Posterior Reversible Encephalopathy Syndrome Complicating Septic Shock

Ayal Romem MD[1], Ori Galante MD[1], Ilan Shelef MD[2] and Yaniv Almog MD[3]

[1]Department of Medicine, [2]Division of Radiology and [3]Medical Intensive Care Unit, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

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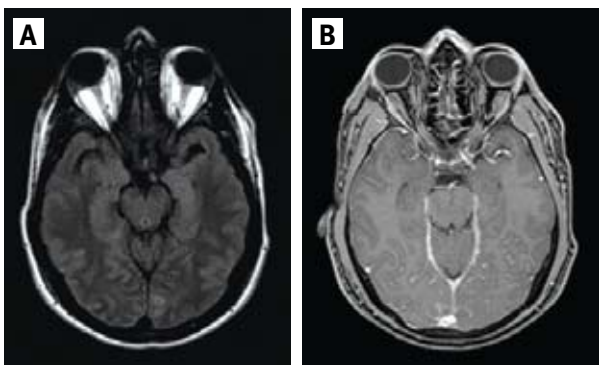
Posterior reversible encephalopathy syndrome is an acute neurologic injury characterized by unique computed tomography and magnetic resonance imaging findings. Clinical symptoms may range from headache, vision changes, paresis and altered mental status to generalized seizures and coma. In approximately 70% to 80% of patients moderate to severe hypertension is observed. PRES has been described in association with preeclampsia, autoimmune diseases, cancer chemotherapy and transplantation. Lately it was also described in the context of infections and severe sepsis [1,2]. PRES is usually characterized by reversibility of the clinical and radiological abnormalities once the underlying disease process is resolved. Since there is no specific therapy, stabilization of the hemodynamic status, eradication of the infectious agent, and control of seizures are the mainstay of its management [3,4].

PATIENT DESCRIPTION

A 33 year old man was admitted to the medical intensive care unit due to septic shock. Two days before admission he developed fever with chills but denied headache or any other localizing symptom. His past medical history was remarkable for stable Crohn's disease for which he underwent surgery at the age of 14 (ileal resection with ileo-colic anastomosis). He was not taking any medications. The patient was admitted following an episode of generalized seizure. On arrival his temperature was 38.6°C, blood pressure 80/26, heart rate 123, and saturation 90% while breathing room air. He was alert and oriented and his physical examination, chest X-ray and laboratory findings were uninformative. Intravenous metronidazole and ceftriaxone were initiated and he was admitted to the medical intensive care unit with a presumptive diagnosis of septic shock. Shortly after admission he developed a generalized seizure with left upward eye gaze deviation that lasted several minutes. Upon regaining consciousness he complained of complete loss of vision. Ocular reflexive response to motion was preserved but he denied any light perception. In addition, he demonstrated partial retrograde amnesia, confusion, and temporal disorientation with no motor or sensory loss. The course was complicated by multi-organ failure comprising hemodynamic instability requiring vasopressors, acute renal failure, disturbed liver functions and coagulopathy.

The abrupt onset of neurological symptoms preceded by a febrile illness had led to an initial working diagnosis of infectious viral encephalitis versus PRES. Since the latter is a diagnosis of exclusion, alternative considerations included central nervous system vasculitis, acute and subacute neurological disease (acute disseminated encephalomyelitis, cerebral venous thrombosis), cerebral hypoperfusion/ischemia, and mitochondrial disease such as the MELAS syndrome (**m**itochondrial **e**ncephalomyopathy, **l**actic **a**cidosis and **s**troke-like episodes). A lumbar puncture revealed a normal opening pressure. CT-angiography/venography of the head as well as the cerebrospinal fluid analysis were within normal limits. Brain MRI showed bilateral occipital lobes high signal on T2 and flair [Figure A], and abnormal enhancement after contrast administration on T1 [Figure B]. Chest and abdomen CT without contrast were significant for bilateral pleural effusions and well-healed ileal resection and ileo-colic anastomosis. All

PRES = posterior reversible encephalopathy syndrome



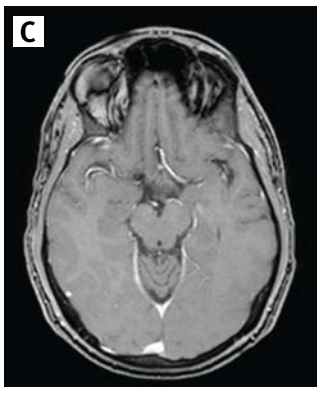
[A] Axial flair study (on day 2) demonstrating high signal intensity of the occipital lobes bilaterally
[B] T1 after contrast administration demonstrating minimal enhancement of the abnormal area

cultures were sterile (blood, urine, sputum, CSF). Serologic evaluation for *Ricketsia typhi* and *conorii*, Q fever and Brucella were negative, as were human immunodeficiency virus and Epstein-Barr virus; and tests for immunoglobulin M, antinuclear antibodies, C-reactive protein, rheumatoid factor, and cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies were normal. Electroencephalogram showed pathological bilateral occipital slowing without alpha wave response upon eye opening. Normal lumbar puncture, negative serologies, sterile blood cultures and MRI images consistent with bilateral occipital region edema excluded most of the differential diagnoses, leading by exclusion to the diagnosis of PRES.

With supportive care and antibiotic therapy the multi-organ failure gradually resolved, followed by significant neurological improvement and return of near-normal sight on ophthalmologic examination. A follow-up MRI prior to discharge (3 weeks after his initial admission) revealed a significant decrease in the regions of high signal on T2 and flair. T1 post-contrast administration showed diminished enhancement due to reconstitution of the blood-brain barrier [Figure C]. Today, 3 years after his initial presentation, the patient is well with normal vision.

CSF = cerebrospinal fluid

[C] Follow-up T1 image after contrast administration study reveals decreased enhancement without any signs of delayed ischemic sequel



COMMENT

The case under discussion illustrates the following important clinical issues: a) the clinical spectrum and radiological characteristics of PRES; b) its association with sepsis; and c) the tip of the iceberg phenomenon, i.e., under-diagnosis, since the true incidence of PRES is unknown among critically ill sedated patient.

- ***Clinical spectrum and radiological characteristics of PRES.*** The first to describe a reversible neurological syndrome characterized by headache, confusion, seizures, and impaired vision in associated with typical neuroimaging changes were Hinchey et al. in 1996 [1]. They coined the term posterior reversible leukoencephalopathy. Since this term is rather misleading as both the white and grey matter can be affected, the current acronym of PRES was adopted. The diagnosis of PRES is based on clinical history, characteristic imaging, and proof of reversible viability. Typically, PRES is an acute encephalopathy manifesting as vomiting, headache, altered mental status, seizures and visual impairment. The full neurological presentation is often heralded by convulsions, the most common presenting symptom in up to 74% of patients [3]. Convulsions are usually generalized and multiple. Status epilepticus is not uncommon. Visual disturbances are one of the hallmarks of this entity; they are found in up to 20% of patients [3] and may range from hemianopsia to cortical blindness as described in the present case [4]. Recognition of the characteristic imaging findings is the key diagnostic clue. Computed tomography can be used to detect hypodense lesions typical of posterior encephalopathy, but magnetic resonance imaging is the gold standard. In the acute phase, MRI reveals hyperintense signals on both T2-weighted and flair sequences and either iso- or hypointense on T1-weighted images, including both gray and white matter. The characteristic pattern associated with PRES resembles the brain watershed zones, with the cortex and subcortical white matter involved to varying degrees. The parietal and occipital lobes are predominantly affected, similar to the case under discussion, followed by the frontal lobes, the inferior temporo-occipital junction and the cerebellum [5]. The findings in the present case may initially be attributed to cerebral hypoperfusion and ischemia. However, in the diffusion weighted MRI, a distinctive feature of ischemic lesions was lacking. Moreover, the quick and complete resolution of the clinical and radiological findings in a young man with no atherosclerotic disease provides the final evidence for the probable nature of the process. Taken together, the clinical findings and the course are highly suggestive of PRES. Treatment of patients with PRES must focus on prompt correction of the mean arterial blood pressure, proper hydration, adequate oxygenation, and correction of electrolyte disturbances. Removal of precipitating factors is of utmost importance in order to halt the hemodynamic and inflammatory cascade that perpetuates the pathophysiologic process of PRES. Treatment of seizures and especially status epilepticus is crucial. When available, the use of continuous electroencephalographic monitoring is advised. Prognosis is usually favorable, and with prompt diagnosis and adequate therapy most patients are expected to fully recover within a few weeks [4].
- ***Pathophysiology and association with infection and sepsis.*** PRES is almost always seen in the setting of significant systemic processes. The most common etiologies are acute severe hypertension, toxemia of pregnancy, and immunosuppressive therapy (with cyclosporine as the most often reported drug). Other less frequent etiologies include autoimmune dis-

ease, cancer chemotherapy and, as reported recently, infection and sepsis. In a review of 120 patients with PRES, hypertension was the most common etiology and was found in 61%, followed by immunosuppressive therapy (19%). Although a well and commonly described etiology, toxemia of pregnancy was the cause in only 6% of the patients reviewed, while sepsis was the cause in 7%. Forty-five percent of the patients described had a history of autoimmune disease, most commonly thrombotic thrombocytopenia purpura and systemic lupus erythematosus. Interestingly, 6% had Crohn's disease similar to our patient [3].

The pathophysiology of PRES is still poorly understood. The initial cytotoxic theory suggested that vasoconstriction and hypoperfusion lead to brain ischemia and subsequent vasogenic edema. The vasogenic theory proposed that severe hypertension leads to failed autoregulation, subsequent hyperperfusion with endothelial dysfunction, and vasogenic edema. This concept is corroborated by the fact that significant hypertension is found among 50% of patients. Nonetheless, PRES is seen in increasing frequency without hypertension, as in our patient. Moreover, even when hypertension is documented, the mean arterial blood pressure does not typically reach the limit of failed autoregulation. Indeed, in a retrospective review of 25 patients diagnosed with PRES in the setting of severe infection, 40% had normal blood pressure [2]. The present case illustrates the association between severe infection, occurring in a patient with autoimmune disease, and PRES. It further suggests that it may complicate the course of hypotensive patients with sepsis. Current research has led to a new unifying theory explaining the pathogenesis of PRES [5]. In the majority of patients with PRES an underlying systemic cytokine-mediated inflammatory response is present. T cell activation and elevated inflammatory cytokines (tumor necrosis factor-alpha, interleukin 1, interferon-gamma and interleukin 6) are common. Cytokines upregulate endothelial surface antigens (P-selectin, E-selectin, intercellular and vascular cellular adhesion molecule-1) and increased leukocyte adherence leading to microcirculatory dysfunction. The developing vasculopathy is accompanied by altered intrinsic vascular tone and vasodilatation. The common final pathway culminates in brain and systemic hypoperfusion and the development of vasogenic edema.

- ***The tip of the iceberg:*** Recognizing neurological impairment in the critically ill may be difficult. Visual disturbances, which are distinctly characteristic, are even more elusive in the sedated patient. PRES may be more frequent than previously reported. It has a broad clinical spectrum, and differentiating PRES from other more common causes of neurological impairments may be difficult since PRES may have normal findings on initial CT, highlighting the importance of MRI when the clinical context is suggestive. Thus, PRES should be included in the differential diagnosis of unexplained seizures and altered mental status in the critically ill patient. As with other rare clinical entities, a high index of suspicion may lead to earlier diagnosis and appropriate treatment.

In summary, this case serves as an important reminder that PRES may complicate the course of sepsis. The exact incidence of PRES is difficult to determine among the critically ill, but conceivably a certain proportion of patients with critical illness-associated cognitive dysfunction may actually represent a form of PRES. Even though there is no specific therapy, early diagnosis is probably important and requires a high index of suspicion.

Corresponding author:
Dr. Y. Almog
Medical Intensive Care Unit, Soroka University Medical Center, P.O. Box 151, Beer Sheva 84101, Israel
Phone: (972-8) 640-0640
Fax: (972-8) 640-0166
email: almogya@bgu.ac.il

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"We're here to put a dent in the universe"

Steve Jobs (1955-2011), American entrepreneur and inventor, co-founder, chairman, and chief executive officer of Apple Inc

"A cult is a religion with no political power"

Tom Wolfe (born 1931), American author and journalist

"History is a vast early warning system"

Norman Cousins (1915-1990), American political journalist, author, professor, and world peace activist