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Routine use of contrast-enhanced MR scans in AIDS.

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FORUM

Editor's note: The following letter concerns a rather controversial subject. For this reason, the reply is somewhat longer than the usual letter to the editor. Because of the controversial topic, several additional individuals were asked to comment. The replies are, therefore, presented as a neuroradiologic forum.

Routine Use of Contrast-Enhanced MR Scans in AIDS

We read with interest the article by Tuite et al, "Efficacy of Gadolinium in MR Brain Imaging of HIV-Infected Patients" (1). Based on their data, we do not think that the authors have made a convincing argument for the use of gadolinium except in a very small minority of cases. In the group of eight patients without focal or mass lesions on precontrast scans and with new focal or mass lesions on postcontrast scans, it is not clear how three patients had a change in therapy. It is difficult to believe that two lesions seen only on enhanced magnetic resonance (MR) were large enough to be biopsied yet too small to be seen on intermediate T2-weighted images. In the third patient with multiple lesions seen only on postcontrast scans, it is also very surprising that all of these "lesions" were missed on intermediate T2-weighted scans. What were the toxoplasmosis titers in these three patients? Interestingly, the authors chose not to illustrate any of these unusual cases.

Regarding the group in which additional masses were detected on postcontrast scans, several questions may be raised. Why did the detection of more masses lead to biopsy in two cases? At the authors' institution, patients with multiple masses are treated empirically with antitoxoplasmosis therapy. Despite their explanation in the Discussion, the authors have yet to make a convincing argument that the three patients started on antitoxoplasmosis therapy would not have received empiric therapy anyway. Why are there no precontrast T2-weighted illustrations of the presumed cases of progressive multifocal leukoencephalopathy? Where were these lesions located? Did they have mass effect? Why could the authors not make a confident diagnosis of progressive multifocal leukoencephalopathy on the unenhanced images alone? In our opinion, the case of syphilis is the only definite example showing the benefit of contrast administration. However, the atypical features of the precontrast T2-weighted images (cortical infarction and subcortical vasogenic edema) would make contrast enhancement mandatory.

We also believe that the flow chart (Table 1) does not do the radiologist's interpretive skills justice: all solitary masses are *not* equivalent. For example, a solitary 3-cm subcortical mass is more suspicious for lymphoma than a 5-mm basal ganglia lesion. In addition, the authors do not provide evidence to substantiate the claim that "gadolinium-enhanced MR is useful . . . if the unenhanced MR does not explain all the patient's symptoms" (particularly if the measure of usefulness is a change in patient management).

A recent study (2) did not support the routine use of gadolinium administration for MR imaging of the brain in patients with acquired immunodeficiency syndrome (AIDS). Tuite et al are to be congratulated for reporting their own experience; however, we believe that they should have emphasized the negative result of their study. Outcome research is assuming an increasingly prominent role in the medical literature, and it is important for radiology research to interpret results accurately in the context of patient outcomes. Based on the authors' data, only a *very small* percentage of human immunodeficiency virus (HIV)-infected patients will benefit from contrast administration; moreover, clinical and laboratory data and the precontrast study will help to identify this subgroup of cases.

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Editor's Note: The above letter was referred to the authors of the original article. Their reply follows.

Reply

We are pleased that the comments of Drs Friedman and Rapoport and the report by Jensen and Brant-Zawadzki are in agreement with our conclusions that gadolinium-enhanced MR is useful in the management of *selected* patients infected with HIV. We do not advocate the routine use of gadolinium in such patients; rather, we recommend that a decision to use gadolinium should be made individually for each patient.

Regarding the specific concerns of Drs Friedman and Rapoport, we think that Figures 2–4 amply illustrate that postcontrast images reveal lesions that are not evident on precontrast T2-weighted scans. Lesions adjacent to cerebrospinal fluid (CSF) spaces are often difficult to detect on heavily T2-weighted images yet may be seen in locations accessible to biopsy, with contrast-enhanced scans (eg, Fig 4).

Although patients with multiple mass lesions are usually treated with antitoxoplasmosis therapy at our institution,

biopsy is sometimes pursued first in patients with absent toxoplasmosis antibody titers, unusual lesion locations, or atypical clinical presentations. For example, the two patients with multiple lesions who underwent biopsy had persistent CSF pleocytosis and low CSF glucose levels, which would be unusual for toxoplasmosis. The three patients with solitary masses on precontrast images and multiple lesions on postcontrast scans were treated with empiric antitoxoplasmosis therapy because the clinical picture (including MR) was most consistent with toxoplasmosis. As we stated, MR imaging contributes to and helps guide therapy but is not the sole factor in reaching therapeutic decisions. Even still, therapeutic decisions are not always correct (eg, patient in Fig 2).

Few radiologists would confidently diagnose progressive multifocal leukoencephalopathy on MR imaging alone. The absence of contrast enhancement in a lesion supports a diagnosis of progressive multifocal leukoencephalopathy; however, it is not confirmatory because it is difficult to exclude other causes including infarctions, which also occur in HIV.

Our Table 1 excluded the details of detected lesions in the interest of brevity. There is little data to support the contention that either the size or location of a solitary lesion is *reliably* predictive of the cause.

In our two patients with cognitive impairment (Figs 2 and 5) the additional findings on postcontrast images helped explain the patients' symptoms.

We take exception to the tone of the comments of Drs Friedman and Rapoport. Perhaps their skepticism about our findings and conclusions is because of an unfamiliarity with the complexities of MR imaging in HIV-infected patients. Jensen and Brant-Zawadzki, in the other large series reported, reached similar conclusions. We stand by the integrity of our research and continue to recommend the selective use of contrast enhancement in MR imaging of HIV-infected patients.

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Editor's Note: The letter of Drs Friedman and Rapoport was also referred to Drs Jensen and Brant-Zawadzki. Their reply follows.

Reply

The article by Tuite argues that gadolinium is efficacious in this patient population because it alters care of the patient. However, as pointed out by Friedman and Rapoport, it is not clear why the management was changed. Indeed, in at least one case the change in management may not have been appropriate.

Friedman and Rapoport raise numerous legitimate points in their letter, with which we agree. These points underscore the difficulty in managing these patients be it without or with contrast-enhanced MR as a guideline. The nonspecificity of the lesions the patients exhibit and the potential for multiplicity of disease causes within any given HIV-infected patient make care decisions based on imaging difficult. The authors fail to demonstrate that gadolinium aids such decisions. More importantly, they illustrate at least one case in which the gadolinium-enhanced study possibly led to erroneous management. In Figure 2, they depict a patient with multifocal disease and enhancing nodular lesions in the posterior fornix (or septum pellucidum?) who, presumably based on the MR study, was treated empirically for toxoplasmosis. In fact, the lesion proved to be lymphoma at autopsy. In Figure 3, they illustrate a focal lesion (not truly a mass lesion given the lack of mass effect) that easily could be lymphoma. Yet, because it was a second "mass," the patient was empirically treated for toxoplasmosis.

Our own recently reported experience suffers from its small sample size (63 versus Tuite's 103 MR studies) in Tuite's experience. We emphasized the importance of a screening negative unenhanced scan. In no case was a normal unenhanced MR study rendered abnormal solely after the administration of gadolinium. Our experience mirrors a report of 261 consecutive HIV-infected patients (totaling 332 scans) from San Francisco General Hospital by Gean-Marton, et al (Gean-Marton AD, et al. The utility of gadolinium administration in the evaluation of HIV-positive patients with suspected CNS pathology, presented at the 29th Annual meeting of the American Society of Neuroradiology, Washington, DC, June 1991) who found "gadolinium enhancement does not add useful information if the T2-weighted examination is normal." In fact, the current policy at San Francisco General is not to administer contrast if the T1-weighted image is normal (Dr Alisa Gean, personal communication). Thus, in the article by Tuite et al, the eight cases with focal or mass lesions seen only after contrast administration (one with multiple lesions and two who underwent biopsy) are of particular interest. In addition to the already-mentioned criticisms above, it should be pointed out that we are not told the results of the biopsies based on the enhanced MR images or whether they were useful. Did they lead to change in subsequent management? Certainly, the questions raised by Friedman and Rapoport as to whether the biopsy was appropriate in the first place are valid. In this context, an additional patient from the article by Tuite is interesting. This patient, one of five in whom new lesions were seen after contrast administration, was not acted upon, and the lesion disappeared. Would the authors' data be different had that patient been biopsied? Could vessels explain the new focal lesions after contrast administration in five additional patients (whose care did not change)?

We also would like to draw attention to the eight patients whose only cited abnormality was the presence of meningeal/ependymal enhancement. According to the authors, this sole finding did *not* alter patient care in a single case.

In fact, in the authors' case showing meningeal enhancement (actually dural enhancement; their Fig 1), the patient did not receive treatment because the CSF cultures were negative. This emphasizes that meningitis remains a diagnosis based on the results of CSF analysis, whereas MR is performed to exclude other pathologic processes that might present clinically in a similar fashion. Indeed, in this case the dural thickening is shown on the precontrast T1-weighted image (not truly a "normal" precontrast study). Incidentally, the type of dural thickening and subsequent enhancement shown in this case is nonspecific and certainly would not lead to any particular management decisions other than perhaps historic correlation. The neurosyphilis case raises similar issues. By the authors' own admission, this patient would have been treated based on history alone, given the findings of multiple infarcts, positive serum rapid plasma reagin, and CSF lymphocytosis. It is highly doubtful that the presence or absence of meningeal enhancement influenced management in any way. Thus, the authors' own data do not support their recommendation that gadolinium should be administered to patients whose symptoms suggest meningeal involvement.

Obviously, the addition of any further information to an already existing data set can be desirable in the context of a diagnostic conundrum. Any time contrast is administered, and a region of the brain enhanced, only two additional points of information are garnered. The first is that perfusion of that area is present. The second is that there is a breech, or absence, of the blood-brain barrier. The value of that information can be significant in selected cases. However, it is well known that the ability to characterize lesions in the HIV-infected patient even with the use of contrast is limited (1–3). Thus, establishing the efficacy of gadolinium use in this patient population is difficult. This is particularly so when one takes into account the difficulties in clinical management of this population. When one then adds the broad issue of outcome analysis, the efforts at defining efficacy for contrast-enhanced MR clearly may end in frustration. One can arrive at decidedly different conclusions using similar data depending on preconceived bias regarding routine gadolinium administration. Indeed, some authors have recommended routine gadolinium administration for every brain MR study "except for perhaps children and young adults with normal precontrast images" (4). Certainly, additional imaging information allows the *radiologic* impression to be stated with greater confidence. Taken to the extreme, however, such insistence on obtaining maximum information argues for use of triple-dose gadolinium in every case. But does the additional information truly affect clinical management? More and more, these questions are being raised in every clinical arena. If radiologists are to assume an increasingly prominent role as partners in cost containment, it is essential to produce fair and credible assessments regarding efficacy and outcome analysis.

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Editor's Note: The letter was also referred to Dr Robert D. Zimmerman for his comments, which follow.

Reply

To Gad or Not to Gad?

Growing up, my best friend Rick and I devoted the better parts of five summers to arguing the relative merits of Mickey Mantle and Willie Mays. We threw impressive statistics at each other to prove that our hero was clearly superior and discounted as false or aberrant any data that supported the opposite point of view. Experts were quoted and praised when they agreed with our views and dismissed as fools when they did not. It has struck me that discussions concerning the appropriate use of contrast agents are similar to these childhood arguments. A case in point is the paper by Tuite et al and the heated response it engendered from Drs Friedman and Rapoport.

Tuite et al reported that enhanced MR provided additional imaging information in approximately 20% of patients, and that this information affected care in 10% of patients. These findings compare favorably with those obtained from studies on the efficacy of contrast-enhanced scans in patients with metastatic disease (1). Based on this data the authors conclude that contrast administration is useful in AIDS patients with: 1) symptoms suggesting meningeal disease; 2) focal lesions (with or without mass effect); and 3) clinical abnormalities not explained by the findings on unenhanced MR scans.

Drs Freidman and Rapoport emphatically disagree with the findings and conclusions of this report. Although I will leave it to Dr Tuite and his coauthors to defend their work, I am distressed by the tone of this letter. In essence the authors are accused of not telling the truth about the value of enhanced scans and of purposefully withholding unenhanced images that would have damaged their hypothesis. The unique quality of scientific knowledge is that it is public and therefore can be disproved. The appropriate response to a paper with which one disagrees is to repeat the experiment. Pending such repetition it is imperative that we accept the work of our peers as honest (although not necessarily correct), because without this acceptance scientific discourse would be impossible. In addition, it is

difficult to understand how Freidman and Rapoport can be so skeptical of the claim that small parenchymal lesions may produce no abnormality (at least in prospect) on long-repetition-time scans and yet be detected on enhanced scans, when Figures 2 and 3 of the Tuite paper clearly document this phenomenon, and Jensen and Brant-Zawadzki report similar findings in two lesions.

Drs Freidman and Rapoport do provide legitimate support for their views about the efficacy of contrast by citing a recent publication by Jensen and Brant-Zawadzki, which concluded that the routine administration of contrast in patients with AIDS was not indicated, because in only one of 63 cases did findings on contrast-enhanced images provide information that could alter diagnosis and care.

A comparison of the seemingly contradictory Tuite and Jensen papers provides insight into the sources of the controversy concerning the use of contrast in patients with AIDS. Because the number of cases in both investigations is small, neither can be viewed as definitive, in particular with reference to uncommon but clinically important processes such as meningitis and ventriculitis. The experimental designs of the two papers are sufficiently different to make direct comparison of results difficult. For instance, Tuite evaluated the precontrast scans first and then the enhanced scans to determine whether new information was obtained with these postcontrast short-repetition-time studies. In the Jensen study, the precontrast long-repetition-time and postcontrast short-repetition-time images were compared for lesion detection, but, unfortunately, because the pre- and postcontrast scans were viewed simultaneously it is not possible to determine objectively whether additional information was provided by the contrast exams.

Given the differences between these papers, in particular their conclusions concerning the overall usefulness of contrast, it is striking that *the two groups agree on one major indication for contrast administration: the presence of focal/mass lesions on unenhanced T2-weighted scans.* Based on this criterion alone at least 20% of Tuite's and 33% of Jensen's patients would have received contrast, a higher percentage than Freidman and Rapoport suggest is necessary. Jensen stresses that no cases were encountered in which unenhanced long-repetition-time scans were normal and enhanced scans abnormal, leading to the recommendation that contrast not be given unless the unenhanced scan is abnormal. This negative result is surely a consequence of the small number of cases in this series. In my experience, the situation is analogous to that encountered in metastatic disease. Meningeal, ependymal, or small parenchymal lesions detected on contrast-enhanced scans in patients with normal unenhanced scans occur infrequently (approximately 1%), but even this small yield is *medically* advantageous, because the contrast agent produces essentially no adverse reactions.

Further studies will resolve some of these conflicts (after all, when their respective careers were over, Willie's superiority over Mickey was established even to us diehard Yankees fans), but I believe that controversy will persist, because its source lies outside the scientific issues under investigation. As Jensen explicitly states in her introduction, the contraindication to routine contrast administration is economic rather than medical, and therefore the focus of this debate must shift to a careful analysis of the cost.

It is simple to determine the cost of the contrast agent. It is more difficult, but equally important, to assess the economic effects of not giving contrast. If, by failing to give contrast, accurate diagnosis and therapy are delayed or prevented, the increased cost of the patient's hospitalization (including that of a repeat MR examination) will far outstrip the cost of the contrast agent.

These costs will vary significantly from institution to institution depending on the nature of the patient population, the caseload, and the time and energy required of both the professional and support staff to perform these studies. Freidman and Rapoport indicate that the combination of clinical information and the findings on unenhanced scans yields a correct diagnosis in the majority of cases and that those few patients who would benefit from contrast can be easily identified. This approach to contrast use is similar to that advocated by both Tuite and Jensen. Each group believes in "customizing" the exam to the individual patient. They disagree only on the number of patients likely to require contrast agents under these circumstances.

This approach should work well when volume is low, patients are relatively healthy (eg, outpatient exams), and staffing is adequate to assess the patients and monitor the examination. It has proved unsuccessful at my institution. At New York Hospital, we perform five to 10 cranial MR scans on hospitalized patients with AIDS per week. The clinical findings in these patients are often nonspecific, and information supplied to us by the house staff may be inaccurate or insufficient (eg, "rule out brain lesion"). The patients are usually quite ill, and therefore it requires a major effort on the part of the clinical staff, the transportation team, and the MR staff simply to get the patients on and off the MR table. It is not unusual for these patients to require twice the time in the scanner as other patients. Motion degradation is a frequent problem, especially on long-repetition-time scans, and even the most astute radiologist may fail to detect subtle lesions by sequentially viewing the images on the MR console. Because of all these problems *we have found it to be most efficient to perform exams routinely with contrast.* This "mass production" technique eliminates the need to return patients to the scanner and reduces the time that the fellows and residents must spend tracking down the clinical information and monitoring the MR exam. For us, at least, the routine use of contrast is the most cost-effective way of studying these patients.

Let me add one further element that affects individual views of the issue of contrast use, called, for lack of a better term, the "compulsiveness factor." Some of us are willing to pursue diagnostic accuracy with imaging studies to greater lengths than others, and each of us is likely to have some diseases to which we are willing to devote more time than others. This phenomenon, rooted in human nature, will survive even the current rage for outcome analysis (which makes me nostalgic for the good old days of 1992 when the most alien concept I had to wrestle with

was K space). It is particularly important to look at how the compulsiveness factor is operating with regard to patients with AIDS. The social stigmata that are often associated with this disease and the fear of contamination by blood products cannot be allowed to influence the decision-making process. At several points in this commentary I have compared the situation in AIDS with that of metastatic disease. I believe this analogy holds not only for the results of imaging studies but for the effect of these studies on outcome. Both diseases have a poor overall prognosis, but in both there are effective palliative measures for the treatment of central nervous system involvement. Therefore, it is reasonable to use contrast material in AIDS in the same manner as in metastatic disease.

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