MR Imaging Investigations in a Non-Human Primate Model of Multiple Sclerosis

MR imaging has emerged as a spectacular tool for noninvasive investigations of the human demyelinating disorder, multiple sclerosis (MS). MR imaging is useful in supporting the diagnosis of MS, in predicting disease outcome, and in monitoring disease activity in clinical trials (1, 2). MS is a chronic, relapsing-remitting disorder of the CNS white matter, characterized pathologically by plaques of perivascular inflammatory infiltrates accompanied by concentric demyelination, proliferation of astrocytes, and progressive gliotic scarring (3). The etiology of MS has not been established, and factors contributing to the prognosis and progression of this disease remain unknown. To a large extent, our current understanding of the pathogenesis of MS lesions is based on observations of experimental allergic encephalomyelitis (EAE), an autoimmune CNS disorder that has been studied extensively as a disease model for human MS. In EAE, the initial event thought to trigger CNS inflammatory lesions is the migration of autoggressive T cells sensitized against myelin antigens into the brain parenchyma, which creates a disruption of the blood brain barrier (BBB). These T cells are believed to be activated by recognition of the sensitizing myelin antigens presented by human leukocyte antigen class II molecules on resident brain antigen-presenting cells (4), which initiates a cascade of inflammatory reactions, and results in tissue damage and further alterations in BBB permeability. Several mechanisms have been proposed as factors that ultimately cause tissue destruction, including direct toxicity of infiltrating T cells, secretion of proinflammatory cytokines, antibody-mediated toxicity, and complement and macrophage activation (5). In MS, these diverse mechanisms for tissue injury could act in concert, in succession, or separately, which may in part explain the heterogeneity of clinical presentation and pathologic features encountered (6, 7).

Observations of EAE also account for our current interpretations of MR findings in MS. Contrast agents injected in the circulation are markers for areas of BBB breakdown, and GdDTPA enhancement is regarded as a sensitive marker for disease activity. Cross-sectional MR studies and, more recently, longitudinal assessment of MR abnormalities, have established the natural behavior of most MR lesions observed in MS (8). The initial MR imaging “event” appears to be an area of increased T2 signal intensity with GdDTPA enhancement, and in most cases evolves into a permanent lesion characterized by an increased T2 signal intensity, which no longer enhances. These T2-characterized lesions may later increase in size and become reactivated, as indicated by GdDTPA enhancement, but rarely disappear. Obviously, the value of MR investigations in MS would increase considerably if MR events could be precisely correlated to neuropathologic events that accompany the formation of MS lesions and their transformation as the disease is progressing or is modified by therapeutic intervention. This information is difficult to obtain from human studies, and must be derived from the imaging of animal models for MS. MR studies of EAE have been conducted in rats (9), guinea pigs (10), and nonhuman primates, most notably macaques (11). A major problem associated with these initial studies is that the models used most often do not offer an adequate representation of all features encountered in human MS, may be difficult to study by noninvasive techniques, or both. Thus, macaque monkeys that have easily identifiable gray and white matter structures similar to that of the human brain usually develop EAE in hyperacute, hemorrhagic, and destructive forms. Unless treated, the first attack is fatal in 50% of the animals, unlike human MS (11). Models of chronic-relapsing EAE exist in mice, but the brain of these animals is difficult to study by conventional imaging techniques.

In this issue of the AJNR (page 965), Jordan et al characterize in vivo MR-revealed brain lesions in the newly available model of marmoset EAE, and correlate these observations with clinical disability and histopathologic findings. C. jacchus marmosets are small, New World primates weighing 300–400 g (approximately the size of a guinea pig) in which a form of EAE with a relapsing-remitting clinical and neuropathologic course can be induced. Widespread CNS white matter lesions are the hallmark features of most MS lesions, eg, mild inflammation, prominent demyelination, and, at later stages, significant remyelination (12, 13). The Jordan study, which includes nine animals induced for disease and two control animals, represents the first account of systematic serial in vivo MR examinations in C. Jacchus EAE, and closely follows another report by t’Hart and colleagues that included 11 animals with EAE studied in a cross-sectional analysis to establish the histopathologic characteristics of MR-detectable lesions in the model (14).

These two studies differ with respect to imaging techniques, design, and immunization protocols employed for induction of EAE, and provide complementary information. Jordan and colleagues used a 1.5-T scanner to image the marmoset brains in interleaved slices of 2- to 3-mm thickness, and followed animals by weekly to bimonthly MR imaging, from control state (preimmunization with myelin antigens) to up to 70 weeks after EAE induction, including a terminal examination immediately before euthanasia and histopathologic evaluation. Their study begins to
describe the dynamics of MR-revealed lesions in marmoset EAE, which, as in human MS, become visible as T2 hyperintensities accompanied by BBB opening as detected by GdDTPA enhancement (triple dose of 0.3 mmol/kg). Interestingly, some initially large lesions appeared to condense to smaller permanent abnormalities, some other lesions disappeared later in the course of the disease, and a significant proportion of GdDTPA-enhancing lesions did not have detectable pathologic correlates, perhaps indicative of active repair processes in this form of EAE. The time course of BBB opening is reported to vary somewhat between lesions, but the average course is 2 weeks. The strong points of the study are the demonstration that the majority of MR-revealed lesions are clinically silent, and the discrepancy between clinical and MR scores appears to be the most apparent in animals with the least demyelination around inflammatory infiltrates. The authors estimate that 44% of GdDTPA-enhancing lesions progressed to detectable demyelinating lesions on neuropathologic examination, and indicated a loose correlation between the frequency of MR-revealed lesion activity and perivascular cuffing and demyelination. Nonetheless, compared to histologic analysis, the rate of lesion detection by MR imaging was only 60% in some cases.

The t’Hart study is more focused on the correlation between imaging characteristics and histologic staging of marmoset EAE lesions obtained by high-resolution MR imaging (4.7-T magnet with 1-mm slices) and a sophisticated immunohistochemical analysis that has been recently proposed as a tool to evaluate the heterogeneity of lesions of human MS (6). Unlike Jordan and colleagues, these authors conclude that with MR imaging they can detect most lesions found at autopsy, and that GdDTPA enhancement is only seen in lesions that display criteria of active demyelination. Both studies, however, show that T2-weighted images do not distinguish inflammatory lesions from those associated with demyelination, or from remyelinating lesions; a finding that parallels emerging concepts in human studies (15, 16).

Certain technical issues exist in both studies. The immunization regimens employed to sensitize the animals for EAE are not identical in all cases studied. Most animals in the Jordan study were immunized with a chimeric recombinant protein that combines immunogenic domains of myelin-basic protein and proteolipid apoprotein. These myelin proteins, in contrast to whole white matter homogenate, do not induce pronounced demyelination in marmosets (17). Similarly, the adjuvants employed differ, and there are no control imaging studies provided for this source of variability. The main concern (which is acknowledged by the authors) is the possibility of positioning errors between serial MR examinations, and the discrepancies that may be introduced by the differences in slice thickness between MR imaging (1–3 mm), and histologic evaluation (5–10 μm).

Despite these obstacles, the reports discussed here underscore the value of marmoset EAE as a tool to investigate the pathophysiologic correlates of neuroimaging studies in human MS. Sensitive neurologic examinations are possible in marmosets that permit accurate clinical assessment of the disease and serial laboratory studies, such as peripheral blood reactivity to myelin antigens and cerebrospinal fluid analyses. These can be performed simultaneously with MR imaging during the course of the disease. The immunopathogenesis of MS-like lesions in C. jacchus (a synergy between myelin-reactive T cells and demyelinating antibodies) is now understood in great detail (18). This allows one to manipulate the model in order to produce different pathologic phenotypes, such as inflammatory and demyelinating forms of disease. Finally, C. Jacchus EAE has been successfully used in preclinical trials that included serial MR evaluation (19). The data of Jordan et al suggest that in such experimental studies important information may be missed in the absence of noninvasive assessment. There is need to standardize experimental protocols of EAE MR acquisition (as in human studies) in order to address specific questions relevant to clinical imaging. Perhaps more important is what this animal model offers to the understanding of the pathophysiologic substrates of abnormalities that can be detected by refined MR imaging techniques such as spectroscopy or magnetization transfer in apparently uninvolved white matter in human CNS demyelinating disorders (20).

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References
The Roles of Diffusion and Perfusion MR Imaging in Acute Stroke Management

The development of new therapies for treating the acute stroke patient has produced demands for sophisticated imaging and physiologic evaluation, as demonstrated in the excellent article by Ueda et al appearing in this issue of the AJNR (page 983). Anticoagulant and antiplatelet therapy have been used for years to prevent intraarterial thrombus formation. A thrombolytic agent, tissue plasminogen activator (tPA), was approved for intravenous use by the FDA in June 1996. The favorable results of the multicenter, prospective, and double-blind study revealing the efficacy of intraarterial Pro-urokinase (Pro-UK), when administered within six hours of the onset of acute ischemia, have been announced (1). Numerous articles reference the intraarterial use of urokinase and tPA (2–4). Many mechanical devices have been recommended for opening the occluded vessel. Although many neuroprotective agents have been evaluated, to date none have been found to be efficacious.

The pretreatment exclusion of hemorrhage by imaging is essential if anticoagulation, antiplatelet therapy, or thrombolysis is to be used. Nonetheless, the morbidity from the use of new thrombolytic agents requires far more from imaging, such as the use of perfusion and diffusion MR imaging techniques that are described in the article by Ueda et al in perspective.

Intravenously administered tPA produces intracranial hemorrhage in 6% to 20% of cases, depending upon the time of treatment after onset of the ictus (5, 6). Pro-UK also produces bleeding in a significant percentage of cases, although not always productive of increased symptoms. Given the morbidity and mortality of these risky therapies, it is essential to maximize the risk-benefit ratio. The potential for salvaging the ischemic brain must be defined. The reversibility of the ischemic process not only depends on the time after ictus, but is primarily a function of the degree of persistent collateral flow to the affected tissues. Brain tissue without sufficient collateral flow will die within minutes, whereas tissue with good collateral flow will remain viable. In the latter circumstance the ischemic process potentially can reverse for hours, beyond the limits of 3 to 6 hours that have been established for thrombolytic agents (7). A myriad of image-based techniques are currently available to evaluate cerebral blood flow (CBF), or “perfusion,” and the status of the cerebral parenchyma. A brief review of these methods will help put the MR techniques and results described by Ueda et al in perspective.

Plain CT is widely available and rapid, but relatively insensitive to the subtleties of differentiating reversible from irreversible ischemia. Xenon-enhanced CT provides a rapid, quantitative determination of CBF. Identification of the extent of infarction can be made based on the measurement of CBF flow (mL/g of tissue/minute) within combined white and gray matter. A measurement of 10 mL/100 g of tissue/minute indicates infarction has occurred within minutes, a value of 10–22 mL/100 g/minute suggests potentially reversible neurologic dysfunction, and a flow of 22–40 mL/100 g/minute reveals the presence of oligemic tissue (8). Perfusion CT is a qualitative evaluation of the intracranial transit time of a bolus of contrast agent after intravenous injection (9). Single-photon emission CT (SPECT) after the intravenous injection of a radionuclide, such as radioactive technetium attached to the carrier hexamethylpropyleneamineoxime (Tc-99m-HMPAO), is also a qualitative technique for evaluating “perfusion.” This technique, with the use of tPA, recently has been shown by Ueda et al to be capable of differentiating those patients who are at risk for hemorrhage from those who have potentially reversible ischemia, regardless of the time elapsed after stroke onset (7). Perfusion MR is currently qualitative, but provides information regarding numerous perfusion parameters, such as cerebral...