

## DO EARLY HIPPOCAMPAL IMAGING CHANGES PREDICT LATER SCLEROSIS?

**Acute Symptomatic Seizures and Hippocampus Damage: DWI and MRS Findings.** Parmar H, Lim SH, Tan NC, Lim CC. *Neurology* 2006;66:1732–1735. The authors describe diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) changes in the hippocampus within 48 h of acute symptomatic seizures or status epilepticus in 12 patients. DWI showed increased signal and a decreased apparent diffusion coefficient (ADC) in all patients, with corresponding lactate detected on MRS in six patients and EEG seizure activity in nine patients. On follow-up, the atrophic hippocampus had an increased ADC in six patients. DWI and MRS may predict development of hippocampal sclerosis.

### COMMENTARY

Only a few years ago, diffusion-weighted magnetic resonance imaging (DWI) was used almost exclusively for the diagnosis of acute ischemia (1). However, the technique since has been shown to be useful in the localization of the epileptogenic zone, when performed periictally (2–4). The signal in DWI depends on the translational motion of tissue water. Therefore, when ischemia is present, a restriction in the diffusion of free water occurs because of a shift of water from the outside to the inside of the cell. These differences in variation of water mobility in extracellular spaces are expressed quantitatively as changes in the apparent diffusion coefficient (ADC) and qualitatively as changes in DWI signal intensity. As a consequence, a restriction in the diffusion of free water is seen not only in ischemia, but in status epilepticus as well, and is referred to as a “high signal” in the DWI images. Concomitantly, the ADC is low. However, ADC measures water diffusivity as well as factors such as barrier permeability and diffusion time, since the diffusion of water molecules is guarded by biologic barriers in the brain tissue (e.g., cell membranes and cellular organelles). ADC values are measured in several directions, and ADC maps are created to produce a direction-insensitive measurement of the diffusion.

Not only are the changes in ADC seen during a seizure or status epilepticus similar to the ones seen in ischemia, but they also are similar in how rapidly they happen and in some cases, the reversibility of them. The reasons for these alterations are still a matter of controversy, but they are likely related to changes in water compartmentalization, restricted space, permeability, and, of course, ischemia. What is known is that the localization of these changes correlates with the localization of the epileptogenic focus.

Similarly, magnetic resonance spectroscopy (MRS) is another relatively new, noninvasive technique; however, it permits the *in vivo* and *in situ* measurement of specific brain metabolites. The main <sup>1</sup>H-MRS signal intensities are from *N*-acetylated compounds, mainly *N*-acetyl aspartate (NAA),

creatine and phosphocreatine, and choline compounds. Because of the predominant neuronal distribution of *N*-acetylated compounds, they are considered markers of neuronal cell loss and/or dysfunction (5). The application of this property to MRS makes MRS very useful as a diagnostic tool in the presurgical evaluation of patients with epilepsy. Parmar et al. combined the neuroimaging techniques of DWI and MRS to evaluate acute seizure-associated damage and to attempt to predict subsequent hippocampal sclerosis. Although efforts to predict hippocampal sclerosis are not novel, Parmar and colleagues bring new insights to this continuously revisited issue.

In a previous study, Farina et al. found that an increase in signal seen on DWI studies of patients with new-onset, prolonged seizures do correlate with the development of unilateral hippocampal sclerosis (6). The follow-up procedures used in the work by Farina and colleagues were better designed than those in the study by Parmar et al., as they repeated MRI studies in three of their five patients after 6 months of the initial event and after only 2 months in the other two patients. In the group of three patients, the authors found clear evidence of hippocampal sclerosis, while the other two patients showed no sign of hippocampal sclerosis—perhaps, because of the very short latency time.

Serial MRI studies in children experiencing febrile status epilepticus have unequivocally demonstrated that prolonged febrile seizures can result in hippocampal atrophy and sclerosis (7). These observations, along with those of Parmar et al. and Farina et al., confirm that injury occurring during status epilepticus or prolonged seizures can produce the lesion of sclerosis. Currently, it is unknown whether these seizures and the hippocampal changes seen on DWI are an initial precipitating injury; the issue will need to be determined by longitudinal observation of the hippocampal lesion and of the incidence of development of unprovoked seizures.

The factor that made the study by Parmar and colleagues so interesting was the use of MRS, which also has been used to evaluate the progression of disease in patients with established temporal lobe epilepsy. However, the majority of studies associating severity of hippocampal atrophy with duration of epilepsy or with estimated number of seizures have been cross-sectional (8,9), which precludes establishment of cause and effect or of

the interpretation that repeated seizures produce volume loss. It has not yet been clarified whether hippocampal sclerosis is more prevalent within specific subtypes of temporal lobe epilepsy and whether some subtypes have progressive neuronal loss and dysfunction, while other subtypes do not. What has been shown with certainty is that NAA reductions at a single point in a refractory temporal lobe epilepsy group do not support progressive NAA reductions (10). The need for a longitudinal study that controls for age, age of onset, seizure frequency, frequency of secondarily generalized seizures, and duration of epilepsy is indisputable.

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