Diffusion-Weighted Magnetic Resonance Imaging in Nonconvulsive Status Epilepticus

Kon Chu, MD; Dong-Wha Kang, MD; Joo-Yong Kim, MD; Kee-Hyun Chang, MD; Sang Kun Lee, MD

Background: In human and experimental models, diffusion-weighted magnetic resonance imaging (DWI) findings in status epilepticus (SE) have been reported to show that apparent diffusion coefficients are reduced during the initial phase and normalized or increased in the later phase of prolonged SE. This effect is caused by cytotoxic edema induced by excitotoxicity. In humans, only focal DWI abnormalities have been reported in partial SE.

Objectives: To report and discuss the DWI findings suggesting diffuse neuronal injury in a patient with nonconvulsive SE.

Design and Methods: A 56-year-old man was admitted because of changing levels of consciousness over 3 days. On admission he was comatose. He had nystagmoid eye movement, forced eye blinking, and oroalimentary automatism. The results of a search for possible infectious and metabolic etiologies were negative, and electroencephalographic findings showed continuous, semirhythmic, bifrontal sharp waves of 2 Hz. Phenytoin and midazolam hydrochloride were infused to alleviate the seizure activities. He underwent DWI initially (3 days after the onset of seizure) and at the 5-month follow-up.

Setting: The neurology department of a tertiary referral center.

Results: During SE, DWI findings showed marked, diffuse gyriform cortical hyperintensity throughout the brain. The apparent diffusion coefficient decreased in the corresponding areas, especially in the occipital lobes. Findings from T2-weighted magnetic resonance imaging showed the intense cortical hyperintensity with gyral swelling and no involvement of brainstem, basal ganglia, thalamus, and white matter. The follow-up DWI findings showed marked atrophy and hypointensity in the corresponding regions. The apparent diffusion coefficient increased in the corresponding regions.

Conclusions: Diffusion-weighted imaging in our patient indicated that the magnetic resonance imaging abnormalities of the affected cortex were due to cytotoxic edema caused by neuronal excitotoxicity during prolonged SE. Diffusion-weighted imaging can be used in the localization of seizure focus for predicting the prognosis of the affected tissue and for researching the basic pathophysiology of SE.

Arch Neurol. 2001;58:993-998

STATUS EPILEPTICUS (SE) is one of the most common life-threatening neurologic disorders. It is defined as more than 30 minutes of (1) continuous seizure activity or (2) 2 or more sequential seizures without full recovery of consciousness between seizures.1 Data from animal studies suggest that seizures lasting longer than 30 minutes may be associated with increased neuronal injury.2 The pathophysiologic characteristics of SE involve a complex interaction of excitatory and inhibitory mechanisms, which both initiate and maintain generalized convulsive SE and nonconvulsive SE. Diffusion-weighted magnetic resonance imaging (DWI) is based on the translational movement or diffusion of water,3 and has been known to identify early brain ischemic injury as a hyperintense region.6 The apparent diffusion coefficient (ADC), which is a measure of water diffusion and is independent of T1 and T2 relaxation times, can be calculated. In the acute stage of cerebral ischemia, the depletion of metabolic substrates leads to the failure of the sodium-potassium ion adenine triphosphatase pump and subsequently to cytotoxic edema. This in turn hinders water diffusion.7 In animal models, DWI abnormalities similar to ischemia have been reported in status epilepticus.8-10 An early decrease and late increase of the ADC have been observed. The mechanism of the early decrease of the ADC has been proposed to be cytotoxic edema due to excitotoxicity.
PATIENTS AND METHODS

CASE HISTORY

A 56-year-old man was admitted for altered consciousness. Three days before admission, his family members found him unresponsive in the morning. Gross convulsive movement was absent. They observed forced eye blinking, nystagmoid movements in both eyes, and intermittent chewing movement. The patient was afibrile and acyanotic. He had a history of pontine hemorrhage 4 years previously; however, he had since enjoyed good health. He had no history of seizure or hypoxic damage. He was admitted to another hospital on the day of onset.

In the emergency department at the initial hospital, the patient was comatose and did not respond to painful stimuli. Vital signs, electrocardiographic results, and laboratory findings, including those from arterial blood gas analysis, were normal. He was not cyanotic and had no convulsive movement. He had only eye movements and lip smacking. The results of brain magnetic resonance imaging (MRI) performed at the hospital on the day of onset showed diffuse high signal intensities and cortical swelling on the T2-weighted image and no involvement of basal ganglia, thalamus, or white matter. The patient was diagnosed as having nonconvulsive SE, and diazepam was infused intravenously but did not correct the clinical status. The patient was transferred to our hospital on the second day of onset.

On admission the altered consciousness, eye signs, and chewing movement were persistent. Vital signs and laboratory findings were normal. The results of a cerebrospinal fluid (CSF) examination showed normal cell count and chemistry profile; IgG index was normal, and an oligoclonal band was negative for bacteria, fungi, and mycobacteria. Viral polymerase chain reaction and antibody analysis of cerebrospinal fluid were negative. The results of electroencephalography (EEG) performed on the third day of onset showed continuous, semirhythmic, bifrontal sharp waves of 2 Hz (Figure 1A). Continuous EEG monitoring showed the sudden development of 8-Hz rhythmic waves on the left temporal area (Figure 1B). After a 42-second run of rhythmic activity, the neurologists (K. C. and S. K. L.) observed a rhythmic chewing movement (oralomotor automatism) (Figure 1C).

Brain MRI (including T2-weighted, T1-weighted, fluid-attenuated inversion recovery, and diffusion-weighted) and magnetic resonance (MR) angiography were performed on the third day of onset. Phenytoin and lorazepam were infused intravenously but did not correct the clinical status and EEG findings. A continuous infusion of midazolam hydrochloride was tried, and when the dose was increased to the extent of burst suppression, the eye signs disappeared. Midazolam administration was continued for 2 days and then tapered. The results of EEG performed on hospital day 6 showed a generalized, diffuse, and mixed slowing of background activity. The administration of diphenylhydantoin and valproic acid was continued, and he was discharged in a persistent vegetative state on hospital day 60.

DATA ACQUISITION AND ANALYSIS

The patient underwent DWI with conventional MRI on a 1.5-T system (Signa Horizon, Echospeed; General Electric Medical Systems, Milwaukee, Wis) equipped with an echo planar imaging capability. Diffusion-weighted images were obtained in the transverse plane using a single-shot echo planar spin echo pulse sequence with 6500/107 milliseconds, 1 excitation, and 2 b values (0 and 1000 s/mm²). The diffusion gradient pulse duration was 31 milliseconds with a gradient separation of 33 milliseconds and a gradient strength of 2.16 G/cm. The diffusion gradients were applied simultaneously along 3 axes (x, y, z). From the Stejskal-Tanner equation, the ADC was calculated as the negative slope of the linear regression line best fitting the points on the b value vs natural log plot, where the signal intensity is from the image region of interest acquired at each b value. Maps of the ADC were created using this calculation on a pixel-by-pixel basis.

RESULTS

In humans, there have been a few reports of DWI abnormalities in partial SE13-16 in which DWI hyperintensities occurred in the epileptic foci. However, DWI abnormalities suggesting diffuse neuronal injury in nonconvulsive SE have not been reported in humans.

During SE, DWI findings showed marked, diffuse gyriform cortical hyperintensities throughout the brain. The signal intensities in the corresponding areas on the ADC map were hypointense (Figure 2A-B). The ADC decrease ranged from 341 to 570 × 10⁻⁶ mm²/s and was most severe in the occipital lobe. The spared cortex showed normal ADCs (Figure 2B, arrow). The DWI in the underlying white matter showed hypointense areas, and the corresponding ADC increased. Absolute ADCs are summarized in the Table. The T2-weighted and fluid-attenuated inversion recovery images demonstrated diffuse cortical hyperintensities in the abnormal regions on the DWI; elsewhere they showed normal white matter, basal ganglia, and brainstem. The results from the MR angiography were normal. In the results of the 5-month follow-up DWI (Figure 3A-B), the cortical hyperintensities on the previous DWI were reversed, ie, hypointense and accompanied by cortical atrophy and ventricular enlargement. Atrophy was at its most severe in both occipital lobes, which had the lowest ADC during SE. The ADC map showed diffuse hyperintensities. The low signal intensities of the underlying white matter on the initial DWI were normalized.

COMMENT

Our patient had nonconvulsive SE. The classification of the type of seizure in our patient was rather obscured because of the time delay from the onset to the diagnosis (3 days) and lack of convulsive movement. The definition of nonconvulsive SE is still evolving, so it is difficult to determine the complications associated with it, although classifications based on clinical presentation and underlying pathophysiologic characteristics have been proposed.17-20 According to the classification, our patient can belong to

(REPRINTED) ARCH NEUROL/VOL 58, JUNE 2001 994 www.archneurol.com

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the indeterminate group. However, there was evidence of focal seizure onset in our patient. First, the focal, rhythmic, 8-Hz waves preceded the rhythmic chewing movement. Second, the ADCs differed in various lobes, with the lowest in the occipital lobe and the highest in the frontal lobe.

During this study, we observed for the first time diffuse DWI abnormalities of nonconvulsive SE in a human. The ADC during SE in our patient decreased significantly, and there were some regional differences. We did not measure the relative decrease of the ADC because of the bilaterally widespread cortical involvement. The MRI findings of our patient were not possibly caused by cerebral ischemia or hypoxic damage. The results of the MR angiography were normal. The predilection site of the hypoxic-ischemic encephalopathy is basal ganglia and thalamus, which was not involved in our case. Furthermore, such a “cortex only” involvement is not possible in cerebral ischemia.

There have been previous reports of DWI abnormalities in experimental SE models and human epilepsy partialis continua. In rats, ADC decreases from 14% to 49% have been observed in kainate- or flurothyl-induced SE. Ebisu et al demonstrated that during the time course of ADC decreases in kainate-induced SE models, decreased ADC was observed at 12 hours, with little evidence of histologic or T2-weighted MRI changes. Fujikawa reported that the longer SE was sustained, the more neuronal death occurred in a pilocarpine-induced SE model. Righini et al observed that the initial decrease in ADC could be reversed, and the ADC later increased. The area of hyperintensity on DWI was concordant with the histologic distribution of neuronal pyknosis and neuropile vacuolation.

The decrease in the ADC in SE is believed to be due to cytotoxic edema; however, it cannot be a consequence of ischemia. In SE, cerebral blood flow has been shown repeatedly to rise severalfold in most parts of the brain to the highest level recorded during any condition. The ADC decline has been shown to correlate with a decrease in the extracellular space volume fraction and an increase in extracellular tortuosity, both of which are manifestations of massive cell swelling (ie, cytotoxic edema). The study of the N-methyl-D-aspartate–induced excitotoxicity model demonstrated that the disorganization of the cytoplasmic matrix can be crucial in raising intracellular obstacles. Swelling of cell organelles, disaggregation of polyribosomes, progressive cytoplasmic and karyoplasmic condensation, proliferation of intracellular membranes, and an increase in the number of cytoplasmic fibrillary structures may contribute to an increased resistance to the mobility of intracellular compounds. Wang et al reported an increase in sodium concentration in the pyriform cortex of rats during SE. They proposed that this might have been due to an energy failure of the sodium-potassium ion adenosine triphosphatase pump, which in turn could lead to sodium ion and water influx. However, other studies that have found increased oxygen pressure in the draining vessels of the epileptic region and no change in adenosine triphosphate levels do not support this hypothesis. Other proposed mechanisms of cytotoxic edema in SE include excessive release of excitatory amino acids (such as glutamate) and increased membrane ion permeability.

In our patient, the initial decline of the ADC was reversed during follow-up, and cortical atrophy occurred in the corresponding areas. This is in accord with several ani-
mal studies that have histologically demonstrated neuronal cell death following SE, and with 2 previously described human cases of radiologically confirmed brain atrophy following SE. The possible cause of increased ADC in follow-up DWI may be gliosis, extracellular volume expansion, neuronal cell death, and partial volume effect. Our patient had intractably prolonged nonconvulsive SE, resulting in neuronal injury. The theoretical basis for neuronal injury resulting from nonconvulsive SE may be identical to that from generalized convulsive SE; however, the underlying pathophysiologic characteristics of the various subtypes of nonconvulsive SE have not been investigated, so this remains speculative. There is evidence

<table>
<thead>
<tr>
<th>Region</th>
<th>Initial DWI</th>
<th>Follow-up DWI</th>
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<tbody>
<tr>
<td>Cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>412 ± 39</td>
<td>1575 ± 42</td>
</tr>
<tr>
<td>Temporal</td>
<td>570 ± 36</td>
<td>1474 ± 47</td>
</tr>
<tr>
<td>Parietal</td>
<td>356 ± 50</td>
<td>1772 ± 46</td>
</tr>
<tr>
<td>Occipital</td>
<td>341 ± 37</td>
<td>1842 ± 51</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying</td>
<td>1338 ± 64</td>
<td>1162 ± 59</td>
</tr>
<tr>
<td>Periventricular</td>
<td>820 ± 35</td>
<td>924 ± 41</td>
</tr>
</tbody>
</table>

*ADC indicates apparent diffusion coefficient; DWI, diffusion-weighted magnetic resonance image. All data are mean ± SD (×10⁻⁶ mm²/s).
of neuronal injury in complex partial SE and nonconvulsive SE associated with severe brain injury.²⁰,³³-³⁵

Some areas in the frontoparietal lobes of our patient were spared at the time of the initial and follow-up DWI. These findings suggest that more selective involvement can occur, even in diffuse EEG change. The ADCs of the occipital lobes were much lower in the initial study, and the cortical atrophy was the most profound finding in the posterior temporal and occipital lobes in the follow-up. Persistent eye blinking and nystagmoid eye movements might be explained by the greater involvement of the occipital lobes. The reason why the occipital predilection occurred is not understood. We would like to suggest some explanations: First, the patient's initial seizure onset might be in the occipital lobe and precede the secondary generalization. Second, occipital involvement might have been due to spreading from elsewhere, such as the temporal lobe. Ebisu et al²² reported that their observations by MR spectroscopy and DWI, which showed little histologic change, suggested that these modalities may detect epileptic foci. Signal changes were present in regions known to exhibit electrographic seizure activity in this model.³⁶,³⁷ In contrast, signal abnormalities were not present in regions that are not susceptible to kainate. Zhong et al²⁸ observed that

Figure 3. A-B, Follow-up diffusion-weighted image performed at 5 months after onset shows diffuse low signal intensities in the cortical regions and cortical atrophy. The atrophy is most severe in the temporo-occipital lobes. C-D, Follow-up apparent diffusion coefficient map shows diffuse high signal intensities in the corresponding cortical areas (marked by squares).
the ADC of brain water rapidly decreases in portions of the brain after cortical electric shocks and that the magnitude of the drop in seizure-related ADC correlates with the duration of brain activation. In their experiment, 10 seconds of bifrontal electroshock resulted in a 14% drop. Stimulation for shorter periods caused smaller changes. Only portions of the parietal and temporal lobes showed changes, not the whole brain. This suggests that the volume of cortex with an altered ADC might define regions of chronically discharging tissue in an epileptic brain. Hence, all this evidence suggests that DWI may play a crucial role in clarifying the epileptic focus and predicting the clinical or histologic prognosis, even in cases with diffuse EEG changes.

Wieshmann et al. observed that the ADC of underlying white matter increased 27%; however, Lansberg et al. reported normal ADCs in white matter. The ADCs of the white matter in our patient increased (13.88 ± 6.4 × 10⁻³ mm²/s). Our findings are concordant with those of Wieshmann et al. and with experimental studies that showed vasogenic edema in the underlying white matter. Wieshmann et al suggested that a possible mechanism involved water shift, which is caused by a breakdown of the blood-brain barrier. During SE, the extracellular space expands in areas remote from the neuronal activity, and this may explain the increase in the ADC in white matter. Diffusion-weighted imaging in our patient indicated that the MRI abnormalities of the affected cortex were due to cytotoxic edema caused by neuronal excitotoxicity during prolonged SE. Our findings suggest that DWI can be used to locate the seizure focus and arrive at the tissue prognosis as well as research the basic pathophysiologic characteristics of SE.

Accepted for publication on December 11, 2000.

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REFERENCES