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CLINICAL CASE REPORT

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Posterior Reversible Encephalopathy Syndrome Complicating Traumatic Pancreatitis

A Pediatric Case Report

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Abstract: We are reporting a case of posterior reversible encephalopathy syndrome (PRES) developed in an unusual clinical scenario without the presence of the most described symptoms. PRES is a neurological and radiological syndrome described in many different clinical conditions. In children it has been mostly reported in association with hematological and renal disorders.

Our patient was a 15 years old boy, admitted to our intensive care unit for pancreatitis after blunt abdominal trauma.

During the stay in the intensive care unit, he underwent multiple abdominal surgical interventions for pancreatitis complications. He had a difficult management of analgesia and sedation, being often agitated with high arterial pressure, and he developed a bacterial peritonitis. After 29 days his neurological conditions abruptly worsened with neuroimaging findings consistent with PRES. His clinical conditions progressively improved after sedation and arterial pressure control.

He was discharged at home with complete resolution of the neurological and imaging signs 2 months later.

The pathophysiology of PRES is controversial and involves disordered autoregulation ascribable to hypertension and endothelial dysfunction. In this case both hypertension and endothelial activation, triggered by sepsis and pancreatitis, could represent the culprits of PRES onset. Even if there is no specific treatment for this condition, a diagnosis is mandatory to start antihypertensive and supportive treatment. We are therefore suggesting to consider PRES in the differential diagnosis of a neurological deterioration preceded by hypertension and/or septic state, even without other ''typical'' clinical features.

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Abbreviations: CT = computerized tomography, IV = intravenous, MR = magnetic resonance, PRES = posterior reversible encephalopathy syndrome.

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INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a neurological syndrome defined by clinical and radiological features. The typical pattern includes headache, confusion, visual symptoms, and seizures, with magnetic resonance (MR) findings consistent with vasogenic edema predominantly localized to the posterior cerebral hemispheres.[1] Patients in all age groups appear susceptible,[2] but the real incidence of this condition is not known. A recent study estimated an incidence of 0.4% in a pediatric critical care unit.[3] PRES most often occurs in the setting of hypertensive crisis, preeclampsia, or with cytotoxic immunosuppressive therapy, however many other clinical settings are reported (Table 1). In pediatric population it is mostly described in association with hematological or renal disorders.[4] The pathophysiology is not completely understood but it appears to be related to disordered cerebral autoregulation and endothelial dysfunction. PRES is usually benign, being fully reversible in many cases within 2 weeks after removal of the inciting factor and control of the blood pressure. However, a small number of patients could experiment refractory intracranial hypertension,[5] leading to residual neurological deficits or even decease.[6]

PATIENT INFORMATION

A 15 years-old Egyptian boy was admitted to the emergency department of our hospital because of accidental abdominal trauma while playing. His medical history was negative. He arrived at the hospital complaining of abdominal pain; he was fully awake, without cardiovascular nor respiratory impairment. Contrast enhanced computerized tomography (CT) scan of the abdomen demonstrated pancreatic injury with edema of the pancreatic head and uncinate process. Because of the high suspicion of perforation, he underwent an exploratory laparotomy that was negative for visceral lesions. After the surgery, the patient was extubated and admitted to our intensive care unit.

CLINICAL FINDINGS, DIAGNOSTIC ASSESSMENT, AND THERAPEUTIC INTERVENTION

During the following week he was hyperthermic (Figure 1, Panel B) and developed severe abdominal pain, partially controlled with epidural infusion of ropivacaine and sufentanil, and intravenous (IV) administration of paracetamol, nonsteroidal antiinflammatory drugs and opiates. He was agitated despite the amount of analgesia: so an IV infusion with propofol was started. His blood pressure was basically high (Figure 1, Panel A), with peak values around 150/80 mm Hg. On day 9 after admission he underwent a second exploratory laparotomy, demonstrating extended bowel ischemia. He was treated with

TABLE 1. Clinical Conditions Associated With Posterior Reversible Encephalopathy Syndrome

Hypertension
Acute or chronic renal diseases
Solid organ/bone marrow transplantation
Preeclampsia/eclampsia
Infection/sepsis/shock
Vasculitis
Systemic lupus erythematosus
Polyarteritis nodosa
Cryoglobulinemia
Wegener's granulomatosis
Immunosuppressive, immunomodulatory, and chemotherapeutic drugs
Bevacizumab
Cisplatin and other platinum-based agents
Combination chemotherapy
Cyclosporine A
Cytarabine
Gemcitabine
Intravenous immunoglobulin
Tacrolimus
Tyrosine kinase inhibitors (pazopanib), sorafenib, sunitinib
Porphyria
Hypercalcemia, hypomagnesmia
Blood transfusion
Contrast media exposure (cerebral, coronary angiography)
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

a small bowel resection and the placement of a vacuum assisted closure system that was removed after 12 days and multiple surgical revisions.

After the surgical intervention he was mostly hyperthermic (Figure 1, Panel B). Procalcitonin increased, reaching a peak of 19 ng/ml on day 11 (Figure 1, Panel C). An empirical antimicrobial therapy with vancomycin and piperacillin–tazobactam was started. After the isolation of extended-spectrum beta-lactamase producing *E. coli* in the abdominal fluid, the antimicrobial therapy was shifted to meropenem and amikacin. The CT scan of the abdomen performed on day 13 showed a diffuse peritonitis and the evolution of the pancreatitis with formation of a pancreatic pseudocyst. Sedation and analgesia were difficult to manage, due to a persistent status of agitation and pain, unresponsive to epidural analgesia. He was kept intubated under IV infusion of propofol, midazolam, morphine and ketamine, and inhalatory anesthesia with sevorane was also used for 5 days. Despite the significant amount of sedative drugs his blood pressure was normal tending to hypertension (Figure 1, Panel A).

After the surgical closure of the abdominal wall on day 21, his clinical conditions seemed to improve: procalcitonin dropped to values less than 1 ng/ml, and the amount of antipyretic drugs required to control his body temperature was progressively lowering. On day 25, sedation was reduced and he was extubated. Antimicrobial therapy was also suspended. He was awake for a few days but his blood pressure rose to value of 160/90 mm Hg. His body temperature rose as well, without any new microbiological isolation or procalcitonin increase. He had several vomit episodes. Few days later, on day 29, his neurological status dramatically worsened with stupor and neck rigidity; he was therefore intubated. Head CT scan showed bilateral cortical and subcortical hypodense lesions in both occipital and parietal lobes and bilateral frontal lobe white matter hypodense lesions. A lumbar puncture was performed, demonstrating no signs of infection of the central nervous system. The electroencephalogram was negative for electrical seizures. The radiological findings, together with the absence of signs of meningoencephalitis, raised the suspicion of PRES. Brain MR confirmed the diagnosis, while excluded the presence of venous thrombosis (Figure 2). Furthermore he underwent a CT scan of the abdomen that showed an enlargement of the pancreatic pseudocyst, compressing the stomach and the duodenum. The lesion was percutaneously drained. The antimicrobial therapy was restarted.

Sedative drugs were continued for 5 days with good control of the arterial pressure values. His neurological status improved and on day 35 he was extubated. He was alert and calm, and his blood pressure was corrected with transdermal clonidine. Four days later he was moved to the pediatric ward without neurological deficits. The antihypertensive therapy was no longer necessary and was suspended after a few days.

OUTCOME

Fifty days later he was discharged at home in good general conditions, after a brain MR demonstrating complete resolution of the lesions (Figure 2).

DISCUSSION

PRES is a clinical syndrome consisting of acute neurological symptoms usually including seizures, headache, visual disturbance, mental status alterations, and paralysis.[7]

At CT/MR imaging, the brain typically demonstrates focal regions of symmetric hemispheric edema. In a recent study of 96 PRES patients by Liman et al, edematous lesions, although detectable within the entire brain, involved the occipital and parietal lobes in the majority of cases. Frontal and temporal lobes were affected in about 50% of cases, the basal ganglia in about one-fourth of cases, the thalamus in about one-fifth of cases. In more than half of cases there were infratentorial lesions, mostly in the cerebellum and the pons.[8]

The pathophysiology of PRES involves disordered autoregulation and endothelial dysfunction.[9] This has been classically attributed to severe rise in blood pressure, but it is now evident that direct endothelial damage, seen in immunosuppressant drugs use, autoimmune diseases, or eclampsia, can be the leading cause of this condition.[10]

The role of hypertension in the onset of this syndrome is supported by the evidence that acute hypertension frequently accompanies PRES.[11–13] Abrupt blood pressure rise, exceeding the threshold of cerebral blood flow autoregulation, can lead to hyperperfusion and blood–brain barrier disruption, inducing leakage of plasma and macromolecules in the interstitium.[10]

However, PRES is commonly seen even without hypertension or with only minor increase of blood pressure.[14,15] This observation promotes the hypothesis that hypertension would be a consequence and not the trigger in PRES pathogenesis. Endothelial activation and dysfunction would play a crucial role, representing the common pathway shared by all clinical conditions associated with PRES onset.[16] Endothelial dysfunction is a well-established feature in eclampsia.[17] The cytotoxic effects of immunosuppressive therapy on the vascular endothelium could explain the relationship between immunosuppressive drugs and PRES.[18] Endothelial activation and injury is

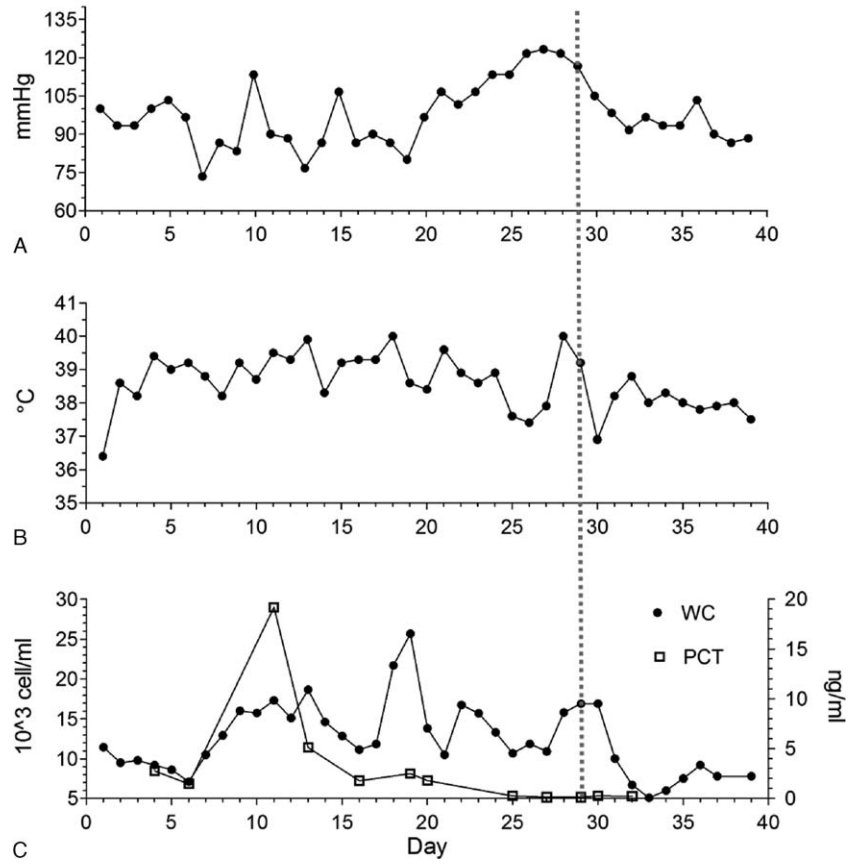

FIGURE 1. Time-line of mean arterial pressure (Panel A), body temperature (Panel B), and white cells count and procalcitonin (Panel C) during the stay in intensive care unit. The dotted gray line highlights day 29, when the brain CT was performed and the diagnosis of PRES was made. WC, white cells count; PCT, procalcitonin.

a crucial step in the progression of the septic response secondary to an infective event,[19] and could explain the association of PRES with infection and sepsis.[20]

In our case, the clinical onset of PRES was characterized by a deterioration of the neurological status without the presence of seizures, a symptom described in 60% to 75% of patients with PRES[10] and in 9 of 10 cases from a pediatric intensive care unit.[3] Furthermore, in the pediatric population, PRES is mostly described in association with hematological diseases, neoplasms, or renal diseases,[4] making our case an unusual clinical scenario.

The neuroimaging has been the pivotal element for the diagnosis, showing bilateral hypodense lesions in both occipital and parietal lobes, consistent with literature findings. Other rare diseases have a similar radiological pattern, in particular acute disseminated encephalomyelitis (ADEM). However, the lack of a viral infection preceding the neurologic deterioration and the absence of pathological findings in the liquor make the diagnosis of ADEM unlikely.

Before the onset of PRES, our patient was mostly hypertensive although without exceeding the values typically associated with loss of cerebral autoregulation.[21] However, his blood pressure values were similar to those reported in a pediatric population of patient with PRES[3] and are consistent with the endothelial pathophysiological hypothesis. Moreover the patient presented a status of sepsis with hyperthermia, high PCT levels and leukocytosis and isolation of *E. coli* in the abdominal fluid and this could represent a trigger for the onset of PRES.

Interestingly a few cases of PRES in the setting of acute pancreatitis[22–26] with or without other possible triggers for PRES (alcohol withdrawal, systemic lupus erythematosus, acute intermittent porphyria) have been reported. In acute pancreatitis there is a local and systemic activation of inflammatory pathways that could play a major role in the development of extra pancreatic complications.[27,28] Experimental models of pancreatitis have suggested that the proinflammatory cytokines, produced during pancreatitis, may have a pivotal role in vasogenic brain edema formation,[29] a pathogenic mechanism similar to PRES. The development of brain edema has also been implicated in the pathogenesis of pancreatic encephalopathy,[30] an uncommon complication of acute pancreatitis.

There is no specific treatment for PRES, but the disorder is usually reversible once the precipitating cause is eliminated or treated. General consensus among clinicians suggests that treatment of hypertension is important, although no studies have been done to measure the effect of hypertension control on the resolution of PRES.[10] Patients with PRES have been treated with dexamethasone,[31] but, because of its associated risk of hypertension, fluid overload, and electrolyte disturbance, this is not a recommended therapy. In our case a supportive therapy was carried out along with correction of hypertension.

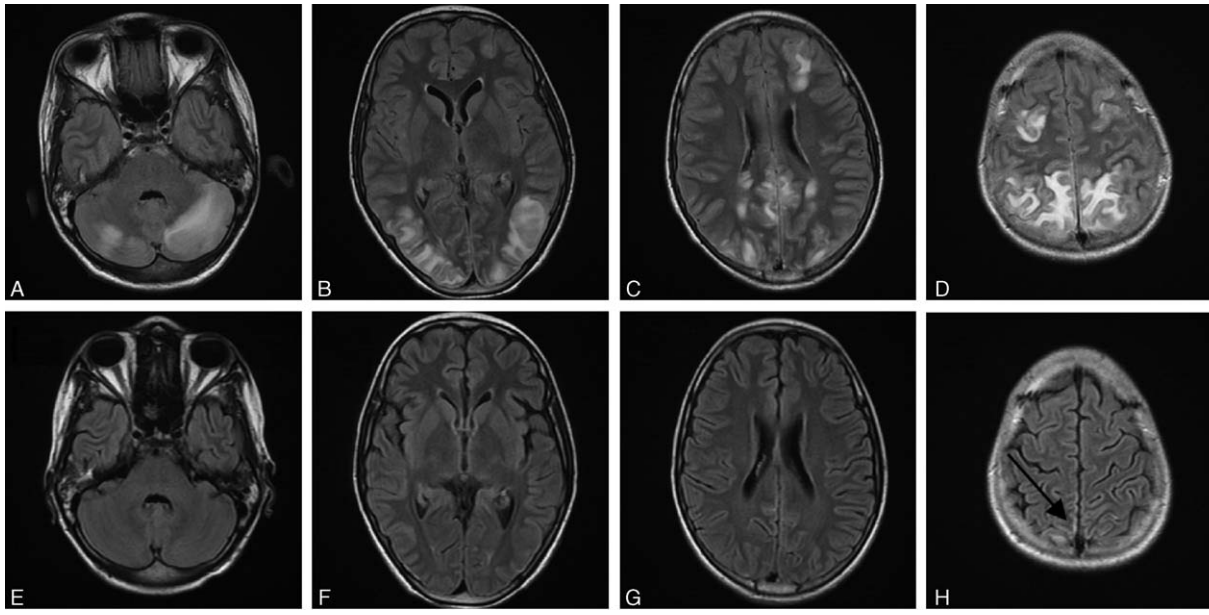

FIGURE 2. Magnetic resonance (MR) findings. Panels A–D: At the time of diagnosis, axial FLAIR images demonstrated multiple, bilateral areas of hyperintensity and edema in cerebellar hemispheres and temporo-parieto-occipital lobes with cortico-subcortical distribution and predominant white matter involvement. Smaller similar foci were present in bilateral frontal and right posterior periventricular white matter. Panels E–H: 50 days later, axial FLAIR images demonstrated complete regression of edema and signal alteration in both cerebellar and cerebral hemispheric white matter. MR showed marked improvement with only small foci of cortical hyperintensity and thinning in parietal parasagittal regions (Panel H, black arrow).

Given the unusual association between PRES and pancreatitis and the lack of the most typical symptoms seen in this case, we would like to stress the importance of considering PRES in the differential diagnosis of neurological deterioration in children with mild hypertension and/or other potential triggering factors like sepsis.

CONCLUSIONS

We reported a case of PRES in a 15 years old boy admitted to our intensive care unit for abdominal trauma with acute pancreatitis. The clinical presentation was a sudden deterioration of the neurological status and the brain CT and MR showed the presence of typical PRES lesions. Hypertension, the septic state of the patient and the intense proinflammatory response triggered by the pancreatitis could represent the culprits of PRES developing. Even if there is no specific treatment for this condition, a diagnosis is mandatory to start antihypertensive and supportive treatment. We are therefore suggesting to consider PRES in the differential diagnosis of a neurological deterioration preceded by hypertension and/or septic state, even without other ''typical'' clinical features.

INFORMED CONSENT

Patient's parents provided their informed consent for the publication of this case report.

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