Imaging offers insight into blood-brain barrier permeability

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"Manipulation of the blood-brain barrier may provide a means for selectively targeting tumors for drug delivery," according to Dr. James M. Provenzale, a professor of radiology at Duke University. Provenzale and colleagues reviewed an extensive body of clinical literature and noted the most effective imaging techniques used to assess permeability and the strategies required to manipulate it (AJR 2005; 185:763-767).

Radiologists understand that high-grade tumors interrupt the blood-brain barrier, which presents as contrast enhancement on CT and MRI. Renewed interest in the phenomenon of permeability, however, has researchers looking beyond the simple contrast enhancement and toward molecular mechanisms involved in permeability that may help them treat brain tumors more effectively.

"The key point of dynamic contrast enhancement MRI is not just seeing blood-brain barrier changes — that's what we do every day when we look at postgadolinium images," said Dr. A. Greg Sorensen, director of the Center for Biomarkers in Imaging at Massachusetts General Hospital. "The key is the ability to quantify these changes in response to a therapy that might have a subtle effect."

Sorensen was not involved in the Duke study.

Changes in permeability may serve as a surrogate marker for angiogenesis, signaling whether a particular therapy designed to shut down vascular growth is working or not. Familiarity with the molecular mechanisms behind permeability would aid in understanding how therapeutic agents enter the brain. Taking this understanding further, researchers could then increase permeability to selectively alter the blood-brain barrier to enhance drug delivery.

Dr. Edward A. Neuwelt, a neurosurgeon at Oregon Health and Science University, pioneered a method of outwitting the brain's protective shield. By temporarily opening the blood-brain barrier with a concentrated sugar solution, he allowed chemotherapy and tumor-specific antibodies to pass into the brain and reach the tumor.

Vascular endothelial growth factor is dominant in tumor angiogenesis, and it also produces vascular permeability. Fluorescence microscopy in mice has proved an effective tool to gauge VEGF-caused permeability. Surgical samples from human brain tumors have shown a significant correlation between VEGF messenger RNA levels and capillary permeability and vascular volume (Neurosurgery 1999;44:732-740).

A small series of patients with rectal cancer treated with a monoclonal VEGF antibody showed a decrease in vascular permeability as gauged through a decrease in tumor interstitial fluid pressure (Nat Med 2004;10:145-147). Provenzale and colleagues suggest that intracranial tumor permeability may be a valuable surrogate marker for assessing effectiveness of VEGF antibodies.

Animal studies, including MRI of breast tumors in mice and in rats with human glioblastoma multiforme cell lines, have shown similar disruption of vascularity after treatment with VEGF antibody.

T1-weighted dynamic contrast-enhanced MR has become the most used imaging technique in humans to assess leaks in the blood-brain barrier. It provides short imaging times, requires only a single dose of contrast material, and can be analyzed by several reconstruction programs already available with MRI workstations.

Many researchers choose to use a 3D spoiled gradient acquisition steady-state technique, which monitors gadolinium over several minutes, rather than observing the first-pass phenomenon such as in T2*-weighted imaging methods, according to the study. Because temporal resolution is low, investigators have used different analysis methods, such as calculating the T1 values before infusion of contrast material.

Dr. Heidi C. Roberts and colleagues used this form of analysis in humans and found very good correlation between microvascular permeability and tumor grade (AJNR 2000;21:891-899).

Researchers at the University of Manchester in the U.K. used iterative analysis of first-pass dynamic
contrast-enhanced MRI data, simultaneously mapping blood volume and permeability in gliomas. The technique proved robust and reproducible and may be useful for therapeutic trials, they said (Br J Radiol 2003;76:39-50).

Many therapeutic agents used to treat tumors show efficacy in vitro, but they typically fail when applied in vivo. Strategies that increase drug permeability sometimes permit nonselective opening of the blood-brain barrier, allowing substances to cross into normal brain tissue. Researchers note, however, that receptor-mediated agents such as bradykinin can increase permeability at the tumor site.

Liposomes can be engineered for size, chemical affinity, and thermal sensitivity to optimize target-specific delivery of chemotherapeutic agents. Liposomes' temperature sensitivity raises interesting therapeutic possibilities, according to Provenzale and colleagues. Physicians could apply heat to brain tumors after IV infusion of heat-sensitive liposomes. The ensuing hyperthermia would both increase permeability of the liposomes across the blood-brain barrier and act to promote release of liposome-borne therapeutic agents into the tumor.

Knowledge of the workings of the blood-brain barrier is important, Provenzale and colleagues concluded, in order to understand the imaging features of brain tumors, and the ways in which blood-brain barrier permeability may be used as a surrogate marker for drug therapeutic response.

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