

## Brief Communication

# Magnetic Resonance Imaging and Spectroscopy Findings After Focal Status Epilepticus

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**Summary:** The etiology of cerebral abnormalities after focal status epilepticus (SE) is unknown. Possible causes include hypoxia and the excessive release of excitatory amino acids. Magnetic resonance imaging (MRI) of a 21-year-old patient with "cryptogenic" continuous motor seizures showed swelling and signal hyperintensity of the contralateral parietotemporal cortex, the thalamus, and the ipsilateral cerebellum on T<sub>2</sub>-weighted images. These regions are connected by glutamatergic pathways. Proton magnetic resonance spectroscopy (MRS) of the cortical lesion yielded a signal peak at the resonance frequency of 2.29 ppm, suggesting a focal increase of glutamate or its

degradation product glutamine. At 3-month follow-up, structural alterations had disappeared, but the *N*-acetyl-aspartate/choline ratio was still reduced in the previously abnormal area. These findings are the first to demonstrate the contribution of MRS to pathophysiologic studies of focal SE in humans and, in combination with the pattern of imaging abnormalities, support a major role of glutamate for seizure-related brain damage. **Key Words:** Magnetic resonance imaging—Magnetic resonance spectroscopy—Focal status epilepticus—Transient signal abnormality—Glutamate.

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Brain scans obtained soon after partial status epilepticus (SE) may show focal abnormalities that subsequently disappear (1-3). These transient phenomena probably reflect seizure-related brain damage. Suggested mechanisms include hypoxia, whether absolute due to hypoventilation or relative due to the high metabolic demand of brain tissue involved in the seizure (4), and the excessive release of excitatory amino acids such as glutamate and aspartate (5). Both substances are ubiquitous excitatory neurotransmitters and, in high concentrations, have the potential to cause receptor-mediated neuronal injury. The results of animal experiments indicate that such excitotoxins play a crucial role in the pathophysiology of SE (6). Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) may now serve as non-

invasive tools for investigating such conditions in humans.

### CASE REPORT

A patient had experienced her first generalized tonic-clonic seizure at age 20 years. The interictal EEG showed irregular generalized spike-wave discharges and diffuse slowing of the background activity. Brain MRI was normal. The patient was first treated with phenytoin (PHT) and phenobarbital, later replaced by carbamazepine (CBZ) because of side effects. Having discontinued her antiepileptic drug (AEDs) on her own initiative for 2 weeks, she was readmitted in generalized convulsive SE 16 months after the first seizure. Although the SE could be interrupted with diazepam, fentanyl, and PHT, the patient continued to have seizures four to six times daily in the next 3 days. Seizures were stereotyped and began with tonic-clonic activity of the left arm that rapidly spread to involve the entire body. This secondary generalization was stopped on hospital day four by adding CBZ and clobazam to the AED regimen. However, convulsions limited

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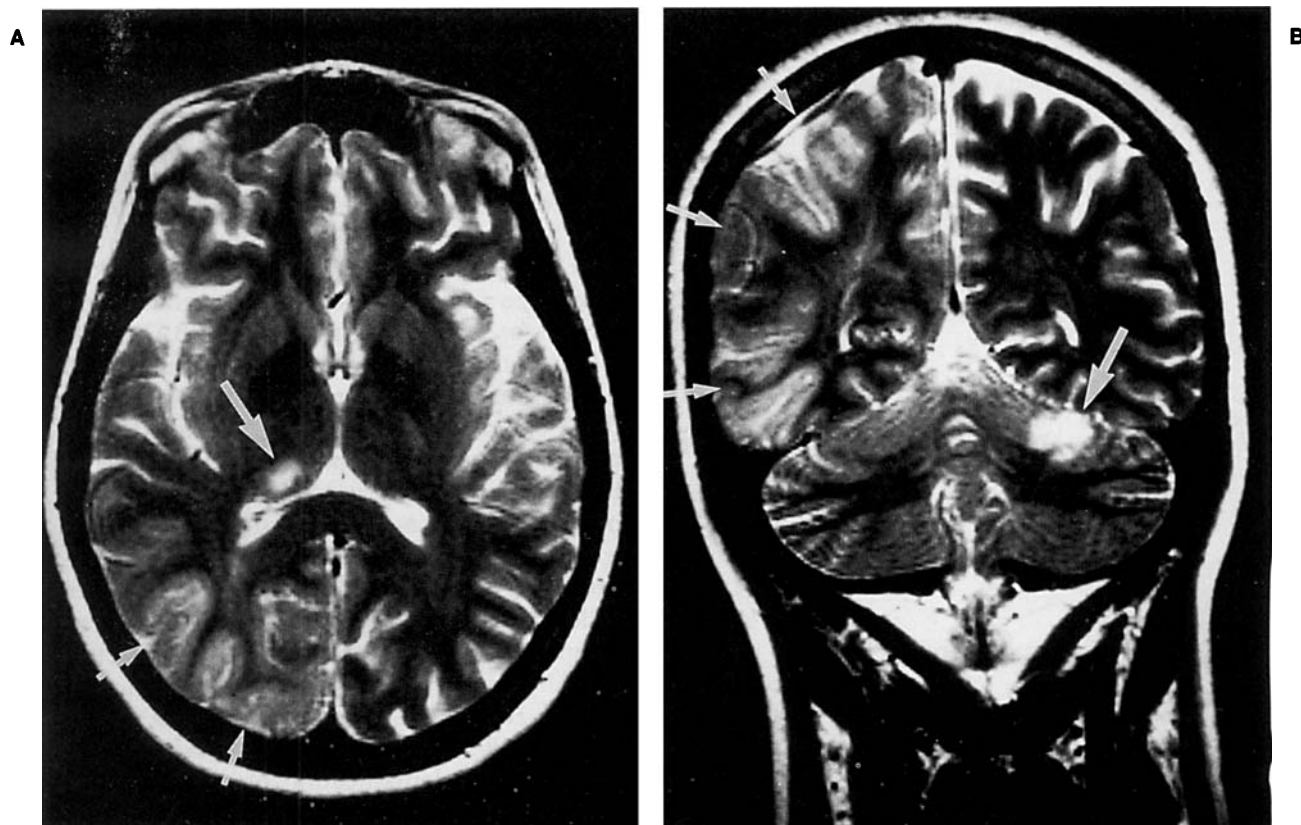
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to the left side of the body recurred and three times persisted for hours as focal SE. Interictal neurologic examination showed a flaccid left hemiparesis 2 days after admission, which evolved to hemiplegia. EEG obtained during a focal seizure showed fast spikes, polyspikes, and slow wave-sharp wave complexes of higher voltage over the left hemisphere. Interictal EEGs were repeatedly characterized by an overall amount of reduced background activity with focal slowing over the right frontoparietal cortex and irregular epileptic discharges more prominent over the right hemisphere.

MRI was performed on hospital day 6 ~20 min after a focal seizure. With a 1.5-T system (Gyrosan ACS II, Philips, The Netherlands) and a rapid T<sub>2</sub>-weighted imaging sequence (turbo spin echo), extensive swelling and abnormal signal were noted in the right parietotemporal region involving predominantly the cortex. Hyperintense signal was also noted in the posterior thalamus on the right and in the upper part of the left cerebellum (Figs. 1 A and B).

For better understanding of these findings, we subsequently obtained proton spectra of the abnormal parietotemporal region and the corresponding

contralateral area. MRS was also performed on the Gyrosan ACS II system with a 1.5-T Oxford super HIHO thickshield magnet and a conventional 10-mT/m gradient system. A circular polarized "bird-cage" resonator served as the transmit and receive coil. The volume of interest was defined by a cube with a side length of 20 mm and was placed well distant from the scalp to reduce field inhomogeneities and avoid signal contamination by fat. Data acquisition was performed with the PRESS sequence (7) under the following conditions: automatic shimming, water suppression by frequency selective adiabatic pulse, repetition time (TR) = 1,500 ms, echo time (TE) = 136 ms, flip angle 90°, 1,024 samples, spectral bandwidth = 2,000 Hz, and number of signal averages = 256. The spectra were then filtered in the time domain by Gaussian and exponential multiply (line broadening = 1.5 Hz). The reconstruction was performed with Fourier transformation, phase correction, and baseline correction by a semiautomatic algorithm with cubic splines. Amplitude ratios of signal peaks served for side to side comparison. The software used for this investigation is part of the spectroscopy package of the system (Philips).



**FIG. 1.** Turbo spin echo T<sub>2</sub>-weighted magnetic resonance imaging (MRI) showing swelling and signal hyperintensity (arrows) of the right parietotemporal cortex (**A**, and **B**), the right thalamus (**A**) and the contralateral cerebellum (**B**). MRI was completely normal 3 months later (data not shown).

Proton MRS of the abnormal parietotemporal region showed a marked peak of resonance frequencies at 2.29 ppm. The *N*-acetyl-aspartate/choline amplitude ratio was slightly lower than that in a corresponding voxel of the left hemisphere (1.49 vs. 2.15), which yielded a normal spectrum (Fig. 2A and B). There was no evidence of a lactate peak on either side.

The patient's left hemiparesis began to resolve as soon as the seizure activity had ceased. A cerebral angiogram was normal. Repeat MRI on hospital day 13 showed regression of the swelling and of the size of the hyperintense areas. Three months later, the MRI was completely normal, and MRS was repeated according to the same protocol used for the first study. There was no longer a signal peak at 2.29 ppm, but the *N*-acetyl-aspartate/choline amplitude ratio of 1.77 was still slightly reduced (Fig. 2C).

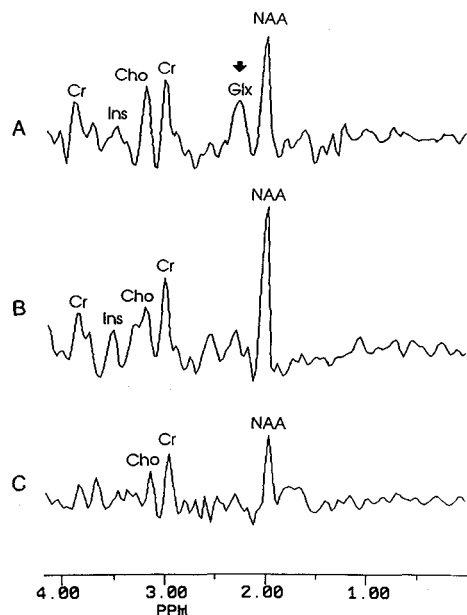
## DISCUSSION

Transient cortical abnormalities on computed tomography (CT) and MRI after focal SE have commonly been attributed to the development of edema in and around the seizure focus, but experimental proof of this is lacking (1–3). In addition to MRI signal changes in the region of the presumed cortical

focus, we noted abnormalities in structures anatomically remote from the focus; the ipsilateral thalamus and the contralateral cerebellum. This distribution of morphologic abnormalities exactly matches the findings of a single photon emission CT study by Duncan et al. (8) in a similar setting. Injecting the blood flow tracer  $^{99}\text{Tc}$ -HMPAO during left-sided motor SE, these investigators observed transient hyperactivity of the right frontoparietal cortex, the right thalamus, and the left cerebellum, which subsided postictally. These findings presumably reflect abnormalities from focal cortical activation and propagation of the severe discharge through specific pathways. Glutamatergic corticothalamic, corticopontine, and afferent cerebellar pathways have been documented in the mammalian CNS (9), which would be in accord with the spread of signal changes observed in our patient.

Simultaneous seizure-related cortical and distant thalamic damage has also been produced experimentally. Various facts suggest an excessive release of the excitotoxic neurotransmitters glutamate and aspartate as crucial event (6). First, local application of these amino acids causes ultrastructural tissue changes almost identical to those resulting from seizures due to continuous electrical stimulation (5). Second, remote seizure-related damage is detected predominantly postsynaptic to glutamatergic pathways on glutamine-rich receptor neurons (10). Seizure-induced tissue changes can be prevented by glutamate receptor-blocking agents (11).

In our patient, the proton MR spectrum of the area of cortical signal abnormality after partial seizure SE showed a marked abnormal peak of resonance frequencies at 2.29 ppm. A signal peak at this resonance frequency is related to glutamate, glutamine, or  $\gamma$ -aminobutyric acid (GABA) (12–14). It is unfortunate that the MRS technique used does not permit separating the individual contribution of these compounds. However, accumulation of glutamate or glutamine appears to be the most probable explanation. In a recent microdialysis study of 6 patients with localization-related epilepsy and intractable complex partial seizures, During and Spencer (15) observed marked increases in extracellular glutamate levels in the epileptogenic hippocampus. During seizures, the increase reached potentially cytotoxic concentrations and tended to persist. High levels of glutamine would lead to one same conclusion, because brain glutamine is largely derived from detoxification of glutamate by glutamine synthetase. In the patients of During and Spencer (15), GABA levels also increased during the course of seizure activity, but with a greater increase in the nonepileptogenic hippocampus and a



**FIG. 2.** Proton magnetic resonance spectroscopy (MRS) from the right epileptogenic (A) and left normal (B) parietotemporal region after focal seizure status. C: A proton spectrum from the right obtained after 3-month follow-up. Major signal peaks are identified as follows: NAA, *N*-acetyl-aspartate; Glx, glutamate/glutamine; Cr, creatine/phosphocreatine; Cho, choline; Ins, inositol. (A possible further peak of Glx resonance at 3.8 ppm may have been missed because of J-coupling.)

more rapid decrease back to initial concentrations. Furthermore, ictal extracellular GABA concentrations were only  $\sim 1/1000$  those of glutamate (15) rendering a significant spectral contribution from this inhibitory neurotransmitter very unlikely. There was no evidence of lactate in the area of morphologic damage, which is a strong argument against a role of hypoxia/ischemia for MRI signal abnormalities.

A reduction in *N*-acetyl-aspartate, as occurred in our patient, is generally considered to be a marker of neuronal damage. Such reduction was evident at the time of MRI signal abnormality and persisted to a lesser extent even after the disappearance of the MRI changes, suggesting that MRS is more sensitive for epilepsy-related tissue damage than structural imaging. This underscores the potential of combined MRI/MRS studies for investigating the pathophysiological consequences of recurrent epileptic seizure.

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