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Gliomatosis Cerebri has Normal Relative Blood Volume: Really?! Who cares? Should you?

In this issue of the *AJNR*, Yang et al (pages 350–355) report on the dynamic contrast-enhanced T2*-weighted MR imaging characteristics of gliomatosis cerebri. Gliomatosis, also known as diffuse glioma, is characterized by diffuse neoplastic glial infiltration of the brain, without a distinct tumor mass and with the preservation of the underlying neuronal architecture. According to the World Health Organization classification, gliomatosis is categorized as a high-grade (grade III or IV) neuroepithelial tumor of uncertain origin; at least three distinct subtypes exist. Gliomatosis can arise in either gray matter or white matter, and it can occur in supratentorial areas, in infratentorial areas, or in the spinal cord. Hypertrophy of affected CNS structures—most often the centrum semiovale—may be present. Reported survival times vary from months to years; this variation may, in part, reflect the difficulty in recognizing and diagnosing this disorder. Radiation treatment may have some benefit.

The conventional MR imaging findings of gliomatosis cerebri are nonspecific. Extensive, diffuse hyperintense signal, without enhancement, is usually present on T2-weighted images (1, 2). Therefore, the differential diagnosis is broad and includes, but is not limited to, demyelinating lesions (eg, multiple sclerosis or acute disseminated encephalomyelitis), other low- or intermediate-grade tumors (eg, diffuse fibrillary astrocytoma or oligodendroglioma), infections (eg, acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy), posttreatment changes (eg, those after irradiation), and various metabolic disorders.

Yang et al found diffuse T2 abnormality in seven patients with gliomatosis, with the absence of contrast enhancement in all cases but one. Mean relative cerebral blood volume (rCBV) values, normalized to normal-appearing white matter, averaged 1.02 ± 0.42 (range, 0.75–1.26). Histopathologic review showed the absence of vascular hyperplasia in all specimens. The authors concluded that their “low MR rCBV measurements . . . are in concordance with the lack of vascular hyperplasia . . . and thus provide useful adjunctive information that is not available from conventional MR imaging techniques.”

Overall, these are interesting, if not surprising, results of some physiologic importance to researchers. After all, at first glance, what we think we know from certain histologic and positron emission tomographic (PET) studies of gliomatosis has been confirmed. Because the fact that rCBV imaging reflects the degree of vascular proliferation in glial cell line tumors has been established (3) and because gliomatosis cerebri is known to be a diffusely infiltrative and minimally vascular lesion, one would expect a priori that gliomatosis should be associated with normal rCBV values. Because this study was based on a small

sample of both patients and histologic findings, however, we should consider these results preliminary and exercise caution before generalizing them to all patients with gliomatosis cerebri.

Are these results likely to be true? Is gliomatosis cerebri really characterized by a diffusely normal blood volume? Probably yes, most of the time, although this study has some minor methodologic flaws. Foremost among these is the authors' decisions to use targeted regions of interest (ROIs) based on the T2 abnormality for their analysis and to average these ROI values, rather than simply selecting the maximal rCBV ROI, as is routine in the design of such studies; the maximal is typically used because it better accounts for lesion heterogeneity and because the grade of a brain tumor is determined by its highest grade component, no matter how small. Normalization of rCBV values to normal-appearing white matter might also be problematic if widespread T2 abnormality is present. The reader is also not explicitly told the time interval between image acquisition and definitive histologic analysis. Additionally, the spectroscopic data, although welcome, is limited in that it was acquired in only three patients, and it was not obtained contemporaneously with the rCBV data (in some cases, MR spectroscopic data were acquired as long as 2 years after biopsy).

Moreover, the authors' claim that gliomatosis cerebri lesions are known to be hypometabolic, and their conclusion that such lesions have low rCBV values may be unjustified when applied to a larger, more heterogeneous population. Indeed, findings from some PET studies have suggested that both *hypermetabolism* (^{11}C -methionine) and *elevated* cerebral blood flow (^{15}O -H₂O) can be present in gliomatosis cerebri and that these derangements can reverse after radiation therapy (1). I would not be surprised if further studies reveal scattered foci of elevated cerebral blood volume (CBV) in some gliomatosis cerebri lesions. Similar considerations apply to MR spectroscopy. In a study (2) of eight patients cited by Yang et al, one with results similar to theirs, the maximal choline-creatine and choline-*N*-acetylaspartate ratios were heterogeneous and nonspecific, ranging from a normal value to one 2.5 times greater than normal.

Nonetheless, Yang et al have produced an important result that adds to our body of knowledge concerning brain tumor physiology, specifically with regard to differences in blood-pool values in gliomatosis compared with those reported in other high-grade astrocytomas. Will this result, however, change our clinical practice? Should it? Will the awareness that gliomatosis has normal relative blood volumes, as the authors suggest, increase our diagnostic confidence that a diffuse, nonenhancing, hyperintense lesion on a T2-weighted image is gliomatosis cerebri? I think not,

because most mimics in the differential diagnosis of gliomatosis are also likely to appear as normal or low-blood-volume lesions. Indeed, the availability of relevant clinical history may be more useful in narrowing the differential diagnosis than normal rCBV values. The rCBV findings of gliomatosis are likely no more specific than those of conventional MR imaging.

Finally, the work of Yang et al begs the question: What is the current clinical role of rCBV imaging in brain tumor evaluation? Does it add to or complement other functional techniques, such as PET or MR spectroscopy? One potential clinical application that may benefit from rCBV imaging is stereotactic biopsy guidance. Regions of elevated rCBV have been shown to be better correlated with high-grade malignancy than foci of enhancement on conventional MR images (3). Another potential clinical application of rCBV imaging is in the staging or subtyping of malignancy, in an attempt to predict the prognosis or response to treatment. Rather than concluding from their MR spectroscopic data that functional techniques, such as MR spectroscopy or rCBV imaging, may be a useful adjunct to conventional imaging to increase diagnostic confidence, Bendszus et al (2) conclude that "[MR spectroscopy] might be used to classify gliomatosis cerebri as a stable or progressive disease, indicating its potential therapeutic relevance." Lastly, rCBV imaging may be a useful modality for monitoring the response to treatment or early recurrence (3).

Despite widespread recent interest in the visualiza-

tion of brain tumor angiogenesis, surprisingly few reports in the literature describe the rCBV imaging appearance of diverse, nonastrocytoma brain tumors, including lesions such as oligodendrogliomas. The literature about lymphomas has been contradictory, with some authors reporting low-CBV lesions and some, high-CBV lesions (the difference may depend on steroid use) (3). What are the false-negative and false-positive rates with the use of rCBV imaging for assessing brain tumor grade? After nearly a decade of research, our answers to many of these questions are still anecdotal. Clearly, this article represents a good first step—but only a first step—in more fully describing the physiologic imaging appearance of diverse, atypical, intracranial neoplasms. Much important, basic work remains to be done.

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The Emergence of Time-Resolved Contrast-Enhanced MR Imaging for Intracranial Angiography

Time-resolved contrast-enhanced MR angiography (MRA) (1), which was developed primarily for use in the diagnosis of abdominal and peripheral occlusive vascular (2), is emerging as a tool for use in the diagnosis of intracranial vascular disease. In recent years, due to advances in gradient hardware and the development of new pulse sequences, contrast-enhanced MRA can produce the high frames rates needed for intracranial applications.

In the initial intracranial application of thick-slab multiphase T1-weighted projection angiography, Wang et al (3) acquired 0.9×1.25 -mm voxels with a thick-section (5.0-cm) two-dimensional (2D) imaging technique. They showed the feasibility of imaging the intracranial circulation with the simultaneous acquisition of two projection angles after the bolus injection of a gadolinium-based contrast agent with a rate of one frame 2.2 s. Hennig et al (4) adopted these ideas to image the pulmonary arteries with subsecond frames rates. More recently, Klisch and co-workers (5) were able to track the progress of intravascular embolization of arteriovenous malformations (AVMs) and dural arteriovenous fistulae. They obtained serial measurements of the ce-

rebral circulation in response to endovascular treatment with a rapid 2D projection angiographic technique with an in-plane spatial resolution of 0.98×0.98 -mm and a rate of less than one frame per second. In this issue of the *American Journal of Neuroradiology*, Coley and co-workers (6) report on the detection and classification of dural AVMs in three patients.

The use of MR techniques has several advantages compared with x-ray DSA; primarily, MR techniques are much less invasive than x-ray DSA. In addition to the fact that MR techniques produce images without the use of ionizing radiation, MR contrast agents are not nephrotoxic and have lower complication rates than those associated with x-ray contrast materials. The spatial localization possible with MR techniques also allow for the selection of a limited through-plane field of view so that targeted acquisition of the relevant vasculature is possible. Furthermore, since MR contrast agents are infused by means of a venous access site, such as that in an antecubital vein, MR angiography does not have the risk and complications associated with arterial punctures or the placement of a catheter.

Compared with nonenhanced MR imaging, such as