Clinical and Radiological Features of Brainstem Variant of Hypertensive Encephalopathy

Abstract

Background: The "posterior reversible leukoencephalopathy" syndrome, generally observed in the setting of severe, acute hypertension, often correlates with radiological abnormalities that involve the occipital lobes and other hemispheric areas. A predominant involvement of the brainstem in this syndrome is rare.

Patients: We report three patients with previously known or newly diagnosed severe hypertension, who presented with a combination of headache and visual disturbances, along with diffuse abnormalities demonstrated on magnetic resonance imaging in the brainstem and cerebellum. The absence of clinical features of brainstem or cerebellar dysfunction contrasted with the severity of the radiological abnormalities.

Conclusions: We discuss the pathophysiological, clinical, and radiographic features of this variant of posterior reversible leukoencephalopathy.

Keywords: Hypertensive encephalopathy, brain stem posterior reversible encephalopathy, vasogenic edema, papilledema

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Hypertensive encephalopathy is a syndrome characterized by headache, cortical blindness, seizures, depression of consciousness, and papilledema, in the setting of severe hypertension.[1] The imaging finding consists of vasogenic edema that affects predominantly the white matter of the cerebral hemispheres, especially posterior regions.[2] These features, along with the reversible nature of most of the clinical and radiological features subsequent to therapeutic control of hypertension led to the labeling of this condition as the "posterior reversible leukoencephalopathy" syndrome.[3] A variant of this syndrome with predominant involvement of the brainstem has rarely been reported. We present three cases and discuss pathophysiological, clinical, and radiographic features of this variant.

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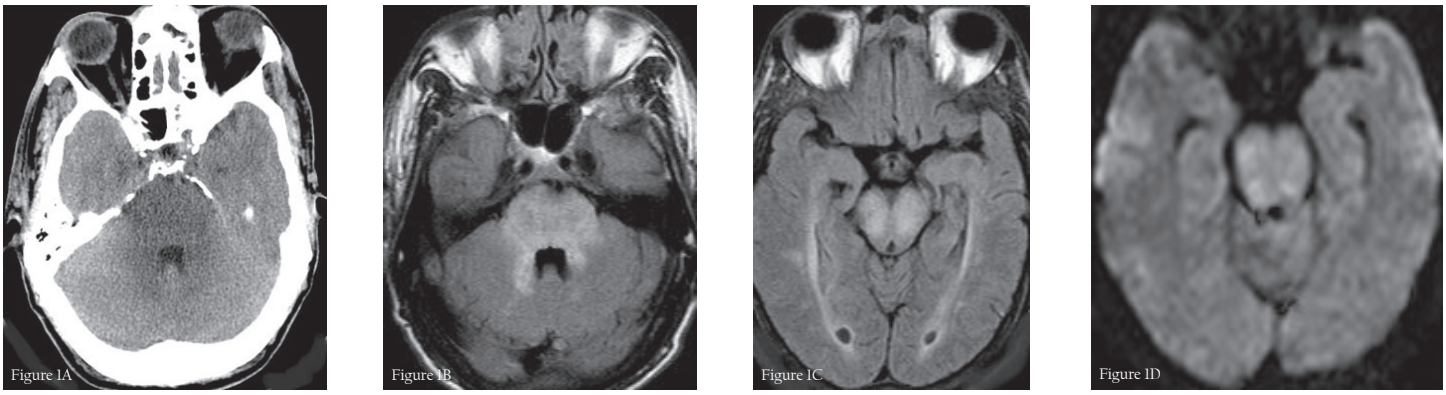

Figure 1: Head CT scan without contrast showing diffuse hypoattenuation in the pons (A). MRI FLAIR sequence images demonstrating diffusely increased signal in pons (B) and midbrain (C) and DWI sequence showing slightly increased signal in the pons (D).

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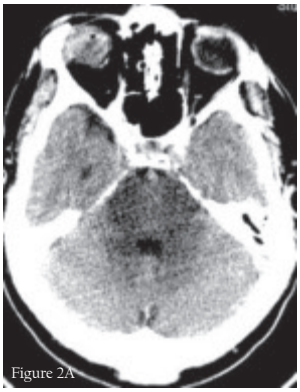
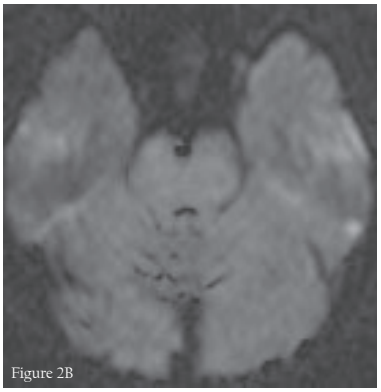
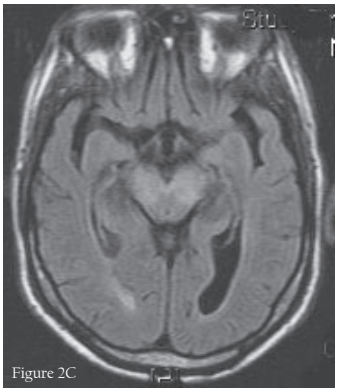
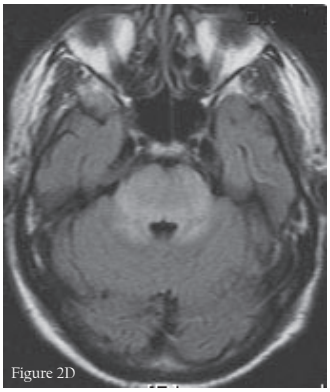








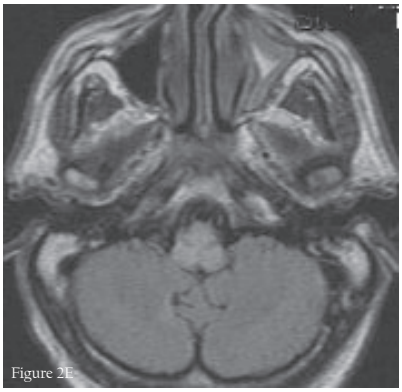


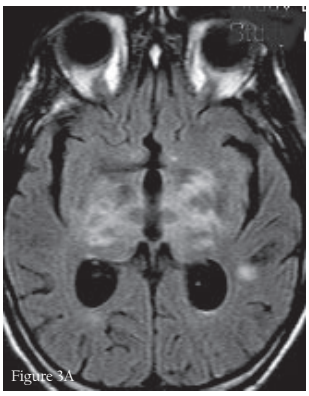
Figure 2: Head CT without contrast demonstrating hypoattenuation in the pons (A). MRI DWI sequence image demonstrating minimal increase in signal in the pons (B), and FLAIR images showing increased signal in the midbrain (C), pons (D), and medulla (E).

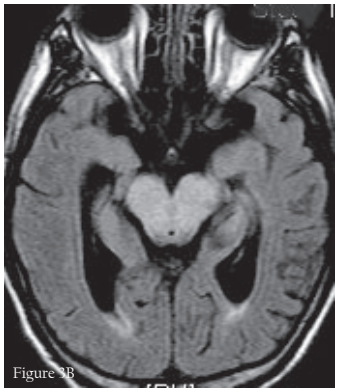
Case presentations

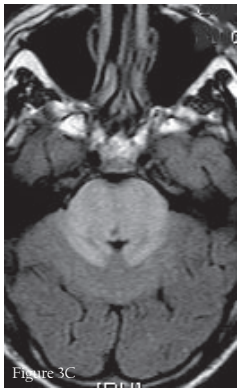
Patient 1. A 51 year old man with history of poorly controlled hypertension, hyperlipidemia, and substance abuse, presented after a few hours of sudden onset of unsteady gait. Physical examination revealed blood pressure (BP) of 250/150 mm Hg, unsteady gait, and mild bilateral limb ataxia. Laboratory data showed mild renal impairment (creatinine 1.4 mg/dL and blood urea nitrogen [BUN] 22 mg/dL) and anemia (hemoglobin 11.7 g/dL); urine was positive for cocaine and opiates. A computed tomographic (CT) scan of the head showed diffuse hypoattenuation throughout the whole extent of the pons (Fig. 1A). Magnetic resonance imaging (MRI) fluid attenuation inversion recovery (FLAIR) sequences demonstrated extensive increased signal in the pons and midbrain (Fig. 1B, C), in addition to the thalamus and cerebellar white matter bilaterally. On diffusion weighted (DWI) sequences, there was slightly increased signal in the pons (Fig. 1D), without corresponding abnormalities in the apparent diffusion coefficient (ADC) maps. Magnetic resonance angiography (MRA) of the intra- and extra-cranial circulation was normal. A transthoracic echocardiogram (TTE) showed severe concentric left ventricular hypertrophy with preserved ejection fraction. The patient's symptoms and examination rapidly improved with control of the hypertension, and he was discharged home three days later.

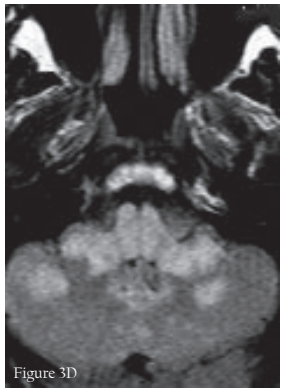
Patient 2. A 50 year old man with known history of uncontrolled hypertension, bipolar disorder, and alcohol dependence, presented with a few days history of headache and decreased vision bilaterally. On examination, he had bilateral visual acuity of 20/200, papilledema, and retinal hemorrhages, without any other findings on neurological examination. CT scan of the head showed diffuse hypoattenuation throughout the pons (Fig. 2A). MRI of the brain showed minimally increased signal in the pons on DWI sequences (Fig 2B), without abnormalities on ADC maps, while T2 and FLAIR sequences showed increased signal diffusely in the midbrain, pons, and medulla (Fig. 2C, D, E), without any enhancement after intravenous gadolinium infusion. The diagnostic work-up for secondary causes of hypertension, including CT scan of the abdomen, renal ultrasound, thyroid function tests, plasma renin and aldosterone levels, and 24 hour urine catecholamine levels, was unrevealing. A TTE showed severe concentric left ventricular hypertrophy with grade I diastolic dysfunction and normal ejection fraction. Despite aggressive management of BP, the visual acuity did not improve.

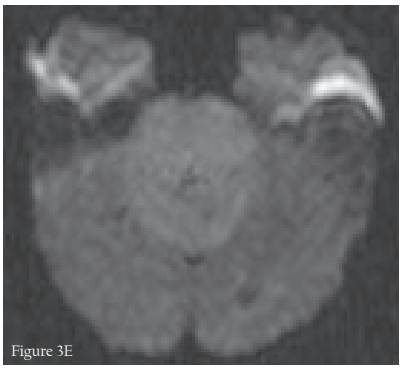
Patient 3. A 47 year old man without known medical illnesses presented with history of three weeks of headache of gradually increasing severity, nausea, and vomiting. Examination showed a BP of 240/120 mm Hg and mildly edematous optic discs with preserved visual acuity and fields; neurological examination was otherwise unremarkable. Laboratory tests revealed creatinine of 3.17 mg/dL and BUN of 45 mg/dL; his urine tested positive for cocaine. Head CT scan without contrast showed hypodensities in the thalami, midbrain, pons, medulla and cerebellum, with effacement of the fourth ventricle and a mild degree of supratentorial hydrocephalus. Initial MRI without contrast showed T2 and FLAIR hyperintensities in the aforementioned

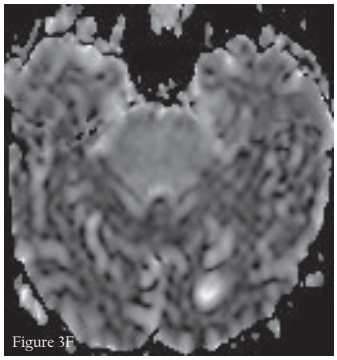












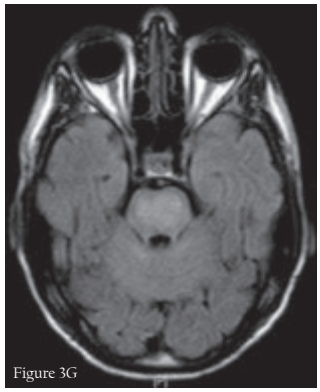


Figure 3: FLAIR MRI sequence images showing increased signal in the thalami (A), midbrain (B), pons (C), medulla, and cerebellum (D); mildly increased signal is identified in the pons on DWI sequence (E) and ADC maps (F), consistent with vasogenic edema. Follow-up FLAIR MRI one week later showed marked resolution of abnormalities (G).

areas (Fig. 3A, B, C, D), in addition to the internal capsule and the basal ganglia bilaterally; DWI sequences showed mildly increased signal in the affected areas (Fig. 3E), and the corresponding ADC maps showed increased signal (Fig. 3F). These findings were consistent with vasogenic edema.[4] A TTE showed moderate to severe concentric left ventricular hypertrophy with grade I diastolic dysfunction and preserved ejection fraction. Renal ultrasound was unrevealing. Follow-up brain MRI with intravenous contrast one week later showed marked improvement (Fig. 3G). The patient's headache resolved with management of the hypertension, and he was discharged home four days later, without residual deficits.

Discussion

Among patients presenting with hypertensive emergencies, up to 16% have hypertensive encephalopathy,[5] with headache, seizures, decreased level of consciousness (including coma), visual disturbances, and papilledema as its main clinical features. The posterior reversible leukoencephalopathy syndrome (PRES)[3] is the clinico-radiological syndrome consisting of clinical features of hypertensive encephalopathy accompanied by reversible vasogenic subcortical edema without infarction on neuroimaging. It is typically seen in the setting of a severe, acute rise in BP, including conditions such as eclampsia, pheochromocytoma, exposure to sympathomimetic drugs (such as cocaine), glomerulonephritis, autonomic instability (in patients with spinal cord injuries, Guillain-Barré syndrome), and treatment with erythropoietin.[1] PRES has also been documented in patients on immunosuppressive therapy, without concomitant hypertension.[3] Although the radiological abnormalities predominantly involve the parieto-occipital areas, they often extend into the basal ganglia, thalamus and, rarely, the brainstem.[6] In a large series, 22 (58%) of 38 episodes of PRES involved brainstem and/or cerebellum on neuroimaging.[7] A literature review of 26 reported cases of patients with brainstem involvement[8] suggested that most patients are men in the fourth decade (as opposed to the fifth or sixth decade presentation of typical PRES cases). Previously or newly diagnosed uncontrolled hypertension is the predominant mechanism (no case related to immunosuppression has been reported).[8] The presentation consists of symptoms of increased intracranial pressure and seizures, and the neurological examination reveals bulbar, cerebellar, and/or long tract signs in about one-third of the cases, with retinal abnormalities in a similar proportion of cases.[8-10] Most patients, including two of our cases, improve clinically and radiologically within a period of days to a few weeks. However there have been reports of a chronic clinical course,[11] as well as recurrent brainstem involvement.[12] In children, Prasad et al. reported instances of PRES with brainstem predominance in 2 of 19 cases, also followed by clinical and radiological improvement after BP control.[13]

The relative selectivity for the brainstem in these cases of PRES remains unexplained. In humans, the sympathetic nerves for the intracranial vasculature course along the carotid and the vertebral plexuses. The former arise from the superior cervical ganglion.

The latter originate from the vertebral ganglion (between the middle and inferior cervical ganglia), with a large branch that arises from the stellate ganglion, while smaller branches originate from the superior and middle cervical ganglia.[14] From anatomical studies of fetal brains between 19 and 23 weeks of gestation, Edvinsson et al.[15] documented more advanced development of the adrenergic system in the rostral intracerebral vasculature than in the brainstem area. This observation suggests that the innervation is generally more developed in the anterior circulation, implying a lesser degree of development (and functional capability) of the adrenergic vascular system in the posterior circulation.[15] In turn, this anatomical difference in vascular sympathetic innervation may translate into different degrees of permeability of the blood-brain barrier between the two vascular systems of the brain.

Sympathetic mediated vasoconstriction maybe protective during acute hypertension and increased perfusion pressure.[16] Due to the differences in sympathetic innervation between the anterior and posterior circulation, the latter is thought to be more vulnerable to the excessive perfusion pressure that results from systemic hypertension.[17] The differential vulnerability may explain the posterior cortical predominance of PRES,[18] but preferential involvement of the brainstem is more difficult to explain. Proposed mechanisms have included possible "sparing" of the distal vertebro-basilar system due to excessive fluid leakage in the brainstem and a potentially protective effect of "collateral" sympathetic innervation to the occipito-parietal areas through a dominant posterior communicating artery.[19] Also, approximately 40% of the reported patients with this syndrome were not known to have chronic hypertension, leading to the speculation that a very rapid increase in BP may result in vasogenic edema predominantly in the brainstem.[9] In support of this view, animal studies have shown that mild acceleration of hypertension produced edema predominantly in the supratentorial white matter, while severe BP elevations produced vasogenic edema infratentorially, as well as in the basal ganglia and thalamus.[20] A greater involvement of the brainstem and deep structures at higher BP maybe related to presence of small arteries that originate directly from larger trunks such as the middle cerebral artery and the basilar artery or its branches and thus subjected to high perfusion pressure levels. A severe elevation of BP may be required for a breakdown of the blood-brain barrier to occur in this location.[21] The presence of sympathomimetic drugs in the urine toxicology screen in 2 of our 3 patients suggests a scenario of rapidly accelerated hypertension.

DWI in the early stages of PRES usually shows no restricted diffusion, while the ADC maps, T2-weighted and FLAIR sequences typically show increased signal consistent with vasogenic edema. If the BP remains severely elevated, infarction with or without intraparenchymal hemorrhages may develop.[7] In one study,[4] DWI sequences showed high signal intensity foci in 27% of the cases in areas where the ADC values were either normal or slightly elevated. The relative normalization of ADC values was termed "pseudo-normalization," and thought to result from intravoxel averaging of values in areas of cytotoxic and vasogenic edema. The finding may indicate onset of irreversible changes and transition from vasogenic to cytotoxic edema in PRES. Post-contrast enhancement is absent in more than two-thirds of patients with PRES.[4] One possible explanation is that the severity of the blood-brain barrier disruption in hypertensive encephalopathy may differ from that seen in infections, inflammatory conditions such as multiple sclerosis, and in brain tumors.[22]

The differential diagnosis of this rare combination of clinical and radiological findings includes brainstem infarction, osmotic myelinolysis, infectious rhombencephalitis, post-infectious or autoimmune encephalomyelitis, post-radiation changes, and tumor (glioma, lymphoma). The onset and evolution of the symptoms, its association with severe hypertension, the lack of other features supportive of the aforementioned conditions, the characteristic findings in the neuroimaging, the prominent disassociation between the clinical and the radiological picture, and the rapid and often complete recovery with normalization of the BP, all facilitate correct diagnosis and avoidance of unnecessary interventions and treatments (e.g. brain biopsy, steroids, antibiotics, etc.).

Conclusion

Brainstem hypertensive encephalopathy is a rare variant of PRES. Early diagnosis and urgent BP management may prevent potential occurrence of secondary ischemic and hemorrhagic complications in the affected areas of the brain.

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