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Diffusion-Weighted MR Imaging in Hypertensive Encephalopathy: Clues to Pathogenesis

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PURPOSE: **Hypertensive encephalopathy, a complex of cerebral disorders, including headache, seizures, visual disturbances, and other neurologic manifestations, is associated with a variety of conditions in which blood pressure rises acutely. It has been ascribed to either exuberant vasospasm with ischemia/infarction or breakthrough of autoregulation with interstitial edema. Diffusion-weighted MR imaging may be used to determine whether the edema in hypertensive encephalopathy is cytotoxic or vasogenic in origin.**

METHODS: **Diffusion-weighted imaging was performed using the double line scan diffusion imaging technique on a 1.5-T MR system. Seven patients with hypertensive encephalopathy were imaged within 1 day of the onset of their symptoms. Apparent diffusion coefficient maps as well as low and high b-factor images were acquired. The two-tailed paired Student's *t*-test was used to compare the apparent diffusion coefficients in edematous brain regions with those of normal white matter.**

RESULTS: **In all cases the apparent diffusion coefficient maps of the patients with hypertensive encephalopathy showed increased signal in regions corresponding to increased T2 signal on standard T2-weighted (low b-factor) images. Quantitative apparent diffusion coefficients in regions of abnormal T2 signal were 1.36 ± 0.14 μm^2/ms, compared with 0.80 ± 0.05 μm^2/ms in normal white matter. Diffusion-weighted (high b-factor) T2-weighted images did not show abnormal signal.**

CONCLUSION: **Diffusion-weighted MR imaging shows that the edema in hypertensive encephalopathy is of vasogenic origin and does not represent ischemia or infarction. This finding may have therapeutic implications.**

Hypertensive encephalopathy (HTE) is a potentially devastating neurologic syndrome characterized by rapidly progressive signs and symptoms, including headache, seizures, altered mental status, visual disturbances, and other focal and/or diffuse neurologic signs (1). HTE occurs in the setting of acute hypertension, often in association with endothelial dysfunction, and has been reported in patients with preeclampsia-eclampsia syndrome, lupus nephritis, or those receiving immunosuppressive drug therapy with cyclosporine (1, 2). CT and MR imaging in uncomplicated cases show edema in the cortex and subcortical white matter of the posterior brain regions (occipital lobes, posterior parietal and temporal lobes, and posterior fossa structures). Although clinical and radiologic findings generally resolve after normalization of blood pressure, intracerebral hemorrhage may occur, especially in patients with thrombocytopenia or in those in whom hypertension cannot be controlled.

Over the past century, two theories have been advanced to explain the pathogenesis of HTE. The conception that has historically been the most widely advocated by clinicians postulates that HTE results from spasm of the cerebral vasculature in response to acute hypertension (overregulation), resulting in decreased blood flow and intraarterial thrombosis. This in turn produces ischemia and cytotoxic edema in the borderzone between arterial territories (3, 4). An alternative view is that the syndrome results from overdistention of cerebral vessels (breakthrough of autoregulation), resulting in the extravasation of fluid into the interstitium at the periphery of arterial territories, termed hydrostatic edema. This theory appears to be favored by the bulk of experimental and clinical data (1, 5, 6), but direct evidence is limited. The distinction between these points may be of great importance in directing therapy. If spasm-induced

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thrombosis and ischemia were responsible for the findings of HTE, a clinician might be inclined to increase systemic blood pressure and decrease intracranial pressure in order to maintain cerebral perfusion or to prescribe anticoagulants to forestall further ischemic events. However, if breakthrough of autoregulation were the cause of the syndrome, reduction in blood pressure alone would be the more appropriate management; anticoagulation, in fact, might result in hemorrhage.

Diffusion-weighted MR imaging techniques may be used to measure the microscopic mobility or diffusibility of protons (7, 8). In areas of acute ischemia or infarction, intracellular diffusion is apparently restricted or reduced; these areas of cytotoxic edema appear as regions of increased signal on heavily diffusion-weighted MR images (9). However, vasogenic or interstitial edema does not elicit increased signal on diffusion-weighted images. Thus, diffusion-weighted imaging is well-suited to address the issue of whether HTE is caused by ischemia or by breakthrough of autoregulation. Although diffusion imaging using echo-planar methods is well established (9), it has recently become possible to perform diffusion imaging on standard 1.5-T MR units without echo-planar gradient capabilities (6, 7). We present the results of diffusion-weighted imaging in seven patients with HTE who were examined with this technique.

Methods

The patients' ages ranged from 32 to 72 years (mean age, 52 years). Each patient was acutely hypertensive for several hours or days and had headache, seizures, and/or visual disturbances that prompted a CT or MR imaging examination within 1 day of the onset of signs or symptoms. A variety of conditions were responsible for inducing the acute hypertension, including pre-eclampsia-eclampsia, hemolytic uremic syndrome, systemic lupus erythematosus, antiphospholipid antibody syndrome, severe pain due to bone metastasis or nephrolithiasis, and anxiety.

MR imaging was performed with a GE 1.5-T Signa scanner using the 5.4 hardware/software configuration. In each case, T1-weighted sagittal images (600/25/1 [TR/TE/excitations]) and T2-weighted axial images (3000/30,80/1) were acquired with 5-mm contiguous sections. Four diffusion-weighted images per section were generated with one image having minimal diffusion weighting and the other three having heavy diffusion weighting along the *x*-, *y*-, and *z*-axes, respectively. A total of 12 sections were sampled in approximately 6 minutes 40 seconds using a modification of the line scan diffusion imaging (LSDI) sequence described elsewhere (7). The modification involved successive excitation of two spatially separated but parallel planes that were both inclined at approximately 50° to the imaging plane (8). This allowed for direct and simultaneous single-shot imaging of two columns per TR period, arranged to sample adjacent axial sections, and is thus referred to as double line scan diffusion imaging (DLSDI). The technique has been described in detail elsewhere (8) but its salient features are briefly reviewed below.

As in the original LSDI method, DLSDI retains the motion insensitivity of the original LSDI technique without the need for echo-planar imaging gradient hardware. DLSDI, however, doubles the volume coverage per unit of time compared with LSDI at the expense of introducing slightly different T2-weighting factors for adjacent sections. This effect has been shown to have minimal impact on the appearance of stroke on the diffusion-weighted images or on the isotropic apparent diffusion coefficient (ADC) and the estimated anisotropy maps generated for the different sections in the brain (8). In the present study, 96 columns were sampled per plane for each b-factor and each direction of the diffusion sensitizing gradient using a TR of 170. With the DLSDI method, this resulted in approximately 8 seconds per "raw" image. Skipping 16 columns each TR resulted in an effective TR, for T1 saturation calculation purposes, of approximately 1 second, since the same columns were sampled with different diffusion sensitizing gradient directions and/or b-factors. The different TE values of the DLSDI used for adjacent sections were approximately 90 and 120, with maximum b-factors of approximately 855 s/mm^2. The complete four-image data per section allowed for the evaluation of isotropic ADC maps. These were generated directly on the Signa console using software specifically developed for this purpose.

Advantages of the LSDI approach over conventional two-dimensional Fourier transform (2DFT) diffusion imaging sequences have been discussed in detail previously (7, 8). The use of a direct excitation of selected columns in a single shot avoids the use of phase-encoding multiple signal acquisitions from the entire plane each TR period. This minimizes the diffusion sensitivity to motion that may degrade non–echo-planar 2DFT spin-echo–based diffusion imaging. In each patient, ADC measurements were made from 1.0 cm^3 regions of interest within areas of normal-appearing white matter and from regions of interest within areas of high signal on T2-weighted images. Statistical differences between the ADC values were determined using a two-tailed paired Student's *t*-test with significance at the .05 level.

TABLE 1: Patient information

Patient No.	Diagnosis	Age, y	Clinical History	Maximal Blood Pressure (Mean Arterial Pressure)*	Baseline Blood Pressure (Mean Arterial Pressure)*	Percentage of Difference, %†
1	Pneumonia	60	Seizures	238/124 (162)	140/80 (100)	62
2	SLE	38	Headache, visual dist., seizures	150/90 (110)	100/70 (80)	38
3	APA	49	Headache	200/110 (140)	120/82 (94.7)	47
4	Eclampsia	32	Seizures, headache	188/126 (146)	118/86 (96.7)	52
5	Bone metastases	72	Headache, visual dist., seizures	184/100 (128)	130/70 (90)	42.2
6	HUS	49	Headache, visual dist.	192/120 (144)	140/90 (107)	35
7	Nephrolithiasis	66	Headache, visual dist., seizures	200/106 (137.3)	120/70 (87)	58

Note.—SLE, systemic lupus erythematosus; APA, antiphospholipid antibody syndrome; HUS, hemolytic uremic syndrome.

* Maximal blood pressure measured during neurologic event; baseline blood pressure measured at least one week prior to the event; mean arterial pressure (systolic blood pressure, calculated as follows: [systolic blood pressure + 2 (diastolic blood pressure)]/3.

† Percentage of difference in blood pressure between baseline and maximum levels, calculated as follows: [(maximal mean arterial pressure − baseline mean arterial pressure)/baseline mean arterial pressure] × 100%.

Results

For each patient, the maximal mean arterial pressure obtained during the hypertensive crisis and the baseline mean arterial pressure obtained at least one week prior to the onset of neurologic symptoms are shown in Table 1. The increase in blood pressure ranged from 35% to 62% (average, 48%). No patient was chronically hypertensive. In all patients, symptoms of HTE resolved after blood pressure was satisfactorily controlled; one patient with thrombocytopenia suffered a right parietal hemorrhage and was discharged 2 weeks later with mild left-sided weakness.

In all seven patients, foci of increased T2 signal were noted in the occipital regions bilaterally. Other brain regions were also affected in five cases. The ADC maps of the patients showed areas of increased ADC in regions corresponding to increased T2 signal seen on standard T2-weighted images. The ranges and means of the ADC values in these regions as well as in normal-appearing white matter are presented in Table 2. The mean ADC within the lesions in the patients with HTE were elevated by approximately 70% over the ADC in normal white matter. This difference was statistically significant ($P < .0001$). Although the ADC values in the affected regions were higher than in normal brain tissue (Table 2), they generally did not appear hypointense on the diffusion-weighted T2 images.

TABLE 2: Comparison of ADC values of normal and abnormal white matter in patients with HTE

	Range (μm^2/ms)	Mean (SD) (μm^2/ms)
Normal white matter	0.70–0.87	0.80 (0.05)
White matter in HTE patients	1.14–1.52	1.36 (0.14)

Figure 1A is an axial calculated ADC map of a patient with HTE showing increased ADC in the occipital lobes. Note that the regions of edema yielded considerable signal on the low b-factor T2-weighted image (Fig 1B) but not on the high b-factor image (Fig 1C). Acute ischemia or infarction routinely produces hyperintense signal on high b-factor (diffusion-weighted) T2 images (9, 10).

Discussion

The line scan approach to diffusion-weighted MR imaging is readily implemented on standard 1.5-T MR units without echo-planar gradient capabilities, and provides images that are equivalent to those obtained with echo-planar techniques (7, 8). Diffusion-weighted imaging provides a means of identifying cytotoxic edema caused by acute ischemia or infarction (9) through a reduction in the diffusibility of protons, represented by the ADC parameter. This elicits bright signal on heavily diffusion-weighted (high b-factor) images, and is believed to reflect increased intracellular and decreased extracellular fluid resulting from sodium pump failure. Vasogenic or interstitial edema, on the other hand, is associated with unchanged or decreased signal on high b-factor images (10).

All seven of our patients were previously normotensive and had experienced several hours to days of acutely elevated blood pressure (an average of 48% over that of premorbid baseline) before HTE developed. The autoregulation of cerebral blood flow,

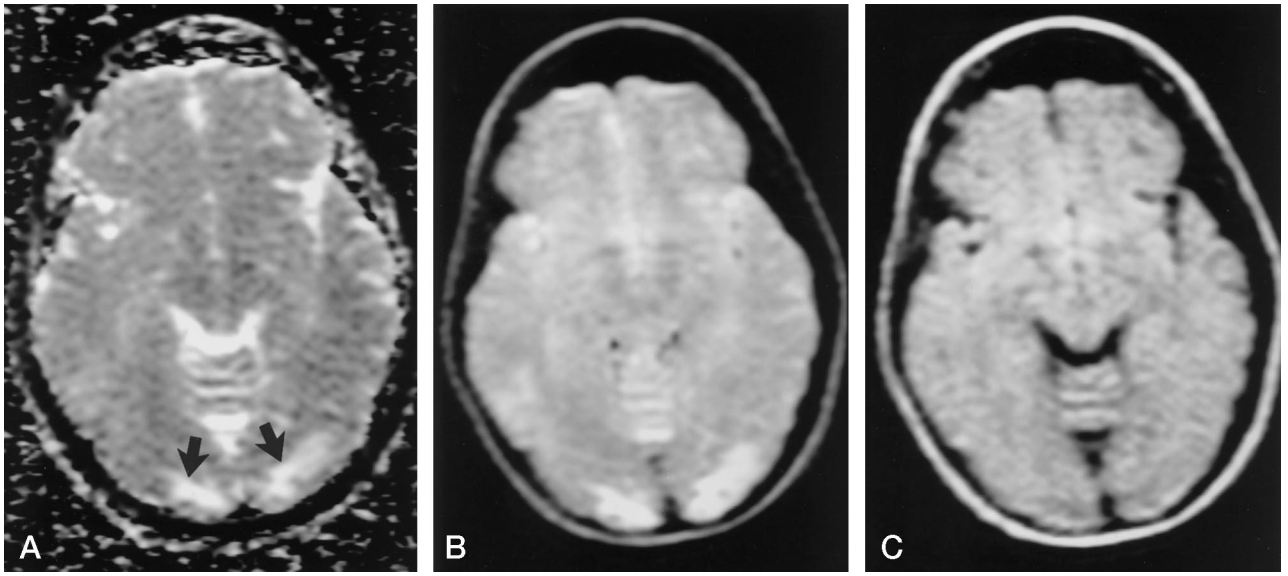

FIG 1. Axial MR images in a patient (case 1) with hypertensive encephalopathy. She had been treated for Legionella pneumonia and was extubated, but she became anxious and hypertensive (maximum blood pressure, 238/124) after experiencing difficulty breathing as a result of mucus plugging. She had a generalized seizure the next morning.

A, An ADC map shows increased signal in both occipital regions *(arrows)*.

B, A low b-factor T2-weighted image shows increased T2 signal in the occipital regions.

C, A high b-factor T2-weighted image does not show abnormal signal, indicating that the increased T2 signal represents interstitial or vasogenic edema.

which has both myogenic and neurogenic components, ensures the vasoconstriction of small arteries and arterioles to counteract increased systemic pressure. Previous reports have suggested that the clinical and radiologic findings in HTE are ischemic in nature, owing to intense or prolonged vasospasm, resulting in intravascular thrombosis or emboli. However, the edema in HTE is predominantly subcortical in location, often sparing the cortex entirely; and, as was the case in our patients, is generally reversible with reduction in blood pressure. Ischemic injury, on the other hand, almost always involves the cortex along with the subjacent white matter, and often progresses to infarction. Furthermore, both ^{99m}Tc-hexamethylpropyleneamine single-photon emission CT (1) and perfusion MR imaging (11) in patients with HTE show preserved or increased perfusion to edematous portions of the brain during the neurologic event; acute ischemia is generally associated with decreased perfusion. Our findings of increased ADC values and lack of high signal on the diffusion-weighted images indicates that the edema in HTE is not cytotoxic in nature but represents increased interstitial fluid. This finding is consistent with the hypothesis that HTE results from breakthrough of autoregulation. At the extreme level of acute hypertension experienced by our patients, the myogenic autoregulatory response may be overwhelmed, resulting in leakage of plasma through the vascular wall and into the interstitium (hydrostatic edema). Further, experimental evidence has shown that under these conditions, sympathetic nerves traveling along the adventitial layer may be stimulated to induce vasoconstriction (12); however, the vertebrobasilar system and in particular the posterior cerebral arteries are sparsely innervated (13), so the occipital lobes and other posterior brain regions are at relatively increased risk for hydrostatic edema. This may account for the characteristic posterior distribution of signal abnormality in patients with HTE.

Conclusion

HTE may occur as a result of a variety of conditions associated with acute increases in systemic blood pressure, but it may be difficult to distinguish clinically or radiologically from ischemia or infarction. Diffusion-weighted MR images indicate that the edema of HTE is primarily vasogenic, most likely representing hydrostatic leakage of intravascular fluid into the interstitium (breakthrough of autoregulation). Therapy, therefore, should be directed toward lowering blood pressure and maintaining adequate platelet levels to avoid hemorrhage.

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