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Brain Edema from a Hypertensive Emergency: A History Before the PRES Designation

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The diagnosis of posterior reversible encephalopathy syndrome (PRES) is both commonly made and not considered. Far before the introduction of the moniker PRES, clinicians and pathologists linked hypertension to damage of the brain, particularly when blood pressure was out of control. White matter abnormalities were seen earlier in eclampsia and particularly with cyclosporine-induced leukoencephalopathy [1, 2], raising the possibility that immunomodulation was involved in the pathogenesis. As early as 1988, reports surfaced on reversible cortical and white matter lesions on magnetic resonance imaging (MRI) acquisitions [3], but a report on white matter brain edema on a computed tomography (CT) scan in severe hypertension was already known in 1980 [4]. There is an interesting history of severe hypertensive encephalopathy, a condition seen regularly in intensive care units.

Early Descriptions

Hypertensive encephalopathy was best documented in an article by Oppenheimer and Fishberg [5] (Fig. 1), which described the setting of acute glomerulonephritis, seizures, coma, and focal findings such as hemiplegia and aphasia. Their major contribution was to distinguish it from acute uremia. Patient blood pressures were 200 mm Hg systolic and 110 mm Hg diastolic on average and seizures, including focal seizures, were the predominant presentation. A clearer relationship between rising blood pressure and seizures was found. They also found blindness, which they called *uremic amaurosis.* Their pathology revealed that patients, in fact, had brain edema. They noted that similarities were found with lead encephalopathy being associated with hypertension, which manifested similar symptoms. The mechanism here was considered cerebrovasoconstriction, but they also considered cerebral edema because they observed "fluid pressed through the capillary walls." They specifically pointed out that acute uremia did not have any brain edema which would distinguish between these symptoms of "hypertensive encephalopathy and acute uremia." They also described a case of recurrent hypertensive encephalopathy; repeated many times with different presentations that appeared within 2 years.

Chester et al. [6] published another pre-CT, pre-MRI study from the Department of Medicine and Neuropathology and Neurology at Case Western Reserve University School of Medicine (the senior author was the legendary Maurice Victor). Notably, they felt that cerebral edema was unimportant in the pathogenesis of hypertensive encephalopathy because of the absence of edema in most of their cases. Their neuropathologic changes showed parenchymal microinfarcts and petechial hemorrhages in their series of 20 patients who died of malignant hypertension, defined as a diastolic blood pressure of 130–160 mm Hg. Most notably, the vascular and parenchymal lesions were multiple and distributed diffusely, frequently in the brainstem (basis pontis) but also in the basal ganglia and diencephalon, cerebral white matter, cerebral cortex, and spinal cord. These findings suggested that the manifestations of white matter brain edema were part of the spectrum and occurred early in the process (Fig. 2) ;brain edema early, microinfarcts and microhemorrhages later.

The acute effect of hypertensive emergency on the brain became better characterized after Hinchey et al.

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HYPERTENSIVE ENCEPHALOPATHY *

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In the course of acute glomerulonephritis and less commonly in other varieties of chronic interstitial nephritis, there may occur acute episodes of cerebral phenomena, such as epileptiform convulsions, coma, headache, amaurosis, hemiplegia and aphasia. In the past, these episodes were generally included under the concept of uremia and were termed acute uremia. Since the beginning of the present century, convincing evidence that these cerebral episodes are not uremic in nature has gradually accumulated. This evidence will be summarized later in the paper. It has become clear that these cerebral symptoms are correlated with hypertension, being a manifestation of circulatory disturbances in the brain consequent on the hypertension. For this reason, we have termed the cerebral syndrome the hypertensive encephalopathy. The nature of the hypertensive encephalopathy is well illustrated in the following case. We have had the patient under continuous observation over a period of twenty months at the Mount Sinai and Montefiore Hospitals.

Fig. 1 Title page

[7] from the New England Medical Center published in 1996 a large series of CT scans and MRIs from 15 patients evaluated from 1988 to 1994. These patients presented with "altered mental functioning," seizures, and loss of vision, which were associated with edema in the posterior region of the cerebral hemispheres but also in the brainstem and cerebellum. Approximately half the patients were on immunosuppressive therapy after transplantation or as treatment for aplastic anemia. Three had eclampsia for acute hypertensive encephalopathy associated with renal disease. They named the disorder *reversible posterior leukoencephalopathy syndrome* as a better explanation for the more common moniker, hypertensive encephalopathy. They hypothesized a multifactorial cause but predominantly explained it by brain capillary leak syndrome related to hypertension, which could involve the cytotoxic effect of immunosuppressive agents on the vascular endothelium.

However, their designation was immediately challenged. The radiologist Richard Schwartz felt the term was inaccurate because it was not always reversible [8], to which they snappishly countered, "The word reversible means 'able to be reversed.' This does not mean that the condition will always be reversed. Reversibility is contingent on controlling the condition that caused the encephalopathy." What is not commonly known is that patients have died of increased intracranial pressure that was associated with severe brain edema and hemorrhages. Schwartz suggested "hyperperfusion encephalopathy," but that term, albeit physiologically correct, would be unworkable knowing that such a syndrome already exists after

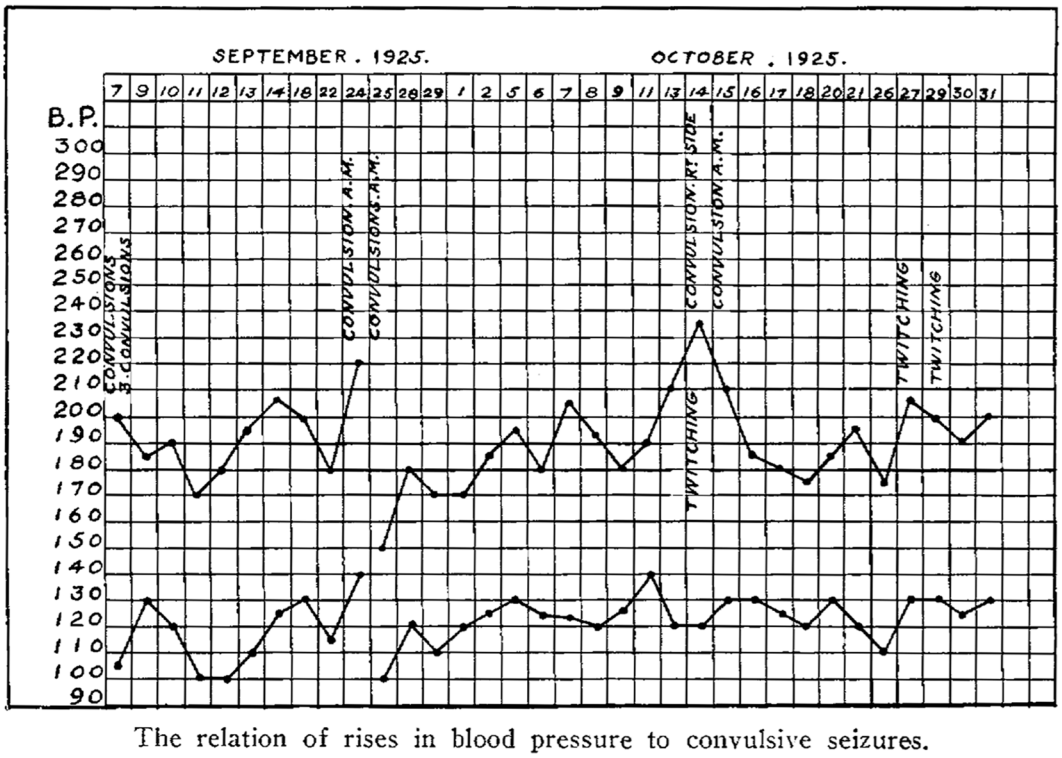

Fig. 2 Blood pressures and related symptoms. B.P., blood pressure

carotid endarterectomy. Several years later, in 2000, cortical lesions were found on MRI acquisitions, and Casey and colleagues in 2000 implied that the prefix, "leuko," was not entirely correct. This led to recoining it as *posterior reversible encephalopathy syndrome* and the introduction of the acronym, PRES [9]. Many subcortical areas other than the posterior regions are involved with frontal and temporal lobe edema just as typical. Brainstem, basal ganglia, and, in particular, cerebellum involvement is seen in at least a third of the cases [10]. Reversibility is common, but regions with restricted diffusion on MRI acquisitions or on areas of hemorrhage mark strokes and irreversible injury. Intraparenchymal, sulcal subarachnoid, and petechial hemorrhages can be seen, but this was already noted by neuropathologists when the entity was still called hypertensive encephalopathy. Nevertheless, the insertion of encephalopathy in the moniker PRES remains problematic; some patients are confused because they cannot see (cortical blindness) or are postictal (generalized tonic–clonic seizures). Further, not every patient with PRES is encephalopathic. Focal findings, uncharacteristic of a global encephalopathy, are not infrequent (5–15% of cases). This clinical entity is therefore much more diverse in presentation and thus clinically more difficult to diagnose and difficult to fully encompass in an acronym. However, the term PRES was an immediate attention grabber, and it did stick.

I suspect many patients previously (and perhaps even now) diagnosed with "toxic-metabolic encephalopathy" may have PRES. MRI is often needed to clinch the diagnosis, but it is most useful to exclude alternative diagnoses. Many clinicians believe that PRES cannot be diagnosed without seeing the characteristic pattern of vasogenic edema on MRI acquisitions, but that is not true. MRI findings can be atypical, the extent of edema may not correlate with the severity of the clinical presentation, and some patients presenting with typical clinical features of PRES (altered consciousness, cortical blindness, seizures, and acute hypertension) have a normal MRI result and still follow the typical evolution of PRES.

Current Knowledge

Posterior reversible encephalopathy syndrome is a major manifestation in intensive care units in patients who are

hypertensive or have a sepsis syndrome. Hemorrhage in the areas of vasogenic edema occurs in 10–20% of cases, and there may be mild subarachnoid hemorrhage. PRES can be expected with a sudden surge of hypertension, poor kidney function, autoimmune disease, and evolving gram-positive sepsis. Neurointensivists have induced it by increasing blood pressure with vasopressors in aneurysmal subarachnoid hemorrhage [11] and may have driven up the blood pressure even more when the patient did not respond. In any unexplained "altered mental status" in a patient with advanced kidney disease (with or without hypertensive urgency), it is important to consider PRES and to pursue the diagnosis. What has become clear over the years is that PRES is a major manifestation of acute renal disease and end-stage renal disease. Mostly, PRES is related to major flare-ups of hypertension or new presentation of severe hypertension, but this relationship is not necessary to see this complication. PRES can be expected with a sudden surge of hypertension, poor kidney function, autoimmune diseases, and evolving gram-positive sepsis. When the cerebral perfusion pressure exceeds 150 mm Hg, there is no further possibility for arterial vasoconstriction, and arteries come under significant pressure. When the mean arterial blood pressure increases above this upper limit of autoregulation, the resistance arteries are unable to maintain vasoconstriction, and a so-called sausage stringing, with dilated segments and local areas of constriction, will eventually lead to more dilatation of the arterial bed and a passive increase in cerebral blood flow. These arteries may leak, and vasogenic brain edema may occur.

Hinchey et al. [7] concluded their responses to the letters to the editor with "Once the medical community becomes aware of this condition, there should be many new insights into its pathogenesis." That is what happened since their publication, and the new abbreviation "PRES" can be found in thousands of PubMed titles.

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