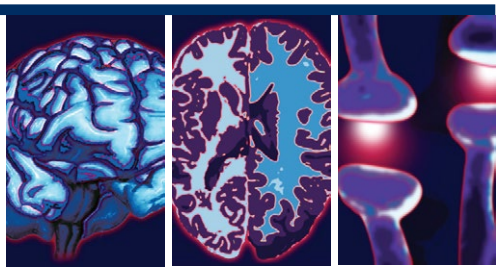
Review



Brainstem Variant of Posterior Reversible Encephalopathy Syndrome Revisited

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiologic entity with several well-known causes such as hypertensive encephalopathy, eclampsia, uremia, antirejection therapy, chemotherapeutic agents, characterized as rapid onset of symptoms (including headache, visual disturbance, seizures, altered consciousness) and typical neuroimaging features, which usually resolve over several days to weeks if promptly recognized and treated.

Keywords

Diffusion-weighted imaging (DWI), Apparent diffusion coefficient (ADC), Posterior reversible encephalopathy syndrome (PRES), Brainstem variant of PRES

Discussion

On brain CT or MR imaging studies, the edema is often widespread but predominates in the parietal and occipital lobes, likely leading Hinchey, *et al.* to suggest the "posterior" description [1]. A diagnosis of typical PRES was confirmed based on clinicoradiologic findings mostly predominating edema in the parietal and occipital lobes on MR T2-weighted images and fluid-attenuated inversion-recovery (FLAIR) images and sparing of the infratentorial regions. The possibilities of ischemic infarct or infection or demyelination or venous thrombosis or tumor growth should be ruled out. PRES is commonly associated with hypertension. Moderate-to-severe hypertension is seen in approximately 75% of patients with PRES, usually termed "hypertensive encephalopathy". PRES pathophysiology remains a mystery even after almost twenty years since its initial description. Hypertension with failed autoregulation and hyperperfusion remain a popular theory for the developing brain edema [2]. On the other hand, endothelial dysfunction/injury of the blood vessels, hypoperfusion, and vasoconstriction may result in altered integrity of the blood-brain barrier [3]. This alteration consists in a weakening of brain vessel tight junctions, which allows fluid leakage and edema. In a healthy status, cerebral autoregulation mechanisms that have both myogenic and neurogenic components conserve constant brain perfusion [4]. The effectiveness of the neurogenic component of autoregulation is directly related to the degree of sympathetic innervation [5]. The tendency for posterior circulation territory involvement is generally accepted to result from the relatively sparse sympathetic innervation of the vertebrobasilar circulation [6]. In patients with PRES, the myogenic response is diminished by either passive over distention of the blood vessel due to elevations in blood pressure [7] or direct toxic effects on the endothelium of the blood vessels [8]. Because brain autoregulation mechanisms are more dependent on the neurogenic response, the more poorly innervated areas in the posterior circulation are most vulnerable. The result is the leakage of fluid into the interstitium and

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developing vasogenic edema [1,4,7]. Recently, a more widely accepted hypothesis, based on several MR diffusion-weighted imaging (DWI) and quantitative apparent diffusion coefficient (ADC) analysis studies, suggests that increased systemic blood pressure may break through the upper limit of the autoregulation of the cerebral blood flow, causing brain hyperperfusion and passive distension of the cerebral arterioles, with resultant interstitial extravasation of proteins and fluid, and focal parenchymal hydrostatic edema. This is consistent with the imaging findings of increased ADC values representing as vasogenic edema [7,9].

Exclusively involvement of the brainstem in PRES has rarely been described. Reversible brainstem hypertensive encephalopathy (RBHE) was first recognized by Chang and Keane in 1999 [10]. PRES rarely presents with predominant involvement of the brainstem (brainstem variant of PRES), and involvement of only the medulla oblongata is uncommon. We reported two cases of brainstem variant of PRES with only medulla oblongata involvement in 2009 [11]. The cases presented illustrate MR imaging findings of a variant of PRES with only involvement of the medulla oblongata and emphasize the diagnostic value of MR diffusion-weighted imaging (DWI). Some reports which attempt to correlate clinical severity or reversibility of PRES with lesion distribution suggest a poor outcome of brainstem variant of PRES [12]. However, the findings of others and the present case disclose a complete reversibility of the brainstem lesions [13]. So it is a debated issue.

A diagnosis of brainstem variant of PRES was exclusively edema involving the brainstem area confirmed by MR FLAIR and T2-weighted images, sparing of the supratentorial regions. The possibilities of ischemic infarct or myelinolysis or glioma or encephalomyelitis should be ruled out. Previous studies have revealed that vasogenic edema represent the changes observed in typical PRES and brainstem variant of PRES cases. A breakdown in cerebral autoregulation results in the fluid leakage into the interstitium, which is detected as vasogenic edema. MR DWI was instrumental in creating and consistently validating that the areas of abnormality represent vasogenic edema [7,9]. Since PRES is usually caused by hypertensive crisis (systolic pressure over 180mmHg or diastolic pressure over 110mmHg), which should have a systemic effect and global manifestations on the brain tissue, we thus proposed that some microscopic abnormalities of the supratentorial regions could be detected with MR DWI using apparent diffusion coefficient (ADC) analysis in the brainstem variant of PRES and hypothesized that "normal-looking" supratentorial regions will increase water diffusion, similar to the vasogenic edema of brainstem. Recently we retrospectively reviewed the medical records of PRES patients at Chi-Mei Medical Center and identified patients with PRES who underwent brain MR imaging studies. For all patients, the MRI studies were performed between the first and third days of the onset of clinical symptoms. All were examined with isotropic DWI. According to previous literature, nineteen regions of interest (ROIs) with locations including cortex, deep gray matter nuclei, subcortical white matter and deep white matter were drawn semiautomatically and systematically placed for quantitative ADC analysis. The mean ADC values were measured and compared. All brainstem variant of PRES patients and typical PRES patients had hypertensive crisis (systolic pressure over 180 mmHg or diastolic pressure over 110 mmHg). According to unpublished data, higher ADC values are consistent with highly mobile water in areas of vasogenic edema in typical PRES and brainstem variant of PRES patients, as multiple prior studies have shown. ADC values in areas of typical PRES group were consistently elevated compared with those in normal control subjects ($P<.017$). ADC values in areas of brainstem variant group were consistently elevated compared with those in normal control subjects ($P<.017$). ADC values in areas of typical PRES group and brainstem variant group did not differ significantly, except for pons area ($P<.017$). The pons ADC values of the brainstem variant group were significantly higher than that of typical PRES group. The results of our study showed that the mean ADC of "normal-looking" supratentorial regions of the brainstem variant of PRES group was significantly higher than that of normal controls. And all of the brain regions that appeared normal on T2-weighted and FLAIR images showed a tendency to have higher ADC values compared with those in the normal control subjects. And also the higher ADC values returned to normal in the followed-up diffusion-weighted images if clinical condition under control. This preliminary finding suggests that ADC values may be more sensitive to vasogenic edema than findings on conventional T2-weighted and FLAIR images. The major point of this diagnosis is vasogenic edema, which can be reliably differentiated from cytotoxic

edema in other etiologies by using DWI and by calculating the ADC values. It may help us to differentiate from other entities of brainstem T2 hyperintensities such as acute ischemia or myelinolysis or glioma or encephalomyelitis. Nevertheless, these subtle changes in quantitative ADC analysis indicate that the pathophysiology of this phenomenon may be more global than previously thought. It supposed that even the more richly innervated territories of the "normal-looking" supratentorial regions maybe vulnerable to brainstem variant of PRES.

It is not clear that the predilection for brainstem variant of PRES. Because the parietal and occipital lobes, as well as the brainstem, are within the territory of the vertebrobasilar artery and its branches, two tentative explanations have been discussed [14]. By allowing fluid to accumulate, the brainstem may simply absorb much of the hypertensive "tidal wave", dissipating pressure before other parts of the brain are reached. Essentially, the brainstem serves as a buffer to protecting cerebrum and the distal parieto-occipital region in the vertebrobasilar system, more distal in blood supply. Another explanation is that the parietal and occipital lobes may be resistant to relatively rich sympathetic innervation via the posterior communicating artery. A well-developed posterior communicating artery, also known as fetal-type posterior communicating artery, is thought to have the same degree of sympathetic innervation as the anterior circulation. In this fashion, individuals with a fetal-type posterior communicating artery may be protected from paroxysmal hypertensive crisis. In our series, however, all brainstem variant of PRES patients enrolled did not have a fetal-type posterior communicating artery. Therefore, it is obvious that at least one of these theories is inconsistent and that more effort is needed to clarify the pathophysiologic mechanisms of brainstem variant of PRES.

Conclusion

Brainstem variant of PRES occur as a consequence of paroxysmal malignant hypertension. Thoroughgoing neurologic examination, combined with MRI and DWI, is essential for the correct diagnosis. The diagnosis has important therapeutic and prognostic implications because the reversibility of the clinical and radiologic abnormalities is depending on the prompt control of blood pressure [11]. As more studies are performed and as more case reports and case series are published, additional clinical associations will be made with PRES and brainstem variant, further enlightening our understanding of the syndrome.

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