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Commentary

Fluid-Attenuated Inversion-Recovery Fast Spin-Echo MR: A Clinically Useful Tool in the Evaluation of Neurologically Symptomatic HIV-Positive Patients

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With the introduction of the fast fluid-attenuated inversion-recovery (FLAIR) magnetic resonance (MR) technique, the routine use of this imaging sequence to enhance the detection of intracranial lesions in the cortical and subcortical regions and deep white matter has become practical, as illustrated so well in Thurnher et al's article in this issue of *AJNR* (1). The diagnostic advantages of FLAIR can now be applied to patient treatment on a daily basis because of the time savings allowed by the coupling of the fast spin-echo technique to the FLAIR sequence (2–7). This achievement has been made possible by recent technical advances in imaging hardware (2). Whereas FLAIR performed with the conventional flow-compensated spin-echo sequences was diagnostically valuable (8–19), the long acquisition times made it too cumbersome for daily use (especially in today's climate of managed health care). However, the decrease in acquisition time offered by the fast spin-echo technique has generated renewed interest in the diagnostic utility of FLAIR. Typically, total acquisition times have decreased from roughly 13 minutes for FLAIR to between 5 to 8 minutes for fast spin-echo FLAIR (3, 4, 6). Even shorter acquisition times of between 2 minutes 8 seconds to 4 minutes 16 seconds have been achieved with a modified fast FLAIR technique (5).

The nulling of cerebrospinal fluid (CSF) signal on FLAIR images gives FLAIR its diagnostic advantage. With CSF devoid of signal, lesions exhibiting high signal intensity in the white matter adjacent to the ventricles or cortical sulci can be more easily detected (2–5). The contrast between the signal void of CSF and the adjacent hyperintensity of white matter lesions on this still heavily T2-weighted sequence enables the imager to appreciate abnormalities that might otherwise have gone undetected on routine spin-echo T2-weighted images (3, 4). Those hyperintense lesions in the periventricular white matter that are often obscured on T2-weighted images because of volume averaging with the even brighter CSF are more easily appreciated on FLAIR images (4, 5). Furthermore, some lesions on conventional proton-density spin-echo images might also not be as apparent as on FLAIR images because of the similarity in signal between the lesions and adjacent gray matter on this sequence and a lower lesion-to-background ratio than T2-weighted images (3). Multiple sclerosis plaques, for example, have been reported to be isointense with gray matter on proton density–weighted images (3).

As emphasized by Hashemi et al (3) in cases of multiple sclerosis and now by Thurnher and colleagues in patients with human immunodeficiency virus (HIV) encephalitis and progressive multifocal leukoencephalopathy (PML), the detection of demyelinating lesions is particularly aided by this FLAIR technique, especially when combined with fast spin-echo. The value of this sequence has also been acknowledged in the diagnosis of acute cerebrovascular disease, acute carbon monoxide poisoning, mesial temporal sclerosis, and partial epilepsy, herpes encephalitis, tuberous sclerosis, acute subarachnoid hemorrhage, and intracranial tumors (3, 5, 6, 14–19). Potential pitfalls with the FLAIR technique have, of course, also been acknowledged (2–6, 13). These include CSF flow and misregistration artifacts, increased fat signal, decreased sensitivity to the detection of low-signal lesions caused by magnetic susceptibility effects such as those containing hemosiderin and, on FLAIR fast spin-echo, lack of white matter

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tract detail (2–6, 13). However, despite reports describing the potential limitations of this technique, those papers touting the diagnostic advantages of FLAIR fast spin-echo have received the most attention in the recent literature (2, 3, 5, 6, 14–19).

The diagnostic benefits of FLAIR fast spin-echo, captured so well in the case illustrations of Thurnher et al, are made even more obvious by the fact that white matter lesions in HIV-positive patients have been notoriously difficult to detect in the past (20–22). The diagnosis of intracranial infections such as HIV encephalitis, cytomegalovirus encephalitis, and PML have been especially elusive on computed tomography (CT), particularly early on in the course of these disease processes (20–24). Numerous papers have alluded to the fact that the clinical diagnosis of HIV encephalitis has usually antedated the CT diagnosis (20, 21). Similarly, with PML and cytomegalovirus encephalitis, the CT diagnosis has often remained elusive (23, 24). This drawback of CT can be attributed to its limited contrast resolution as well as to the difficulty of detecting low-density lesions against a background of normally hypodense white matter. This difficulty is compounded even further by the routine lack of mass effect and contrast enhancement in HIV encephalitis and PML and in many (albeit not all) cases of cytomegalovirus encephalitis.

Because of its superior contrast resolution over CT, the detection of these white matter lesions has been made easier by MR (22, 25). MR, displaying hyperintense signal abnormalities on T2-weighted images against a background of normally hypointense white matter, has made the detection of demyelinating lesions in HIV-positive patients easier (25). Nevertheless, the relative paucity of findings on serial MR images in asymptomatic HIV-positive patients in multidisciplinary longitudinal studies of the neurologic complications of HIV have pointed out the limitations even of MR and its lack of early detection of HIV encephalitis and PML (20, 21, 25–34).

The desire to detect and characterize lesions earlier at a time when early treatment might be beneficial has focused attention on additional techniques that might supplement conventional MR imaging, such as MR proton spectroscopy, CSF volumetrics, calculations of magnetization transfer contrast ratios, functional imaging, and imaging fusion techniques (25, 34–44). These latter techniques have shown some promising results in lesion detection and characterization and differential diagnosis in the neurologically symptomatic HIV-positive patient (25, 37, 42–44). In the neurologically asymptomatic HIV-positive patient, the possibility of detecting abnormal metabolites in the brain when conventional MR images are negative has been alluded to as well (37). However, the additional time needed to perform these studies, especially proton MR spectroscopy, combined with limitations in equipment used for clinical purposes, has restricted their routine use.

Onto this stage now comes a technique, FLAIR fast spin-echo, that is cost-effective, rapid, and easy to perform on an institution's available equipment, and that can, as exquisitely illustrated by Thurnher et al, show periventricular, subcortical, and cortical lesions that do not enhance and that are not apparent on T2-weighted fast spin-echo images. One has only to view the figures in Thurnher and colleagues' paper to appreciate the impact of this technique on diagnosis. These authors obtained their case material by prospectively examining 44 consecutive neurologically symptomatic HIV-positive patients with both FLAIR fast spin-echo and T2-weighted fast spin-echo techniques on 1.0-T or 1.5-T systems. They then compared the differences in lesion detection rate between these two techniques. Of these 44 patients, they identified 33 subjects who had lesions shown on either sequence. The pathologic findings in these 33 patients (documented in 13) were varied and included infections causing white matter lesions (such as HIV encephalitis, PML, and cytomegalovirus encephalitis) as well as lesions typically associated with mass effect and contrast enhancement (such as toxoplasma encephalitis and lymphoma). Comparison of the two techniques revealed that FLAIR fast spin-echo had both an improved rate of lesion detection as well as greater overall lesion conspicuity as judged independently by this group's two experienced neuroradiologists, who had good and excellent interobserver reproducibility for lesion conspicuity for the T2-weighted and FLAIR fast spin-echo sequences, respectively. In 24 of the 33 patients in whom lesions were detected, a greater number was detected with FLAIR than with T2-weighted fast spin-echo images. Although there was no patient having normal T2-weighted fast spin-echo and abnormal FLAIR findings, or vice versa, 28 additional le-

sions were found with FLAIR. Statistically significant higher contrast ratios between lesion and CSF and contrast-to-noise ratios were found for FLAIR fast spin-echo. Although lesions larger than 2 cm and lesions in the basal ganglia and posterior fossa were equally well delineated with both techniques, FLAIR was found by Thurnher's group to be superior in the detection of small lesions and those located in the cortical and subcortical regions and deep white matter.

Thurnher and colleagues also found (at least in their one patient with toxoplasma encephalitis illustrated in their Figure 1) that more lesions were seen on FLAIR fast spin-echo images in the cortical and subcortical regions than on the corresponding contrast study. This raises the intriguing question of whether lesions such as toxoplasma encephalitis that typically enhance with contrast can be identified on FLAIR fast spin-echo before there is a breakdown in the blood-brain barrier. One could certainly counter that those lesions that did not enhance were not from toxoplasma encephalitis but rather from coexistent disease, but nevertheless the observation that FLAIR showed a greater number of lesions in this one patient than did the contrast study is an interesting one. Despite the recent report by Tsuchiya et al (45) showing the superiority of contrast-enhanced T1-weighted images over fast FLAIR in brain abscess, meningitis, and epidural empyema in immunocompetent patients, perhaps a comparison of FLAIR fast spin-echo and contrast-enhanced MR in HIV-positive patients with disease that is known to enhance typically would make an interesting subject for future investigation by these authors. However, no matter what the results of such a future investigation, the authors' current study clearly shows the ability of FLAIR fast spin-echo to show lesions (whatever their cause) that are not apparent on T2-weighted fast spin-echo and that might not even be apparent on some contrast-enhanced images.

Despite the obvious benefits of FLAIR fast spin-echo demonstrated by Thurnher's group, a word of caution is necessary when comparing this technique to older pulse sequences. It should be pointed out that many papers that have compared FLAIR fast spin-echo to other imaging sequences have emphasized the differences between FLAIR or FLAIR fast spin-echo and T2-weighted imaging (either with conventional spin-echo technique or with fast spin-echo technique) (5, 14, 17). Not all papers have concentrated on a comparison of FLAIR (with or without fast spin-echo) to proton-density imaging done with a conventional spin-echo technique (3, 4, 6, 11). This emphasis is important to appreciate, because proton-density images with conventional spin-echo technique certainly come the closest to resembling FLAIR sequences in regard to the signal of CSF, which is low on both sequences. While the physics behind these two sequences is not the same, and the reason that lesions appear bright on one sequence versus the other is different, nevertheless the diagnostic advantage of silhouetting hyperintense lesions against low-signal CSF either in a periventricular or in a cortical or subcortical location seems intuitively similar. One has to be careful, then, when reading about the advantages of FLAIR fast spin-echo not to assume immediately that many lesions are necessarily obscured with proton density– and T2-weighted conventional spin-echo imaging.

A case in point is this paper by Thurnher et al, in which the authors so convincingly show the diagnostic utility of FLAIR over T2-weighted fast spin-echo imaging in the detection of intracranial lesions in neurologically symptomatic HIV-positive patients. The comparison done by these authors is between FLAIR fast spin-echo and T2-weighted fast spin-echo, and not between FLAIR fast spin-echo and conventional proton density– and T2-weighted spin-echo imaging. Investigations, therefore, such as those in the past describing the findings in neurologically asymptomatic HIV-positive patients on MR performed with both proton density– and T2-weighted conventional spin-echo techniques are not necessarily invalidated. Just how many small white matter lesions might have gone undetected in these neurologically asymptomatic HIV-positive persons on routine dual-echo imaging with conventional spin-echo technique remains to be seen. Although one could certainly argue (based on prior comparisons between these two techniques done in immunocompetent and neurologically symptomatic patient populations [3, 4, 6]) that some small lesions might have gone undetected with dual-echo conventional spin-echo imaging, nevertheless formal comparisons between FLAIR fast spin-echo and conventional proton density– and T2-weighted spin-echo cranial imaging in the HIV-positive asymptomatic and symptomatic populations are not yet available in the lit-

erature. Furthermore, since the imaging hallmark of HIV encephalitis is cortical atrophy and demyelinating lesions, not cortically based focal gray matter lesions, it seems unlikely that conventional spin-echo imaging with both proton density– and T2-weighted images would have missed many white matter lesions.

Yet another word of caution concerns the questions of whether FLAIR fast spin-echo should complement dual-echo spin-echo images or eliminate them. Lest we become overzealous and want immediately to eliminate T2-fast spin-echo without further comparative trials, we should first consider the recent study by Keiper et al (46) describing the limitations of FLAIR sequence in the detection of multiple sclerosis plaques in the spinal cord. Keiper and colleagues caution against blind acceptance of the diagnostic advantages of FLAIR without first having data from well-documented, well-controlled comparative studies. These authors point out that a new technique can seem potentially very promising, but those new sequences must withstand the scrutiny of time and of many large controlled comparison studies. A previously valued technique should not be totally abandoned until investigations show the clear superiority of one technique over the other in a myriad of situations. As astutely observed by Keiper et al in the spinal cord studies of their patients with multiple sclerosis, FLAIR may be better suited for detection of diseases only in certain stages of their evolution. For example, in their series FLAIR sequences were unsuccessful in showing chronic multiple sclerosis plaques in the spinal cord, whereas acute and subacute lesions were well seen. This raises the interesting possibility that lesions in the brain might also have better or worse conspicuity with FLAIR fast spin-echo, depending on whether they are in the acute, subacute, or chronic stages. As pointed out by Alexander et al (5), mixed low and high signal intensity can be encountered on fast FLAIR images in chronic brain infarctions because of liquefaction or gliosis. The signal intensity of these chronic infarctions could then match that of CSF and consequently be nulled. Although such infarctions would still be evident on T1-weighted images as low-signal intensities, nevertheless scenarios such as these, along with the potential pitfalls alluded to above, emphasize the diagnostic difficulties that might be encountered with FLAIR fast spin-echo. The diagnostic information it yields might also be made more complicated by the addition of different treatment regimens and their uncertain effects on different types of lesions. Because of these uncertainties, the jump from adding a FLAIR fast spin-echo sequence to our routine imaging protocols to eliminating proton density– and T2-weighted conventional or fast spin-echo completely when FLAIR-FSE is done seems too great at this time. Large, well-controlled series are needed before such a determination should be made.

Despite these cautionary words, it is my opinion that we should definitely use FLAIR fast spin-echo routinely to complement our everyday diagnostic imaging of neurologically symptomatic HIV-positive patients. The evidence, as presented and illustrated so beautifully by Thurnher and colleagues, is indisputable. FLAIR fast spin-echo is a rapid technique that can provide valuable diagnostic information in neurologically symptomatic HIV-positive patients and it should be used routinely, as Thurnher et al recommend, in the work-up of these patients. Given the time advantage of fast spin-echo in today's environment, which demands that more patients have imaging in shorter periods, the question of how many more lesions FLAIR fast spin-echo might show than proton density– and T2-weighted images with a conventional spin-echo technique is moot. As demonstrated by Thurnher et al and as described by other authors with different patient populations, FLAIR fast spin-echo imaging does increase the conspicuity of cortical, subcortical, and periventricular white matter lesions over T2-weighted fast and conventional spin-echo images. The detection of cortical lesions with FLAIR fast spin-echo is of special importance because these are the lesions in the HIV-positive patient population that are often treatable with current medical regimens.

Thus FLAIR fast spin-echo imaging would appear to be a technique we do not want to miss the opportunity of using, because it can be acquired in a time-effective manner and because it gives us diagnostic advantages over T2-weighted fast spin-echo. Here is a noninvasive, rapidly acquired sequence. It is easy to obtain and does not involve extensive physician input as other techniques, such as MR proton spectroscopy or magnetization transfer (MT) with calculations of MT contrast ratios, do. Why not add this valuable diagnostic technique to our imaging armamentarium? It is well known that

demyelinating lesions such as are seen in HIV encephalitis, PML, and cytomegalovirus encephalitis, can be difficult to detect early in the course of the disease, especially when the patient's neurologic symptoms are minimal. It is also well known that infections such as herpes encephalitis can be difficult to detect before neurologic symptoms and signs become fulminating. Why not then use a sequence that might identify such disease processes earlier, so that as new therapeutic regimens become available these therapies can be instituted earlier? But whether it be a neurologically symptomatic HIV-positive patient or an asymptomatic one being followed on a clinical trial, let us implement this sequence now. The advantages have been clearly shown. Early detection, early diagnosis, early treatment, and ease of patient monitoring while using various therapeutic regimens are all potential benefits that might be encountered—all worthwhile goals that make us aware of the benefits of using this new technique in the evaluation of neurologically symptomatic HIV-positive patients. Based on the fact that 80% to 100% of all patients with the acquired immunodeficiency virus have central nervous system disease evident on neuropathologic examinations (47), it seems only prudent to explore fully and then use those imaging techniques that are the most sensitive in detecting these lesions when patients first become neurologically symptomatic. Thurnher et al are to be congratulated for making us aware of the benefits of FLAIR fast spin-echo imaging in this patient population.

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