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Pathophysiology of "Reverse" Edema in Global Cerebral Ischemia

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A small percentage of patients who suffer a global cerebral hypoxic/ischemic event develop reversal of the normal density relationships of gray and white matter on CT. CT and pathologic findings in the three cases presented indicate that this phenomenon appears to result from distension of deep medullary veins secondary to partial obstruction of venous outflow from elevated intracranial pressure. The "reverse" edema sign indicates a severe hypoxic/ischemic injury to the brain and has a poor clinical prognosis.

A peculiar reversal of the normal densities of gray and white matter occurs in a small percentage of patients who have suffered a diffuse hypoxic/ischemic injury to the brain. This phenomenon has been previously termed the "reversal" sign [1]. The purpose of this article is to (a) report three patients who demonstrated such a finding on CT acquired after a diffuse hypoxic/ischemic insult; (b) describe the pathologic basis for its appearance; and, (c) propose an etiologic mechanism by which this change occurs.

Case Reports

Case 1

A 2½-year-old boy in good health was noted, on the morning of admission, to slump over on his right side after eating breakfast. His mother attempted cardiopulmonary resuscitation (CPR). When the paramedics arrived, he was apneic and pulseless. Upon admission to the emergency room he was hypotonic and areflexic, with no spontaneous movements. His pupils were fixed and dilated. There was no obtainable blood pressure and the arterial blood gas showed a pH of 6.65. He was resuscitated and placed on life support systems. There was an approximately 2 to 2½-hour period of hypotension until a recordable blood pressure was obtained. Blood pressure was maintained at normal levels during the remainder of the hospitalization. Over the next 24 hr his neurologic status (clinically brain dead) remained unchanged. After a radionuclide brain scan showed no evidence of flow on the day after admission, the patient was taken off the respirator. A nonenhanced CT scan done approximately 2 hr after admission showed diffuse cerebral swelling with marked hypodensity in the basal ganglia and cerebral cortex and prominent hyperdensity in the cerebral white matter (33–35 H) (Fig. 1). The brain grossly appeared swollen and diffusely necrotic on postmortem examination. Gross sections of the brain showed discoloration of the cerebral white matter and multiple distended deep medullary veins (Fig. 1C). Microscopic sections showed diffuse necrosis. Pickworth stains of sections from the frontal, temporal, and occipital regions showed distension of deep medullary veins by intact red blood cells (Fig. 1D). No distended vessels were identified in the cortex or basal ganglia and there was no evidence of cortical vein or dural sinus thrombosis.

Case 2

A 1-month-old girl was found (in her crib) on the morning of admission, cold, apneic, and pulseless. She was last noted to be moving approximately 30 min earlier. No CPR was
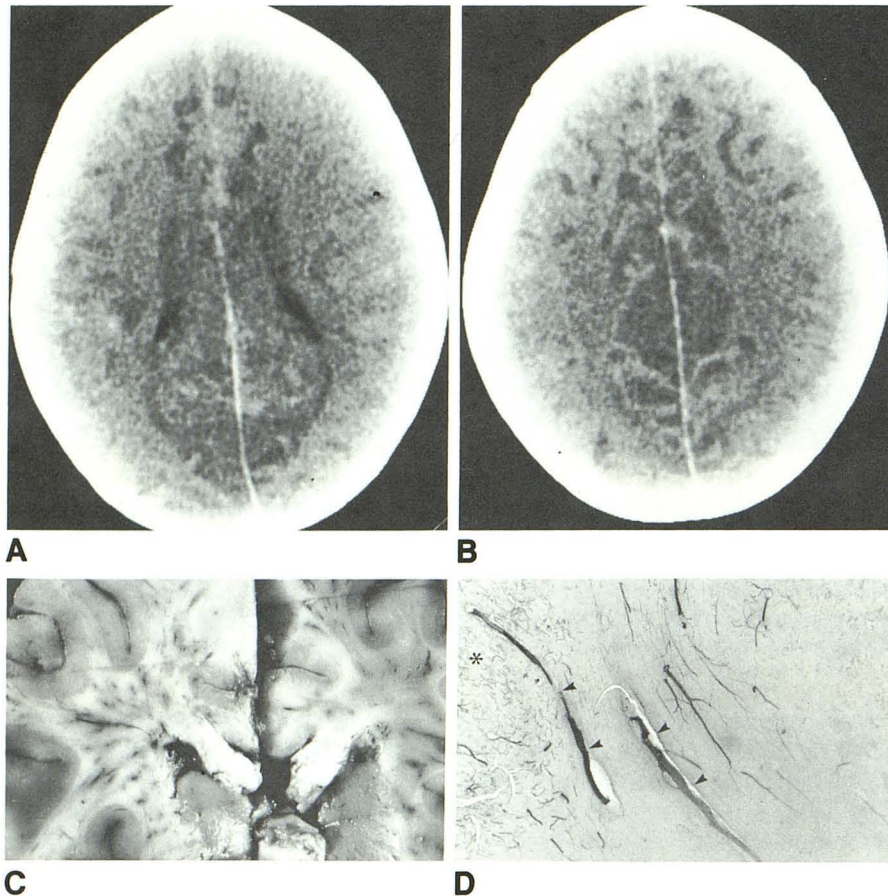
Fig. 1.—Case 1.
A and *B*, Noncontrast CT scans show diffuse increased density of deep cerebral white matter (33–35 H) and marked cortical edema.
C, Coronal section of brain at level of frontal horns shows distended vessels throughout deep white matter but not in cortex.
D, Microscopic section of frontal lobe (Pickworth stain) reveals distended medullary veins filled with red blood cells in deep white matter (*arrowheads*) and corticomedullary junction but not in cortex (*asterisk*).

attempted and the infant was driven by her parents to the emergency room. On admission she was apneic, pulseless, and nonresponsive. Arterial blood gas showed a pH of 6.9. She was resuscitated and placed on life support systems. There was an approximately 1½ to 2 hr period of hypotension prior to establishment of a normal blood pressure. Blood pressure was maintained at normotensive levels during the remaining hospitalization. A CT scan done approximately 1 hr after admission showed diffuse cerebral edema with decreased density of the cerebral cortex and compression of the ventricular system and subarachnoid spaces (Fig. 2). The cerebral white matter showed abnormal increased density measuring 30–35 H. Twenty-four hours after admission the child was declared brain dead and removed from the respirator.

Case 3

A 3-year-old girl was in a chronic care facility because of a spinal cord injury suffered 2 years previously. On the evening of admission the child had a prolonged seizure and a period of hypoxia and hypotension that lasted approximately 2½ hr. On admission to the hospital she was comatose with minimal response to noxious stimuli. A CT scan at the time of admission showed diffuse cerebral edema. There was abnormal hypodensity in the cortex and abnormal hyperdensity (30–33 H) in the cerebral white matter (Fig. 3). Normal blood pressure was maintained during the remainder of the hospitalization. Approximately 24 hr after admission a radionuclide brain scan demonstrated absent cerebral blood flow and the child was removed from the respirator.

Discussion

Although the "reversal" sign has been described in patients who have suffered a diffuse hypoxic/ischemic episode to the brain from various causes, its pathologic basis and etiology have remained obscure [1–3]. On the basis of the pathologic findings in case 1, it appears that the increased density of the cerebral white matter in such patients is due to distension of the deep medullary veins by intact red blood cells. The deep medullary veins originate just beneath the cortex and drain capillary blood from the cerebral white matter to the subependymal veins along the margin of the lateral ventricle. They are oriented in a radial fashion as they course through the cerebral white matter to converge on the subependymal veins [4].

In the majority of patients who suffer a severe irreversible hypoxic/ischemic insult, the cerebral blood vessels are collapsed and contain a very small amount of blood. The collapse occurs secondary to increased intracranial pressure. With progressive edema the cerebral veins collapse in an effort to decrease the intracranial volume and prevent a further rise in the intracranial pressure. If intracranial pressure further increases and reaches the level of mean arterial pressure, a similar mechanism occurs in the arterial system. Ultimately, the cycle of increasing intracranial pressure results in the cessation of cerebral blood flow.

Fig. 2.—Case 2.
A and B, Noncontrast CT scans show increased density in deep cerebral white matter (30–35 H) and diffuse cortical edema.

A   B
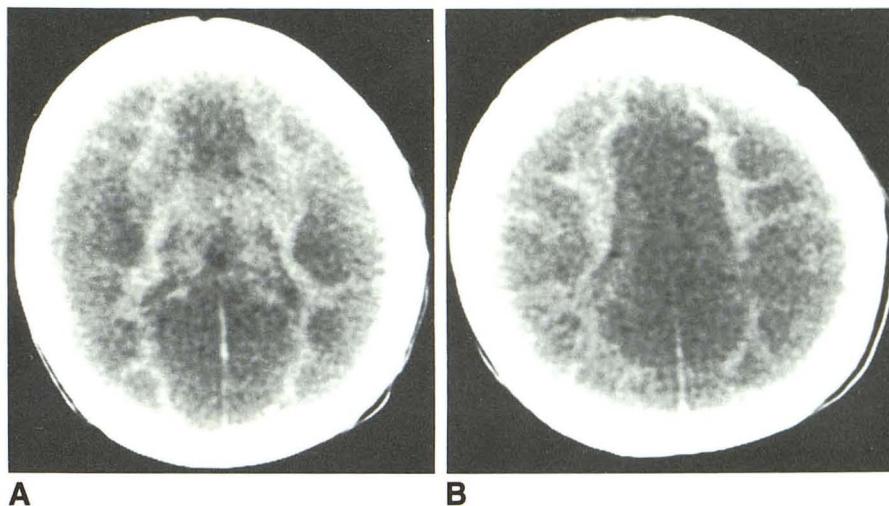
Fig. 3.—Case 3.
A and B, Noncontrast CT scans show patchy increased density of deep cerebral white matter (30–33 H) and multifocal areas of cortical edema.

A   B
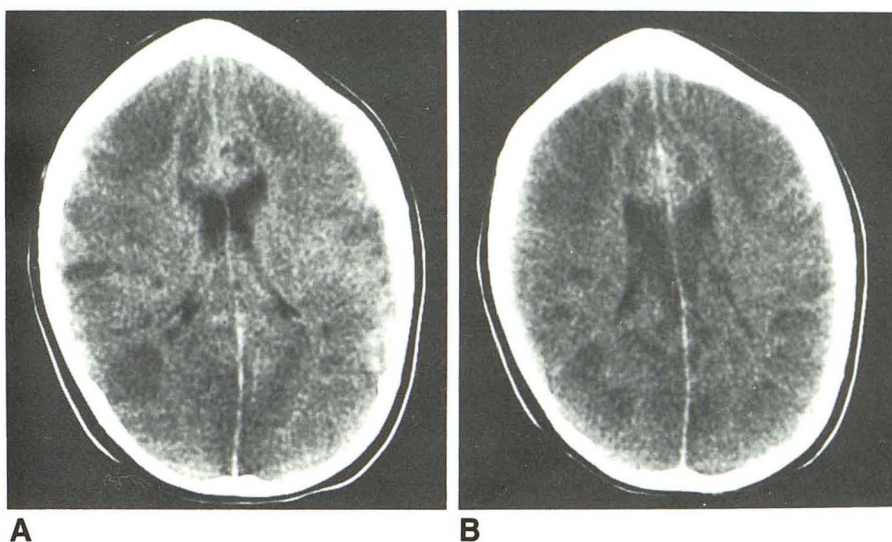
Why, then, in cases of "reverse" edema, is there the paradoxical finding of distended deep medullary veins in the face of markedly elevated intracranial pressure? The proposed mechanism by which this occurs is presented in Table 1. The common clinical feature resulting in this characteristic CT appearance may be the prolonged period of severe hypotension and hypoperfusion that has been shown to produce white matter edema as well as cortical edema [5]. During this period, the intracranial pressure increases enough to at least partially occlude the subependymal veins and impede deep venous outflow. When the systemic hypotension is corrected, cerebral blood flow increases and this partial venous obstruction causes distension of the deep medullary veins. This venous distension produces the increased density of the cerebral white matter noted on CT. The reason why such venous distension does not occur in gray matter is not clear but at least two factors are likely involved. First, anatomically the venous drainage of the cortex is superficial and has a much shorter course. Second, and perhaps more important, the cortex has higher regional cerebral blood flow, and during

TABLE 1: Proposed Mechanism for Development of "Reverse" Edema

Cerebral hypoperfusion
↓
Elevated intracranial pressure
↓
Collapse of deep veins
↓
Reperfusion
↓
Venous stasis

hypoxic ischemic periods edema formation is more rapid and severe [6]. This causes a higher local tissue pressure and may lead to an earlier collapse of the superficial venous drainage system [7, 8].

Similarities exist between these cases of "reverse" edema and those with so-called "respirator brain." Vascular conges-

tion is commonly present in respirator brain; however, it is usually cortical in location [9, 10]. More severe deep white matter involvement is less common but can happen and in this instance might be expected to show "reverse" edema on CT scans [9]. The underlying pathophysiologic mechanism in both these entities is in fact probably largely related to cerebral hypoperfusion [11].

In conclusion, "reverse" edema on CT is characterized by an absolute increased density of the deep cerebral white matter accompanied by diffuse cerebral swelling. Pathologically, this increased density is caused by a distension of deep medullary veins related to venous obstruction at the level of the subependymal veins. Clinically, this finding is indicative of a severe, prolonged hypoxic/ischemic insult and signifies a poor prognosis.

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