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Case Report

Recurrent posterior reversible encephalopathy syndrome with cerebellar involvement leading to acute hydrocephalus

Paul Hage[a], Cedric Kseib[a,*], Ghassan Hmaimess[b], Pauline Abou Jaoude[b], Peter Noun[b]

[a] Department of Neurosurgery, Saint George Hospital University Medical Center, Beirut, Lebanon
[b] Department of Pediatrics, Saint George Hospital University Medical Center, Beirut, Lebanon

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ABSTRACT

Posterior reversible encephalopathy syndrome or PRES is a proposed cliniconeuroradiological entity that is characterized by headache, confusion, seizure, cortical visual disturbances or even blindness and, to a lesser extent, focal neurological signs. The etiology of this entity includes a sudden increase in blood pressure, renal failure, immunosuppressive drugs, infections, and intravenous immunoglobulin (IVIG). Classically, magnetic resonance imaging (MRI) findings show a symmetric reversible vasogenic edema in the parietooccipital lobes. PRES can involve the brainstem and cerebellum and sometimes can leave irreversible lesions but it can also recur, which is a very rare presentation. In this article, we report a case of recurrent PRES with cerebellar involvement associated with non-communicating hydrocephalus in a 2-year-old child with renal failure on peritoneal dialysis after receiving Etoposide for macrophage activation syndrome.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a proposed cliniconeuroradiological entity that is characterized by headache, confusion, seizure, cortical visual disturbances or even blindness and, to a lesser extent, focal neurological signs. The etiology of this entity includes a sudden increase in blood pressure, renal failure, immunosuppressive drugs, infections, and intravenous immunoglobulin (IVIG). Classically, magnetic resonance imaging (MRI) findings show a symmetric reversible vasogenic edema in the parieto-occipital lobes. On another note, PRES can involve the brainstem and cerebellum and sometimes can leave irreversible lesions [1,5]. In this article, we report a case of recurrent PRES with cerebellar involvement associated with non-communicating hydrocephalus in a 2-year-old child with renal failure on peritoneal dialysis after receiving Etoposide for macrophage activation syndrome.

2. Case report

A previously healthy 2-year-old boy developed a high-grade fever of unknown origin and was treated symptomatically. As fever subsided, he acquired a generalized descending blanching maculopapular rash. Blood tests showed a CRP of 15 mg/dL, hemoglobin of 11.6 g/dL, platelet count of 80,000 per mL, and white blood count of 20,000 mcL. Further investigation showed a high LDH of 4,408 U/L, a ferritin of 5,500 U/L, and a CPK of 247 mcg/L followed by an abnormal blood smear showing 4–5% schistocytes. ADAMTS13 test revealed to be normal ruling out thrombotic thrombocytopenic purpura (TTP). Viral infection investigation was positive for parvovirus B19 (HPV B19). On the second day, he suddenly developed facial and nuchal edema, a sequelae of HPV B19, and was started immediately on high dose steroids and antihistamines as a treatment for angioedema. Bone marrow biopsy was done showing a normocellular marrow with numerous macrophages exhibiting hemophagocytosis suggesting macrophage activation syndrome (MAS).

The following day, he developed status epilepticus refractory to midazolam and phenytoin and then controlled by continuous thiopental infusion. Brain CT scan showed no abnormalities. Creatinine levels reached 4.8 mg/dL with associated electrolyte imbalances and hypoalbuminemia. Complement system studies showed a decreased complement C3 levels. He was promptly started on peritoneal dialysis due to persistent anuria despite IV albumin and continuous furosemide infusion. A kidney biopsy displayed thrombotic microangiopathy coupled with acute tubular necrosis suggestive of atypical hemolytic uremic syndrome (aHUS).

Eculizumab treatment was started for aHUS and the child began recovering. A month later, blood tests normalized except for thrombocytopenia, elevated triglycerides, cholesterol, and ferritin which is associated to MAS. The child was then admitted to the hospital to receive IVIG treatment for persistent thrombocytopenia. After receiving

* Corresponding author.
E-mail address: cedkseib@gmail.com (C. Kseib).

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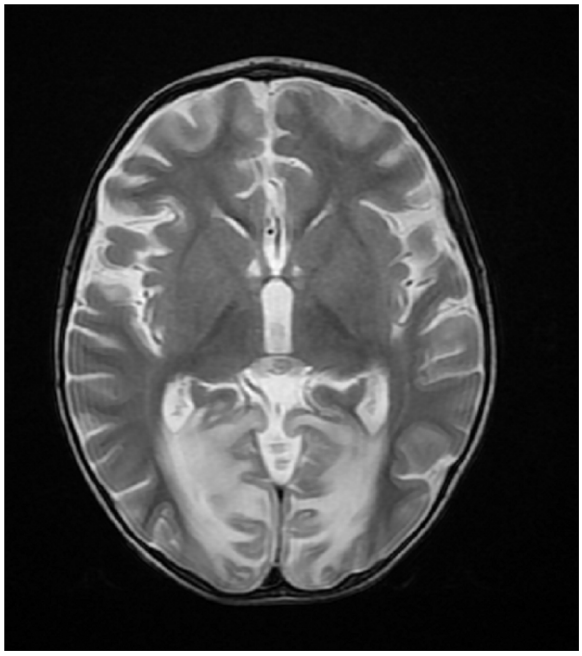

Fig. 1. T2-weighted MRI scan of patient's brain: hyperintensity in the occipital and parietal lobes due to vasogenic edema.

his first dose, he became obtunded. His blood pressure was elevated and was managed with a calcium channel blocker. Urgent brain MRI showed a vasogenic edema within the occipital, and parietal lobes typical of classical PRES (Fig. 1). IVIG was withdrawn and the patient was started on high dose of solumedrol. He responded to the treatment and continued his recovery with intensive physiotherapy. Eculizumab was reinitiated uneventfully followed by a repeat bone marrow biopsy showing high numbers of normal macrophages still suggestive of MAS. A repeat brain CT scan showed increased cortical and subcortical edema in both fronto-parietal lobes with microhemorrhages in both parietal lobes. Nevertheless, the patient was still improving clinically.

A month later, he returned to the hospital to receive etoposide (VP16) treatment for MAS. After his first dose, the patient developed a partial seizure in the form of repeated jerky movements of his left arm associated with a decreased level of consciousness and hypertension (systolic blood pressure (SBP): 180 mm of Mercury and diastolic blood pressure (DBP): 120 mm of Mercury). Seizure evolved to status epilepticus for which he was transferred to the pediatric intensive care unit where he was intubated and was managed with IV anti-epileptics (diazepam, midazolam, and phenytoin). Etoposide (VP16) was suspended. Note that the patient was anuric on peritoneal dialysis with a 4.9 mg/dL creatinine blood level. Emergency CT brain showed diffuse cerebellar edema with compression of the fourth ventricle and brainstem with minimal early tonsillar herniation associated with supratentorial subcortical hypodensities sparing the cortex and a non-communicating hydrocephalus (Fig. 2). Recurrent PRES with cerebellar involvement and hydrocephalus was diagnosed. He immediately had a ventriculostomy to relieve the hydrocephalus. High dose dexamethasone was started to relieve the edema and labetalol for hypertension. The patient remained comatose for 2 weeks. After that his vitals improved and started to regain consciousness. Ventriculostomy was removed without complications. After 2 months, follow-up brain MRI showed extensive supratentorial white matter abnormalities with cortical hemorrhagic sequelae in the occipital and parietal lobes, subacute ischemic lesions in the periventricular white matter, in the body and splenium of corpus callosum, in the basal ganglia, and in the cerebellar hemispheres (Fig. 3a, b, and c).

Follow-up a year after, the child regained all his neurologic functions with no noticeable deficiencies. Last brain MRI showed near total clearance of any white matter abnormalities consistent with the diagnosis of PRES (Fig. 3d and e).

3. Discussion

PRES is defined by the association of neurological signs such as headache, vomiting, visual disturbance, decreased level of consciousness, seizures and radiological abnormalities in the occipitoparietal white matter, usually involving both hemispheres in a symmetrical pattern, characterized by cerebral edema with hypodense signals on CT scan and hyperintense signals on T2 weighted images by MRI that are reversible after resolution of the underlying cause.

The pathophysiology of PRES remains unknown. The classical explanation is based on two theories. The first one links the etiology of PRES to a severe systemic hypertension disabling the auto-regulatory capacity of the cerebral vasculature leading to hyper-perfusion, arteriolar dilatation, injury to the capillary bed and vasogenic edema. The predilection to the posterior brain is linked to the lack of sympathetic innervation. Nonetheless the degree of hypertension hasn't been proportionate to the degree of vasogenic edema and in many cases PRES happens without any elevation in the blood pressure and involves other regions than the posterior brain [1].

The second theory is based on cerebral vasoconstriction resulting in hypo-perfusion, ischemia with concomitant vasogenic edema due to capillary leak. It postulates that PRES occurs in the context of systemic diseases where the immune system is activated causing endothelial dysfunction. Excessive cytokine production induces a cytokine storm stimulating astrocytes to produce vascular endothelial growth factor (VEGF) weakening endothelial cells' tight junctions. The result is blood brain barrier disruption causing cerebral edema. Other inflammatory cytokines drive the expression of endothelin-1 in endothelial cells causing vasoconstriction [1]. A combination of endothelial dysfunction, leukocyte trafficking, vasoconstriction, and leaky tight junction lead to brain edema.

Our patient was first infected by HPV B19. The virus is known to bind to P antigen or globotetraosyl ceramide (Gb4, a globoside) highly expressed on pronormoblasts and on endothelial cells, megakaryocytes, platelets, and fibroblasts [2]. Anti-HPVB19 monoclonal antibodies were found in vascular endothelial cells of the dermis in patients with erythema infectiosum [2]. Since our patient developed a maculopapular rash and angioedema, we can postulate that dysfunction of blood brain barrier endothelial cells were affected by HPV B19.

Another complication of HPV B19 our patient acquired was MAS, a syndrome of uncontrolled activation and proliferation of T cells and well-differentiated macrophages. MAS leads to a highly stimulated but ineffective inflammatory immune response with cytokine overproduction (mainly TNF-α, IL-1, IL-6) called a cytokine storm that also drives endothelial cell dysfunction [3].

Endothelium dysfunction is also linked to the development of aHUS which our patient also developed, led him to renal failure and dialysis alongside the diseases mentioned above. Therefore endothelial dysfunction from a heightened immune system activation would explain our patient's susceptibility to develop PRES.

First attack of PRES occurred after IVIg infusion. How IVIg is implicated in PRES development is still unknown but one of IVIg complications is hypertension. Hypertension with a background of endothelial cell dysfunction would explain PRES occurrence in our patient