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The diffusivity of water in tissue depends in a complex manner on local microstructure and physicochemical properties. Diffusion tensor imaging (DTI) provides, in the form of the diffusion tensor, a complete description of the intravoxel diffusion characteristics of tissue water. Appropriate manipulation of the diffusion tensor within a given voxel provides information about the degree of anisotropy, as well as the direction of greatest diffusivity. Of particular interest in the CNS is the observation of significant intravoxel diffusion anisotropy in white matter tracts; water diffusivity is greater along the fiber axis of a white matter tract than perpendicular to it. This diffusion anisotropy in white matter is believed to reflect local microstructural anisotropy, with increased diffusion anisotropy reflecting increased parallel ordering of intravoxel axons. Furthermore, by identifying the degree to which the preferred diffusion direction within a voxel is correlated with adjacent voxels, it is now possible to map principal white matter tracts in the human brain.

In this issue of the *AJNR*, Filippi et al (page 277) report that DTI detects a significant reduction in white matter anisotropy and a significant increase in average water diffusivity (D_{av}) with increasing viral load in HIV-infected patients whose MR findings, other than mild atrophy in some cases, were normal. Several issues are raised by this provocative report. Is the finding real and, if so, does it assist us in understanding the pathogenesis of HIV dementia or other HIV-related CNS diseases? Also, are these findings predictive of the development of clinically relevant neurologic disease, in particular HIV dementia, which is a major cause of morbidity in AIDS?

White matter abnormalities are frequently observed in patients with AIDS, and have been considered to be among the most important neuropathologic lesions seen with HIV dementia. Pathologically, the reduced staining of subcortical and deep white matter with sparing of subcortical ''U'' fibers observed in HIV dementia has been referred to as ''progressive diffuse leukoencephalopathy'' and ''diffuse myelin pallor.'' MR spectroscopy studies have also identified metabolic abnormalities in white matter as one of the early hallmarks of HIV dementia (1, 2). Thus, the finding in Filippi et al's study of diffusion abnormalities in white matter appears consistent with previous findings. If, as suggested, the changes were present in patients prior to the onset of dementia, this would have important implications for the early detection and treatment of this common and debilitating complication of HIV infection. Nonetheless, the results should be treated as highly preliminary for several reasons. First, the study cohort was very small, and there appear to be no corrections for multiple comparisons in the statistical analysis, increasing the likelihood of false-positive results. Second, the cognitive and motor deficits that attend early HIV dementia may be subtle and detected only with a thorough history, neurologic examination, and neuropsychological battery. The characteristic features of HIV dementia (eg, slowness of thought and movement, impairment of memory, postural instability, and appearance of primitive reflexes) may be overlooked on cursory neurologic examination, rendering the examination ''nonfocal.'' Could the mild ''age-inappropriate atrophy'' observed by Filippi et al on routine brain MR images have been a reflection of underlying HIV dementia, and was there an association between atrophy and the abnormalities seen on DTI?

Does this study tell us anything about the pathogenesis of HIV dementia? Viral entry into the brain has been detected very early after systemic infection. Despite the apparent rapidity with which the brain is infected, only about one third of HIV-infected persons ultimately develop HIV dementia. The best evidence suggests that the virus, although not neurotropic, leads to cellular injury of the brain in two major fashions. In one, viral proteins such as gp120 and tat are neurotoxic (3). In the other, products of inflammation (4), various chemokines and cytokines, result in cellular injury. The latter may possibly persist as a consequence of inflammatory cell activation despite the relative clearance of HIV from the CNS.

Several of Filippi et al's observations are consistent with the hypothesis that the diffusion changes observed, if real, may reflect activation of inflammatory pathways. In cases of multiple sclerosis, inflammatory (contrast-enhancing) lesions exhibit the greatest reduction in diffusion anisotropy, whereas destructive (nonenhancing, T1-hypointense) lesions show the greatest increase in D_{av} (5). Perivascular macrophages, serum protein infiltrates, and multinucleated giant cells characterize HIV infection of the brain. Both perivascular extracellular fluid space and blood-brain–barrier permeability are increased. The increased D_{av} and decreased anisotropy are consistent with increased diffusion across white matter fibers, suggesting a loss of myelin integrity secondary to activation of inflammatory pathways.

Some investigators (6) have suggested, on the basis of different patterns of myelin disease in HIV infection, that several distinct mechanisms lead to its development. Blood-brain–barrier impairment is postulated to account for angiocentric foci of myelin damage, impaired methylation of myelin to vacuolar changes, coalescence of angiocentric foci, and a diffuse spread of infected macrophages with

elaboration of toxic products to HIV leukoencephalopathy (6). Supportive of this latter hypothesis is the correlation between the severity of myelin damage in the brain of HIV-infected patients with the extent of astrocytic and microglial reactions (7). Future DTI studies that attempt to correlate abnormalities with CSF markers of inflammation (eg, tumor necrosis factor-alpha, beta-2 microglobulin, quinolinic acid, membrane cofactor protein), and with markers of endothelial integrity (eg, matrix metalloproteinase 9) may prove very useful in attempting to determine the mechanisms of myelin injury.

Despite the great emphasis on white matter, specifically myelin abnormalities, in the initial reports of HIV dementia, subsequent studies indicate that they are not invariably present. In a pathologic study, Glass et al observed myelin pallor in only 33% of patients with HIV dementia (compared to 6% dying without HIV dementia), and found that its frequency did not differ significantly with duration of antiretroviral therapy (4). The authors question the value of myelin pallor detected by routine histopathologic examination as a marker for HIV dementia (4). If real, are the white matter diffusion changes observed in Filippi et al's study correlated with or predictive of HIV dementia? Perhaps the DTI is more sensitive than routine histopathologic study for detecting subtle white matter changes; this issue begs further study. In addition to correlative studies with autopsy material, serial evaluations of HIV-infected persons by DTI coupled with neurologic and neuropsychological examinations would be extraordinarily useful in determining whether these abnormalities in the white matter were of predictive value for the development of HIV dementia. If so, it may suggest the need for more aggressive antiretroviral therapies or other treatment strategies directed toward the mechanisms of HIV dementia to prevent significant brain injury.

As is often the case with scientific investigation, the results of an intriguing study only open the door for further inquiry. Many questions remain to be answered regarding the white matter changes observed with HIV infection before DTI is widely applied.

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