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REVIEW ARTICLE

Posterior reversible encephalopathy syndrome (PRES) and infection: a systematic review of the literature

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is an encephalopathy characterized by a rapid onset of symptoms including headache, seizures, confusion, blurred vision, and nausea associated with a typical magnetic resonance imaging appearance of reversible subcortical vasogenic edema prominent and not exclusive of parieto-occipital lobes. Vasogenic edema is caused by a blood-brain barrier leak induced by endothelial damage or a severe arterial hypertension exceeding the limits of cerebral blood flow autoregulation. Although the exact pathophysiological mechanism is still unclear, frequent conditions that may induce PRES include severe hypertension, eclampsia/pre-eclampsia, acute kidney diseases and failure, immunosuppressive therapy, solid organ, or bone marrow transplantation. Conversely to other conditions, which may induce PRES, the link between severe infection or sepsis and PRES, often associated with gram-positive bacteria, is still poorly understood and less well known. Clinicians from multiple disciplines, such as neurologists and internists, may encounter during their profession patients with severe infection or sepsis and should consider the possible association between PRES and these conditions. We systematically reviewed the literature about this association in order to provide a helpful clinical insight of such complex pathophysiological mechanism, highlighting the importance of recognizing PRES in such a complex clinical scenario.

Keywords PRES · Infection · Sepsis · Posterior reversible encephalopathy syndrome

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a term used for the first time by Hynchey et al. in 1996 in order to describe a syndrome characterized by the association of specific clinical and neuroradiological findings [1]. Presenting symptoms usually are a subacute onset encephalopathy with generalized seizures, headache, and visual disturbances [2]. Brain imaging performed with magnetic resonance imaging (MRI) commonly shows vasogenic edema affecting, almost symmetrically, subcortical regions of the occipital, posterior temporal, and parietal lobes with a watershed distribution (Fig. 1) [3–6].

When promptly diagnosed and treated, PRES is often a benign and reversible condition, as most of the patients reach a complete clinical recovery within few days, with a MRI abnormalities' disappearance within few weeks or sometimes months [3, 7–10]. Posterior brain areas are more frequently affected due to a minor sympathetic posterior circulation vessels innervation compared to anterior circulation one [8].

This syndrome has been recognized for the first time during severe hypertension, acute kidney diseases, eclampsia/pre-eclampsia, and immunosuppressive therapy [11–17]. To date, several predisposing factors have been reported as causes of PRES including autoimmune diseases, solid organ or bone marrow transplantations, chemotherapy, thrombotic thrombocytopenic purpura, drugs causing hypertension or endothelial dysfunction, and severe infections and sepsis (Table 1) [18–52].

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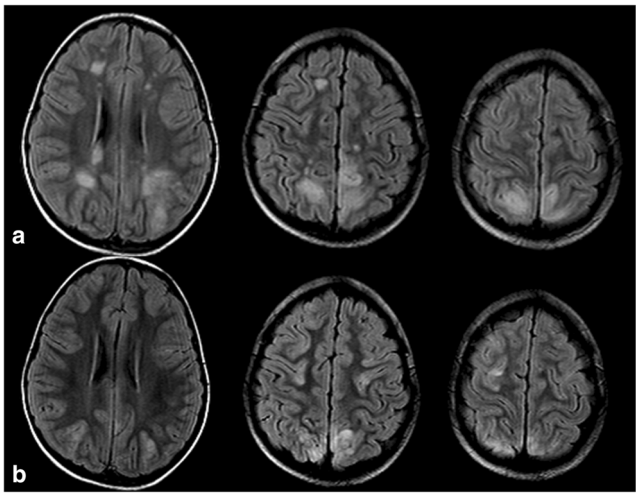

Fig. 1 FLAIR MR images at onset (A) and at a distance of 5 days (B). Baseline MR confirms the presence of multiple small high-signal foci at gray matter-white matter junction. A more typical involvement of "watershed" cortical territories is present. Follow-up examination shows a significant reduction in lesion load (B)

The exact pathophysiological mechanisms responsible for this condition are still unclear, although it is known that the vasogenic edema could be caused by a disruption of the blood-brain barrier and a capillary leakage of fluids into the interstitial space. The whole process can be triggered by a sudden elevation of systemic blood pressure exceeding the autoregulatory limits of the brain arterial vessels or by an endothelial dysfunction occurring during many neurotoxic systemic conditions such as transplantations, immunosuppressants, chemotherapy, autoimmune diseases, and severe infections and sepsis [1, 6, 7].

While the correlation between PRES and hypertension, pre-eclampsia/eclampsia, cytotoxic/immunosuppressive drugs, and autoimmune disorders is widely demonstrated, the association with severe infection and sepsis is less known.

Clinicians from multiple disciplines, such as neurologist, frequently may encounter patients with severe infection or sepsis, and it would be important at least to consider PRES as the possible cause of acute neurological symptoms. When promptly recognized, PRES is often a benign and reversible condition, conversely if not treated, patients may develop life-threatening complications, such as cerebral hemorrhage, cerebellar herniation, and refractory status epilepticus or neurological sequelae including long-term epilepsy [53, 54]. We systematically reviewed the literature about the link between PRES and severe infection or sepsis in order to emphasize the importance of recognizing this condition in a complex clinical scenario and highlighting the risk in avoiding the proper diagnosis of PRES in septic patients.

Table 1 Risk factors for posterior reversible encephalopathy syndrome

Risk factors for PRES	
Medical conditions	Drugs (20–60%) [10]
- Arterial hypertension (20–60%) [10]	- Immunosuppressive agents (cyclosporine A, tacrolimus, methotrexate, sirolimus, etc.) [11]
- Infection, sepsis, systemic inflammatory response syndrome, multiple organ failure (25%) [18]	- Chemotherapy (cytarabine, cisplatin, gemcitabine, oxaliplatin, bevacizumab, fluoropirimidin, tiazofurin, ipilimumab, thalidomide, apatinib, etc.) [27, 28]
- Renal diseases (acute glomerulonephritis, acute renal failure, parenchymal diseases) (45%) [19]	- Erytropoietin [29]
- Toxemia of pregnancy (eclampsia/preclampsia) (5–15%) [10, 19]	- Indinavir [30]
- Autoimmune diseases (systemic lupus, scleroderma, vasculitis, Polyarteritis nodosa, cryoglobulinemia, Wegener's granulomatosis) (5–11%) [10, 19]	- Ivabradine [30]
- Bone marrow transplantation or solid organ transplantation (40%) [19]	- High-dose steroids (methylprednisolone) [31]
- Hematologic conditions (Henoch-Schonlein purpura, thrombotic thrombocytopenic purpura, blood transfusion, leukemia and lymphomas, sickle cell anemia, uremic syndrome) [20–22]	- Sympathomimetic agents (amphetamine, benzylpiperazine, cathine, cathinone, cocaine, ephedrine, mephedrone) [32]
- Guillain-Barrè Syndrome [23]	- Intravenous immunoglobulin treatment [33, 34]
- Tumor lysis syndrome [24]	- Triple H therapy for subarachnoid hemorrhage (prevent and treat cerebral vasospasm with hypervolaemia, hypertension, and haemodilution) [35, 36].
- Porphyria [25]	- Withdrawal from antihypertensive agents (amlodipine, triamterene, prazosin) [37]
- Hypercalcemia, hypomagnesemia [26]	- Tyrosine kinase inhibitors (pazotanib, sorafenib, sunitinib) [38]
	- Contrast media exposure (coronary or cerebral angiography) [39]

Methods

We conducted a literature search using Medline (National Library of Medicine) electronic database looking for the following keywords associations: "infection" and "posterior reversible encephalopathy syndrome," "sepsis" and "posterior reversible encephalopathy syndrome," "endothelial dysfunction" and "posterior reversible encephalopathy syndrome," "gram-positive," and "posterior reversible encephalopathy syndrome," between 1st of February 1996 and 12th of January 2018.

Since our review is focused on understanding the relationship of PRES and infection, we excluded from the analysis papers which are not mainly focused on this topic, as well as ones focusing mainly on technical aspects or non-English language ones.

Results

A literature search of the keyword "posterior reversible encephalopathy syndrome" found 1.990 papers, in the period between 1st of February 1996 and 12th of January 2018. In order to better filter these results, we decided to combine this keyword with other ones, focusing mainly on the real association of PRES with infection/sepsis. We found 109 papers with the "infection" and "posterior reversible encephalopathy syndrome" keyword association; 47 results for "sepsis" and "posterior reversible encephalopathy syndrome"; 73 results for "endothelial dysfunction" and "posterior reversible encephalopathy syndrome"; and 3 results for "gram-positive" and "posterior reversible encephalopathy syndrome". A total of 232 papers were evaluated for the final selection in this review. Among these 232, only 67 papers (28%) fulfilled the abovementioned inclusion criteria and were further selected for this review accordingly to their relevance and unicity.

Discussion

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome presenting with acute-subacute neurological symptoms (e.g., seizures, encephalopathy, headache, and visual disturbances) and characteristic neuroradiological findings [1, 3, 6, 10]. With the improvement of the neuroradiology evaluation, PRES has becoming progressively more often recognized [6, 10]. Neuroimaging usually reveals cortical-subcortical vasogenic edema located predominantly in bilateral parieto-occipital regions and, in decreasing order of frequency respectively in high posterior, frontal, temporal, cerebellar, basal ganglia, and brainstem locations [6, 10].

Currently, the precise pathophysiological mechanism of PRES is not entirely understood. The endorsed theory states that hypertension could cause the loss of autoregulation in cerebral blood flow with a subsequent increase in vascular permeability, damage to the blood-brain barrier, and secondary vasogenic edema [1, 6, 7]. This theory is called the *vasogenic theory* and it is supported by the fact that 50% of patients during PRES had an episode of severe hypertension, which exceeds the upper limit of the autoregulation and usually occurs at mean arterial pressures greater than 150–160 mmHg [7, 10]. Nevertheless, debuting against this hypothesis 30% of patient with PRES show normal or only slightly elevated arterial blood pressure values that do not necessarily exceed the normal upper autoregulatory limit [7, 10]. For this reason, another pathophysiological model has been proposed recently: the endothelial dysfunction may cause vasoconstriction, hypoperfusion, and ischemia, resulting in vasogenic edema, which characterize PRES [18, 19, 54–56]. According to this hypothesis, called *the endothelial damage hypothesis*, blood pressure elevation may occur as a consequence of a primary endothelial dysfunction [18, 19, 54–56]. Some authors such as Marra et al. and Gao et al. reported different theories of endothelial damage causes, which may lead to PRES with similar mechanisms leading to hypoperfusion and ischemia [10, 19, 54]. One of these is the *immunogenic theory*, in which a primary inflammatory involvement with T cell activation and cytokine release is the mechanism involved in this process [10, 18, 19, 54]. Another hypothesized mechanism has been described by Gao et al. in the *neuropeptide theory:* the release of endhotelin-1, prostacyclin, and thromboxane A2 could lead to an endothelial dysfunction, causing PRES vasogenic edema [6, 7, 10, 18, 19, 54–56].

It is noteworthy to notice that cytokine-mediated mechanism inducing sepsis is very similar to those underlying PRES [6]. During a severe infection or a condition of sepsis with a valid host immune response, the increased release of tumor necrosis factor α, interleukin 1 and the upregulation of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1), may cause an increase in vascular permeability of brain vessels with interstitial edema development and interstitial extravasation of plasma and macromolecules, detectable as a typical neuroradiological pattern for PRES [6, 7, 10].

Since its identification as a distinct nosological entity in 1996, PRES has been associated with immunosuppressant therapy as a major cause [1]. This particular event mostly occurs in patients receiving immunosuppressant therapy after solid organ or bone marrow transplantation [41–43]. The drugs involved are usually cyclosporine and tacrolimus, together with other medications reported in isolated cases (see Table 1). PRES is associated with different clinical conditions, such as severe hypertension (20–60%), pre-eclampsia/

eclampsia (5–15%), cytotoxic or immunosuppressive drugs (20–60%), autoimmune disorders (5–11%), severe infection or sepsis (25%), renal failure (45%), thrombocytopenia, hypocalcaemia, and alcohol withdrawal [6, 10, 19] (see Table 1). According to our systematic review, compared to the other clinical conditions, the association of PRES and severe infection or sepsis is less well known.

Bartynsky et al., in a retrospective study, suggested the association between PRES and severe infection or sepsis. In 2006, they found that over a population of 106 patients, 25 patients (21.6%) developed PRES in association with severe infection or sepsis. In all of these cases, prominent clinical signs of infection preceded the occurrence of PRES and 18/25 patients (72%) developed a multiple organ dysfunction coincident with a condition of neurotoxicity. Mean arterial blood pressure was significantly elevated only in 15/25 patients (60%) while in the remaining 10 (40%) patients, it was normal. Among tissue and blood culture, the most frequent identified organisms were gram-positive cocci. This condition is probably due to a probably more powerful stimulation of systemic inflammatory response by the peptidoglycan rather than the one caused by the lipopolysaccharide, which is typical for gram-negative bacteria. [9]

Yoon et al., in a retrospective study, including 16 patients with clinical and radiological diagnoses of PRES, found that 4 patients were affected from sepsis. They suggest that PRES can occur in patients with systemic conditions like sepsis. Among this group, the same rate of PRES cases (25%) were related to arterial blood hypertension, typically considered the most frequent associated condition [57]. In a larger study of 113 cases of PRES, Fugate et al. identified that severe infection was the third etiologic agent, occurring in 8 patients (7%). In this study, a cortical involvement is considerably higher in patients with severe infection or sepsis in comparison with other patients, with parieto-occipital involvement in all of cases [6].

Although the most frequently recognized organisms responsible for PRES are the gram-positives [9], few papers, mostly regarding isolated case reports, have been published on infection-associated PRES, reporting other possible responsible organisms, such as viruses (especially HIV and influenza viruses) bacteria and protozoa agents [58–89].

Nightingale et al. described a case of PRES in a patient with HIV infection, in the absence of an active virus replication, opportunistic infection or others “typical” predisposing factors.

The authors suppose that HIV infection, particularly when untreated, is associated with endothelial dysfunction, which in this case was probably the main cause of PRES [61]. The endothelial dysfunction due to generalized immune activation, in the setting of HIV infection, particularly when untreated, may have been sufficient to induce PRES [61].

Recently, Birner et al. in a case report also discussed the hypothesis that persistent HIV-associated cerebrovascular reactivity in combination with endothelial dysfunction may represent an unknown risk factor for PRES in virologically and immunologically stable patients [66], even if this interesting hypothesis should be proved in large epidemiological studies. An unusual lesion location, limited to the pons, is described in two cases of PRES triggered by HIV [82–84]. Mohanty S. et al. in a recent MRI study of 11 patients investigated the correlation of *Plasmodium falciparum* malaria infection and PRES, suggesting that blood-brain barrier damage with endothelial dysfunction and microvascular obstruction by *Plasmodium falciparum*-infected erythrocytes, the so-called sequestration, could be responsible for the reversible brain alteration of PRES [88].

PRES related to severe infection or sepsis is infrequently reported also during severe acute pancreatitis or in complicated post-operative course of abdominal surgery with subsequent sepsis in Crohn disease patients [80–81]. In a recent report, Pereira et al. described a case of PRES in the contest of an acute setting of pancreatitis in a patient with a thrombophilic defect. The authors reviewing the literature found nine cases of PRES in patients with pancreatitis, postulating that acute pancreatitis might complicate, or even cause PRES. In experimental studies with rat models, a proinflammatory cytokine pathway following acute pancreatitis may induce brain vasogenic edema with damage of blood-brain barrier [80].

Papaconstantinou et al. in a case report described a case of PRES in a Crohn disease patient who developed during a complicated post-operative course with sepsis due to abscess formation [81].

In most cases, the condition of patients who developed PRES in a contest of abdominal severe infection or sepsis were severely compromised with frequent renal impairment, alteration of coagulation and liver function, and respiratory failure. The neurological symptoms and the neuroradiological findings in these cases did not differ from other causes of PRES. Neuroimaging mostly shows vasogenic edema in typical locations reported for PRES [3–6, 10].

Moreover, considering that any kind of severe infection may induce PRES, the exact occurrence of this correlation could be underestimated probably due to a poor emphasis on the importance of this risk factor.

Larger epidemiological studies are needed to clarify the real link between PRES and severe infection in order to better understand specific prognostic factors related to different kinds of infections.

Typically, PRES has a favorable prognosis, but when not promptly recognized, patients may develop life-threatening complications, such as cerebral hemorrhage, cerebellar herniation, and refractory status epilepticus or neurological sequelae including long-term epilepsy [53–54]. So timely and

appropriate therapy is essential; therefore, everyone approaching infection/sepsis patients should consider PRES as the cause of acute neurological clinical symptoms; syndrome that can be easily diagnosed with MRI.

Conclusions

Severe infection or sepsis may be a relevant cause of PRES. The management of infection-septic patients concerns a lot of clinicians from multiple disciplines, such as neurologists and internists that in a complex clinical scenario, should also consider PRES as a cause of acute neurological symptoms.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not necessary because the present study consists of a literature revision.

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