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### **Diffusion-weighted MR Imaging of Multiple Sclerosis: Added Clinical Value or "Just Another Pretty Face?"**

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## Preoperative Identification of the Facial Nerve Achieved Using Fast Spin-echo MR Imaging: Can It Help the Surgeon?

In this issue of the *AJNR*, Dr. Sartoretti-Schefer et al (page 810) present a novel study investigating imaging of the facial nerve and its relationship with acoustic tumors. They point out that it has been reported in the literature that the facial nerve lies anteriorly to the tumor 98% of the time. With the T2-weighted fast spin-echo MR technique, they could identify consistently the entire course of the facial nerve in small tumors and found its position where expected (anterosuperior). Their article calls further attention to the kind of detailed preoperative imaging anatomy that is now available to the neuro-otologist with this technique. Other useful imaging data for the surgeon includes distance from the lateral tumor margin to the fundus of the internal auditory canal (IAC), and in smaller tumors, the nerve origin.

One of the major advances in the treatment of acoustic tumors has been the development of trans-temporal approaches (translabyrinthine and middle fossa) for their removal. These new surgical approaches allow positive facial nerve identification in the proximal fallopian canal (labyrinthine segment) where it is normal, and not involved with the tumor. Routine facial nerve preservation in most published series exceeds 90% as a result of the surgeon's confident facial nerve identification (1). For small tumor removal through the retrosigmoid approach, facial nerve identification in the lateral IAC is also routinely possible.

The other important advance in acoustic tumor treatment has been intraoperative facial nerve monitoring. This consists of continuous electromyographic monitoring of facial muscle activity, and allows identification and mapping of the course of the facial nerve by using electrical stimulation during surgery. This technique has led to improved postoperative facial nerve function (2).

With the combination of anatomic facial nerve location and intraoperative facial nerve monitoring, the facial nerve can be identified routinely during acoustic tumor surgery. Preoperative imaging of the facial nerve probably would not change the surgical approach or the intraoperative surgical technique. For acoustic tumors, the choice of surgical

approach is usually based on tumor size, tumor location, and hearing level. At our institution, we use the translabyrinthine approach for patients with poor hearing or who have large tumors. For patients with good hearing, we use the middle fossa approach for small tumors involving the lateral IAC, and the retrosigmoid approach for small tumors in the cerebellopontine angle and the medial IAC (3). There is debate regarding the tumor type associated with the unusual posterior course of the facial nerve (approximately 2% of cases, as stated by the authors). In my experience, this unusual facial nerve position is found only with facial nerve neuromas and meningiomas, and is not seen in association with acoustic tumors.

We have found preoperative fast spin-echo MR imaging to be helpful in our center in predicting the course of the facial nerve (and the eighth nerve) in patients with posterior fossa meningiomas. In these cases, the relationship of the facial nerve to the tumor is quite variable, and preoperative knowledge of its course can influence surgical technique and selection of surgical approach (4). Depending on the course of the facial nerve in relationship to the meningioma, an approach may be selected that leads to decreased manipulation of the nerve, improved visualization of the nerve, or transposition and rerouting of the nerve to augment access.

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## Diffusion-weighted MR Imaging of Multiple Sclerosis: Added Clinical Value or "Just Another Pretty Face?"

In this issue of the *AJNR*, Castriota-Scanderberg et al (page 862) describe the diffusion-weighted

imaging (DWI) findings from 10 patients with relapsing-remitting multiple sclerosis (MS), 10 pa-

tients with secondary-progressive MS, and 11 control subjects. Orientationally averaged apparent diffusion coefficient (ADC) values (" $\langle D \rangle$ ", equal to one-third the trace of the diffusion tensor) were computed for selected white matter regions of interest within T2-hyperintense plaques for each of the MS patients, as well as for selected normal white matter regions in the control subjects. Mean  $\langle D \rangle$  values were found to be significantly higher in the secondary-progressive group ( $1.45 \times 10^{-3}$  mm<sup>2</sup>/sec) than in the relapsing-remitting ( $0.95 \times 10^{-3}$  mm<sup>2</sup>/sec) or control groups ( $0.73 \times 10^{-3}$  mm<sup>2</sup>/sec). Also, these values correlated highly with disease duration and disability. This is not surprising, given the two clinical subgroups of MS that were studied. Additionally, for a smaller number of regions selected within MS plaques characterized by both T2-hyperintense and visually evident T1-hypointense signal intensity, a strong inverse correlation was found between the  $\langle D \rangle$  values and the T1 signal intensities. The authors conclude that  $\langle D \rangle$  values can be used "to distinguish between MS lesions of different severity, which are associated with a different degree of clinical disability."

These results are certainly intriguing, but they beg the following question. Does DWI contribute any new, clinically relevant data about MS that cannot already be determined using conventional T2- and T1-weighted MR imaging? For a new imaging technology, such as a novel pulse sequence, to displace older, more established techniques, it must either do a better job at detection (sensitivity) or diagnosis (specificity) of disease, or do an equally accurate job, but more quickly or less expensively. In the case of MS, DWI may satisfy the requirements of specificity, speed, and, possibly, of sensitivity, by providing visually evident "functional" data not otherwise easily obtainable. Clearly, further work is required to establish fully the role of DWI in the clinical evaluation of MS, but based on the preliminary results of Castriota-Scanderberg et al and others, we can answer "yes" to the question, "Does DWI offer added clinical value?"

MR imaging is the most sensitive test for detecting MS lesions of the craniospinal axis, and has become essential in the evaluation of this disease. The definitive diagnosis of MS, however, continues to be based on a spectrum of findings, the most notable being the occurrence of focal neurologic deficits that vary with time in both degree and location. The caveat that the diagnosis of MS remains primarily clinical cannot be over-emphasized (1). The characteristic MR appearance of MS plaques is that of multiple ovoid, well-circumscribed, T2-hyperintense foci, which may show halos of T2-hyperintense signal probably caused by inflammatory edema. Rarely, such lesions can be quite large, with a pseudotumor-type appearance. Approximately 10–20% of T2-hyperintense MS plaques are also hypointense on T1-weighted images (2). In the acute phase, this probably reflects vasogenic edema without underlying tissue destruction, and may be

reversible as inflammation wanes; in the chronic phase, this "black hole" appearance more likely reflects severe, irreversible tissue damage (2). The presence of contrast enhancement suggests blood brain-barrier disruption in acutely inflammatory lesions; without steroid treatment, enhancement may persist for 2 to 6 weeks (2). The extent of the T2 signal abnormalities at initial presentation, together with a history suggestive of demyelination, is strongly predictive of the risk of developing clinically definite MS within the next few years. In established MS, however, the correlation between the extent of the T2 signal abnormalities and disability is modest (1).

Although conventional T2-weighted MR imaging is highly sensitive in the detection of the white matter lesions of MS, it is limited, as is pointed out by Castriota-Scanderberg et al, by its lack of histopathologic specificity. Demyelination, inflammation, edema, gliosis, and axonal loss all may appear as foci of T2-hyperintense signal. These different pathologic entities not only reflect different stages of the disease, but are associated with different prognoses.

MS can manifest clinically in one of two major forms. Relapsing-remitting disease is characterized by repeated, acute bouts of exacerbations or relapses, separated by weeks or months of partial or complete clinical remission (3). The underlying histopathologic process of this form of disease appears to be remodeling of the demyelinated axonal membranes, such that they acquire a higher-than-normal sodium channel density, permitting increased action potential conduction velocity despite their loss of myelin (3). Progressive forms of MS, however, are characterized by an unrelenting downhill course, either beginning with the first clinical presentation (primary-progressive), or after a period of relapsing-remitting disease (secondary-progressive).

The pathologic substrate underlying progressive forms of MS has been elucidated only recently. Surprisingly, although every medical student "knows" MS to be the poster child for demyelinating disease (indeed, the demonstration of slowed nerve-conduction velocities as measured by evoked potential studies—a hallmark of demyelination—remains an important diagnostic feature of MS), MS recently has been proven to have components of both demyelination and axonal transection (3, 4). In a 1998 study using confocal microscopy and computer-based three-dimensional reconstruction techniques, axonal transection was shown to occur commonly in active MS plaques (both acute and chronic), and was postulated to be the pathologic correlate of the irreversible neurologic impairment found in this disease (4).

The idea that progressive axonal loss, in addition to demyelination, may be a feature of MS, is supported by radiologic studies. Early MR spectroscopy investigations using *N*-acetyl aspartate (NAA) as a neuronal marker showed reductions in cerebellar NAA that correlated with persistent disease

progression (5). In a more recent proton MR spectroscopy study, T1-hypointense MS plaques were found to correlate with axonal loss at autopsy and biopsy (6). In this work, NAA concentration correlated highly with the degree of T1-relaxation time prolongation within the spectroscopic voxels. Visually evident T1-hypointense lesions showed a lower concentration of both NAA and creatine compared with deranged but normal-appearing white matter, which showed less severe reductions in NAA only. These findings provide *in vivo* evidence of axonal damage in severely T1-hypointense MS lesions, and underscore the point that T1 relaxation, in itself, could be an important parameter in monitoring disease progression in MS (6). Thus, the presence of visually detectable, persistent, T1-hypointense signal within an MS plaque appears to have greater specificity than T2-hyperintense signal alone in identifying lesions associated with axonal loss, and therefore, could potentially aid in identifying MS patients with a more severe, progressive clinical course (6).

Other radiologic studies have suggested that the integrated use of "functional" MR imaging techniques, such as magnetization transfer and spectroscopy, might provide a more complete description of the pathologic features of MS than conventional MR imaging alone (7, 8). In a recent *AJNR*-published study that compared the combined magnetization-transfer and proton-spectroscopic MR imaging results of patients with relapsing-remitting, primary-progressive, and secondary-progressive MS with those of control subjects, the magnetization-transfer ratio (MTR) of normal-appearing white matter in MS patients was found to be significantly lower than that of the control subjects. MS lesions showed a large reduction in MTR, with old lesions exhibiting lower MTR than new lesions. Average lesion MTR and relative NAA concentrations correlated positively in patients with relapsing-remitting MS, and more strongly in regions containing new lesions (8). Importantly, the results of this study, as well as those of previously discussed studies by Trapp et al and van Walderveen et al, suggest that: 1) axonal damage is not exclusively a late feature of MS, and 2) even white matter that appears normal on conventional MR images may be histopathologically deranged. Although a number of the acute imaging changes of MS are reversible, persistent reduction in MR parameters such as NAA concentration, MTR, and T1 signal intensity, suggests the presence of demyelination, irreversible axonal degeneration, or both in many chronic MS lesions (1).

Could the addition of DWI further strengthen this imaging assessment of MS? DWI already has been shown to have great clinical benefit in the radiologic evaluation of acute stroke, as well as in the differentiation of arachnoid cysts from epidermoid tumors, and in the differentiation of epidural abscesses from sterile extraaxial fluid collections. Pilot investigations assessing the role of DWI in the evaluation of MS have shown that, unlike the

reduced or "restricted" ADC values found in regions of acute infarction, which reflect the presence of cytotoxic edema, the typical DWI abnormality found in MS plaques is that of truly elevated ADC values (9, 10). In early studies, this increased diffusivity of MS plaques, compared to that of normal white matter, appears to be more pronounced than corresponding T2 signal intensity changes (9).

The results reported by Castriota-Scanderberg et al present a compelling case for the specificity of DWI in distinguishing relapsing-remitting from secondary-progressive MS. A careful reading of Castriota-Scanderberg et al's method for region-of-interest selection additionally suggests the possibility that, because fewer T2-hyperintense plaques with concurrent T1 hypointensity were identified than T2-hyperintense plaques with concurrent elevated  $\langle D \rangle$  values, the finding of a markedly increased diffusion coefficient within an MS plaque might also be a more sensitive predictor of axonal injury, and thus of clinical progression, than the finding of T1-hypointense signal only. Although the authors did not report sufficient data either to prove or refute this hypothesis, their observations do support the assertion that DWI probably provides added clinical value regarding MR imaging's accuracy in the clinical subtyping of MS patients.

Like all good studies, this one raises far more questions than it answers. Does the degree of elevation of diffusivity within an MS plaque truly correlate with axonal injury? Is marked elevation of diffusivity within plaques really a more specific and sensitive indicator of a clinically progressive disease subtype than the degree of T1 prolongation is? What is the correlation between  $\langle D \rangle$  values and NAA concentrations? Between  $\langle D \rangle$  values and MTRs? Between  $\langle D \rangle$  values and enhancement? At my institution, we have observed only a poor correlation between the enhancement found in "new" MS plaques and their DWI signal changes. Only four enhancing lesions were noted in the study by Castriota-Scanderberg et al, and these were excluded from analysis. Might diffusivity changes correlate more highly with the axonal transection of "chronic" plaques than with inflammatory demyelination of "new" plaques? Under what clinical circumstances, if any, are reduced  $\langle D \rangle$  values found within plaques? Might the clinical value of DWI in MS be further refined, as has been suggested by some (and successfully applied in the setting of acute stroke), by a detailed assessment of diffusion anisotropy, the "shape" of the diffusion tensor, within and around plaques (11-13)?

Finally, how can discrepancies between the results of the study by Castriota-Scanderberg et al and those of others be explained (10)? Such discrepancies might be attributed to subtle yet important differences in the criteria for patient inclusion, or in the methods used for region-of-interest selection. Future MS imaging studies must carefully distinguish "acute" from "chronic" plaques based not only on their current MR imaging characteristics and clinical presentation, but on comparison with

prior studies. A well-designed study might also attempt to correlate conventional and "functional" MR imaging findings directly with those of serial follow-up MR examinations and long-term clinical outcome. The subtypes of relapsing-remitting, primary-progressive, and secondary-progressive MS would need to be defined rigorously according to a strict clinical standard of reference.

In conclusion, conventional MR imaging is a sensitive but not specific test for MS. MR imaging findings may be present in asymptomatic individuals; conversely, clinically definite MS may present occasionally with a normal T2-weighted MR examination of the brain and spinal cord (2). If the findings of Castriota-Scanderberg et al could be confirmed and expanded upon in a larger, well-controlled study, this could have important consequences with respect to MR imaging's ability not only to help one determine more accurately the clinical subtypes of MS patients, but to be predictive of prognosis or response to treatment. Conventional MR imaging, because of the poor correlation between MR signal abnormalities and clinical disability in established disease, is of only limited value as a surrogate marker of disease progression in MS clinical trials. DWI and other "functional" techniques have the potential to improve further the detection and characterization of clinically relevant lesions in MS patients, which could impact positively on patient care.

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## What More Can MR Imaging Teach Us about Brain Injury?

Head trauma is a major public health problem in the United States. As many as 75% of head-injured patients are classified as having "mild head injury." Mild head injury is associated with a significant morbidity, which may be associated with deficits in information processing on neuropsychological testing. These tests, as pointed out by McGowan et al in this issue of the *AJNR* (page 875), may also be sensitive to factors not related directly to the cognitive sequelae of the injury. Therefore, the severity of brain injury should not be evaluated exclusively by the extent of impairment as determined by neuropsychological tests; imaging techniques also should be used to detect anatomic and physiologic abnormalities of tissue in various parts of the brain.

Some investigators recently have proposed that CT should provide the basis for updated classification schemes of head injury. However, Mittl et al (1) showed in their study that MR imaging

should play a major role in any classification scheme of injury, especially in mildly head-injured patients. Their results revealed MR imaging changes compatible with nonhemorrhagic and hemorrhagic diffuse axonal injury (DAI) after mild head injury, which were not shown by CT in approximately 30% of cases. It has been accepted for some time that the greater sensitivity of MR imaging makes it a better study than CT for detecting the extent of injury and for predicting patient outcome.

Several different MR sequences have been studied in the evaluation of head trauma. The utility of fluid-attenuated inversion-recovery (FLAIR) MR imaging in head trauma has been studied by several authors. Ashikaga et al (2) examined 56 patients with head injury by using T2-weighted spin-echo and FLAIR sequences, and found the sensitivity of FLAIR images to be equal or superior to spin-echo images in evaluating traumatic lesions. Diffusion-

weighted MR imaging findings in traumatic brain injury were studied by Liu et al (3). They studied nine patients with conventional MR imaging as well as echo-planar diffusion-weighted MR imaging. They found that decreased apparent diffusion coefficient values can be demonstrated in patients with DAI in the acute setting and may persist into the subacute period, beyond that described for cytotoxic edema.

The article by McGowan et al in this issue investigates the possible relationships between quantitative magnetization transfer imaging (MTI) and neurocognitive findings in a set of patients who had experienced mild head trauma and had negative conventional MR imaging results. They found that the magnetization transfer ratio (MTR) in the splenium of the corpus callosum was lower in the patient group than in the control group, but no significant reduction in MTR was found in the pons. All of the patients demonstrated impairment of at least three measures of the neuropsychological tests, and in two cases a significant correlation was found between regional MTR values and neuropsychological performance. One of the important aspects of this study is that the authors are trying to find an even more sensitive study than conventional MR imaging, because the set of patients studied had negative conventional MR results. Their hypothesis was that quantitative MTI analysis would offer increased sensitivity over conventional MR imaging for the detection of traumatic brain injury in patients at risk for cognitive deficits secondary to mild traumatic brain injury (TBI).

Preliminary work using MTI has shown success in the detection of DAI in both animal and human studies, even when conventional T2-weighted images do not show the lesion. MTR can be used to detect changes in the structural status of brain parenchyma, which may or may not be visualized on conventional MR images. A clear physiologic explanation for lowered MTR in head trauma, how-

ever, has not been established. It is reasonable to suppose, as the authors in this issue have stated, that a lower MTR portends a less favorable outcome.

What is the future for imaging of head trauma? In a comparison of CT with 99-technetium hexamethylpropyleneamine oxime single-photon emission CT (SPECT) of the brain in TBI patients, the effects of brain trauma on regional cerebral blood flow (rCBF) were evaluated. SPECT showed differences in rCBF more often than lesions diagnosed with CT. Does this mean that there also may be a role for perfusion scanning in head trauma? What about MR spectroscopy (MRS)? While MTI provides structural information, MRS permits the detection of in vivo neurochemical alterations. Preliminary work using MRS in animal models and human TBI studies has shown changes indicating neuronal damage. Current animal studies are directed at preventing secondary neuronal damage from mechanisms such as ischemia, apoptosis, and excitatory amino acids. Imaging strategies and algorithms must be directed at the best means of early identification of patients at risk after mild TBI, to determine which patients may benefit from a specific treatment.

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