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Visual disturbances, confusion and seizures in the setting of high blood pressure and endothelial dysfunction: differential diagnosis of Posterior Reversible Encephalopathy Syndrome

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Abstract

Background: Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by headache, seizures and altered mental status, coupled with a pattern of predominantly transient, posterior cerebral hyper intensities on T2-weighted images at magnetic resonance imaging (MRI). The initial symptoms in these patients often include a diverse array of visual disturbances, such as blurred vision, hemianopsia or cortical blindness. PRES is very rare in children and its exact pathophysiology is not yet established but severe hypertension is perhaps the most common cause.

Patients and Methods: Eleven children (6 male, 5 females; aged 4 to 17 years, median age of 9.7 years) diagnosed with PRES have been retrospectively (years 1998-2013) studied at our Institutions. Each patient's chart, was reviewed and their demographic, clinical, laboratory and radiological findings critically analyzed.

Results: Associated co-morbidities included acute renal failure, sepsis, Schonlein-Henoch Purpura (SHP), Hemolytic Uremic Syndrome (HUS), Mediterranean Spotted Fever (MSF), immunosuppressive therapy and corticosteroid therapy. Headache was the commonest symptom followed by seizures, visual disturbances, drowsiness and confusion. Acute elevation of blood pressure (BP) was recorded in 7 patients, 4 patients had normal BP values at the time of diagnosis. Normotensive and previously unreported presentations and associated co-morbidities were recorded including MSF by *Rickettsia conorii* and normotensive sepsis complicated by PRES. Atypical imaging findings have been also documented including isolated reversible brainstem involvement and unilateral not reversible hematoma.

Conclusions: Children might be prone to PRES due to an overall immaturity of auto regulatory capacities. Endothelial injury and/or dysfunction may have an important pathophysiological role for PRES in normotensive children. Pediatricians and neuroradiologists should recognize and treat promptly this condition to avoid neurological sequelae. Also ophthalmologists should recognize PRES and include it in the differential diagnosis of visual loss in a patient with the predisposing factors of hypertension, preeclampsia, collagen vascular disease, sepsis or exposure to immunosuppressive or cytotoxic agents.

Background

Posterior reversible encephalopathy syndrome (PRES) is a clinical-radiological entity that is predominantly symmetric and potentially reversible. It is marked by acute neurological symptoms such as headache, seizures, visual disturbances, and altered consciousness [1]. Children with PRES usually present headache, seizures, visual disturbances, and altered mental status, as well as a pattern of predominantly transient, posterior cerebral hyperintensities on T2-weighted magnetic resonance imaging (MRI) [2]. Atypical cases in which PRES may not be posterior, reversible, or confined to white matter, also occur, albeit less frequently [3]. PRES could be caused by a breakdown of autoregulation in the cerebral circulation, blood-brain barrier failure due to increased local cerebral perfusion pressure, and/or endothelial dysfunction [4]. A diverse array of comorbidities are described in the literature, but PRES is most commonly associated with hypertensive encephalopathy, autoimmune diseases, collagen vascular disorders such as systemic lupus erythematosus and polyarteritis nodosa, eclampsia, and thrombocytopenic syndromes. It is also commonly associated with the use of immunosuppressive agents and cytotoxic drugs . [1-4]. The ophthalmologist's role in care of the patient with PRES is paramount. The initial symptoms in these patients often include visual loss. A thorough examination can efficiently differentiate a cerebral cause for visual loss from ocular disease. The ophthalmologic examination may not reveal signs of acute or chronic hypertension such as optic disc edema, hemorrhages or exudates. Alternatively, intraretinal hemorrhages, disc edema, arterio–venous nicking, and macular exudates can all be present. The cause of visual loss may be multifactorial in these patients, and a high degree of suspicion for concomitant cortical disease is necessary.The potential for complete reversibility of vision loss in these patients is an extremely satisfying result for the physician astute enough to make the diagnosis [3, 4]. While PRES has been widely studied in adults, data describing its clinical presentations and etiological peculiarities in the pediatric age group are limited.

Methods

We conducted a retrospective study in 5 pediatric neurology tertiary care centers in Italy (University Hospitals from Messina, Catania, and Rome), the United Kingdom (Great Ormond Street Hospital for Children, London) and Japan (Tokyo Medical and Dental University, Tokyo). Familial and institutional consents were acquired. We reviewed the medical records of 11 children (5 girls, 6 boys) identified from the abovementioned Institutions' databases for the period between 2008 and 2013 with a confirmed diagnosis of PRES based on the clinical presentation and neuroimaging abnormalities. Children with sepsis were defined by the *International Consensus Conference on Pediatric Sepsis* as presenting ¾ criteria (mean heart rate > 2 SD above normal for age in the absence of external factors, core temperature > 38.5°C, elevated leukocyte count) for systemic inflammatory response syndrome (SIRS) together with localized infection as demonstrated by positive cultures. All children underwent MRI. Magnetic resonance venography (MRV) and cerebrospinal fluid (CSF) examination were also performed in some cases to rule out other conditions (arterial stenosis, venous sinus thrombosis, post infectious encephalitis, and demyelinating disorders). All neuroimaging findings were reviewed by 2 pediatric neuroradiologists blind to clinical aspects of the patients.

Results

Demographic features and comorbidities

We identified 11 children (6 boys and 5 girls). The median age was 9.7 years. Comorbid conditions include acute renal failure (n = 1), peritoneal dialysis (n = 1), sepsis (n = 2), Schonlein-Henoch purpura (SHP, n = 1), Hemolytic Uremic Syndrome (n = 1), Mediterranean Spotted Fever (n = 1) and conditions requiring cyclosporine therapy (n = 1), tacrolimus therapy (n = 1) and corticosteroid therapy (n = 2). At the onset of clinical symptoms, 7 children (63.6 %) presented elevated blood pressure (BP). The median peak systolic and diastolic BP in these 7 patients during the acute stage were 152.5 mmHg (range, 95–210 mmHg) and 112.5 mmHg (range, 65– 160 mmHg), respectively. Normal median BP values were recorded in 4 children for our series (28.6%) who had associated sepsis (n = 2), rickettsiosis (n = 1), and SHP (n = 1).

Clinical and laboratory findings

On clinical evaluation, headache was found to be the most common symptom (11/11), followed by seizure (8/11), visual disturbances (5/11), and drowsiness and confusion (4/11). Eight patients underwent lumbar puncture examination and their CSF was analyzed. The CSF cultures were negative, and no oligoclonal bands were found. These children were also negative for neurotropic viruses, as assessed through polymerase chain reaction. All the 8 children had normal white cell counts (range 0–2/ml). A mild elevation in protein level was found in 4 patients (range 30–140 mg/dl). An elevation of intracranial pressure was found in 3 children (range 220–350 mm H_20). None of these 3 patients had papilledema at fundus examination and the MRV ruled out sinus venous thrombosis. Extensive work-up including tests on coagulopathies and immunological tests (ANA, ENA, ANCA, and anti-phospholipid antibodies) were performed in all 11 patients and yielded normal results. All 7 children with hypertension received timely treatment, with aggressive control of BP and seizures and reversion of neurological and ophthalmological symptoms occurring within a mean of 6 days (range 3–9 days).

PRES in children with normal BP

In this series, we report 4 children with normal BP values at onset PRES and during the hospitalization period. A child with a history of acute otitis media accompanied by retro-auricular inflammatory signs developed headache and confusion 7 days after admission and underwent MRI. The MRI showed hyperintensity in the left mastoid and pericranial soft tissue swelling, as well as a mild hyperintensity in the pons and midbrain (Figure 1).

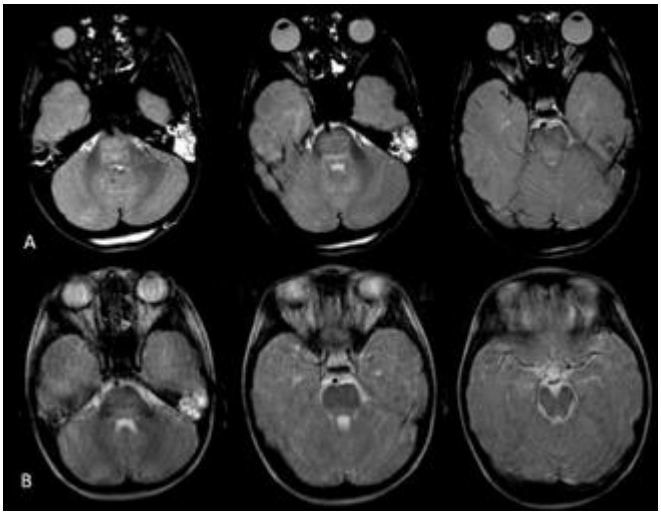

Fig.1 *Posterior Reversible Encephalopathy Syndrome (PRES) with brainstem involvement in a child with acute mastoidits. Axial Spin-Echo T2-weighted images at clinical onset (A) and at a distance of four days (B) Baseline MRI shows a mild hyperintensity of the pons and midbrain. Note the marked hyperintensity of the left mastoid and the peri-cranial soft tissue swelling (arrow). Follow-up examination shows the almost complete resolution of the disease process.*

Because of normal electrolytes and osmolarity values, a diagnosis of pontine myelinolysis was rejected. The patient was normotensive and MRV ruled out venous sinus involvement. He underwent myringotomy, and *Streptococcus pneumoniae* (SP) was collected from his pus specimens. Another child presented onset of clinical sepsis coupled with seizures, visual disturbances, and headache 5 days after central venous catheter insertion. His BP was normal during hospitalization in the intensive care unit. He received blood cultures that isolated coagulase-

negative *Staphylococcus aureus* (SA). These 2 patients who had normal BP with PRES and sepsis were treated with anticonvulsant and targeted antimicrobial therapy as well as intravenous immunoglobulin administration. They showed complete neurological recovery within a mean of 5.5 days (range 4–7 days). In another patient with normal BP, visual changes, confusion, and convulsions occurred together with typical lower extremities purpura and abdominal pain. A diagnosis of HSP was considered. The child showed no renal involvement or hypertension during the hospitalization period, and MRI showed limited cortical signal alteration at both parietal lobes, MR angiography was normal, and CSF examination found no pathological results. The patient underwent anticonvulsant and steroid therapy with resolution of clinical symptoms in 7 days and disappearance of previous MRI abnormalities. Another patient developed convulsions, frontal headache, and visual changes 2 days after the onset of a maculopapular rash on the face and both extremities including the palms. He was positive for the Weil–Felix test, and 10 days after admission, he was tested using an immunofluorescent antibody against*Rickettsia conorii* that showed an increase of titers (IgM 1:1480 and IgG 1:840). This patient received anticonvulsants and started doxycycline therapy with complete neurological recovery in 6 days. MRI findings showed some signal alterations in both the frontoparietal lobes at onset, which were reduced on a 4-day follow-up examination.

Imaging results

All children underwent initial neuroimaging with either computer tomography (n = 3) or MRI (n = 8). MRI was performed at 1.5 T and 3 T. Due to the retrospective study design, protocols and parameters were not homogeneous. However, all studies included axial T1- and T2-weighted images as well as fluid-attenuated inversion-recovery images. Diffusion-weighted imaging (DWI) sequences, apparent diffusion coefficient (ADC) maps, T2-weighted gradient echo sequences, and MR angiography (MRA) were available in 7, 7, 4, and 8 cases, respectively. Neuroimaging showed cerebral subcortical white matter involvement in 10/11 children. Neuroimaging evaluation showed that the parietal lobe was involved in 8 children (72.7 %), the occipital lobe in 6 children (54.5), the frontal lobe in 3 children (27.2 %), and the temporal lobe in 1 child (9%). Isolated brainstem involvement (reversible pons lesions) was found in 1 child (Figure 1); another child had a left parieto-occipital hematoma (Figure 2 A). On MRA, 5/8 (62.5%) patients were found to have attenuation of cerebral arteries. Seven children underwent DWI that yielded hypointensity and ADC maps that showed hyperintensity in all children, except in the child with the left parieto-occipital hematoma that was hypointense on both DWI images and ADC maps. Complete resolution of previously visualized lesions was documented in 9 children (81.8%), 1 child had partial resolution and 1 had irreversible lesions at follow-up MRI (Fig. 2 B).

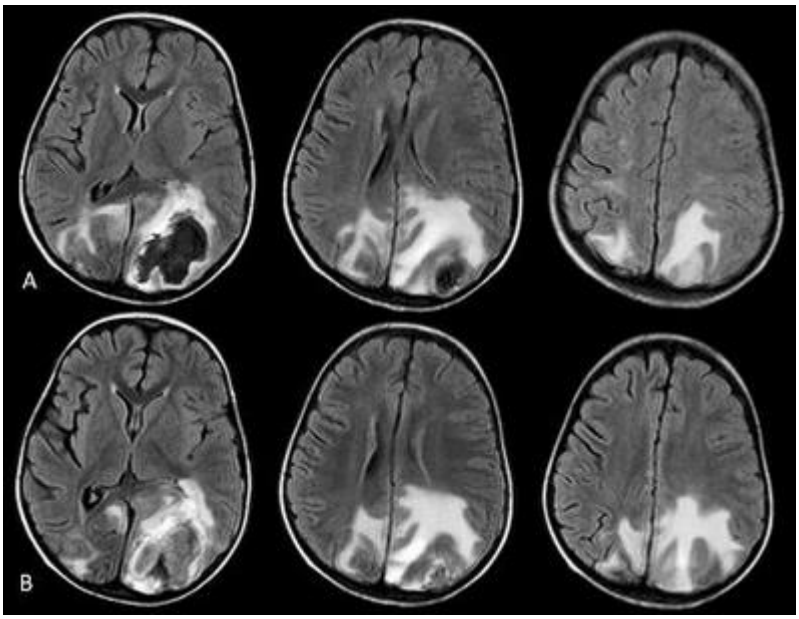

Fig. 2 *Posterior Reversible Encephalopathy Syndrome (PRES) in a 5-years old girl with acute renal failure and hypertension. FLAIR MR images at onset (A) and at a distance of ten days (B). The extent of vasogenic edema with a prevalent involvement of the parieto-occipital lobes is well depicted. A left parieto-occipital hematoma coexisted.*

Discussion

The cause of PRES is controversial but appears to be multifactorial.

Neurotoxicity and PRES are associated with eclampsia, cyclosporine/FK-506 toxicity occurring typically after allo-bone marrow transplantation (or solid organ transplantation) and systemic chemotherapy. It is also seen in patients with autoimmune disease and medical-renal disease. However, severe hypertension is perhaps the most common cause [1-4].

In hypertension, the elevated hydrostatic pressure leads to failed autoregulation and subsequent hyperperfusion that could cause brain capillary leak syndrome related to high BP, hyperpermeability, endothelial dysfunction, and vasogenic edema. The sudden elevation in systolic BP exceeds the autoregulatory capacity of brain vasculature.

The predilection for more involvement of the posterior, rather than anterior, circulation in encephalopathy may be due to a relative lack of sympathetic innervation at the level of the arterioles supplied by the vertebra basilar system [5].

There is rapid resolution of clinical signs and symptoms, and imaging abnormalities of reversible posterior encephalopathy, when the BP is lowered in such patients. It has been suggested that children might be more prone to PRES and its complications since the BP range in which cerebral blood flow is autoregulated is lower in children than in adults.

In adults, the resistance arterioles undergo proliferation of the muscular media adapting to the chronically higher perfusion pressures [2, 4].

Interestingly, the lack of elevated BP in 4 children in our series supports the hypothesis that PRES in cases without hypertension may result from direct endothelial injury and/or dysfunction causing blood–brain barrier breakdown.

The endothelium could be considered as the largest “organ” in the body and plays a critical role not only in separating the vascular wall from the circulation, but also in regulating the BP and inhibiting platelet aggregation, coagulation, inflammation, and oxidative stress [6].

Although rare, involvement of the central nervous system after rickettsial infection has been reported in the literature, and a few case reports (almost all adult) of meningoencephalitis related to MSF with brain lesions detected on imaging were reviewed [7]; in these patients, the clinical onset was correlated to focal neurological deficits.

These occurrences also had devastating outcomes, as most of these patients died, and those who survived had severe and permanent neurological sequel. An additional report of a case of MSF with cerebral vasculitis, in which thrombosis led to a massive cerebral infarct and death, has also been published [8].

In our case, cerebral vasculitis or meningoencephalitis were unlikely, given the normal MRA findings, normal CSF composition, the mild neurological presentation, and the prompt clinical and radiological recovery within 6 days from onset of symptoms.

Because of the characteristic clinical features and MRI findings, a provisional diagnosis of PRES was considered.

Of note, *Rickettsia conorii* invades and multiplies in vascular endothelial cells, resulting in widespread damage to capillaries, arterioles, and small arteries.

The major pathophysiological effect of rickettsial infections is increased microvascular permeability due to the disruption of adherens junctions between infected endothelial cells. Furthermore, patients with MSF can develop a transient pro-coagulant state resulting from rickettsia-induced disseminated endothelial injury, with activation of the coagulation cascade and generation of thrombin, platelet activation, and increased fibrinolytic factors [9].

This results in a combined endothelial-hemostatic dysfunction; of note, a transient hypercoagulable state and related cerebrovascular endothelial dysfunction have been reported as a pathophysiological factor in the onset of PRES, independent from the BP values [10]. Regarding HSP and the risk of developing PRES, patients without hypertension, renal impairment, and/or vasculitis, as in our case, have previously been reported [11]. Its pathophysiology is not completely understood, but it has been hypothesized that in these cases, the mechanism could be related to an endothelial dysfunction due to cytokines and vascular endothelial growth factor [12]. Sepsis is a well-known comorbidity association of PRES since the description of 23 patients in which significant infection and/or bacteremia occurred in close association with the development of PRES [13].

The pathogenic link between PRES and sepsis could be related to cell wall antigens of the infective organisms (endotoxins, exotoxins) that, through stimulation of SIRS, up-regulate inflammatory cytokine release and endothelial surface antigens with consequent increased white cell adhesion, microcirculatory dysfunction, altered vascular tone and permeability, hyper coagulation state, and endothelial injury and/or dysfunction [14].

In our study, in the 2 children diagnosed with sepsis according to *International Consensus Conference on Pediatric Sepsis* [15], CSF examination revealed no pathological findings (negative culture, normal leucocyte count, and normal protein levels). These children manifested typical clinical and radiological features of PRES in a mean of 6 days (5–7) after the sepsis diagnosis.

The BP values were normal at the appearance of neurological symptoms and during the overall hospitalization period, although intermittent episodes of hypertension can occur in sepsis [14], as previously described in some patients with PRES and sepsis [13]. This is related to the release of some mediators, such as endothelin-1.

Our cases are the first description of normotensive sepsis clearly associated to PRES in the pediatric age group, because previously described cases had confounding factors, such as hypertension [16].

Interestingly, from the primary infection site and blood cultures of these 2 children, gram-positive organisms were identified (SP and coagulase-negative SA); this confirms previous findings from other investigators that correlated PRES and gram-positive infections [13].

This may be due to super antigen related T-cell stimulation of cytokine release involving exotoxins (peptidoglycan and lipoteichoic acid) [13].

This study has the limitation of small number of patients and its retrospective design, which can be a confounding factor for the interpretation of clinical results.

In addition, interpretation of radiological results can be partially compromised because imaging protocols and timing differed between the 11 patients both at the onset of clinical symptoms of PRES and during radiological follow-up.

Despite these caveats, our series reports novel PRES-associated comorbidities, such as Mediterranean spotted fever by *Rickettsia conorii* and normotensive sepsis.

This latter factor has been studied as a possible complication of PRES only in adults, and to the best of our knowledge, has never been reported in the pediatric literature.

Pediatricians should be aware of and recognize this potential, although rare, complication of sepsis, which is known to be a more common condition in the pediatric age group than in adults.

The etiological, clinical, and radiological features of children reported here emphasize the emerging role of endothelial injury and/or dysfunction in the pathophysiology of PRES and reflect a possible increasing percentage of cases with normal PB compared to previously reported series.

PRES is a heterogeneous condition that is diagnosed by exclusion; the etiological peculiarities in children should be considered and clinical manifestations should be promptly recognized in order to provide timely treatment and to avoid neurological sequel or irreversible imaging changes.

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