REVIEW ARTICLE

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Posterior Reversible Encephalopathy Syndrome

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Posterior reversible encephalopathy syndrome (PRES)[1,2] is an acute or subacute cerebral syndrome, the main manifestations of which are headache, encephalopathy, seizures, or visual disturbances in various combinations. The disorder typically occurs in patients with acute, severe hypertension or moderate but acute elevations in blood pressure that are outside the accustomed range for the patient, or exposure to certain drugs and toxic agents, mostly from chemotherapeutic drugs and immunosuppressive agents. Both drug and toxic exposures are probably related to cerebrovascular dysregulation or endothelial dysfunction. The most common abnormality detected on neuroimaging is white-matter vasogenic edema in the occipital and sometimes the adjacent parietal lobes. When PRES is promptly recognized and the underlying cause is addressed, most patients recover.

An article by Hinchey et al.[1] on an early series of cases of PRES described 15 patients with acute neurologic deficits that resolved within 2 weeks. Many subsequent articles have described various clinical features, particularly coma or focal neurologic deficits other than visual deficits (described below), an expanded list of triggering pathologic conditions, varied neuroimaging findings, the persistence of deficits, and outcomes of death. Although the term "PRES" has become common, the name no longer captures all the features of the disorder, and other terms have been used, including reversible posterior leukoencephalopathy, as in the article by Hinchey et al.

Epidemiology

The incidence of PRES in the general population has been difficult to determine, but in selected populations, it has been reported to be 0.8% among patients with end-stage renal disease,[3] approximately 0.7% among those with systemic lupus erythematosus,[4] 0.5% among those who have undergone solid-organ transplantation,[5] and from 20.0% to 98.0% among those with preeclampsia or eclampsia.[6,7] The incidence in similarly selected groups of children has been estimated to be 0.04%.[8] Case series show that PRES occurs in all age groups, with the highest incidence among young and middle-aged adults, and it is more prevalent among women than among men.[9-14] In one study based on the National Inpatient Sample of 635 patients who had PRES as an admission diagnosis, the mean age of the patients was 57 years, 72% were women, and 68% were White.[15]

Clinical Features

The most prominent typical feature of PRES (in up to 94% of patients) is a nondescript encephalopathy that may range from mild confusion to coma.[1,14] In up to

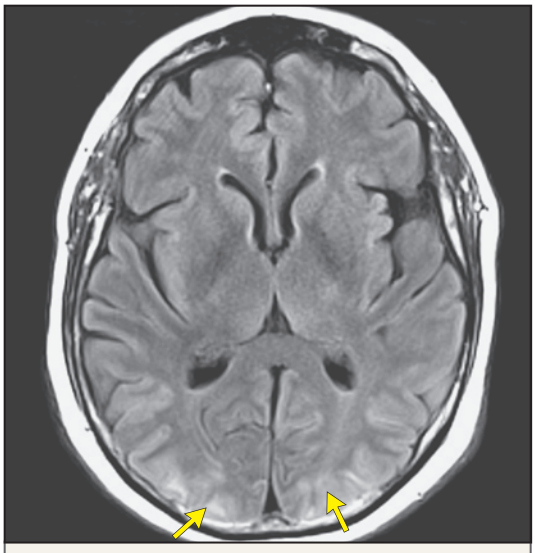

Figure 1. Typical Bilateral Imaging Pattern in Posterior Reversible Encephalopathy Syndrome (PRES).

A 58-year-old man had severe, acute hypertension, acute nausea, vomiting, and altered mental status. A magnetic resonance imaging (MRI) axial fluid-attenuated inversion recovery (FLAIR) scan of the patient's brain shows subcortical and cortical hyperintensities, primarily in the bilateral occipital lobes (arrows). Diffusion-weighted images (not shown) were normal in the affected regions. Computed tomography may not show changes as conspicuously as MRI.

half of cases, dull and diffuse headache develops gradually, but occasionally it may be a sudden "thunderclap" headache.[12,14] Partial or generalized seizures occur in approximately three quarters of patients at some time in the course of PRES. Seizures are only occasionally the initial feature, and they may progress to status epilepticus in up to 18% of patients.[16] Visual abnormalities are prominent in 20 to 39% of patients, and they manifest as vaguely diminished acuity, visual-field deficits, visual neglect, visual hallucinations, or blindness.[1,12] Less frequent features include focal paresis, incoordination, hyperreflexia, and spinal manifestations.[1,12] In a retrospective case series involving 635 patients, the initial manifestation was seizure in half the patients and vision loss or speech difficulty in one fifth.[15]

NEUROIMAGING

Neuroimaging has been considered to be central to the diagnosis of PRES.[1,9] Edema in bilateral cerebral regions supplied by the posterior circulation area is evident on noncontrast computed tomographic (CT) examination of the brain. Magnetic resonance imaging (MRI), when available, is preferred over CT because fluid-attenuated inversion recovery and T_2-weighted sequences are sensitive to vasogenic edema.[9,17] The MRI signal changes occur mostly in the bilateral white-matter regions and typically in the occipital lobes (Fig. 1), but unilateral or gray-matter involvement and other patterns have been reported.

Various case series have described imaging abnormalities in the parieto-occipital region (in 65 to 99% of cases), frontal region (in 54 to 88%), temporal region (in 68%), thalamic region (in 30%), cerebellar region (in 34 to 53%), brainstem region (in 18 to 27%), and basal ganglia (in 12 to 34%).[16,18] Other patterns on MRI are signal changes in the posterior occipital and parietal regions simultaneously (in 22% of patients), the bilateral holohemispheric watershed (the regions supplied by the end territories of major vessels) (in 23%) (Fig. 2), the superior frontal gyri (in 27%), and mixtures of these patterns (in 28%) (Fig. 3).[9] Atypical patterns may involve the cerebellar hemispheres (Fig. 4). Case series with follow-up neuroimaging weeks to months after presentation have shown resolution of MRI abnormalities in 66 to 70% of cases.[16,19]

In extreme circumstances, abnormalities detected on neuroimaging have included large volumes of brain edema with mass effect and transtentorial herniation. Occasionally, there are areas of hemorrhage, restricted diffusion abnormalities on MRI (usually focally or unilaterally), and contrast enhancement in the regions of edema.[18] Digital subtraction angiography, MRI, or CT angiography may show diffuse or focal vasoconstriction with vasodilatation ("string of beads") patterns, but these patterns are also common in many of the pathologic conditions that are associated with PRES and that may occur independent of this syndrome.[20]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PRES includes cerebral infarction, especially posterior-circulation or watershed strokes, central nervous system (CNS) infections, demyelinating diseases, brain cancers, dural venous sinus thrombosis, CNS

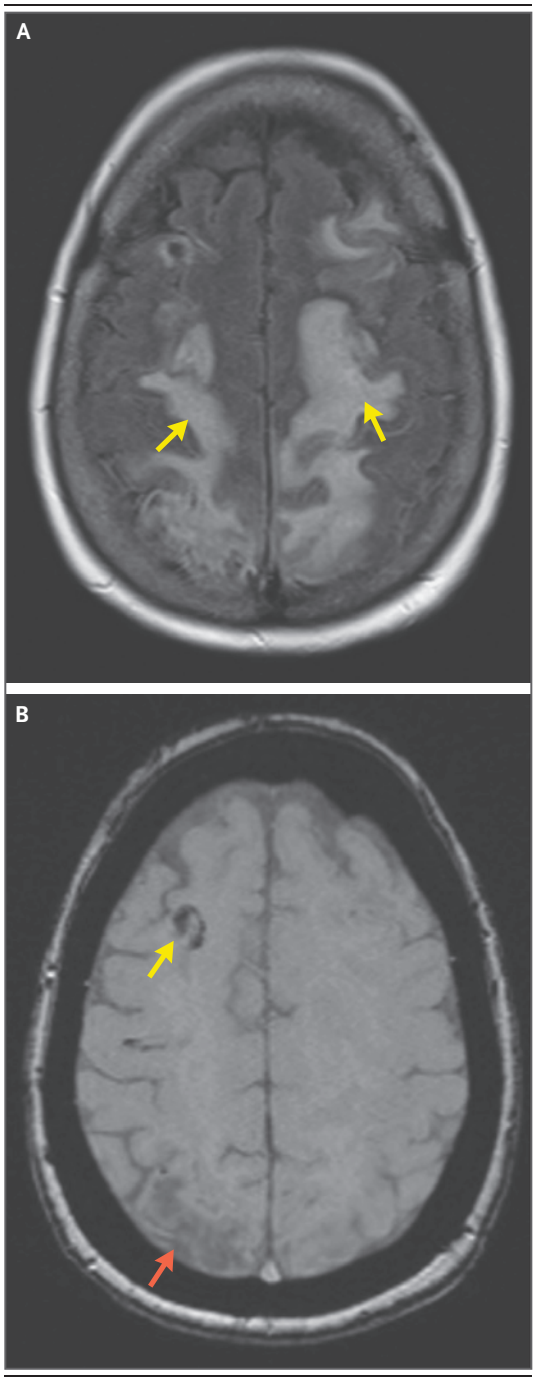

Figure 2. Bilateral Holohemispheric Watershed Imaging Pattern in PRES.

A 63-year-old woman with a history of stroke presented with new-onset seizures and declining mental status. In Panel A, an axial MRI FLAIR sequence of the patient's brain shows white-matter hyperintensity in a bilateral watershed distribution (arrows). In Panel B, an axial susceptibility-weighted image shows a small region of hemorrhage (yellow arrow) within the affected region shown in Panel A. The red arrow indicates an encephalomalacia from a previous stroke in the medial parietal lobe area; this finding was unrelated to PRES.

vasculitis, toxic encephalopathies, and mitochondrial disorders. Some cerebrovascular dysregulation syndromes, particularly reversible cerebral vasoconstriction syndrome, in which there are irregular segments of cerebral vessel constriction, may overlap with PRES, as mentioned above.[21] An assessment of the patient's history, cerebral imaging, blood and urine samples, and cerebrospinal fluid studies — particularly in a patient with extreme and abrupt hypertension or in the presence of one of the known drug triggers — helps to refine the differential diagnosis.

MANAGEMENT

Prompt control of the precipitating cause of PRES and supportive care are probably essential to obtain good outcomes (Tables 1 and 2). Up to 70% of patients with PRES, especially those with severe hypertension, a depressed level of consciousness, or seizures, are admitted to the intensive care unit (ICU), when this care is available.[22] Treatment of PRES is primarily directed at mitigation of hypertension, as discussed below; managing seizures, brain edema, and encephalopathy; or discontinuation or replacement of a precipitating agent (e.g., a chemotherapeutic drug). A small subgroup of patients with PRES are considered to have a "malignant state," with coma at the onset, elevated intracranial pressure, and widespread cerebral edema and herniation syndromes.[23] With supportive care, including management of cerebral edema, these patients may have favorable outcomes.[23]

TREATMENT OF HYPERTENSION

For patients with a hypertensive emergency, pertinent cardiology-based treatment guidelines recommend ICU admission with continuous blood-pressure management.[24] Although a specific blood-pressure target has not been established in the treatment of PRES, there is consensus that blood-pressure reduction generally does not have to exceed 25% of systolic pressure within the first hour, followed by cautious normalization of blood pressure over 24 to 48 hours.[24] The effect of blood pressure in the pathogenesis of PRES is

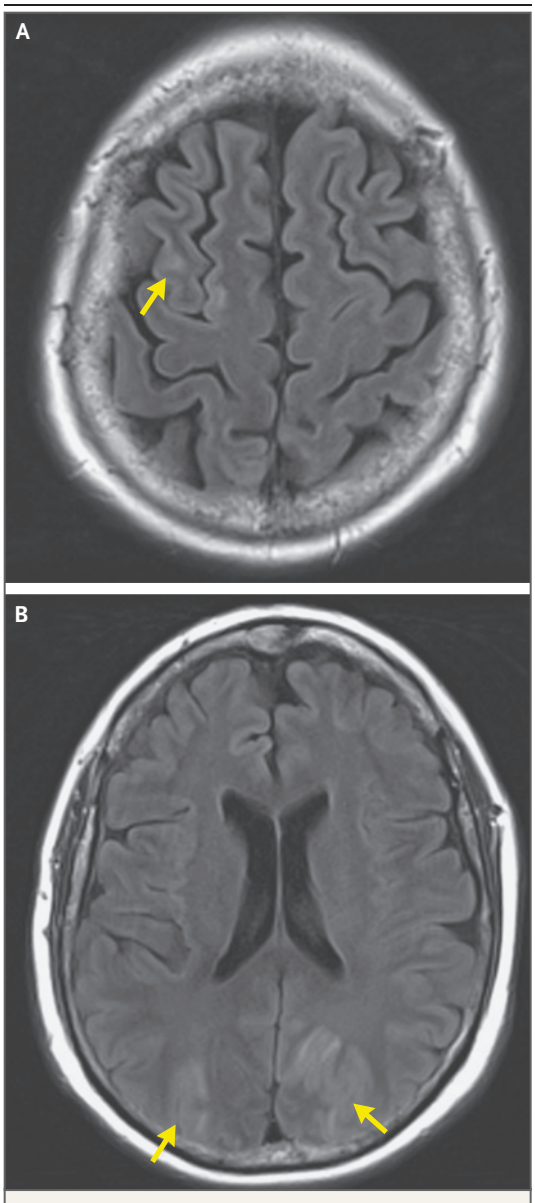

Figure 3. Multilobar Imaging Pattern in PRES.

A 58-year-old man with drowsiness and seizures was receiving immunosuppressive treatment for chronic lymphocytic lymphoma. Panel A shows an MRI FLAIR axial image of the patient's brain, with a subtle white-matter signal change in the right frontal lobe (arrow). Panel B shows an MRI scan 2 days later, with new FLAIR hyperintensity involving the occipital and medial parietal regions (arrows).

not fully understood, but one study suggested that the effect of hypertension is associated with the degree and rapidity of absolute increase in blood pressure from the patient's typical levels, and in those without acute hypertension, the effect is related to fluctuations in blood pressure from the patient's normal range.[13]

The optimal antihypertensive agents have not been determined, but intravenous agents with rapid action, doses that can be adjusted rapidly, and well-defined clinical effects are favored; these agents include nicardipine, clevidipine, and labetalol. The approach to management of hypertension should be undertaken with consideration of potential coexisting conditions, particularly aortic dissection, pheochromocytoma, eclampsia (see below), coronary disease, and renal disease.[24]

TREATMENT OF TRIGGERS OTHER THAN HYPERTENSION

In patients who have PRES without hypertension, it is necessary to identify associated medical disorders or triggering agents that are known to be associated with the condition (Tables 1 and 2). Common disorders include rheumatologic and autoimmune disorders, and common triggers include exposure to drugs used to treat cancer and immunosuppressive agents for transplantation. Table 2 summarizes the classes of drugs and toxic agents that have been associated with PRES. In some case series, investigators have attempted to alter the course of PRES by changing the dose or replacing the agent believed to be causative, with inconsistent results. One retrospective series involving patients with PRES caused by exposure to tacrolimus, which had been administered for hematopoietic stem-cell transplantation, suggested that strategies of withholding the drug, withholding and then restarting, or switching to a similar agent led to similar results.[25] In another series involving patients with cancer in whom PRES developed within 1 month after initiation of chemotherapy or hormonal therapy, discontinuation followed by reinitiation of the same agent did not cause a recurrence of PRES.[26]

TREATMENT OF SEIZURES

Although seizures are common in patients with PRES, they have no characteristic features. The approach to management is similar to that for other medical conditions with seizures. The presence of seizures is first confirmed by means of electroencephalography (EEG), if possible,

Table 1. Syndromes, Disorders, and Procedures Related to Posterior Reversible Encephalopathy Syndrome (PRES).*

Type of Disorder or Condition	Specific Illness or Procedure
Systemic disorders	Acute and chronic renal failure, primary aldosteronism, sepsis and shock, and pheochromocytoma
Pregnancy-related conditions	Preeclampsia, eclampsia, and the HELLP (hemolysis, elevated liver-enzyme levels, and low platelet count) syndrome
Autoimmune or connective-tissue disorders	Systemic lupus erythematosus, scleroderma, Sjögren's syndrome, vasculitis, cryoglobulinemia, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Hashimoto's thyroiditis, primary sclerosing cholangitis, antiphospholipid antibody syndrome, granulomatosis polyangiitis (formerly known as Wegener's granulomatosis), systemic sclerosis, giant-cell arteritis, polyarteritis nodosa, and antineutrophil cytoplasmic antibody–associated vasculitis
Postprocedure conditions	Solid-organ transplantation, stem-cell transplantation, immune globulin transfusion, extracorporeal membrane oxygenation, bone marrow transplantation, blood transfusion, spine surgery, induced hypertension (aneurysmal subarachnoid hemorrhage), carotid surgery, and cardiac surgery
Hematologic disorders	Sickle cell disease, hemolytic–uremic syndrome, thrombocytopenic purpura, acute myeloid leukemia, acute lymphocytic leukemia, and non-Hodgkin's lymphoma
Metabolic disorders	Porphyria (acute intermittent porphyria) and primary hyperparathyroidism
Neurologic disorders	Neuromyelitis optica spectrum disorder, carotid dissection, subacute sclerosing panencephalitis, moyamoya disease, and craniopharyngioma

* The conditions listed may be commonly noted in addition to severe hypertension or moderate but acute hypertension outside the normal range for the patient. These examples do not represent a full listing of conditions related to PRES.

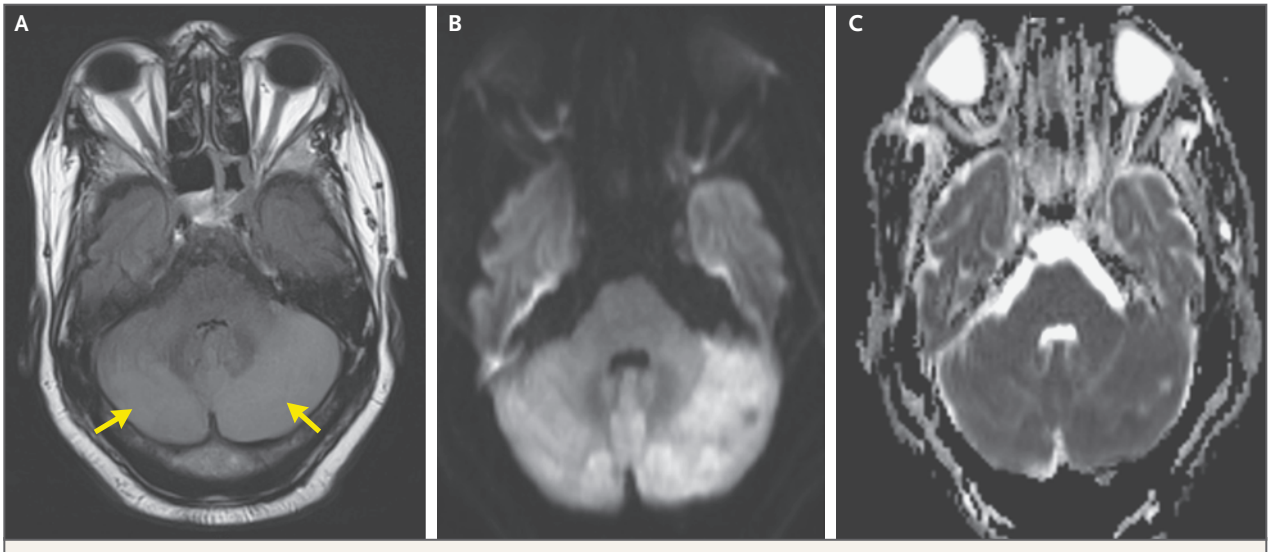

Figure 4. Atypical Imaging Patterns in PRES.

A 57-year-old man had multifocal myoclonus as well as coronavirus disease 2019 and chronic kidney disease after renal transplantation, for which he was receiving immunosuppression. Panel A shows an axial MRI FLAIR image of the patient's brain, with a diffuse, confluent signal change in the cerebellar hemispheres (arrows). Panel B shows a diffusion-weighted image with asymmetric signal changes in these regions. The apparent diffusion coefficient image (Panel C) did not show changes in these regions, findings that indicate there was no tissue infarction. (Images courtesy of Dr. Vivek Yedavalli and Dr. Rafael H. Llinas, Johns Hopkins University School of Medicine.)

Table 2. Drugs and Toxic Agents Related to PRES.*

Drug Class or Exposure	Specific Drugs and Toxic Agents
Chemotherapeutic drugs	Bevacizumab, tyrosine kinase inhibitors, bortezomib, cytarabine, gemcitabine, L-asparaginase, methotrexate, vincristine, and cisplatin (platinum-based agents)
Immune-modifying drugs	Tacrolimus, sirolimus, cyclosporine A, rituximab, interleukin, tumor necrosis factor antagonist, and interferon alfa
Pharmacologic agents	Erythropoietin, granulocyte colony-stimulating factor, voriconazole, butalbital–acetaminophen–caffeine therapy, pseudoephedrine, and antiretroviral therapy for human immunodeficiency virus infection
Intoxications and exposures	Alcohol intoxication, drug overdose (e.g., lithium, dextroamphetamine, acetaminophen, ephedrine, phenylpropanolamine, digitoxin, bismuth), chemical substance (e.g., organophosphates), illicit drugs (e.g., cocaine, amphetamine, mephedrone, kratom, amide of lysergic acid), and natural toxins (e.g., from snake bites, scorpion bites, wasp stings, mushrooms, licorice)

* These examples do not represent a full listing of drugs and toxic agents related to PRES.

and first-line treatment with benzodiazepines is typically followed by the addition of longer-acting antiseizure medications.[27] When EEG is not available, convulsions may be treated in the same way. Although PRES may lead to seizures, it may be helpful to identify and correct other causes of seizures such as hyponatremia.[27] Long-term outcomes in a case series of 84 patients with PRES and seizures who received treatment for 3 months and were followed for 3 years showed that late recurrent seizures occurred in 3% of the patients and epilepsy developed in 1%.[10]

ECLAMPSIA AND PREGNANCY-RELATED PRES

The diagnosis of PRES with eclampsia during or after pregnancy is based on typical clinical manifestations and neuroimaging characteristics.[28] Some disorders such as cerebral venous thrombosis and reversible cerebral vasoconstriction syndrome enter into the differential diagnosis. In consideration of fetal and maternal health, the treatment of choice for hypertension and seizures has generally been intravenous magnesium sulfate. Additional agents for severe hypertension may include intravenous hydralazine and labetalol, and for seizures, diazepam and phenytoin may be used.[28]

PUTATIVE PATHOGENESIS

Although several hypotheses have been suggested regarding the underlying biologic changes of PRES, the two leading ones are cerebrovascular dysregulation in cases of acute hypertension and cerebrovascular endothelial dysfunction in association with or after exposure to toxic agents.[16,17,29] Acute, severe hypertension is presumed to damage the blood–brain barrier, allowing vasogenic edema that is typically most severe in white matter.[30] The distinctive involvement of the occipital and posterior parietal lobes that characterizes PRES may be attributed to less sympathetic innervation in the posterior cerebral areas than in the anterior circulation[13,31] so that these regions are more susceptible to injury with blood-pressure changes.

In patients who have PRES without hypertension,[15] several unspecified processes resulting in endothelial dysfunction have been suggested.[29] Such processes have been reported with exposure to immune-modifying and cytotoxic agents[32,33] or in autoimmune disorders[32] or systemic disorders such as cancer, sepsis, or renal failure, which may, under certain circumstances, disrupt vascular function.[12,16] The mechanisms of injury with all underlying causes appear to converge on the cerebrovascular endothelium with disruption of the blood–brain barrier, which leads to vasogenic edema. The neurologic manifestations, particularly visual changes referable to the occipital lobes, are presumably the result of the edema, but the proximate causes of other aspects such as coma and seizures are obscure.

OUTCOMES AND PROGNOSIS

Perspectives on the outcomes of PRES have evolved since the original descriptions of this

disorder, but PRES generally has a good outcome with appropriate management. In one retrospective case series involving 63 hospitalized patients with a diagnosis of PRES, 2.2% died as inpatients.[15] Another study, as previously mentioned, indicated that patients recovered from neurologic deficits within 2 weeks, and this time period has been recapitulated in subsequent series.[14] However, poor outcomes and death have been reported,[34] especially in patients who had been admitted to the ICU.[12] A meta-analysis of six studies showed that a poor outcome was associated with brain hemorrhage and cytotoxic edema on imaging studies, whereas favorable outcomes were associated with PRES due to preeclampsia and eclampsia.[29] In contrast, in one series involving 5 patients who had cancer and coma, seizures, and massive brain edema, good functional outcomes were reported after aggressive treatment.[23]

CONTROVERSIES AND RESEARCH OPPORTUNITIES

Since the publication of the case series in 1996[1] and the recent addition of an *International Classification of Diseases, 10th revision*, code for PRES (ICD-10CM I67-83),[2] the number of publications on PRES has been increasing. The features of reported cases have deviated from those described in the article by Hinchey et al.,[1] with inclusion of more clinical settings, more triggering factors, nonreversible cases, and varying neuroimaging characteristics. The development of a multidisciplinary collaboration to define the essential aspects of PRES and the core diagnostic criteria on the basis of clinical and neuroimaging features is needed. This may also help us understand the extent to which conditions such as reversible cerebral vasoconstriction syndrome overlap with PRES. With better-defined diagnostic criteria, registries can be established to characterize the epidemiologic features, natural history, best care practices, and long-term outcomes so that controlled trials of treatment may be undertaken.

CONCLUSIONS

PRES is an acute or a subacute syndrome with various neurologic signs and symptoms — typically headache, encephalopathy, and seizures — and characteristic imaging changes in patients who have acute, severe hypertension or other clinical disorders. This syndrome is probably triggered by cerebral vascular dysregulation or endothelial dysfunction. Prompt diagnosis and treatment of underlying triggers along with supportive care usually, but not always, reverse abnormalities detected on clinical examination and neuroimaging.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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