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Measurement of Volumetric Lesion Load in Multiple Sclerosis: Moving from Normal- to Dirty-Appearing White Matter

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Measurement of Volumetric Lesion Load in Multiple Sclerosis: Moving from Normal- to Dirty-Appearing White Matter

It is generally accepted that conventional T2-weighted MR imaging (T2WI) is sensitive in revealing macroscopic multiple sclerosis (MS) lesions. Nonetheless, the definitive diagnosis of MS remains clinical (1). Although MR imaging remains the best diagnostic test for the workup of MS, several studies have shown only modest correlations between the clinical neurologic deficits and lesion count measured by T2WI (2). Therefore, conventional T2WI techniques appear inadequate to characterize MS lesions fully, because that sequence is not specific for tissue abnormalities such as acute edema, demyelination, gliosis, and axonal loss, which share similar hyperintensite appearances at T2WI. On the other hand, other MR images may show better tissue characterization. For example, MS lesions with T1 hypointensity usually indicate axonal loss or transient acute edema (3). Gadolinium-enhanced T1-weighted imaging (T1WI) allows the separation of active MS lesions from inactive ones by showing enhancement due to the increased blood-brain–barrier permeability of acute inflammatory lesions. Nonetheless, these techniques have not successfully balanced sensitivity to MS lesions and accuracy in characterizing subtypes of tissue damage.

More recently, investigators have examined MS lesion burden that exists at microscopic levels by using innovative MR techniques. Specifically, normal-appearing white matter (NAWM) in MS patients was found to have significantly lower magnetization transfer ratio (MTR) than that of healthy control subjects. These findings coincided with a pathology report (4) in which up to 72% of white matter lesions that appeared macroscopically normal were abnormal at the microscopic level. One study showed that microscopic MS lesions in NAWM may portend development of new macroscopic lesions, suggesting NAWM as prelesional white matter changes (5). Similarly, other studies suggested that these early microscopic MS lesions may further evolve to become subtly visible at T2WI before they develop into full-blown acute demyelinating plaques, which are readily seen at conventional MR imaging. These ill-defined MS lesions, which occur mainly in the deep and periventricular white matter, have been described as dirty-appearing white matter (DAWM) at T2WI (6).

Although one may argue that some of these DAWM findings are actually convalescent demyelinating MS lesions, the concept that DAWM should be measured as MS lesion burden should not be overlooked. Nevertheless, this important concept can be challenged by many issues. One of the issues is that the definition of DAWM is not as clear as that of NAWM in terms of the T2WI signal intensity changes, because DAWM may be difficult to differentiate from the normal range of variability in white matter myelination that may also appear "dirty" at fast spin-echo T2WI. Similarly, in acute MS lesions, the often-associated perilesional edema can be misclassified as DAWM bordering the acute lesions. Others may ask whether these DAWM MS lesions are useful in predicting patients' clinical disability or outcome. To answer these questions confidently, a longitudinal correlational study between patients' clinical scores and a robust quantitative analysis of MS lesion burden based solely on DAWM measurement is required.

In this issue of the *AJNR,* Ge et al have taken a further step toward analyzing the MTR behavior in DAWM in patients with relapsing-remitting MS (RRMS). Analysis of MTR histograms from different tissue categories showed clearly distinguishable patterns reflected in several statistical measures (eg, mean MTR and peak height), possibly allowing further understanding of MS lesions in RRMS. Because even in limited-size autopsy specimens MS lesions are generally highly heterogeneous and contain essentially all different stages of disease progress, imaging evaluation of MS by using a single parameter is certainly difficult. Thus, the reported data for MTR in DAWM may be particularly interesting to the neuroscientists, because it may add to our understanding of the complexity and course of MS and may potentially help monitor the response to new therapeutic regimens.

The study by Ge et al represents a classic example of applying advanced imaging techniques (in this case, MTR combined with elegant image segmentation for analysis) to a particular biomedical target (in this case, the DAWM in RRMS), hoping to answer specific questions that are essential in clinical neurology. The study performed by Ge et al should bring to the attention of neuroradiologists the increasing capability of advanced MR techniques to help visualize both the *invisible* and the *uncertain* on routine images. Changes in MTR likely indicate, for example, alterations in chemical exchange of bulk water associated with that bound to the macromolecular environment (7). Therefore, from an analysis of MTR in tissues that are supposedly in different stages of the disease progress (ie, NAWM, DAWM, and lesion plaques), it might be possible to unravel the ongoing pathologic processes related to macromolecular changes in those T2-uncertain tissues (ie, DAWM at T2WI). In fact, techniques other than MTR may be used for such a purpose. Specifically, just as diffusion tensor imaging (DTI) can be used to study traumatic axonal injury (8) in which there is trauma-induced disorientation of neuronal fibers, DTI (9) has also been shown to reveal significant changes of microstructural anisot-

ropy in NAWM (9) and hence may likely be another effective technique to assess MS disease burden. Without doubt, technical developments in modern imaging modalities, together with clear understanding of the pathophysiology behind the diseases, are the essential elements pushing further improvements in the diagnostic efficacy of MR.

As with almost all research reports, however, ample room exists for further improvement. For example, the analysis employed by Ge et al compares histographic parameters (mean MTR, peak height) across multiple lesion types. Because of factors such as technical difficulties in precise control of the radio-frequency power for the magnetization transfer preparation pulses, the reported mean MTR values may not be directly comparable with those of other studies that used similar methods (6). On the other hand, the MTR peak height, which represents the percentage of tissue having MTR values corresponding to the value at the highest occurrence rate in a single tissue category (eg, DAWM), is at least subject to the choice of the number of groups when classifying MTR into a histogram. In such a case, the measure of kurtosis, in which a larger positive value indicates that the distributions are narrower and more "peaked" around its center, can be used as a histogram-free counterpart of the MTR peak height. More important, one needs to bear in mind that a histogram analysis only compares the statistical "trends" among different tissues rather than individually identifying the regional disease progress unambiguously. Even with the potential of cross-validated MTR analysis with T2WI findings and clinical features such as disease duration and the expanded disability status scores, definition of different lesion types continues to be determined manually. Unsupervised statistical or neural-network segmentation techniques, particularly sensitive to "peaks in a multivariate attenuation," might be helpful in this regard, if multitechnique MR imaging combining T2WI, contrast-enhanced T1WI, MTR, and even DTI were used in the future for better tissue classification. Ideally, different lesion types should be visually discernable, which is perhaps the most difficult goal in radiologic diagnosis of MS because of the heterogeneity and different types of the disease.

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CT versus MR for Acute Stroke Imaging: Is the "Obvious" Choice Necessarily the Correct One?

A spate of recent articles, including one by Saur et al in the May 2003 issue of *AJNR* (1), has confirmed the "obvious:" namely, that diffusion-weighted MR imaging is more sensitive and has greater interrater agreement than unenhanced CT for the detection of early ischemic signs of stroke.

Confirming the "obvious" is not an unimportant or trivial task and can sometimes lead to unexpected results. A possibly apocryphal legend has it that up until the time of the Renaissance when the Italian anatomist Andreas Vesalius actually *looked* in a horse's mouth to verify *for himself* what he would find there, textbooks incorrectly described the number of teeth horses have on the basis of centuries-old authority of the ancient Roman physician Galen. Analogously, in one of the first clinical reports of the diagnostic accuracy of diffusion-weighted MR imaging in acute stroke detection, Gonzalez et al (2) surprised us not so much with the finding that diffusion-weighted imaging has greater sensitivity than that of unenhanced CT (100% versus 45% in the small patient cohort studied), but with the revelation that in blinded review the sensitivity of unenhanced CT far exceeds that of conventional T2-weighted and proton density–weighted MR imaging (45% [unenhanced CT] versus 18% [T2- and proton density–weighted MR]). Indeed, until the advent of thrombolytic agents, which proved to be of benefit for acute stroke victims, and the consequent widespread need for imaging triage, the often-subtle unenhanced CT signs of early ischemia had typically been both overlooked by clinicians and underreported in the literature. Such early ischemic signs include: 1) parenchymal hypoattenuation with loss of gray matter–white matter differentiation owing to cytotoxic edema and possibly decreased blood volume (eg, "insular ribbon" sign); 2) sulcal effacement, also owing

to edema; and 3) hyperattenuated vessels owing to intraluminal thrombus (eg, "hyperdense middle cerebral artery [MCA]" sign).

Saur et al considered all of these factors in their CT assessment of early ischemic changes, with a resultant sensitivity of 73% (versus 93% for diffusion-weighted imaging) based on the consensus ratings of three neurologists, and 87% (versus 98% for diffusion-weighted imaging) based on the consensus ratings of three neuroradiologists (P = .04 for neurologist versus radiologist CT interpretation and P = .30 [NS] for neurologist versus radiologist diffusion-weighted imaging interpretation). These results are novel and noteworthy because, as the authors point out, earlier studies comparing CT and diffusion-weighted imaging findings were confounded by the relatively long time interval between the admission CT and initial diffusion-weighted examinations. In this investigation, the mean delay between imaging sessions was a brief 25 minutes. The authors' conclusion that diffusion-weighted imaging depicts early ischemia with higher sensitivity than that of CT has received strong recent confirmation. Fiebach et al (3) clearly showed this in a study in which CT and diffusion-weighted images were randomly obtained. That the radiologists performed significantly better than the neurologists for CT, but not for diffusion-weighted imaging, supports the contention that interpretation of subtle stroke CT findings is a learnable skill that improves with experience, but that interpretation of highly conspicuous diffusion-weighted imaging findings requires little specialized training. To be sure, arguably the greatest benefit of using an objective CT grading scheme, such as the Alberta Stroke Program Early CT Score ([ASPECTS]), for which interrater agreement is superior to that of the "1/3 MCA" rule, is that it compels the inexperienced reader to carefully examine *all* portions of the CT image (4).

The remarkably high sensitivity for acute stroke detection achieved by the neuroradiologists in this study (approaching 90%) is noteworthy and is likely related to the specific population studied, which consisted predominantly of large-vessel embolic stroke patients. Also, each reader was aware of the global suspicion for stroke during image analysis, which may explain why not blinding to the clinical history did not alter the results. Care was taken to optimize both imaging technique and image interpretation; center level and window width settings of the hardcopy CT images were appropriate for the detection of subtle decreases in Hounsfield attenuation. If anything, the tube current (mA) used during scan acquisition was larger than what is minimally required for an adequate signal-to-noise ratio (voltage was not reported, but is assumed to be 120–140 kV). The breakdown by time-to-imaging of the CT and diffusion-weighted sensitivities for detection of early ischemic signs, shown in Table 1 of the article by Saur et al, not only underscores the importance of *time* as a critical determinant of infarct conspicuity, but serves as a reminder that different pathophysiologic phenomena underlie the acute CT and diffusion-weighted imaging findings. Indeed, one wonders from this data if the sensitivity of CT and diffusion-weighted imaging are really all that different beyond a 3–4 hour time window.

Finally and most importantly, Saur et al's conclusion that their results "support the application of 'stroke MR imaging' for the management of acute stroke patients" fails to take into account the evolving use of *contrast-enhanced* CT techniques for neurovascular evaluation. Because, as compared with MR imaging, CT is rapid, inexpensive, and more readily available in a variety of urgent care settings, there is strong current interest in developing a combined unenhanced CT, CT angiography, and CT perfusion protocol for thrombolysis triage. Preliminary studies from multiple groups, including our own, suggest that the sensitivity of postcontrast CT angiography source images for acute stroke detection approaches that of diffusion-weighted imaging for all but the smallest distal emboli and lacunar infarcts (5). Moreover, there is increasing evidence from the MR, CT, and nuclear medicine literature that it is the *degree*, and not simply the *volume*, of ischemic change on blood volume and blood flow maps that may be a critical determinant of clinical and imaging outcome, as well as hemorrhagic risk, in response to thrombolysis. Thus, in the ongoing battle between CT and MR imaging as the first-line technique for acute stroke imaging, the "obvious" choice may not necessarily prove to be the correct one. Stay tuned.

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Suprasellar Monomorphous Pilomyxoid Gliomas

The proposed cell of origin generally forms the basis for the classification of primary brain tumors, a practice highlighted by Bailey and Cushing in 1926 (1) and continued to the present time (2, 3). Despite the

long history of the naming of tumors, "new" tumors continue to be identified when their correct cell of origin is identified by additional studies or modern technology. The cerebral neurocytoma typifies such a tumor whose histogenesis from neuronal lines rather than from oligodendroglial lines was recognized when electron microscopy identified tumor cell synapses. The advent of molecular biology has ushered in a new dimension to tumor classification, or reclassification, most notably in its current potential to distinguish between chemosensitive and chemoresistant infiltrating gliomas.

In 1999, Tihan et al (4) reclassified a subset of previously diagnosed pilocytic astrocytomas of the suprasellar-hypothalamic region on the basis of their more aggressive clinical course, monomorphous histology, myxoid features, and an absence of Rosenthal fibers. They termed these tumors "pediatric astrocytomas with monomorphous pilomyxoid features." Three additional cases were subsequently described by Fuller et al (5) and included the immunophenotype and electron microscopic appearance of these neoplasms. Because of the ultrastructural appearance was similar to the periventricular tanycyte, Fuller et al suggested a tanycytic origin for these tumors, although they concluded that current studies were insufficient to redefine this unique group of third ventricular gliomas as "tanycytomas."

In the present issue of the *AJNR,* Lieberman et al more fully detail the neuroradiologic features of Fuller's cases and add two additional cases with similar histology, immunophenotype, and ultrastructural features.

Are the available data now sufficient to classify these tumors as tanycytomas? Probably not. Location and ultrastructure are suggestive of tanycytic origin, but as Fuller et al have pointed out, they are insufficient for a definite statement regarding the histogenesis of this neoplasm. Additional immunohistochemical studies to examine other tanycytic antigens such as macrophage migration inhibitory factor (6) or a tanycytic-specific antigen such as P5 (7) would strengthen the hypothesis of a tanycytic origin of this suprasellar pilomyxoid tumor. The potential role of molecular biology in identifying the cell of origin is, or course, uncertain, but it has been helpful in distinguishing among the different glial tumors such as astrocytoma, oligodendroglioma, and ependymoma (2) as well as predicting biologic behavior (8). Classification as a "suprasellar pilomyxoid glioma" might be a compromise term until its cell of origin is established.

Sato et al (9) recently propose a tanycytic origin for the choroid glioma (9), a well-circumscribed third ventricular neoplasm. Its histology and more benign clinical course (10) separate it from the suprasellar pilomyxoid glioma and its molecular profile displays an absence of genetic mutations commonly associated with gliomas (11). Currently, there is insufficient information to determine links between the low grade choroid glioma with the more aggressive suprasellar pilomyxoid glioma.

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New Prospects and Ethical Challenges for Neuroimaging Within and Outside the Health Care System

In a recent *AJNR* editorial, Illes (1) described a new discipline of neuroethics emerging at the crossroads of biomedical ethics, research, and clinical neuroscience. With an explosion of studies and unprecedented applications of functional neuroimaging, especially with MR imaging (2), neuroimaging has garnered significant attention from the discipline. New capabilities have enabled functional mapping of

complex human behaviors such as moral reasoning and racial stereotyping never before imaged in the research environment and have begun to provide new forms of quantitative data about neurologic disease that may lead to improved diagnosis and treatment and even to predictive markers of disease. In the past, however, technological advancements have often outpaced consideration of their ethical, legal, and social implications (3). Here we present an initial approach to conceptualizing the neuroethical considerations for advanced neuroimaging, with a focus on the practical translation of capabilities from the laboratory to the clinical environment and outside the health care setting.

In an analysis of the distribution of studies involving functional MR imaging (fMRI) with a clinical component conducted between 1991 and 2001, we found that, collapsed over time, presurgical mapping studies (ie, for tumors and epilepsy; 33% of clinical studies), major psychiatric disorders including depression (18% of the studies) and neurodegenerative diseases including Alzheimer disease (12% of the studies) accounted for 63% of the data. The remaining 37% of the studies were divided among other categories such as drug and alcohol use, nonpathologic changes over the lifespan, and developmental pediatric delays. We also found that of a total of 642 review articles, 74% were devoted to either clinical studies (52%) or methods development (22%).

We infer from these data that there is vigorous momentum to transition imaging capabilities from the research setting into practical application. We are compelled to ask concurrently what moral reasoning will be needed to determine the trade-offs of risk and benefit of such complex new information in the clinical environment. How will a visual activation image affect physician practice patterns or patient insurability? How will this new form of quantitative information be protected, and what impact might the evidence provided by a brain image have on a patient's understanding about his or her own disorder? Such issues may be especially acute for disorders for which qualitative results from clinical or neuropsychological examination were the exclusive basis for diagnosis in the past, for functional images that are discordant with results obtained by using reference standards, and even for behaviors newly "medicalized" by imaging findings and not previously considered pathologic.

The issues for predictive imaging are no less trivial. Well known to the field of genetics is the ethical quandary of predicting the likelihood of a disease, such as Alzheimer disease, for which there is no cure at present. Whether neuroimaging comes to be used alone or adjunctively to genetic testing or others, neuroimagers will have to face old questions for the new domain: who should be tested; what procedures are needed to promote good surrogate decision making for impaired patients; what safeguards are needed for ensuring confidentiality, access to counseling, and protections from inappropriate advertising and marketing (4)?

In the public health arena, how will we manage brain activation information that might predict a propensity for sociopathy and suicide in adolescents and aggression in adults? If we project that neuroimaging services will become openly available in the consumer marketplace—like self-referred body scanning—they may also become available in our school systems. What are prospects for using neuroimages for screening or for justifying remedial training or therapeutic enhancement for behaviorally difficult students, those who have learning disabilities, or students who are gifted? Core issues such as who will have access to interventional programs, who will pay, and what is the duty to inform third parties engender significant moral debate. Further, but perhaps even more in the future, could advanced new medical capabilities such as those afforded by fetal MR imaging for the diagnosis of central nervous system disorders eventually become adopted for predictive screening for complex behavioral traits?

In an era of increasing violence in our society and increasingly powerful imaging capabilities for detecting neurobehavioral phenomena such as lying and deception (reviewed by Illes et al. [2]), the implications for responsible application of the technology in the criminal justice system also quickly surface. With heightened media attention to such scientific advancements and the predilection for juries to give great credence to expert testimony and evidence, appropriate dismantling of information available from visual images—whether they are structural CT studies, or any of an array of functional images including positron emission tomography, single photon emission tomography, electroencephalography, magnetoencephalography (MEG), or MR—by appropriately trained neuroimaging experts is critical to effective communication of the information that may be correlated to either guilt or innocence. In parallel, and as the ubiquity of neuroimaging technology such as fMRI becomes further realized, screening in highly trafficked public areas such as our national airports may become a true possibility. Who will be screened, who will interpret the data, and how the data will be used are but a few of the challenges with which we will be faced.

Once priorities for advancing neuroimaging capabilities are identified by neuroradiologists and others within the health care setting and outside it, a framework for addressing them will evolve through broad acceptance of the issues, a common language for engaging in dialogue about them, and evidence-based approaches to study them. New information available from brain images will also undoubtedly inform beliefs and practice involving mutual influences in the relationship between brain and behavior throughout the lifespan. Neuroethics will invariably be concerned with and call for further discussions of these issues. Whatever shape these discussions may take, it will be imperative to think about how to adjudicate between biologic influences on behavior in health and disease, environmental, and cultural effects and factors that are a function of the choices we make.

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