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Commentary

Hippocampal T2 Relaxometry in Epilepsy: Past, Present, and Future

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Mesial temporal sclerosis (MTS) is the most common known pathologic substrate of epilepsy. Accurate preoperative identification of unilateral MTS by magnetic resonance (MR) imaging has had a tremendous impact on the clinical management of medically refractory seizures. It was well known in the pre-MR era that obtaining a temporal lobectomy specimen that contained MTS conferred a higher probability of excellent postoperative seizure control for the patient than if the temporal lobectomy specimen was free of disease. However, that information was available only after the surgery had been performed. MR imaging now provides this information before surgery and the surgical risk-benefit decision-making process is made in a much better informed fashion. Patients with clear-cut unilateral MTS on MR images can be cited a 70% to 90% probability of being free of seizures after a temporal lobectomy (1, 2). In contrast, patients without MTS (or other epileptogenic lesions) on preoperative MR images have less than a 50% probability of being seizure free after lobectomy (1, 2). In turn, the frequency with which prolonged invasive electroencephalographic monitoring is used has declined dramatically. Invasive monitoring is generally considered unnecessary at this time in patients with clear-cut MR-identified unilateral MTS in whom the scalp-recorded electroencephalographic ictal onset is coincident with the side of the MR-identified abnormality.

End-stage or mature MTS is characterized histologically by cell loss and astrogliosis throughout medial temporal lobe limbic areas, but particularly in the hippocampal formation (3). Although several MR abnormalities have been described in association with MTS, the two principle MR findings in histologically proved cases of MTS are hippocampal atrophy and signal change indicative of increased tissue-free water (increased signal on T2-weighted images). Both of these principle MR correlates of MTS can be quantified. Tissue hydration is quantified via T2 relaxometry (4) and hippocampal atrophy is quantified via hippocampal volumetry (5).

The most common radiologic manifestation of MTS seen in clinical practice is a *unilateral* atrophic hippocampus with increased signal, with a normal-appearing contralateral hippocampus. The surgical approach to temporal lobe epilepsy (temporal lobectomy) is also driven by the concept that MTS is a unilateral phenomenon. However, autopsy studies and, more recently, quantitative MR studies (volumetry and T2 relaxometry) indicate that MTS is present *bilaterally* in a substantial percentage of patients with temporal lobe–onset seizures (3, 4, 6). For the sake of illustration, the entire spectrum of MTS can be divided into four possible conceptual categories (6): (*a*) unilateral hippocampal damage, in which MTS is present unilaterally, and the contralateral hippocampus is completely normal, (*b*) bilaterally asymmetric damage, in which MTS is present bilaterally, but is more severely represented on one side, (*c*) bilaterally symmetric damage, in which MTS is present and of equivalent magnitude in both hippocampi, and (*d*) symmetric normal hippocampi, in which neither hippocampus has changes of MTS. This fourth category is conceptually useful in the context of this discussion, because distinguishing mild MTS from a normal hippocampus is often not straightforward, either with MR imaging or with qualitative pathologic analysis. These four groups represent conceptual points along a continuous distribution of hippocampal damage ranging from normal to severe MTS in one or both hippocampi (6).

Most cases of MTS encountered for presurgical evaluation in general clinical practice will have hippocampal atrophy, increased signal, or, more commonly, both (7–11). The accuracy of visual inspection of an appropriately per-

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formed MR examination in the setting of clear unilateral MTS exceeds 90%. A recent evaluation of fluid-attenuated inversion-recovery imaging sequences showed an accuracy of 97% with pathologic determination of MTS as the standard of reference (12). Quantitative MR is unnecessary in this situation for clinical purposes. Visual discrimination of a normal from an abnormal hippocampus is straightforward when one is clearly normal and the other is grossly abnormal, but the visual binary paradigm breaks down in the presence of symmetric bilateral disease, mild disease, or both. While the clinical implications of identifying classic unilateral MTS on a preoperative MR study are quite clear, the clinical implications of bilateral MTS and mild MTS are not. Quantitative MR techniques (relaxometry and volumetry) useful in assessing bilaterality, and also in assessing the continuous distribution of damage from severe to mild to none, are well positioned to address these issues (5, 13–15). For example, do patients with bilateral MTS have worse surgical outcome than patients with unilateral disease? This can be stated more generically: is a different prognosis for postoperative seizure control associated with each of the four categories of MTS outlined above? Early results (5, 6), based on hippocampal volumetry, indicate that patients with classic unilateral MTS and those with bilateral but asymmetric MTS have essentially the same prognosis for postoperative seizure control, which is very favorable. Conversely, patients with bilateral symmetric MTS and patients with no MTS in either hippocampus have roughly the same prognosis for postoperative seizure control, which is unfavorable. However, these results are based on a relatively small number of patients, and further studies are necessary. If it is shown that surgical outcome is different among the four conceptual groups described above, then the next important research question will involve establishing numeric thresholds or cutoffs along this continuous distribution of bilateral disease, which will segment patients into those with a high probability of good seizure control after surgery versus those with a lower probability of good postoperative seizure control.

Another potentially important research area for quantitative MR imaging in epilepsy is memory. In general, outcome after a temporal lobectomy is thought of in terms of postoperative seizure control. However, the most common surgical complication is a postoperative decline in verbally mediated declarative memory after a dominant temporal lobectomy (16, 17). Given that declarative memory is mediated by medial temporal lobe limbic structures, particularly the hippocampus, this association between memory loss and temporal lobectomy is not surprising. The link between functional and anatomic integrity has led to the evaluation of quantitative MR imaging (the original studies were performed with hippocampal volumetrics) as a means of predicting postoperative memory decline (18–21). Not surprisingly, the neuroanatomic status of the hippocampus greatly influences the risk of a postoperative memory decline (18–21). A definite hemispheric effect is seen. The risk of a decline in memory (either verbal or visual spatially mediated) is not particularly great after a right temporal lobectomy. The risk of a verbal, but not visuospatial, memory deficit is substantially greater after a left temporal lobectomy. This risk is significantly greater if a nonatrophic hippocampus is resected; the risk is minimized if an atrophic hippocampus is resected. In addition, the risk to postoperative verbal memory after a dominant lobectomy is significantly higher in men with nonatrophic left hippocampi than in women with nonatrophic left hippocampi.

In this issue of the *AJNR*, Duncan et al (22) study the feasibility of in vivo hippocampal T2 relaxometry with a dual-echo spin-echo pulse sequence. T2 relaxometry of the hippocampi as a means of identifying MTS was originally described by Jackson et al (4), who used a 16-echo-train Carr-Purcell-Meiboom-Gill (CPMG) sequence fitted to a monoexponential T2 decay curve. Although this pulse sequence generated precise hippocampal T2 relaxometry data, a 12-minute time expenditure and additional imaging sequences with whole-head coverage for clinical imaging diagnosis were necessary. Duncan et al wish to replace the Jackson-Connelly 16-echo CPMG sequence with a double spin-echo pulse sequence that provides whole-head anatomic coverage and serves the dual purposes of routine diagnostic MR evaluation and estimation of hippocampal T2 relaxation.

Despite the efforts of numerous workers, tissue characterization with formal T2 relaxation measurements has not found widespread acceptance in clinical practice (23, 24). To some extent, this may be attributable to imprecision of the T2 relaxation measurements possible

with early MR instruments; this will be addressed in more detail subsequently. However, it may also be that MR-based quantitation (either relaxometry or volumetry) plays a uniquely useful role in the evaluation of MTS. The imprecision of T2 measurements that is caused by tissue volume averaging can be minimized because of the unique neuroanatomy of the hippocampus. Because of its longitudinal orientation, anisotropic imaging voxels oriented with their long axis parallel to the hippocampus may be placed completely within hippocampal parenchyma with minimal or no volume averaging effect. In addition, the knowledge that MTS exists bilaterally and also along a severity continuum, and that the "more abnormal" hippocampus is generally the site of seizure onset, is a paradigm that lends itself to image quantitation for clinical decision making in epilepsy more readily than other central nervous system diseases. However, quantitative techniques are useful only if the results are reproducible and stable and scale precisely with the severity of the disease of interest.

Duncan et al have admirably demonstrated that reliable and stable hippocampal T2 relaxation measurements can be made from a dual-echo conventional spin-echo sequence. Moreover, they have shown fairly good but not perfect scaling between hippocampal T2 values generated via the dual spin-echo pulse sequence and the established Jackson-Connelly 16-echo CPMG sequence (4). However, the clinical role of quantitative hippocampal measurements (either relaxometry of volumetry) centers on the ability of the technique to distinguish precisely *subtle* increments along the continuum of severe, mild, moderate, and no MTS. One of the main reasons often cited for failure of clinical acceptance of early attempts at T2 relaxometry was undersampling of the T2 decay curve (24). Early clinical T2 relaxometric studies often used two sampling points on the relaxation curve. One might expect less accuracy a priori with the dual-echo approach, given that it is a linear approximation (2 point fit) of an exponential phenomenon. When compared with a more thorough sampling scheme (such as the Jackson-Connelly 16-echo CPMG pulse sequence), a sparsely sampled measurement approach is more sensitive to noise, and is also less capable of characterizing the complicated relaxation behavior of biological tissues. The data presented by Duncan et al clearly demonstrate that (*a*) the T2 measurement is highly dependent on the pulse sequence parameters used, (*b*) the longer the second echo the larger the apparent measured T2 values become, and (*c*) the two-point approach used systematically underestimates absolute T2 values in phantoms. The rationale behind the selection of a 120-millisecond second echo is not explained. A second echo time longer than the 120 milliseconds selected might result in less underestimation of the T2 of pathologic tissue (25). It is not clear yet that the technique proposed by Duncan et al is capable of determining tissue T2 relaxation in vivo with sensitivity that is either equivalent to that obtainable with the Jackson-Connelly 16-echo CPMG sequence (4), or with sensitivity that is sufficient to distinguish precisely subtle increments along the continuum of the disease severity. This will await further clinical and pathologic correlative studies.

Finally, the measure of repeatability that Duncan et al use is the coefficient of reliability. This seems to be a useful means of statistically evaluating repeatability, or the test-retest variability inherent in a particular quantitative imaging measure. Unfortunately, it is difficult to assess exactly how well the technique of Duncan et al performs in this regard relative to other quantitative techniques reported in the literature, because of the absence of a universally accepted standard measure of repeatability for continuous quantitative radiologic measures. Continuous quantitative radiologic measures have been assessed by a number of statistical measures—correlation coefficient, coefficient of variation, percent variation, standard deviation, variance, and, here, the coefficient of reliability. It would be most useful if the radiologic community could agree on a single standard measure of reproducibility for continuous quantitative radiologic variables, much as κ values seem to have become accepted as a standard measure of the reproducibility of categorical radiologic data.

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