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## Can Nonenhancing White Matter Lesions Be Disregarded?

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### Can Nonenhancing White Matter Lesions Be Disregarded?

Linda A. Heier<sup>1</sup> and Robert D. Zimmerman<sup>1</sup>

In this issue of AJNR (1), Drs Elster and Chen pose a provocative question that has certainly given us pause as we routinely dismiss a large nonenhancing white matter lesion in a cancer patient. It was with relief that we read the conclusion that white matter lesions in cancer patients that do not enhance with gadolinium-DTPA at the time of the initial MR study have a low probability of representing metastatic disease. However, as the authors remark, a low probability does not mean zero and we feel our continuing paranoia is still justified, although reduced.

Within the limits of clinical practice the authors have performed an excellent prospective study. The study would have been more reassuring if the authors had selected patients with cancers most likely to have cerebral metastases, and those most likely to have white matter disease.

While over 50% of the 50 patients with nonenhancing white matter disease did have cancers with a predilection for CNS seeding (eg, lung, breast, lymphoma, head and neck), the remaining patients have primaries (GI, urinary tract, and reproductive system) less likely to result in metastatic brain disease. Ideally, only patients with focal neurologic deficits and seizures would have been included in the cohort. There are only eight of these patients, and there were six patients who were asymptomatic but referred for MR due to the highly aggressive nature of their primary malignancies with a propensity for cerebral metastases. The remaining 36 patients presented with nonfocal neurologic signs and symptoms that have low probabilities of being due to metastatic disease.

Selecting for the elderly, ie, the over 60 age group, would have increased the incidence of nonmalignant white matter lesions. A white matter lesion, whether enhancing or not, is less likely to occur in a 23-year-old than in an 85-year-old,

23 to 85 years being the age range of patients in this study.

More complete follow-up would also have been helpful. Only 13 of 30 patients who were alive without clinical evidence of metastatic disease a year after their initial MR exam had follow-up CT or MR studies. Of the 20 patients who died, only nine had follow-up imaging and no autopsy data are presented. We feel the conclusion this paper reaches is valid, but it would have been more compelling if all patients had been followed up and if autopsy data were available on the 20 who died, confirming that they had no metastases in the white matter disease.

The authors used the conventional dose of gadolinium-DTPA (0.1 mmol/kg) and began imaging after a 5–10 minute delay. Recent work by Yuh et al (2) indicates that an additional dose of 0.2 mmol/kg at 30 minutes is more efficacious, inasmuch as 46 new lesions were detected in 19 of 27 patients. How many of these lesions were white matter foci that only enhanced with the higher dose of gadolinium-DTPA is not detailed but a case could be made for evaluating cancer patients in the future with higher doses of gadolinium-DTPA.

In our practice we use additional imaging criteria to evaluate white matter disease beside enhancement. The authors only characterize the white matter lesions as being discrete without contrast enhancement. The anatomic location of the lesions and their signal characteristics are not described. We must admit we have a lower suspicion for lesions closer to the ependyma and have a proportionately higher suspicion for lesions that involve the subcortical U fibers. We find a large lesion in the subcortical U fibers hard to dismiss even if it does not enhance—but this is the whole point of this paper. We assume that the white matter lesions in the 50 patients ending up in the cohort were nonspecific and of the usual

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signal intensity (T1-isointense, T2-hyperintense) without mass effect. We raise this point because the authors comment that both Sze et al (3) and Davis et al (4) reported cases where the T2-weighted images demonstrate metastases that were not apparent on the postcontrast T1-weighted sequences. On review, these abnormalities on the T2-weighted images cannot be characterized as nonspecific white matter disease. The case of Davis et al (4) had multiple spherical hypointense lesions involving the periphery of the cerebellar hemispheres on the short TR images. Two of the three cases of Sze et al (3) had hemorrhagic metastases that were identified on the long TR scans as markedly hypointense and would obviously not be characterized as nonspecific white matter disease. The third case had multiple pin point T2 hyperintensities most accurately characterized as cortical rather than white matter (Sze G, personal communication). This only further confirms Dr Elster's and Dr Chen's conclusions and we assume the lesions of their cohort were truly of the white matter and had no unusual signal intensity.

Clinical practice aside, do we know the earliest MR manifestation of metastatic disease in the brain? Zagzag et al (5) have studied the source of CT contrast enhancement in a rabbit brain tumor model. They concluded that the contrast enhancement of intracranial tumors is dependent primarily on the proliferation of the microvasculature. Despite breakdown of the blood-brain barrier in the region of the tumor, without the concomitant presence of angiogenesis, enhancement was not detected. If the principles of CT contrast enhancement can be extrapolated to gadolinium-DTPA, then tumor angiogenesis plays an important role in metastatic detection. Looking at the pathophysiology of tumor growth it has been demonstrated that tumor spheroids grown in vitro or in vivo in the absence of blood vessels will grow until they reach a size at which passive diffusion can no longer provide the nutrients required nor can waste products adequately diffuse out. An equilibrium condition is reached and commonly the diameter of such a sphere will be between 3 and 4 mm in vitro and less than 2 mm in situ in the rabbit cornea. To become larger, the spheroids must acquire vasculature (6). It is not known whether these diameters apply to a cerebral metastases in a patient, but they imply that a tumor could initially grow avascularly and be large enough to be detected by a long TR MR

sequence and yet not enhance on a postcontrast study.

Frank et al (7) have created an animal model of cerebral metastases and studied it with contrast-enhanced MR imaging. Ocular and cerebral metastases developed after the inoculation of a VX2 tumor cell suspension into the internal carotid artery of rabbits. MR imaging with gadolinium-DTPA demonstrated enhancement in cerebral metastases in 14 of the 15 animals 5 to 7 days after the infusion of the tumor cells. The authors fail to mention whether the metastases appeared on the T2-weighted images and they only mention the size of the tumor at necropsy and do not give any diameters on MR images. At necropsy, multiple metastases of varying sizes up to 6 mm in diameter were present in the ipsilateral cerebral hemisphere. Thus contrast imaging detected lesions well under 6 mm since most of the animals were killed 7 days after their imaging. In the future, this type of animal model could be used to study the earliest MR manifestations of cerebral metastases and get a threshold of tumor detection. If we are lucky, the earliest manifestation of metastatic disease will be contrast enhancement rather than a T2 abnormality, but we are not optimistic.

We have encountered white matter lesions that were initially nonenhancing and considered nonspecific that have progressed into both glioma and lymphoma, but none has yet evolved into an obvious metastatic focus. If most initial white matter disease does not represent tumor but rather arteriosclerotic microangiopathy, perhaps we will rarely see seeding of these areas by hematogenously borne tumor cells as the blood flow to these regions is reduced (8, 9).

As Dr Elster and Dr Chen conclude, much larger clinical pathologic studies will be needed to determine the risk of nonenhancing white matter lesions. However, in the interim, their work convincingly supports the general theory that these lesions in cancer patients are benign and unlikely to alter management of clinical outcome.

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