

Posterior reversibl ensefalopati sendromu (PRES): difüzyon ağırlıklı MRG bulguları

Posterior reversible encephalopathy syndrome (PRES): diffusion-weighted MR imaging findings

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ÖZET

Amaç: Difüzyon ağırlıklı görüntüleme (DAG), posterior reversibl ensefalopati sendromu (PRES) tanısında ve serebral iskemi varlığında, sitotoksik ve vazojenik ödem ayırımında önemli rol oynamaktadır. Bu çalışmadaki amacımız DAG' nin, PRES tanılı olgularda sitotoksik ve vazojenik ödem ayırımındaki rolü ve prognostik faydasını değerlendirmektir.

Gereç ve yöntem: PRES tanılı sekiz olgu izotropik DAG ile değerlendirildi. Çalışmaya dahil edilme kriterleri şunlardı: 1) Baş ağrısı, nöbet, vizüel değişiklikler, değişken mental durum veya fokal nörolojik bulgular;2)hipertansiyon, eklampsi, antirejeksiyon ilaçlarla tedavi (örneğin; siklosporin, takrolimus);3)diğer ensefalopati nedenlerinin bulunmaması;4)MRG bulgularının PRES ile uyumlu olması.

Bulgular: Dört olguda eklampsi; iki olguda antirejeksiyon tedavisine bağlı toksisite, bir olguda hipertansif ensefalopati ve bir olguda hemolitik üremik sendrom etyolojik neden olarak belirlendi. Tüm olgularda posterior sirkülasyon alanlarında T2 ağırlıklı görüntülerde sinyal anormallikleri mevcuttu. Yedi olguda (%87.5) anterior sirkülasyon yapıları etkilenmişti. DAG' lerde, sekiz olgunun üçünde (%37.5) sitotoksik ödem mevcuttu ve lezyonlar çoğunlukla kortikal dağılım göstermekteydi. İki olguda (%25), DAG' lerde yüksek sinyalli alanlar, karşılığı olan ADC görüntülerde, psödonormalizasyon ile uyumlu olarak normal ya da hafif artmış sinyal intensitesi gösterdi. Bu iki olgunun takip görüntülerinde, psödonormalize alanlarda infarkt gözlemlendi.

Sonuç: PRES' te vazojenik ödem çoğunlukla posterior dolaşım alanlarında gözlenmektedir, ancak anterior sirkülasyon da sıklıkla etkilenmektedir. DAG' lerde yüksek sinyal ve psödonormalize ADC değerleri serebral infarkt gelişimi ile ilişkilidir ve sitotoksik ödeme ilerleyişin erken prognostik bulgusu olarak karşımıza çıkabilir.

Anahtar Kelimeler: reverzibl posteriyör lökoensefalopati sendromu, manyetik rezonans görüntüleme, difüzyon

Türkçe kısa makale başlığı: Posterior reversibl ensefalopati sendromunda MRG bulguları

ABSTRACT

Objective: Diffusion-weighted MR imaging (DWI) plays an important role in prompt diagnosis of PRES and in distinguishing vasogenic edema from cytotoxic edema in the setting of cerebral ischemia. In this study our aim was to assess the prognostic utility and role of DWI in distinguishing cytotoxic and vasogenic edema in patients with PRES.

Materials and methods: Eight patients with PRES were examined with isotropic DWI. Four inclusion criteria were used: 1) Acute presentation with headache, seizure, visual changes, altered mental status, or focal neurologic signs; 2) the presence of a known risk factor for PRES, such as hypertension, eclampsia, antirejection therapy (eg. cyclosporine, tacrolimus); 3) absence of other likely causes of encephalopathy; 4) MR examination with findings consistentwithPRES.

Results: Four cases involved eclampsia; two, antirejection medication toxicity; one, hypertensive encephalopathy; and one, hemolytic-uremic syndrome. In all the patients there were T2 signal abnormalities in the posterior circulation territories. Anterior circulation structures were affected in 7 patients (87.5%). On DWI three of eight cases (37.5%) presented cytotoxic edema and the lesions were predominantly cortical in distribution. In two patients (25%) areas of high DWI signal intensity were seen with normal or slightly increased ADC values which were consistent with pseudonormalisation. Follow-up images in these two patients showed progression to infarction in pseudonormalised regions.

Conclusion: Vasogenic edema in PRES involves predominantly posterior circulation territories but anterior circulation structures are also frequently affected. High DWI signal intensity and pseudonormalised ADC values are associated with cerebral infarction and may represent the earliest sign of progression to cytotoxic edema.

Key words: posterior reversible encephalopathy syndrome, magnetic resonance imaging, diffusion
İngilizce kısa makale başlığı: MRI findings in PRES

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Introduction

Posterior reversible encephalopathy syndrome (PRES) classically refers to a symptom complex characterised by visual disturbances, seizures, altered mental status, and headaches (1,2).

It was first described as reversible posterior leukoencephalopathy syndrome (RPLS) by Hinchey et al (1) in 1996 and four years later Casey et al (2) proposed the name posterior reversible encephalopathy syndrome (PRES) for RPLS to stress the common involvement of both grey and the white matter. Since then there have been many reports that describe the involvement of anterior circulation structures and that this syndrome sometimes may not be reversible (3-9).

Despite this syndrome needs a new and proper name, it's well known that 'if' promptly recognised and treated, the symptoms and radiologic abnormalities can be completely reversed. (1,2,10-12). It has been shown that diffusion-weighted MR imaging (DWI) plays an important role in prompt diagnosis of PRES and in distinguishing vasogenic edema from cytotoxic edema in the setting of cerebral ischemia (3,6,12).

In this study our goal was to show the diagnostic and prognostic utility of DWI in patients with PRES.

Materials and methods

We retrospectively identified patients with PRES who underwent brain MR imaging studies during a 42-month period. The study was performed with approval from our institutional review board under institutional guidelines that allow for retrospective analysis of patient medical records as long as all patient-identifying information is removed. The inclusion criteria for the patients were: 1) An acute presentation with headache, confusion, visual disturbance, seizures, altered mental status or focal neurologic signs, 2) the presence of a known risk factor for PRES, such as hypertension, eclampsia, antirejection therapy (eg. cyclosporine, tacrolimus), 3) absence of other likely causes of encephalopathy, 4) MR examination with findings consistent with PRES, 5) acquisition of diffusion-weighted images.

We searched the clinical record for information on blood pressure (BP), laboratory data and duration of symptoms in six patients. In one patient (patient 5) no clinical data from outside institution could be obtained.

All patients underwent MR imaging within a 12-hour to 9-day period after onset of symptoms. Three patients had seizures and the time interval between the seizures and MR imaging were between 3-4 days for all three patients. For four patients follow-up MR imaging were performed at a mean of 2.5 weeks.

MR images were performed on a 1.5 T superconducting system (Magnetom Vision Siemens, Erlangen, Germany) using a circularly polarized head coil. The standart MR imaging examination included turbo spin-echo T1-weighted (T1-W) (TR/TE: 650/14 ms) images in three orthogonal planes, T2-weighted (T2-W) (TR/TE: 3800/90 ms) in the axial plane and FLAIR images (TR/TE/TI: 8690/128/2500 ms) in the coronal plane. DWI was performed by using a single-shot, multisection, spin-echo echo-planar imaging obtained in the axial plane using echo-planar sequence with the following parameters: TR 4000 ms, TE 110 ms, number of excitation 1, matrix 96×128, slice thickness 5 mm, FOV: 220–240 mm, number of slices 17, scan time 32 s. The b values were 0, 500, and 1000 mm²/s with diffusion gradients applied in the three orthogonal directions to generate three sets of diffusion weighted images (x, y and z axes). Composite isotropic diffusion-weighted images and apparent diffusion coefficient (ADC) maps were created in all patients by using commercially available software on a separate workstation.

Two senior radiologists interpreted the signal intensity on T2-WI, DWI and ADC mapping through mutual agreement. The anatomical locations of the lesions were also determined by the consensus of these two radiologists. Alteration in signal intensities on DWI was evaluated as hypointense, isointense, slightly hyperintense or hyperintense.

Results

A total of 8 patients (five women, three men, mean age 25 years) with PRES were identified (Table 1).

Table 1. Summary of clinical features in eight patients with PRES

Patient No	Age/Sex	Clinical presentation	Time from onset to scan	Blood Pressure	Risk factor for PRES	Creatinine level (mg/dL)	CSF level (ng/dL)
1	19F	Generalized tonic clonic seizures	3 days	180/120 mmHg	Eclampsia	2.4	
2	19F	Generalized tonic clonic seizures	3 days	220/120 mmHg	Postpartum eclampsia	0.7	
3	19F	Concious blindness, altered mental status	12 hours	135/80 mmHg	Cyclosporin A treatment	1.0	201
4	30M	Headache, lethargy, visual changes	4 days	150/110 mmHg	Ticlidin treatment	2.0	6.0
5	24F	Headache, confusion	N/A	N/A	Eclampsia	0.6	
6	19F	Visual changes	9 days	180/100 mmHg	Eclampsia	0.7	
7	22M	Hemiparesis, altered mental status	1 day	220/130 mmHg	Hypertension induced by chronic renal failure	4.7	
8	48M	Seizures, confusion	4 days	240/140 mmHg	Hemolytic-uremic syndrome	7.6	

Note: -N/A, not available (data couldn't be obtained); CSF, Cerebrospinal A.F. fluid; M, male

Four cases involved eclampsia; two, antirejection medication toxicity; one, hypertensive encephalopathy; and one, hemolytic-uremic syndrome. In three patients combination of multiple factors that may have led to PRES was present and we used the clinical data to decide which factor was most relevant. Patient 4 had other risk factors for PRES such as uremia and elevated BP, but he was classified as antirejection medication neurotoxicity because he responded clinically to discontinuation of the drug.

An acute sustained rise in diastolic blood pressure to >100 mm Hg was determined in six patients and typical elevation of systemic arterial blood pressure was between 30 and 50 mm Hg, and typical elevation of diastolic blood pressure was between 10 and 20 mm Hg for all these six patients. In one patient (patient 3) no significant elevation in BP was recorded.

In patients with immunosuppressant neurotoxicity (patients 3 and 4), had symptoms with therapeutic levels of drugs and no toxic levels were determined before and during the development of PRES. Laboratory studies revealed no evidence of hypomagnesaemia nor hypocholesterolaemia in patient 3 and she recovered quickly after the withdrawal of cyclosporine.

Elevated creatinine levels (range, 2.0-7.6 mg/dl; mean 4.1) were seen in four patients (patients 1,4,7 and 8) in our study group.

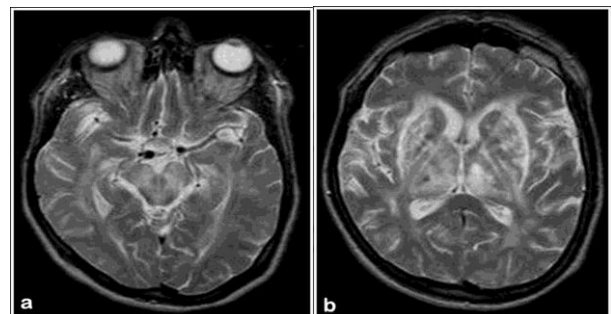
Conventional and DWI findings of the patients in our study group were summarized in the Table 2.

Table 2. Summary of conventional and DWI findings of eight patients with PRES

Patient no.	Distribution of disease	DWI findings	Time interval for follow-up MRI	Findings on follow-up MRI
1	Occipital, parietal, frontal	Isointense on DWI, high ADC values consistent with vasogenic edema	2 weeks	Completely resolved
2	Brainstem, basal ganglia, frontal, parietal, occipital	Cytotoxic edema in left frontal and parietal lobes	Not performed	N/A
3	Parietal and occipital	Isointense on DWI, high ADC values consistent with vasogenic edema	Not performed	N/A
4	Frontal, parietal, temporal, occipital, cerebellum	Increased signal intensity in the left occipitotemporal lobe in DWI, but showed pseudonormalised ADC values	4 weeks	Petechial hemorrhage into a subacute infarct
5	Frontal, parietal, temporal, occipital, cerebellum	Cytotoxic edema in left frontal lobe	Not performed	N/A
6	Frontal, parietal and basal ganglia	Cytotoxic edema in parietal lobes	10 days	Completely resolved
7	Brainstem, cerebellum, temporal, frontal, occipital, parietal, basal ganglia	Isointense on DWI, high ADC values consistent with vasogenic edema	3 weeks	Completely resolved
8	Brainstem, cerebellum, temporal, frontal, occipital, parietal, basal ganglia, thalami	Increased signal intensity in the left parietal lobe on DWI, but showed pseudonormalised ADC values	Not performed	N/A

Note: -N/A, not available (follow-up MRI was not performed)

In all the patients there were T2 signal abnormalities in the posterior circulation territories. Anterior circulation structures were affected in 7 patients (87.5%). Thalamic involvement was seen in one patient (12.5%) and brain stem involvement in three (37.5%). One of the most commonly involved region was basal ganglia, which were affected in four patients (50%) (Fig 1).



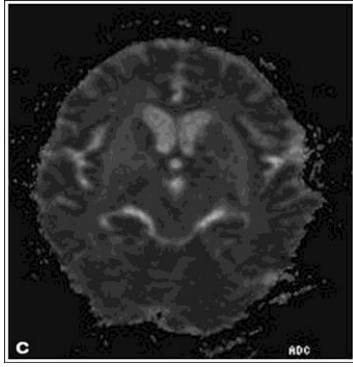


Fig. 1 Magnetic resonance imaging scan of Patient 8. Bilateral high signal intensities are noted in both basal ganglia, internal capsule and brainstem on T2-WI (a,b). ADC values at T2 high signal intensities are increased, representing vasogenic edema rather than cytotoxic edema (c).

On DWI three of eight cases (37.5%) presented cytotoxic edema (patients 2,5 and 6) and the lesions were predominantly cortical in distribution (Fig 2). On the other hand all eight cases manifested increased ADC values in the areas appearing hyper,iso or hypointense on DWI.

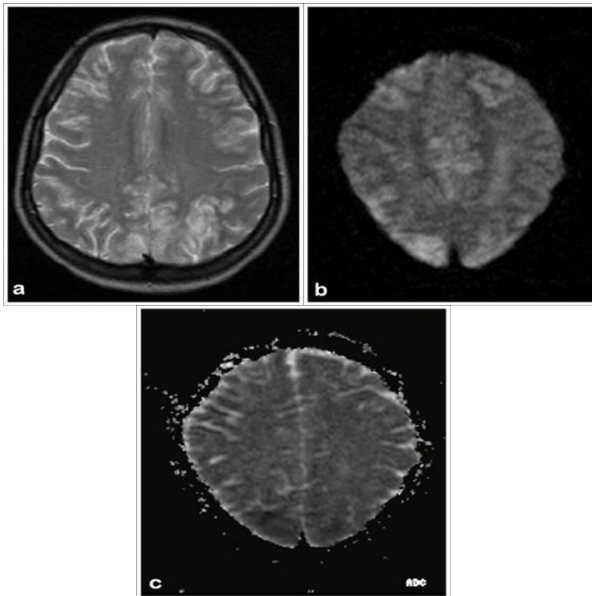


Fig. 2 Patient 6, a 19-year-old female with eclampsia. Axial T2-WI (a) shows hyperintense signal in bilateral cortical-subcortical parietal lobes. DWI image (b) shows apparent high intensity signal at the same level. On ADC mapping (c) most areas that showed high signal intensities on T2-WI demonstrate increased ADC, representing cytotoxic edema.

In two (25%) of remaining five cases areas of high signal intensity on DWI were observed (patients 4 and 8) and these lesions were also cortical in

distribution. These areas were iso or hyperintense on ADC maps and were not hypointense as expected, indicating restricted diffusion in ischemia. And also subcortical white matter surrounding these areas were hyperintense on T2W images and ADC maps indicating severe vasogenic edema. In patient 4 follow-up MR imaging performed 30 days after the initial examination showed increased signal intensity on T2W and FLAIR images corresponding to the area of abnormal findings with DWI at presentation. On follow-up images gyriform, increased T1 signal intensity was also present and this finding was consistent with petechial hemorrhage into a subacute infarct (Fig 3). Platelet counts assessed at the time of presentation were within the normal range ($259 \times 10^9/L$). This patient recovered in two weeks after tacrolimus was withdrawn.

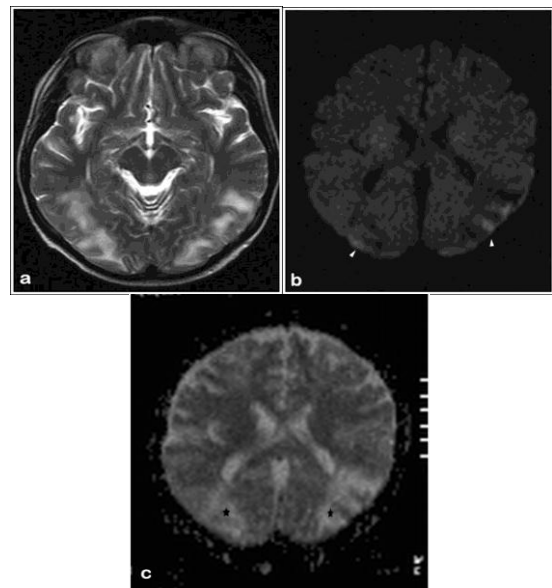


Fig.3 Patient 4, a 30-year-old man with tacrolimus toxicity. On T2-WI (a) cortical and subcortical high signal intensities are demonstrated in both temporal and occipital lobes. DWI image (b) shows increased signal intensity in these areas (arrowheads). ADC map (c) shows increased diffusion in the areas of vasogenic edema (asterisks), as expected. The areas of high signal intensity in b, do not have low ADC values, as would be expected in ischemic brain. Instead, the values are pseudonormalized. Follow-up T2-W (d) and non-contrast T1-WI image (e) obtained four weeks later show increased signal intensity on T2W image (arrows) corresponding to the area of abnormal findings with DWI at presentation and gyriform increased signal intensity (arrowheads) corresponding to the region of abnormal findings at DWI. This finding is consistent with petechial hemorrhage into a subacute infarct.

One patient (patient 8) with high DWI signal intensity died before follow-up MR imaging could be performed. He died of aspiration pneumonia 2 weeks after the initial examination.

Three patients had severe brainstem involvement (patients 2,7 and 8) and in two of them (patients 2 and 8) high signal intensity on DWI was observed. Patient 8 also had areas of high signal intensity in frontal and parietal lobes and died soon after the initial examination. Patient 2 recovered fully after the rapid control of her BP and patient 7 recovered partially despite aggressive intervention with dialysis.

Discussion

PRES encompasses a spectrum of disorders; including hypertensive encephalopathy, eclampsia, thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome, treatment with a number of therapeutic agents (eg, tacrolimus, cisplatin, cyclosporine, cytarabine, 5FU, interferon alfa, gemcitabine, erythropoietin, ciprofloxacin, bevacizumab) (13-19).

At presentation patients usually have marked hypertension, although cases with mildly elevated or even normal blood pressure as in our series, have been reported (3).

Clinical symptoms include headache, nausea and vomiting, abnormalities visual perception (blurred vision, hemianopia, visual neglect and frontal cortical blindness), altered alertness and behaviour, mental status abnormalities, seizure (usually generalised) and occasionally focal neurologic signs (20,21).

The term PRES is a misnomer as the condition is not always reversible (4), as with two of our cases who did not make a full recovery. Furthermore, it is not necessarily confined to the posterior regions of the brain, but might also include areas supplied by the anterior and middle cerebral arteries and also the brainstem (1,2,4,6) as seen in seven of our cases.

In view of these considerations Narbone et al. (22) suggested renaming this entity 'Potentially Reversible Encephalopathy Syndrome'. They also emphasized, by not modifying the acronym again, confusion about the syndrome can be avoided, which is still unfamiliar to many neurologists and the term "PRES" is still more apt.

Pathophysiology of PRES has long been studied and debated nevertheless is still not completely understood. There are two theories on the pathophysiology of PRES. The cytotoxic theory is that a sudden and severe increase in blood pressure causes cerebral vasoconstriction with cerebral

ischemia and cytotoxic edema formation (2, 23, 24, 25). The vasoconstriction occurs as a response to a cerebral vascular damage or, alternatively, vasoconstriction itself induces hypoxic change leading to endothelial cell damage and cytotoxic edema (23). Support for this notion comes from cerebral angiography performed in a patient with clinical and radiological findings consistent with PRES and which revealed vasoconstriction involving the posterior cerebral and middle cerebral arteries (23). Tajima et al., (25) using ¹³³Xenon single photon emission computed tomography, demonstrated hypoperfusion in the posterior white matter, with parallel angiography confirming irregular narrowing of the posterior cerebral artery. In addition Brubaker et al. (26) found decrease in both CBV and CBF in PRES using perfusion-weighted MR imaging, that might be caused by autoregulatory vasoconstriction. However, other cases are not associated with visible large vessel vasospasm (2).

The vasogenic theory holds that elevated blood pressure overcomes cerebral autoregulation leading to cerebral vasodilatation and vasogenic cerebral edema (1,27). Cerebral autoregulation serves to keep cerebral blood flow constant when mean arterial blood pressure (MAP) remains between 60–120 mmHg, thereby protecting the brain from acute changes in blood pressure. As MAP increases, cerebral vasoconstriction limits cerebral hyperperfusion, but at higher MAP cerebral autoregulation fails. This leads to arteriolar vasodilatation and endothelial dysfunction with capillary leakage and disruption of the blood-brain barrier (27). Plasma and cells then accumulate in the extracellular space, particularly the cerebral white matter, which is less tightly packed and organised than the cortex, causing vasogenic cerebral edema (1,2).

The rate of change in blood pressure is also important in the development of acute hypertensive encephalopathy. In chronic hypertension, adaptive vascular changes protect end organs from acute changes in blood pressure and in these patients blood pressure might need to be 220/110 mmHg or higher before encephalopathy develops (27).

MR imaging changes in PRES have been shown to occur typically in the territory supplied by the posterior circulation, with anterior circulation abnormalities only seen in more severe cases (4). The posterior region of the brain might be more susceptible to PRES as a result of less sympathetic

innervation of the vertebrobasilar and posterior cerebral arteries. In comparison, the anterior cerebral vasculature is richly innervated by sympathetic nerves from the superior cervical ganglion (2,3,15). This means there is less ability for the posterior brain to protect itself from acute increases in blood pressure with sympathetic mediated cerebral vasoconstriction (7).

The exact aetiology of PRES associated with immunosuppressant and cytotoxic drugs, such as cyclosporin and tacrolimus (1,28,29) is uncertain. It is thought that a direct toxic effect produced by these drugs might damage vascular endothelium, leading to endothelial dysfunction. This results in vasospasm, reduced tissue perfusion, activation of the coagulation cascade and extravasation of fluid (1). PRES can occur whilst drug levels remain within the therapeutic range (1,2) and in patients who are normotensive (1), as we see in our

two cases in our study group. In over half of the patients with cyclosporin induced neurologic symptoms hypocholesterolaemia and hypomagnesaemia are present (1). Therefore, the cause of cyclosporin induced PRES is probably multifactorial. Laboratory studies revealed no evidence of hypomagnesaemia nor hypocholesterolaemia in our patient with cyclosporine induced PRES (patient 3).

Renal dysfunction might predispose the brain to PRES because of chronic uraemia or fluid overload. Similarly, in eclamptic patients, PRES occurs more commonly in the puerperium, at a time when fluid accumulation might increase the tendency for cerebral oedema to develop (1).

The findings in our series confirm the predilection for posterior circulation territories in PRES, but not to the exclusion of anterior circulation structures. The involvement of anterior circulation structures was seen in seven patients (87.5%) in our study group.

We observed areas of cortical DWI hyperintensity in five (62.5%) of our patients, an incidence that was much higher than those of previous reports. Instead of the low ADC values one would expect in the setting of ischemic injury with irreversible damage, ADC values in areas of cortical DWI hyperintensity were pseudonormalized in two patients. Covarrubias et al. (4) postulated that the paradoxically normal or elevated ADC values in areas of DWI hyperintensity result from intravoxel averaging of both cytotoxic and vasogenic edema in cortex affected by PRES. Because restricted diffusion in cytotoxic edema

lowers ADC values and vasogenic edema elevates them, the effects cancel each other out when the two combine at the subvoxel level.

The progression to subacute infarction that we observed in areas of cortical DWI hyperintensity is consistent with prior case reports of PRES in the literature. Ay et al's (7) original description of cytotoxic edema in a patient with PRES showed large areas of restricted diffusion 3 days prior to their patient's demise. Koch et al (8) describe a case in which areas of cytotoxic edema in PRES led to tissue loss on follow-up images obtained 2 months later. Cooney et al (9) observed gliosis, white matter volume loss, and petechial hemorrhage on follow-up images that corresponded to areas of high DWI signal intensity at presentation. Covarrubias et al. (4) reported that high DWI signal intensity and pseudonormalization were associated with an adverse outcome.

The mechanism by which vasogenic edema in PRES becomes cytotoxic is not well understood. Ay et al (7) suggest that, in areas of massive vasogenic edema, increased tissue pressure eventually impairs the microcirculation and leads to ischemia. In our patient, (patient 4), cytotoxic edema developed in cortex immediately adjacent to areas with intensely elevated ADC values in the subcortical white matter; this finding is consistent with a heavy burden of fluid in the interstitium. The postulation that unchecked vasogenic edema results in cytotoxic edema and infarction seems reasonable.

It has been reported that brain stem involvement indicates poor response to treatment (4). In our series, three patients with brain stem involvement (patients 2,7,8) had also supratentorial structures involvement, therefore interpretation of our findings in these three patients is difficult. Since, one of them (patient 8) died soon after diagnosis and remainder recovered after prompt treatment. Larger studies are needed to establish the precise relationship of brain stem involvement to patient outcome.

In conclusion, the hallmark of diagnosis of PRES is vasogenic edema in the territories of posterior circulation which can be reliably differentiated from cytotoxic edema in other etiologies by using DWI and by calculating the ADC map, which shows elevated ADC

values. Involvement of anterior circulation structures is also common and should not deter consideration of this diagnosis. Diffusion-weighted images may show foci of high signal intensity in cortex that is either undergoing infarction or at high risk of

infarction. ADC values in these areas are normal or slightly elevated, which is called 'pseudonormalised'. This finding may represent an early non-reversibility in PRES and may help guide more aggressive treatment.

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