

of different diseases. For example, demyelinating lesions may have improved conspicuity at lower b values, whereas cortical lesions may be depicted better at higher b values. Although the article by Meyer et al focuses primarily on acute infarction, it also notes that the hypointense appearance of lesions with facilitated diffusion is accentuated with increasing b values. Most striking is an example of an oligoastrocytoma, which appears isointense at $b = 5000 \text{ s/mm}^2$, but markedly hypointense at $b = 5000 \text{ s/mm}^2$ and $b = 3000 \text{ s/mm}^2$. Clearly, much of the advantage of increased b values may lie not with the diagnosis of lesions with restricted diffusion, especially acute infarcts, but with allowing a more complete understanding of other types of disease. For example, in demyelinating and dysmyelinating diseases, the true nature of enhancing lesions may become more obvious. The differences in the diffusion characteristics of the advancing, enhancing rim versus the central portion of the lesion may be accentuated, confirming even more strongly the behavior of these types of diseases as involving not only the destruction of myelin, but also of axons in the central core of the lesion.

Ultimately, all three articles in this issue point out how simplistic much of our current approach to clinical diffusion-weighted imaging is at the moment, and how much room for future exploration

remains. Diffusion imaging has become an essential part of clinical MR imaging, and it is difficult to imagine routine imaging without it. Nonetheless, we are on the threshold of an even higher level of complexity and understanding of diffusion-weighted imaging.

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The Status of Status: Seizures Are Bad for Your Brain's Health

What is the relationship between seizures and brain dysfunction? Because seizures and epilepsy represent symptoms of an underlying disorder, rather than the disorder itself, their relationship to cognitive function is variable. Although 0.5% to 1% of the population suffers from recurrent seizures, most lead productive lives. In some cases, abnormal cognitive function coincides with seizure activity because both represent different phenotypic displays of the underlying etiology, such as in diffuse developmental conditions like the agyria-pachygyria disorders. Cognitive impairment also occurs during and after the ictus, and may accompany treatment with antiepileptic drugs. Two important questions are raised: do seizures directly cause brain damage, and do they augment epileptogenicity? If seizures do cause progressive brain or epileptogenic dysfunction, then early intervention for seizure control is indicated in order to prevent further brain injury.

A number of experimental animal and clinical imaging studies support the idea that seizures by themselves cause brain damage (1). Experimental animal models have shown that intense limbic seizures result in a pattern of hippocampal damage similar to hippocampal sclerosis. Similar imaging changes have been reported in the human hippocampus after prolonged nonfebrile or febrile seizures; the hippocampus initially becomes enlarged

and hyperintense, and then later atrophies. Several MR imaging studies have correlated hippocampal atrophy with duration of epilepsy. Gray matter volume has been negatively correlated with seizure duration, suggesting that neocortical changes may be a consequence of seizures. One study found that generalized seizures appear to cause progressive brain dysfunction in patients with temporal lobe epilepsy. Frequent generalized seizures were correlated with bilateral temporal lobe metabolic dysfunction by use of MR spectroscopy, and ipsilateral atrophy by use of MR volumetry.

When seizure activity is markedly prolonged, as in status epilepticus, brain damage can occur quickly and be profound. Histologic studies from both humans and animal models have shown that brain damage primarily affects the hippocampus, amygdala, and piriform cortex; the cerebral cortex, cerebellar cortex, and thalamus are affected to a lesser extent. MR imaging with long TRs have shown regional hyperintense changes that occur during or immediately after onset of seizure activity in humans with status epilepticus (2). These changes usually resolve with time, followed by regional atrophic changes.

Status epilepticus can also be evaluated by diffusion-weighted MR imaging and apparent diffusion coefficient (ADC) measurements (2, 3). Although a number of studies describe these rela-

tionships in detail, the reports by Men et al (a clinical case report, page 1837) and Wall et al (an animal study, page 1841) in the current issue of the AJNR enhance our knowledge by their wonderful correlation with histopathologic findings. While diffusion changes have been reported in humans with status epilepticus, there is a paucity of histopathologic correlation (2). With regard to animal models of status epilepticus, diffusion changes are well documented. Sequential, correlative diffusion-pathologic changes, however, have not been described for the first 24 hours after the onset of status epilepticus as provided by Wall et al. Correlative studies are imperative for us to understand what seizure-induced imaging findings truly represent, and in turn, the pathophysiology of this type of brain damage.

What is the current understanding of diffusion changes induced by status epilepticus? Transient decreases in ADC (and increased signal changes on diffusion-weighted images) are observed in regions of seizure activity, usually accompanied by hyperintense signal changes on long-TR images. The regions with decreased ADC correspond to regions of transient, increased perfusion and EEG abnormalities. The most affected regions are the amygdala, piriform cortex, and hippocampus. The cerebral cortex, cerebellar cortex, and thalamus are involved to a lesser extent. In animal models, decreases in ADC occur as early as 1 hour after status epilepticus, become most pronounced at about 24 hours, and then normalize over the next week (3). In humans, the time course is less well defined, but also appears to be transient. The diffusion changes, accompanied by signal changes on T2-weighted images, usually resolve when imaged weeks later and atrophy ensues. Hyperintense signal changes on long-TR images may persist, especially in the hippocampus and amygdala. These acute changes can be differentiated from those caused by stroke by using perfusion-weighted MR imaging techniques. Unlike in cases of stroke, there is a focal increase in regional cerebral blood volume and an increased mean transit time.

The diffusion changes appear to be due to seizure-induced changes in cellular membrane permeability and ion homeostasis, with a resulting elevation of extracellular potassium and an influx of sodium and calcium. Swelling of neurons and glial cells occurs as free water rapidly follows the osmotic gradient into the cells. ADC values are

thought to increase because of the rapid shift of water from extracellular compartments to the more restrictive intracellular environment. T2 measurements are prolonged because of the increase in water content. Swelling of cells may lead to irreversible cellular edema, resulting in selective neuronal necrosis as described by Wall et al and Suleyman et al. As the cells lyse, ADC values normalize over time and MR imaging reveals atrophic changes.

While there is now abundant evidence that status epilepticus is detrimental to brain tissue, and that diffusion-weighted imaging (and ADC maps) can document this damage, several questions remain. Does abnormal diffusion (and ADC values) always mean subsequent neuronal death? The answer appears to be no for the retrosplenial cortex, according to Wall et al. Case reports of seizure-induced, transient diffusion changes without associated T2 changes may also represent cases of reversible cellular changes. What is the explanation for the ADC changes in the hippocampus in the study by Wall et al? The answer is not clear. ADC increases in the amygdala and piriform cortex in the pilocarpine model of status epilepticus as reported by Wall et al and the kainic acid model reported by others (3). However, Wall et al report a decrease in hippocampal ADC values, whereas those using the kainic acid model report an increase. The explanation provided by the authors does not appear to be sufficient.

Our understanding of the pathogenesis of seizures is still incomplete, but studies that correlate imaging findings with cellular microenvironment (like the reports in this journal) will help fill in the gaps.

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