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Increased Permeability of the Blood-Brain Barrier after Carotid Renografin-76

Michael R. Sage,^{1,2} Burton P. Drayer,¹
Philip J. Dubois,¹ E. Ralph Heinz,¹
and Dennis R. Osborne¹

Increased permeability or "breakdown" of the blood-brain barrier following the carotid injection of various contrast media has been previously documented [1-6]. Transient opening of the blood-brain barrier may also be produced by injecting hyperosmotic mannitol or arabinose into the internal carotid artery [7-12]. CT scanning has recently been applied to the definition and quantitation of this barrier breakdown [13, 14]. This case report documents, with cranial computed tomography (CT), disruption of the blood-brain barrier after the intracarotid injection of a hyperosmotic iodinated contrast media.

Case Report

A 43-year-old woman was admitted for reevaluation of poorly controlled hypertension and renal artery stenosis. While in the hospital she had the acute onset of left hemiparesis and sensory loss with complete resolution within 4 hours. She reported several similar episodes over the preceding few months.

Arch aortography using Renografin-76 (two injections of 60 ml each) defined a narrowing at the origin of the right internal carotid artery. To obtain better visualization of this abnormality, the angiographer chose to exchange catheters for selective catheterization of the right common carotid artery. By accident, 10 ml of Renografin-76 (rather than Renografin-60) were injected at a rate of 7 ml/sec. About 10 min after injection and after the catheter had been removed from the carotid artery, the patient developed a left body focal motor seizure with secondary generalization lasting for about 2 min. Her blood pressure was stable and no seizure medication was administered. Neurologic examination about 15 min later revealed only a mild left central facial weakness that had disappeared by 3 hr later.

CT was performed about 40 min after the intracarotid injection of Renografin-76. No intravenous contrast medium was injected. Prominent enhancement of the gray matter was demonstrated in the right brain in the distribution of the anterior and middle cerebral arteries (fig. 1). There was no enhancement in the distribution of the right posterior cerebral artery or the left brain vasculature, which had not been injected with contrast material. Diffuse decreased attenuation consistent with generalized vasogenic edema was evident throughout the white matter of the right hemisphere.

An electroencephalogram 2 hr after the carotid angiogram was grossly abnormal with anterior delta activity involving the right frontal and temporal regions. The background activity in the left hemisphere consisted of normal alpha with occasional interspersed low voltage theta. Occasional irregular delta rhythms occurred bilaterally and synchronously, being maximal in voltage anteriorly over the right hemisphere. An electroencephalogram 2 months before admission was normal. A follow-up electroencephalogram was not obtained, but the patient was discharged a few days after angiography with a normal neurologic examination except for the previously noted bilateral carotid (as well as femoral and abdominal) bruits and hypertensive fundoscopic abnormalities.

Discussion

CT scanning provides an anatomically precise means for defining the extent and distribution of many brain abnormalities *in vivo*. In our case, the inadvertent injection of Renografin-76 resulted in disruption of the blood-brain barrier. The persistence of the abnormal gray matter enhancement for 45-60 min after the intracarotid contrast media infusion is consistent with damage to the barrier and leakage of the iodinated contrast media into the extracellular brain space. If the enhancement were due to increased cerebral perfusion as may occur with a seizure, the abnormal enhancement would not persist for 1 hr and would likely have been bilateral, rather than precise right middle and anterior cerebral artery distribution, as the seizure rapidly became generalized after its focal motor onset. In addition, the persistence of electroencephalogram changes is consistent with reversible opening of the blood-brain barrier [15].

The permeability properties of the cerebral capillaries differ from those of other tissues, resulting in the concept of a blood-brain barrier. Tight junctions between nonfenestrated endothelial cells have been demonstrated [16] and appear to prevent the passage of high molecular weight substances from the capillary lumen into the brain parenchyma. The endothelial cells of the brain also have a paucity of micropinocytotic vesicles [17], a further structural peculiarity of the barrier.

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¹Department of Radiology, Box 3808, Duke University Medical Center, Durham, NC 27710. Address reprint requests to B. P. Drayer.

²Present address: Department of Radiology, Flinders Medical Centre, Bedford Park, South Australia 5042.

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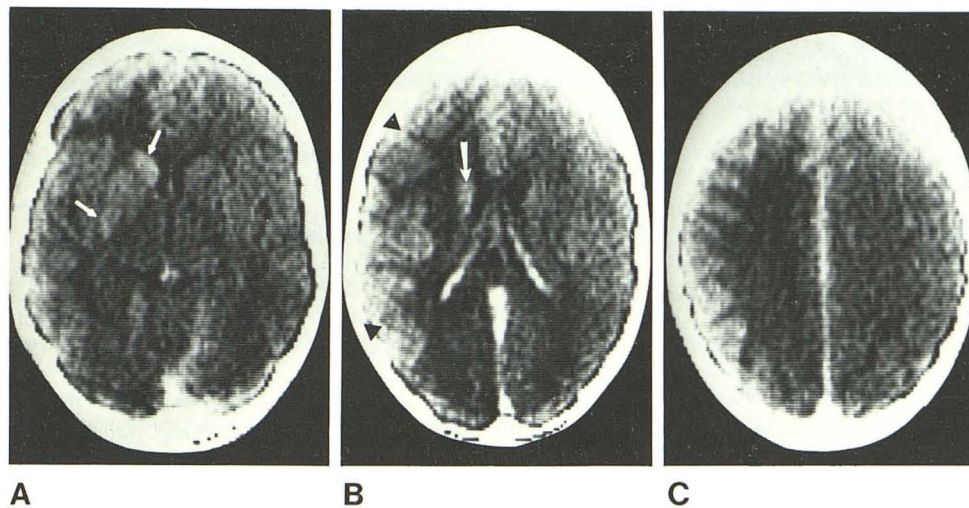


Fig. 1.—Renografin-76-induced blood-brain barrier disruption. A, Enhancement (arrows) of right caudate nucleus, globus pallidum, and putamen. Deep gray nuclear structures are in distribution of right anterior and middle cerebral arteries and have a high capillary density similar to cortical gray matter. B, At level of bodies of lateral ventricles. Caudate nucleus enhancement (arrow). Enhancement in frontal and parietal gray matter (arrowheads) prominent when compared with mild capillary bed blush in right occipital lobe and left hemisphere gray matter. C, At more cephalad level. Abnormal gyral enhancement again apparent in frontal and parietal convexity regions. Diminished density of right hemisphere white matter compared with left centrum semiovale is consistent with vasogenic edema.

TABLE 1: Comparison of Renografin-76 with Pure Meglumine Salts Used in Neuroangiography

Contrast Medium	Anion	Cation	Solution (mg/ml)		Osmolality (mosmol/kg H ₂ O)	Osmolality (mosmol/1 solution)
			Iodine	Sodium		
Renografin-76	Diatrizoate	Meglumine, 66%; sodium 10%	370	4.48	1,940	1,270
Hypaque-60	Diatrizoate	Meglumine	282	0.20	1,340	960
Conray-60	Iothalamate	Meglumine	282	0.03	1,440	1,030

Substances with a high lipid solubility, low ionization at physiologic pH, and poor plasma protein binding have the greatest permeation through the normal blood-brain barrier. On the other hand, hyperosmolar substances have been shown to increase the permeability properties of the cerebral capillaries and thus disrupt the protective barrier in a reversible fashion [7-14].

Breakdown of the blood-brain barrier after the carotid injection of contrast media has been reported in experimental animals [1-6] and the neurotoxicity of such media may be related to this effect. The osmolality of contrast media (table 1) is a definite factor in neurotoxicity [18, 19], presumably by increasing the permeability of the blood-brain barrier to the iodinated contrast media. For this reason Renografin-76 should not be used for direct cerebral angiography [2]. Hypertonic glucose and sodium chloride solutions produce similar, but less pronounced, effects [20].

The specific molecular structure of various contrast media also determines their effects on the blood-brain barrier. However, iodine content of contrast media is not crucial, since similar noniodinated compounds also produce blood-brain barrier disruption [21]. The sodium salts of particular contrast media cause a greater disruption of the blood-brain barrier [1, 4] and greater neurotoxicity [19, 22, 23] than equivalent solutions of methylglucamine salts. On the other hand, there is insufficient evidence to suggest a significant difference between the various anions such as diatrizoate, iothalamate, or metrizoate [23-25]. Because of this, methylglucamine salts of low concentration and osmolality have been recommended for direct cerebral angiography. Recently developed contrast media (sodium and meglumine

ioxaglate [26]; metrizamide [27]; NyegaardC-29 [28]) appear even less toxic to the blood-brain barrier than the conventional monomeric methylglucamine salts.

The mechanism involved in abnormal permeability of the blood-brain barrier remains controversial. Perhaps there is shrinkage of cerebral capillary endothelial cells and associated loosening of the tight junctions [3, 11, 12]; however, contrast media also have a direct chemotactic effect on endothelial cell membranes. Golman [28] speculated that both mechanisms may play a role and the dominant factor may instead relate to the contrast media studied. For example, a water soluble nonionic contrast medium might increase pinocytotic activity in cerebral endothelial cells while a more osmotically active meglumine may act by opening tight junctions. Others suggest that stimulation of pinocytotic vesicular transport across the capillary endothelium may be the key factor [5, 6].

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