aeruginosa*, *Streptococcus constellatus*, and *Bacteroides.*

The patient improved gradually, became afebrile, and was weaned off blood pressure support medications. His wound was closed by delayed primary closure. On post-operative day (POD) 7, blood pressure readings were trending up gradually. The highest reported reading on POD 9 was: 164/117 mm Hg (95th percentile for age, height, and gender is 118/78 mm Hg). On POD 10, he became drowsy and developed two episodes of tonic-clonic seizures. Seizures were treated with intravenous lorazepam. CT of the head was done and showed hypodensities in the bilateral subcortical parietal regions (Image 1). Subsequently, MRI, magnetic resonance arteriography (MRA), and magnetic resonance venography (MRV) were done. These early studies showed abnormal FLAIR hyperintense signal more prominently in the bilateral parietal regions, but also extended to the frontal and occipital regions, mainly in the subcortical regions, with associated gyral and leptomeningeal enhancement. There was no diffusion restriction, venous sinus thrombosis, and no evidence of intracranial hemorrhage (Image 2). In addition, there were no ring enhancing lesions or evidence of septic emboli.

The patient's clinical condition improved quickly, and he returned to his normal mental status in 24 h. Hypertension was treated with oral isradipine. Repeat MRI 48 h later showed worsening of the subcortical FLAIR signal changes in the parietal, occipital, and frontal regions, but a significant improvement in the appearance enhancement pattern seen on the previous exam, still with no diffusion restriction or evidence of bleed (Image 3). The imaging findings with the pattern of evolution of the abnormalities were more consistent with PRES. Four months later, he was seen by pediatric nephrology where he had no reported elevated blood pressure or neurological deficits. He had no further work up at that point since he remained normotensive. No further follow-up imaging was obtained because patient was doing well clinically.

Discussion

As in adults, pediatric PRES is commonly associated with severe hypertension and cytotoxic chemotherapy medications.[1] The exact pathophysiology is still a matter of debate. One theory relates it to severe hypertension resulting in loss of autoregulation in cerebral blood flow with a subsequent increase in vascular permeability. This damage to the blood–brain barrier is traditionally believed to result in vasogenic edema.[6] Another proposed mechanism is cerebrovascular endothelial dysfunction that may be primary or secondary caused by severe hypertension, fluctuations in blood pressure, or by circulating endogenous (eclampsia-preeclampsia, sepsis), or exogenous (chemotherapy, immunosuppressive agents). The key mechanism in autoimmune

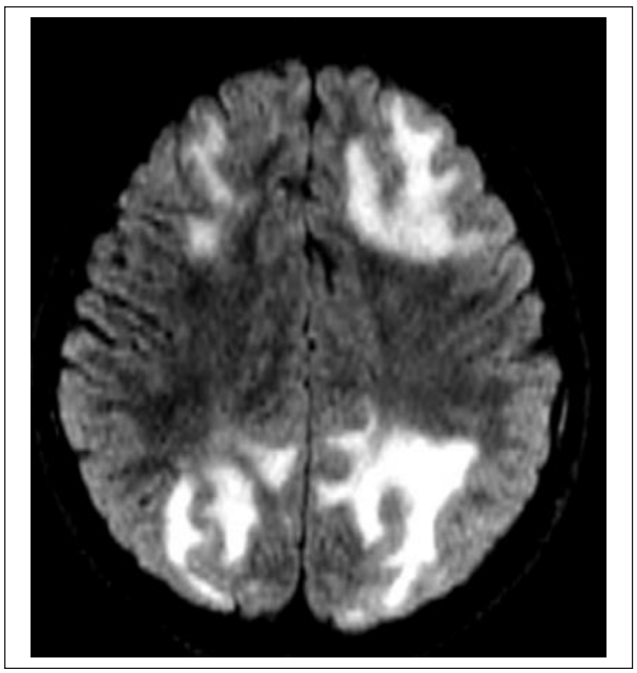

Image 3. FLAIR images showing worsening signal in the same regions and in the right frontal region.

disorders and sepsis is excessive release of pro-inflammatory cytokines resulting in endothelial activation, release of vasoactive agents, increased vascular permeability, and edema formation.[3,6,7]

In children, as in adults, most patients with PRES present with acute encephalopathy, seizures, and hypertension.[2] Seizures are the most common presentation (90%), followed by encephalopathy.[1,3] In a review by Chen et al.,[1] acute encephalopathy was found in all their cases. This underscores the importance of considering PRES in the differential diagnosis of acute encephalopathy in children. Other symptoms include visual disturbances, headache, and focal neurologic deficits.[3] The differential diagnosis of PRES in children includes many conditions including infectious or autoimmune encephalitis, malignancy, cerebral venous sinus thrombosis, acute disseminated encephalomyelitis (ADEM), ischemic stroke, and toxic leukoencephalopathy. Due to the broad clinical presentations, and multiple neuroimaging patterns, a comprehensive evaluation including medical history, neuroimaging, and laboratory investigations is often needed to confirm the diagnosis.[8]

Brain imaging may show the "classical" subcortical, and less often cortical, bilateral parieto-occipital vasogenic edema, that is more clearly seen in the MRI (T2-FLAIR images) than CT. Other commonly involved areas are the superior frontal sulcus or arterial watershed regions. Less commonly affected areas include the cerebellum, brain stem, basal ganglia, or spine. Unilateral abnormalities, diffusion restriction abnormalities, contrast enhancement, and hemorrhage, including microhemorrhages and vasculopathy may also be seen.[3,7,9] In a recent review article, it was reported that atypical imaging findings (locations other than parieto-occipital regions, asymmetry, frontal sulcus involvement, gadolinium enhancement, presence of hemorrhagic changes, and restricted diffusion) are more commonly seen in pediatric cases than adults. Although the exact etiology for such difference is not completely understood, this may make the diagnosis of pediatric PRES more difficult.[8]

Recently, PRES is increasingly recognized in association with infection, sepsis, and Systemic Inflammatory Response Syndrome including most recently an association with COVID-19 infection.[4,10,11] Bartynski et al.[10] reviewed 25 patients who have PRES in association with severe infection or sepsis. In this review, the primary infection was noted mostly in the lungs, abdomen, wound, or urinary tract. The blood pressure measurements were either normal or mildly elevated in 40% of the patients. Vascular instability and PRES developed within 14–30 days of the severe infection. In addition, the authors found an association with gram-positive organisms, inverse effect of severe hypertension on the extent of vasogenic edema, and high frequency of associated cerebral vasospasm. These recent observations in patients with severe sepsis suggest that systemic inflammation resulting in endothelial dysfunction could be contributing to the development of the brain vasogenic edema.[10,12]

We found limited data when we reviewed the literature in search for reported cases of PRES and severe infection or sepsis in the pediatric populations. None of the 25 cases of PRES and associated infection reported by Bartynski et al.[10] were in children. Yoon et al.[13] reported a case of 17-year-old boy who developed PRES after tuberculosis peritonitis and sepsis. Finally, Saley et al.[5] reported a previously healthy 5-year-old patient who developed PRES following laparotomy and appendectomy secondary to perforated appendicitis. Her clinical course was complicated by *E. coli* and *Bacteroides fragilis* peritonitis with intra-abdominal abscess formation. On POD 15, she suddenly developed a seizure requiring benzodiazepine treatment and intubation. She had moderately increased systolic, diastolic, and mean arterial pressures (MAPs) preceding the acute neurological symptoms. She had a normal neurological exam and was normotensive upon the 2-week follow-up post-discharge.

PRES has a favorable prognosis with a complete recovery reported in 75%–90%, which is expected in few days or weeks.[3] However, mortality and persistent neurologic sequelae including seizures, hemiparesis, decreased visual acuity, and dizziness may occur.[3,7] There is no specific treatment for PRES. However, symptoms usually improve when specific triggers are eliminated or treated. As such, recognizing it and including it in the differential diagnosis with subsequent early intervention may help reduce such adverse outcome. This is even more important in children since they may be more vulnerable to cerebrovascular dysfunction than adults, because they have a narrower range of autoregulation in

cerebral blood flow,[14] and the mean blood pressure at the onset of PRES symptoms is lower.[3,14]

Conclusion

Clinicians from multiple disciplines, such as pediatric hospitalists, may frequently encounter patients with severe complicated infections, and it would be important to consider PRES as the possible cause of acute neurological deterioration in such situations. Early recognition and treatment may accordingly be started.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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