

Hypertensive Brainstem Encephalopathy Without Parieto-occipital Lesion

—Two Case Reports—

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Abstract

Two patients presented with malignant hypertension associated with encephalopathy predominantly manifesting as brainstem lesion. T₂-weighted and fluid-attenuated inversion recovery magnetic resonance (MR) imaging revealed diffuse hyperintense areas in the pons and scattered lesions in the cerebellum, basal ganglia, and cerebral subcortex without parieto-occipital lesions. Diffusion-weighted MR imaging demonstrated these lesions as normal intensity, indicating vasogenic edema. These lesions resolved rapidly once hypertension was controlled. Review of clinical findings for 14 other patients with hypertensive brainstem encephalopathy without parieto-occipital lesions suggested that anterior circulation structures supplied by the carotid artery are frequently involved in such patients.

Key words: reversible posterior leukoencephalopathy syndrome, posterior reversible encephalopathy syndrome, malignant hypertension, brainstem swelling, crescentic glomerulonephritis

Introduction

Hypertensive encephalopathy is an acute condition characterized by headache, and visual and consciousness disturbances associated with severe systemic hypertension.^{1,5)} The symptoms are usually reversible if adequate treatment is initiated promptly, but irreversible neurological deficits sometimes develop.¹⁾ A clinico-neuroradiological entity was proposed consisting of reversible leukoencephalopathy located in the posterior lobes of patients with acute renal insufficiency, malignant hypertension, or administration of immunosuppressive drugs.¹⁰⁾ Characteristic magnetic resonance (MR) imaging findings include bilateral white matter abnormalities in the posterior portions of the cerebral hemispheres, often sparing the cortex. However, the term “reversible posterior leukoencephalopathy syndrome” (RPLS) remains contentious, as the adjacent gray matter is also often involved, so the term “posterior reversible encephalopathy syndrome”

(PRES) is now preferred by some authors.³⁾

We treated two patients with reversible extensive brainstem swelling involving lesions in the territory of the carotid artery without parieto-occipital lesions, attributable to malignant hypertension.

Case Reports

Case 1: A 35-year-old man with no past history of hypertension presented with a 5-day history of throbbing headache, nausea, blurred vision, and skin purpura over the entire body. He was brought to the emergency center, where his blood pressure was measured at 180/118 mmHg. Funduscopic examination revealed multiple “cotton wool” exudates on the retina and papilledema (Keith-Wagener grade IV). Urine analysis revealed proteinuria and hematuria. Laboratory examinations indicated anemia (hemoglobin 8.8 g/dl), low platelet count ($11.3 \times 10^4/\mu\text{l}$), and red blood cell fragmentation. Renal dysfunction was also present (creatinine 4.1 mg/dl, blood urea nitrogen [BUN] 50 mg/dl). Serum electrolyte concentrations were: Na 138 mEq/l, K 3.8 mEq/l, and Cl 118 mEq/l. Plasma renin

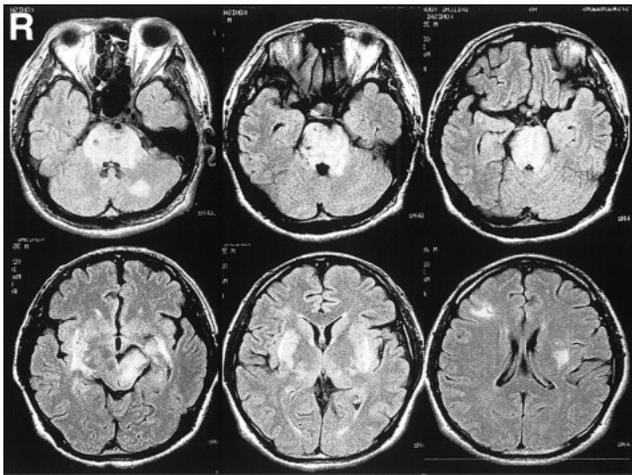


Fig. 1 Case 1. Fluid-attenuated inversion recovery magnetic resonance images showing diffuse hyperintense areas in the pons, and scattered lesions in the left cerebellum, left cerebral peduncle, bilateral basal nuclei, left external capsule, and right frontal white matter, but no parieto-occipital lesions.

activity was 72.0 ng/ml/hr (normal <3.0 ng/ml/hr) and aldosterone level was 310 pg/ml (normal 36–240 pg/ml). Serum epinephrine level was 17 pg/ml (normal <100 pg/ml) and norepinephrine level was 157 pg/ml (normal 100–450 pg/ml). Cerebrospinal fluid appeared normal except for an opening pressure of 240 mmH₂O. All antibodies related to autoimmunity were negative.

Abdominal echocardiography showed no stenosis of the renal arteries. T₂-weighted and fluid-attenuated inversion recovery (FLAIR) MR imaging demonstrated diffuse hyperintense areas in the brainstem and cerebellum, and subcortical lesions in the right frontal lobe and bilateral basal ganglia (Fig. 1). Diffusion-weighted MR imaging detected no signal abnormalities in these regions. MR angiography and MR venography found no abnormalities.

The patient was treated with antihypertensive agents (nifedipine 20 mg/day, atenolol 50 mg/day) and intravenous injection of nicardipine hydrochloride and methylpredonine pulse therapy (1000 mg/day) for 3 days, followed by oral prednisolone (60 mg/day). Brain MR imaging 1 week later showed marked improvement of the abnormalities in the brainstem and other areas. One month later, follow-up MR imaging demonstrated almost complete resolution of the brain lesions (Fig. 2). Reduction of blood pressure resulted in rapid improvement of clinical symptoms and blood cell counts (hemoglobin 12.9 g/dl, platelets $51.7 \times 10^4/\mu\text{l}$), but his

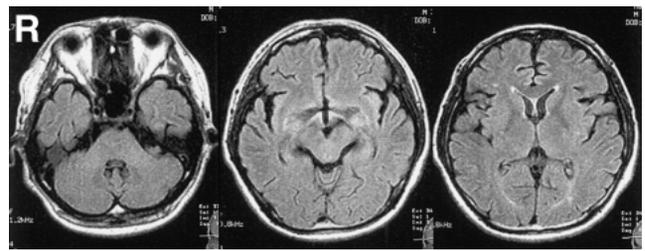


Fig. 2 Case 1. Fluid-attenuated inversion recovery magnetic resonance images 1 month later demonstrating almost complete resolution of the lesions.

visual disturbance and renal dysfunction were still present after 3 months (creatinine 2.6 mg/dl, BUN 33 mg/dl).

Renal biopsy performed 3 months after admission revealed onion-skin lesions of endothelial cells in the renal arterioles and focal crescentic glomerulonephritis, indicative of malignant hypertension.⁵⁾ The rapid resolution after controlling the high blood pressure and subsequent renal biopsy indicated a diagnosis of idiopathic malignant hypertension without underlying disorders such as thrombotic thrombocytopenic purpura (TTP) or pheochromocytoma.

Case 2: A 52-year-old woman with poorly controlled hypertension presented with altered mental state preceded by a 1-week history of headache. Blood pressure on admission was 200/130 mmHg, heart rate was 96 beats/min, and body temperature was 36.5°C. The patient was drowsy and unable to follow commands, but other neurological findings were normal. Fundoscopic examination showed hypertensive retinopathy without papilledema (Keith-Wagener grade III). Laboratory testing yielded the following results: hemoglobin 11.3 g/dl, platelets $23.9 \times 10^4/\mu\text{l}$, and C-reactive protein 0.73 mg/dl. Serum electrolyte levels were: Na 140 mEq/l, K³ 6 mEq/l, and Cl 99 mEq/l. Renal function was slightly disturbed (creatinine 1.48 mg/dl, BUN 23 mg/dl). Plasma renin activity was 8.0 ng/ml/hr and aldosterone level was 90 pg/ml. Serum epinephrine level was 92 pg/ml and norepinephrine level was 420 pg/ml. No autoimmune-related antibodies were detected.

Electrocardiography revealed left ventricular hypertrophy. T₂-weighted and FLAIR MR imaging showed extensive hyperintense areas in the brainstem and cerebellum, as well as in the periventricular areas and basal ganglia (Fig. 3 upper and middle row). Diffusion-weighted MR imaging showed the pons and cerebral lesions as normal intensity.

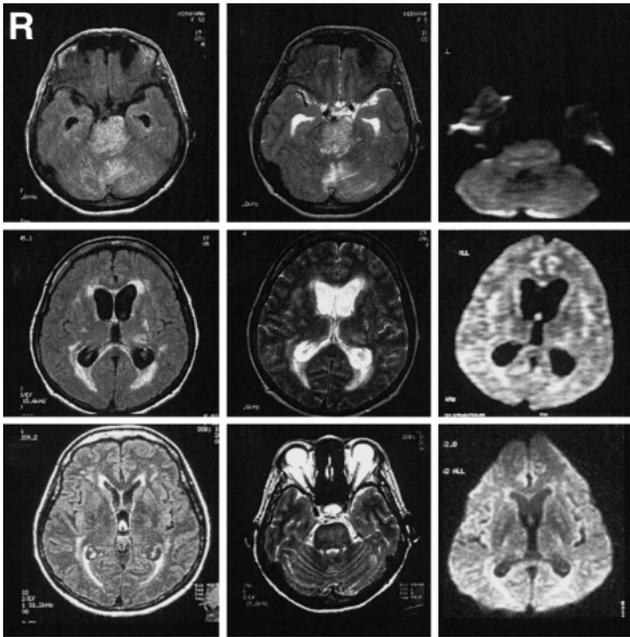


Fig. 3 Case 2. Magnetic resonance (MR) images on admission showing abnormal hyperintense areas in the brainstem and cerebellum (upper row) on the fluid-attenuated inversion recovery (left column) and T₂-weighted images (center column), which appeared as normal intensity on the diffusion-weighted images (right column), and hyperintense areas in the periventricular areas and basal ganglia but without parieto-occipital lesions (middle row), and MR images after treatment of hypertension showing resolution of the signal abnormalities (lower row).

Her consciousness was markedly improved during the 1st week of treatment with antihypertensive agents (nilvadipine 8 mg/day, candesartan cilexetil 16 mg/day) and intravenous injection of nicardipine hydrochloride and glycerol without prednisolone. The lesions completely resolved within 2 weeks (Fig. 3 lower row). Visual acuity recovered completely within 1 month and renal function normalized (creatinine 1.16 mg/dl, BUN 18 mg/dl).

Discussion

The present cases illustrate the characteristic distributions of imaging abnormalities in the brainstem, cerebellum, left middle cerebellar peduncle, frontal lobe, and basal ganglia attributable to hypertensive encephalopathy. Such findings may suggest a diagnosis of brainstem encephalitis, but the normal cerebrospinal fluid findings exclude

such a condition. Brainstem infarction can be excluded by the absence of residual symptoms. Central pontine myelinolysis may produce a similar radiological picture,¹⁸⁾ but no electrolyte abnormalities were noted at any time during the clinical course in either patient. An underlying condition such as TTP had been suspected in Case 1 on admission. Endothelial injury associated with malignant hypertension, which promotes hemolysis, platelet destruction, and renal failure, may result in a clinical picture similar to that of TTP. No causative disorder such as renovascular hypertension or pheochromocytoma was identified in either patient.

The pathophysiological mechanisms of RPLS are considered to be edematous in nature, as the neurological and imaging abnormalities typically resolve within a few weeks.¹⁷⁾ Diffusion-weighted MR imaging may be used to determine whether edema is cytotoxic or vasogenic in origin.¹⁶⁾ Diffusion-weighted MR imaging demonstrated isointense areas corresponding to hyperintense lesions on T₂-weighted MR imaging in both patients, indicating that the lesion did not involve increased intracellular fluid content, but rather accumulation in the extracellular spaces associated with vasogenic edema. The reversibility of the lesions and the absence of major brainstem symptoms support the hypothesis of vasogenic edema without tissue necrosis. This combination resulted in the discrepancy between the absence of clinical findings and the obvious radiological findings of hypertensive encephalopathy, expressed as “the patient looking better than the MR images.”⁴⁾

Both our patients had hypertensive brainstem encephalopathy (HBE) without parieto-occipital lesions.⁴⁾ Similar MR imaging distributions of lesions in the brainstem with hypertensive encephalopathy but in the absence of parieto-occipital lesions have been reported in 16 patients (Table 1).^{4,6,8,9,11-13,19,20)} Lesions are not limited to the parieto-occipital lobes, but are less common in the brainstem, cerebellum, frontal lobe, and basal ganglia. The brainstem is one of the principal sites affected by hypertensive encephalopathy.¹⁴⁾ Gray matter regions such as the basal ganglia are also involved. The past episode of hypertension was involved in nine of the 15 patients. No cases of HBE associated with immunosuppressive drugs, interferons, or eclampsia have been reported. All patients had acute renal failure causing volume overload and resulting in brain edema. The elevation of plasma renin activity may indicate sympathetic overactivity. Moreover, the elevated renin activity may contribute to changes in vascular permeability.

RPLS, PRES, or HBE is very impressive as an

Table 1 Summary of patients with hypertensive brainstem encephalopathy without parieto-occipital lesion

| Author (Year) | Age (yrs) | Sex | HT | Symptom | CD | OF | Involved regions on MR imaging | | | | Blood pressure (mmHg) | |
|--|-----------|-----|----|-------------|----|--------|--------------------------------|------------|---------|-----|-----------------------|-----------|
| | | | | | | | Basilar | | Carotid | | Systolic | Diastolic |
| | | | | | | | BS | Cerebellum | SWM | BG | | |
| Katsumata et al. (1993) ¹¹⁾ | 63 | M | ND | headache | + | KW IV | * | * | * | 270 | 170 | |
| Chang and Keane (1999) ⁴⁾ | 54 | F | + | headache | + | KW IV | * | * | * | 210 | 144 | |
| | 49 | M | + | headache | + | ND | * | * | * | 211 | 156 | |
| | 22 | F | - | convulsion | + | ND | * | | | 213 | 133 | |
| Hasegawa et al. (2000) ⁹⁾ | 48 | M | - | ataxia | + | KW IV | * | | * | 210 | 116 | |
| de Seze et al. (2000) ⁸⁾ | 41 | M | + | headache | - | KW IV | * | | * | 220 | 120 | |
| | 52 | F | - | headache | - | KW IV | * | | * | 220 | 150 | |
| | 50 | M | + | headache | + | KW IV | * | * | * | 250 | 130 | |
| Matsumoto et al. (2000) ¹²⁾ | 50 | M | + | headache | + | KW IV | * | * | * | 250 | 130 | |
| Morello et al. (2001) ¹³⁾ | 36 | M | + | headache | - | KW III | * | * | * | 280 | 180 | |
| Chu et al. (2001) ⁶⁾ | 48 | F | - | headache | - | KW IV | * | * | * | 180 | 110 | |
| Thambisetty et al. (2003) ¹⁹⁾ | 38 | M | + | hemiparesis | - | KW III | * | | | 210 | 130 | |
| | 61 | M | - | hemiparesis | - | ND | * | | * | 219 | 138 | |
| | 46 | F | + | hemiparesis | + | KW IV | * | | * | 203 | 139 | |
| Yasuda et al. (2003) ²⁰⁾ | 45 | M | + | hemiparesis | + | KW III | * | | * | 250 | 160 | |
| Present Case 1 | 35 | M | - | headache | - | KW IV | * | * | * | 180 | 118 | |
| Present Case 2 | 52 | F | + | headache | + | KW III | * | * | * | 200 | 130 | |

Mean age was 46 ± 11.1 years. Mean blood pressure was 222/139 mmHg. Fourteen of the 16 cases including our patients had lesions supplied by the carotid artery. BG: basal ganglia, BS: brainstem, CD: consciousness disturbance, HT: past history of hypertension, KW: Keith-Wagener grade, MR: magnetic resonance, ND: no description, OF: optic fundus, SWM: subcortical white matter.

indicative finding in the MR imaging of patients with malignant hypertension. However, such findings do not mean that lesions are limited to the posterior circulation. Fourteen of the 16 patients (87.5%) with HBE without parieto-occipital lesions also had lesions in the territory of the carotid artery. Our data indicate that anterior circulation structures are also frequently involved in patients with HBE.⁷⁾

No clear explanation has been suggested for the prominence of brainstem lesions over occipital lesions. Both parieto-occipital and brainstem lesions are within the territory of the vertebrobasilar artery and its branches. The posterior circulation has significantly less sympathetic innervation than the carotid circulation.²⁾ More severe and longer-lasting malignant hypertension is unlikely to cause predominantly infratentorial lesions rather than supratentorial lesions. Two mechanisms have been proposed: extensive fluid leakage in the brainstem may spare the parieto-occipital region in the distal portion of the vertebrobasilar artery system; or relatively rich sympathetic nerve innervations occur in the parieto-occipital region, which is mainly supplied via the posterior communicating artery (PCoA) from the anterior circulation. A well-developed PCoA is known as a fetal-type PCoA. If a fetal-type PCoA has tight sympathetic innervation similar to that of the anterior circulation, the parieto-occipital region will

be protected from brain edema caused by increased blood pressure. Nevertheless, MR angiography showed Case 1 had a non-fetal-type PCoA and Case 2 had a fetal-type PCoA. No description of the PCoA has been reported for patients with HBE or RPLS, and further studies are necessary to address the role of the PCoA in those patients.

Case 1 received prednisolone therapy in order to reduce brain edema and stabilize the impaired blood-brain barrier, but Case 2 did not receive prednisolone. An autoimmune disorder such as TTP had been initially suspected in Case 1. Prednisolone is considered to reduce tumor-associated vasogenic edema, but displays mineralocorticoid activity that increases circulating fluid volume and may exacerbate clinical manifestations of neurological deficits. Administration of prednisolone remains controversial and is poorly defined for the treatment of hypertensive encephalopathy. Further studies on the effects of glucocorticosteroids in the treatment of vasogenic edema are warranted.

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