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Posterior Reversible Encephalopathy Syndrome

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Posterior reversible encephalopathy syndrome (PRES) is a complex disorder, our understanding of which continues to evolve. PRES has many clinical associations, many causative factors, a variety of imaging manifestations, and its pathophysiology remains a topic of debate. There are also many other disorders that may mimic PRES. We present a concise review of PRES to enable the radiologist to more readily and easily recognize this treatable disorder with important clinical implications.
Semin Ultrasound CT MRI 35:118-135

Posterior reversible encephalopathy syndrome (PRES) is a complex disorder with many causative factors, it has a variety of imaging manifestations, and its pathophysiology remains a topic of debate. Awareness of these issues, particularly with regard to its less commonly known imaging manifestations, is paramount to diagnose this disorder. Here, we present a concise review of these issues to enable the radiologist to more readily and easily recognize this treatable disorder with important clinical implications.

Background

Early Beginnings

Knowledge of this disorder requires an understanding of its beginnings. Originally described in 1996 as reversible posterior leukoencephalopathy syndrome, Hinchey et al[1] published on a series of 15 patients who presented with headache, altered mental status, seizures, and loss of vision in association with "leukoencepalopathy" on imaging. Nearly half of these patients were receiving immunosuppressive therapy, most had impaired renal function, and all but a few had abrupt increases in blood pressure. By decreasing or withholding immunosuppressive therapy and by treating the hypertension, the neurologic symptoms resolved in all of these patients, all within 2 weeks.

The imaging findings at that time appeared to be that of a leukoencephalopathy, manifest as white matter hypoattenuation on computed tomography (CT) and T2 hyperintensity on magnetic resonance imaging (MRI), predominantly in the posterior cerebrum, specifically the more posterior parietal-temporal-occipital regions. These findings were typically bilateral but asymmetric. In those patients that underwent follow-up imaging, the findings proved to be always reversible, usually complete, but sometimes partial.[1]

In retrospect, the findings likely simulated a leukoencephalopathy for several reasons. First, as PRES typically involves the cortex in the early stages, and the deep white matter later, more severe cases were being described that not only exhibited the cortical edema that is present in mild PRES, but also the deep white matter edema. Second, the cortex is smaller, and it is likely that the cortex was being "dwarfed" by the relatively larger volume of edema in the white matter. Third, at that time, the typical and most common clinical presenting symptoms and signs of PRES were not known, and the term "leukoencephalopathy" was (and still is) of general utility as a "catchall" to describe poorly understood disorders resulting in white matter cell death. However, the terminology of reversible posterior leukoencephalopathy syndrome and "leukoencephalopathy" have fallen out of favor as the pathophysiology, anatomical distribution, and imaging patterns do not support such terminology.

Hypertensive encephalopathy was described with reversible white matter findings on CT as early as 1985,[2] and on MRI as early as 1988.[3] This was soon followed afterwards by several other reports.[4-6]

Even before 1996, central nervous system toxicity in conjunction with white matter changes on imaging as a result of cyclosporine toxicity had also been reported as early as 1985.[7] Although an earlier case report demonstrated more frontal white matter changes on imaging,[8] this toxicity was then described a few months later in a series of 3 patients with a

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http://dx.doi.org/10.1053/j.sult.2013.09.007

more posterior distribution of white matter changes.[9] Later reports exhibited a variety of distribution with regard to the leukoencephalopathy.[10-15]

A New Name

It was not until after the advent of T2-weighted imaging (T2WI) with fluid-attenuated inversion recovery (FLAIR) and its more widespread use that the more modern name of posterior reversible encephalopathy was introduced in 2000.[16] In this landmark paper, Casey et al[16] showed that FLAIR was superior to proton density and T2WI for detecting the lesions in PRES. Perhaps most importantly, the localization of the edema was much better delineated with a near-even split of cortical (46%) and white matter (54%) lesions. Also intriguing was that the milder cases demonstrated a predominantly cortical distribution of lesions, whereas the more moderate or severe cases had a more subcortical distribution of lesions.[16] Thus, the syndrome was clearly not a true leukoencephalopathy, especially as it was shown that the cortex was involved in 94% of cases in that study. The supposition arising from this work is that the more severe cases of PRES had previously been reported on the basis of CT and T2WI, resulting in the syndrome being described as a white matter condition. However, FLAIR imaging later uncovered the milder cortically based cases of PRES.

Clinical Manifestations

PRES is usually subacute in onset, presenting with seizures in approximately 75% of patients, most commonly of the generalized tonic-clonic type.[17,18] Mental status changes are the next most common clinical manifestations, followed by visual disturbances, severe headache, nausea or vomiting, and aphasia.[17,18] Many of these patients present in the setting of hypertension and impaired renal function, which is discussed in more detail later in the article. After recognition of the disorder on MR imaging, the symptoms resolve after a mean of approximately 10 days.[17]

Pathophysiology

A comprehensive analysis of the proposed pathophysiological mechanisms by which PRES occurs is beyond the scope of this review. However, some important points regarding the major theories behind its development are discussed. Although a topic of debate, it is generally agreed upon at this point that PRES is a result of a process involving vascular injury.

Hyperperfusion

The first described mechanism for PRES was that of hyperperfusion, particularly owing to recognition of hypertension and eclampsia as causes early on.[1,19-22] This theory has been described as hypertension with failed autoregulation, forcing otherwise constricted arterioles to dilate, thereby leading to hyperperfusion with injury to the capillary beds downstream.[4,23] This would result in extravasation of fluid, macromolecules, and red blood cells producing vasogenic edema. The vasogenic edema tends to occur in the cortex, which is tightly packed and resists the edema, hence the edema then migrates into the subcortical white matter.[16] The primary evidence supporting this theory is that increases in blood pressure are commonly seen in the setting of PRES, and treatment of hypertension tends to result in a reduction in symptoms. Also, hyperperfusion has been demonstrated on single-photon emission CT (SPECT) with technetium Tc99m-hexamethylpropyleneamine oxime (Tc99m-HMPAO).[4]

However, we now know that PRES develops in patients with only mild increases in blood pressure and in normotensive patients.[24] Also, despite the many patients with PRES who have more substantial increases in blood pressure, the hypertension achieved does not exceed the upper limit of autoregulatory capacity (MAP (mean arterial pressure) > 150-160 mm Hg) in most cases.[26] Further intriguing is the fact that the extent of vasogenic edema is decreased in those patients with severe hypertension.[25]

Hypoperfusion

Other theories attribute PRES to hypoperfusion. The prevailing hypoperfusion theory is that vasoconstriction occurs in the setting of evolving hypertension with resultant overreaction of autoregulatory compensation leading to hypoperfusion and eventual ischemia with subsequent alteration of integrity of the blood-brain barrier and vasogenic edema.[1,30] This theory would account for the watershed distribution of changes often seen in PRES and the ischemia and infarcts observed in a subset of cases. Also, this would explain the petechial hemorrhages that could result from the breakdown of the blood-brain barrier along with transudation of fluid. Furthermore, although not typically encountered, this would also explain why large vessel vasospasm has been encountered on catheter angiography and MR angiography (MRA).[16]

Also, more recent studies demonstrate hypoperfusion in affected areas in patients with PRES on MR perfusion,[26-28] and in patients with eclampsia on Tc99m-HMPAO SPECT.[29] This would tend to favor the theory of hypoperfusion, although an explanation for the associated T-cell activation and inflammatory cytokine production would be lacking.

Endothelial Injury

It has become clear that perhaps hypoperfusion or hyperperfusion alone is not an adequate explanation for the manifestations of PRES. A more novel theory is that of a systemic toxicity, perhaps with increased leukocyte trafficking, which results in endothelial dysfunction.[25] As a result of the systemic toxicity, hypoperfusion and vasoconstriction may lead to hypoxia with upregulation of vascular endothelial growth factor, resulting in increased endothelial permeability. This entire process may be modulated by changes in blood pressure, with increased autoregulatory vasoconstriction in response to increases in blood pressure. Thus, treatment of hypertension would result in less autoregulatory vasoconstriction, and hence improved perfusion.[25] This theory of