Reversible Signal Abnormalities in the Hippocampus and Neocortex after Prolonged Seizures

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PURPOSE: To investigate the phenomenon of reversible increased signal intensity of medial temporal lobe structures and cerebral neocortex seen on MR images of six patients with recent prolonged seizure activity. **METHODS:** After excluding patients with known causes of reversible signal abnormalities (such as hypertensive encephalopathy), we retrospectively reviewed the clinical findings and MR studies of six patients whose MR studies showed reversible signal abnormalities. MR pulse sequences included T2-weighted spin-echo coronal views or conventional short-tau inversion-recovery coronal images of the temporal lobes. **RESULTS**: All six MR studies showed increased signal intensity within the medial temporal lobe, including the hippocampus in five studies. All follow-up MR examinations showed partial or complete resolution of the hyperintensity within the medial temporal lobe and the neocortex. In one patient, results of a brain biopsy revealed severe cerebral cortical gliosis. Temporal lobectomy performed 4 years later showed moderate cortical gliosis and nonspecific hippocampal cell loss and gliosis. **CONCLUSION:** Significant hyperintensity within the temporal lobe is demonstrable on MR images after prolonged seizure activity, suggestive of seizure-induced edema or gliosis. Damage to medial temporal lobe structures by prolonged seizure activity indicates a possible mechanism of epileptogenic disorders.

Index terms: Brain, magnetic resonance; Brain, temporal lobe; Hippocampus; Seizures

AJNR Am J Neuroradiol 17:1725–1731, October 1996

Prolonged seizure activity is associated with long-lasting neurologic damage and even death in humans (1–3); prompt treatment is required to forestall irreversible changes (4). Pathologic studies performed on the brains of adults and children who died after an episode of status epilepticus show marked neuronal loss, particularly within the so-called Sommer's sector, or CA1 subfield, of the hippocampus (1–3). Corsellis and Bruton (1) pointed out that the character of the acute neuronal loss in the hippocampus seen after an episode of status epilepticus is different from the neuronal loss and atrophy of the hippocampus seen in the typical case of mesial temporal sclerosis. In their review of 20 patients who died shortly after status epilepticus, these authors noted that acute neuronal loss in vulnerable areas of the brain was usually accompanied by an intense astrocytic reaction, with the reactive astrocytes replacing the absent neurons.

Several investigators have reported reversible lesions found on magnetic resonance (MR) images after status epilepticus (5–9). We initiated the present study of reversible MR signal abnormalities after we became aware of a patient who had undergone brain biopsy after an episode of status epilepticus and who subsequently returned for temporal lobectomy because of worsening temporal lobe seizures. The purpose of our study was to investigate the phenomenon of reversible signal abnormalities on MR examinations of patients with seizures and

Received September 12, 1995; accepted after revision April 25, 1996.

Presented at the annual meeting of the American Society of Neuroradiology, Nashville, Tenn, May 1994.

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AJNR 17:1725–1731, Oct 1996 0195-6108/96/1709–1725

to determine the clinical significance and outcome associated with these findings.

Materials and Methods

We performed a retrospective review of all patients referred for MR studies for evaluation of seizure disorder during the period from August 1991 to February 1994. From this group, we searched for cases in which abnormally increased signal intensity could be seen within the brain and which then either partially or totally resolved on a subsequent study. We then checked to see if cases of known acute hypertensive encephalopathy, toxemia of pregnancy, cyclosporin toxicity, and MELAS (mitochondrial encephalomyopathy–lactic acidosis syndrome) were included, as these syndromes may be associated with reversible signal abnormalities by other mechanisms (10–14). No case was excluded on the basis of these disorders. Six cases were identified, and a review was performed of the relevant clinical, laboratory, neuroimaging, and neuropathologic data.

The imaging studies were performed on 1.5-T MR units. The pulse sequences obtained during this period included conventional T2-weighted spin-echo axial views, conventional T2-weighted spin-echo or fast spin-echo T2-weighted coronal views through the temporal lobes, and T1-weighted spin-echo coronal views through the temporal lobes. In some patients, conventional short-tau inversion-recovery (STIR) coronal images through the temporal lobes were also obtained. For each of the six patients, the same type of T2-weighted pulse sequence was used in both the initial study and the follow-up study, whether conventional T2-weighted spin-echo, T2-weighted fast spin-echo, or STIR. The parameters for the T2-weighted spin-echo sequences were 2500–3500/85–120/1–2 (repetition time/echo time/excitations); 5- to 6-mm section thickness with 1.5- to 2.5-mm gap; and 192 × 256 matrix. The parameters for the STIR pulse sequence were 2800/43/1; inversion time of 145; 4- to 5-mm section thickness with a 1.0- to 2.5-mm gap; and 256 × 256 matrix. The parameters for the T1-weighted spin-echo pulse sequence were 500–650/20–32/1–2; 4- to 5-mm section thickness with 1.0- to 2.5-mm gap; and 192 × 256 matrix.

Qualitative analysis of signal intensity changes throughout the brain was performed retrospectively by two neuroradiologists who used only the T2-weighted or STIR coronal pulse sequences. The regions studied were formally subdivided into the following: hippocampus, amygdala, lateral temporal lobe cortex, and extratemporal cerebral cortex. These regions were scored as showing either presence or absence of abnormally increased signal intensity. Disagreements were resolved by consensus review between the two neuroradiologists.

The neuropathologic findings were reviewed retrospectively by a neuropathologist. This included review of sections stained with hematoxylin-eosin from one temporal lobe biopsy specimen and one standard temporal lobectomy tissue specimen. These were obtained from the same patient 4 years apart. The specimens were examined for the extent and degree of gliosis. The hippocampus was included on the lobectomy specimen and was qualitatively examined to determine the degree of neuronal loss and gliosis within each subfield.

TABLE 1: Abnormal increased signal intensity on T2-weighted spin-echo or STIR MR images

Patient	Hippocampus	Amygdala	Neocortex
1	+	+	+
2	+	+	−
3	+	−	+
4	+	+	−
5	+	−	−
6	+	+	+

Note.—+ indicates present; −, not present.

Results

The findings on the initial MR studies of these six patients indicate that abnormally increased signal intensity was found within the hippocampus in six patients and within the amygdala in four patients (Table 1). In three patients, the lateral temporal neocortex was involved, and in one patient, the frontal and parietal lobes were involved. In five patients, the abnormalities were unilateral; in one patient, both the hippocampal and neocortical signal changes were bilateral. Confluent bilateral periventricular white matter and bilateral basal ganglia lesions were noted in one patient.

The most dramatic case is illustrated in Figure 1. These MR studies were obtained in 1988 of a 27-year-old woman (patient 6) who was in status epilepticus while 7 months pregnant. An MR scan of the brain obtained 8 days after admission revealed a large area of hyperintensity within the left temporal lobe on T2-weighted images (Fig 1A and B), which was interpreted at that time as compatible with infiltrative brain tumor or edema; herpes encephalitis was considered less likely because of the lack of fever. A closed computed tomographic (CT)-guided stereotactic biopsy of the left temporal lobe was performed, and histologic examination revealed a marked reactive astrocytosis of the temporal neocortex without evidence of malignancy or inclusion bodies (Fig 1C). The patient had no further seizures in the hospital, and was discharged on phenobarbital. Four years later, her seizure pattern changed in character and increased substantially in frequency, despite multiple trials of antiepileptic medications. A repeat

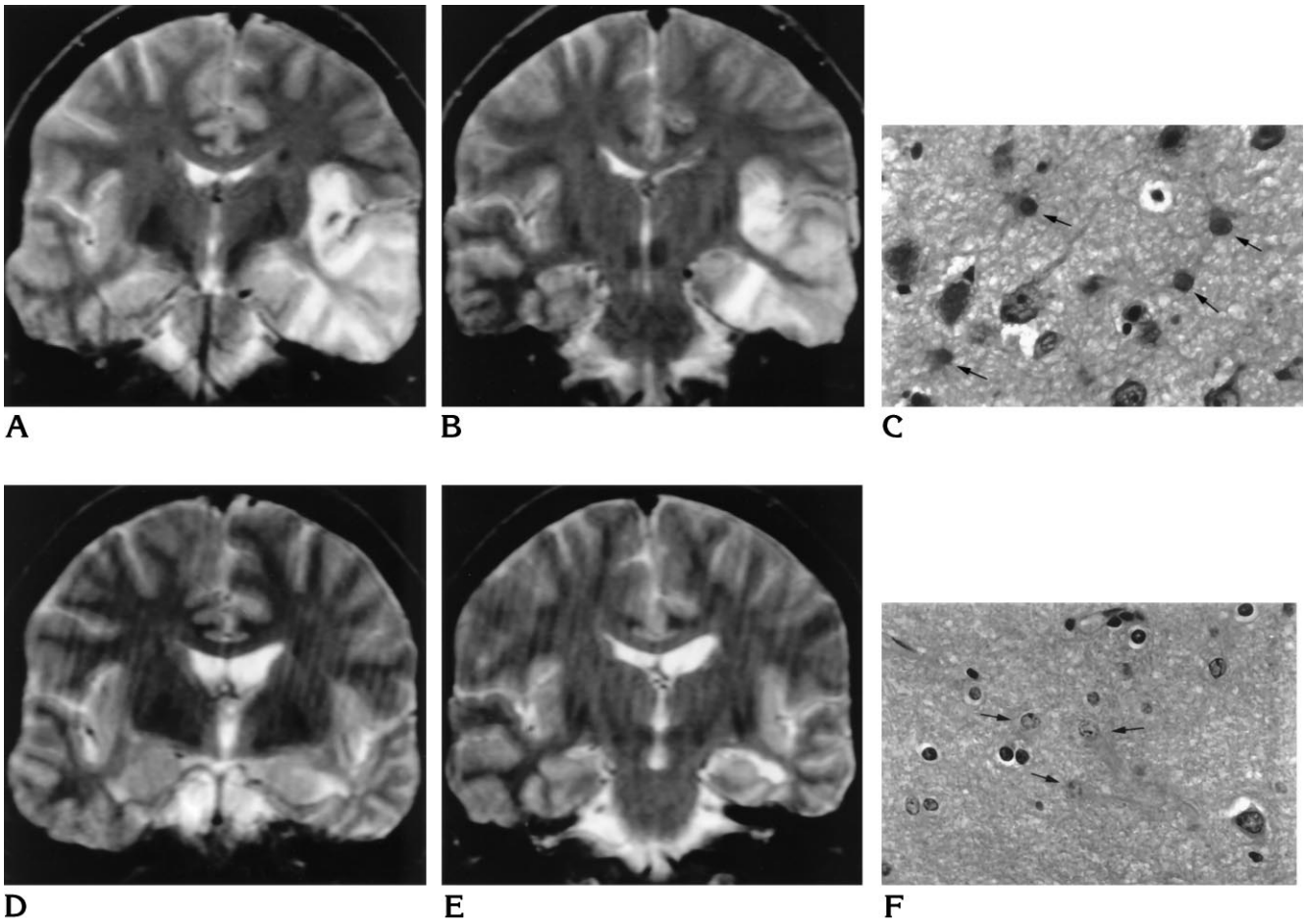

Fig 1. Twenty-seven-year-old woman with status epilepticus.

A and *B*, Coronal T2-weighted conventional spin-echo MR images (3500/80) obtained 8 days after cessation of seizures. Marked hyperintensity throughout the left temporal lobe cortex is identified, with moderate displacement and minimal signal increase of the left hippocampus.

C, High-magnification photomicrograph of biopsy specimen of temporal lobe cortex 2 weeks after episode of status epilepticus. Reactive astrocytes (*arrows*) characterized by hypertrophic nuclei and prominent, homogeneous, eosinophilic cytoplasm are present throughout the biopsy specimen. The surrounding neuropil also exhibited a rarefied consistency, suggestive of edematous changes (hematoxylin-eosin).

D and *E*, Coronal T2-weighted conventional spin-echo MR images (3500/80) obtained 4 years later show interval resolution of the marked signal abnormality with development of diffuse volume loss of the left temporal lobe compared with the right. No discernible atrophy or signal abnormality of the left hippocampus is identified, although mild enlargement of the left temporal horn is seen.

F, High-magnification photomicrograph of the resection specimen of the temporal lobe 4 years after that shown in *C*. Residual chronic gliosis is indicated by astrocytes (*arrows*) with enlarged nuclei associated with eosinophilic cytoplasm exhibiting a fibrillar quality. This is quite distinct from the more homogeneous, "swollen" cytoplasm seen within the acutely reactive astrocytes in the biopsy specimen (hematoxylin-eosin).

MR study in 1992 revealed resolution of the left temporal lobe hyperintensity (Fig 1D and E), but residual diffuse atrophy of the anterior left temporal lobe was noted with sparing of the left hippocampus. A continuous video-electroencephalographic (EEG) monitoring examination revealed seizure onset in the left temporal lobe, with decreased memory function in the left cerebral hemisphere noted on intraarterial amobarbital sodium (Wada) testing. Surgical excision of the epileptogenic region in the anterior temporal lobe was performed, with total removal of the amygdala and hippocampus. Histologic examination revealed moderate cortical gliosis but only mild diffuse gliosis and neuronal loss in the hippocampus (Fig 1F). Since the operation, she has had no further complex partial seizures.

Reexamination of the histologic studies of the two specimens from patient 6 showed the pres-

ence of reactive astrocytes within the cortex and the junction of the gray and white matter. A specimen from the first biopsy, which consisted of a small amount of tissue, contained many acutely reactive astrocytes. These cells exhibited prominent, darkly staining nuclei and abundant eosinophilic, homogeneously staining cytoplasm, features consistent with cytotoxic edema. The surrounding neuropil also appeared to be rarefied, which could be interpreted as evidence of extracellular edema, although the possibility of artifact cannot be ruled out. Subsequent resection of the ipsilateral temporal lobe showed mild to moderate diffuse gliosis that affected the junction of the gray and white matter with extension into the overlying cortex. The glial cells in this specimen also exhibited enlarged nuclei, but these nuclei appeared less basophilic. Additionally, the cytoplasm did not appear as swollen as in the original biopsy specimen, but instead exhibited a characteristic fine fibrillar appearance, commonly seen in chronic reactive gliosis. Examination of the hippocampal specimen showed a nonspecific pattern of mild neuronal loss within the hippocampus, not considered to be typical of mesial temporal sclerosis.

The follow-up MR studies of all six patients were reviewed for signal abnormalities and structural volume loss. Four patients had complete resolution of the temporal lobe signal abnormalities on the follow-up MR study (Fig 2), and two had partial resolution. The periventricular white matter and basal ganglia lesions in one patient (patient 5) did not change significantly in size and signal intensity. No evidence of hippocampal atrophy was noted on any of the follow-up MR studies, although significant atrophy of the anterior temporal lobe was noted in one patient (patient 6). Mild increase in dilatation of a temporal horn was noted in two patients (patients 5 and 6), with increase in dilatation of both lateral ventricles noted in one patient (patient 5).

The clinical results indicate that five of the six patients had either prolonged seizure activity (n = 3) or multiple seizure episodes (n = 2) within the 24-hour period before the MR study (Table 2). Patient 6 was studied 8 days after cessation of status epilepticus. Of the group with prolonged seizures, three had status epilepticus (defined as continuous seizure activity of more than 30 minutes' duration), and one had a seizure of 15 to 20 minutes' duration. The ages ranged from 1 year to 27 years. EEG monitoring showed epileptiform discharges in one or both temporal lobes in five of the six patients. Pathologic studies were performed in two patients. Patient 5 harbored an arteriovenous malformation in the left occipital lobe, which was treated by successive neuroembolization procedures followed by surgical resection and histologic confirmation. The retrospective review of the two sets of histologic studies of patient 6 (temporal lobe biopsy followed by temporal lobectomy 4 years later) are discussed below. The four children who did not have surgery in this series have chronic epilepsy (three with partial epilepsy and one with progressive myoclonic epilepsy) and are currently being treated with antiepileptic medications (Table 3).

Discussion

The results suggest that a reversible T2 signal increase in the temporal lobe is detectable in some patients after a recent episode of prolonged seizure activity or multiple repeated seizures within a short period of time. Although increased signal intensity on T2-weighted images may be due to many kinds of lesions that increase relative water content, such as vasogenic edema, demyelination, and transependymal cerebrospinal fluid resorption, we suggest that the reversible signal abnormality associated with recent seizure activity is related to cytotoxic edema. Patient 6 underwent two biopsies of the affected temporal lobe, first at the time of status epilepticus and second at the time of surgical resection of the temporal lobe 4 years later. The initial pathologic studies showed a pattern of astrocytic cytoplasmic swelling, which is most consistent with cytotoxic edema. The prominence of the astrocytes on the initial specimen also suggest, but do not prove, astrocytic proliferation. The decreased swelling of the astrocytes on the temporal lobectomy specimens obtained 4 years later sug-

TABLE 2: Pertinent clinical epilepsy data

Patient	Age, y	Seizure Period	EEG Findings
1	1	Status epilepticus	Bitemporal
2	3	Multiple per day	Nonfocal
3	6	Multiple per day	Nonfocal
4	7	Multiple per day	L temporal
5	12	Status epilepticus	Bitemporal
6	27	Status epilepticus	L temporal

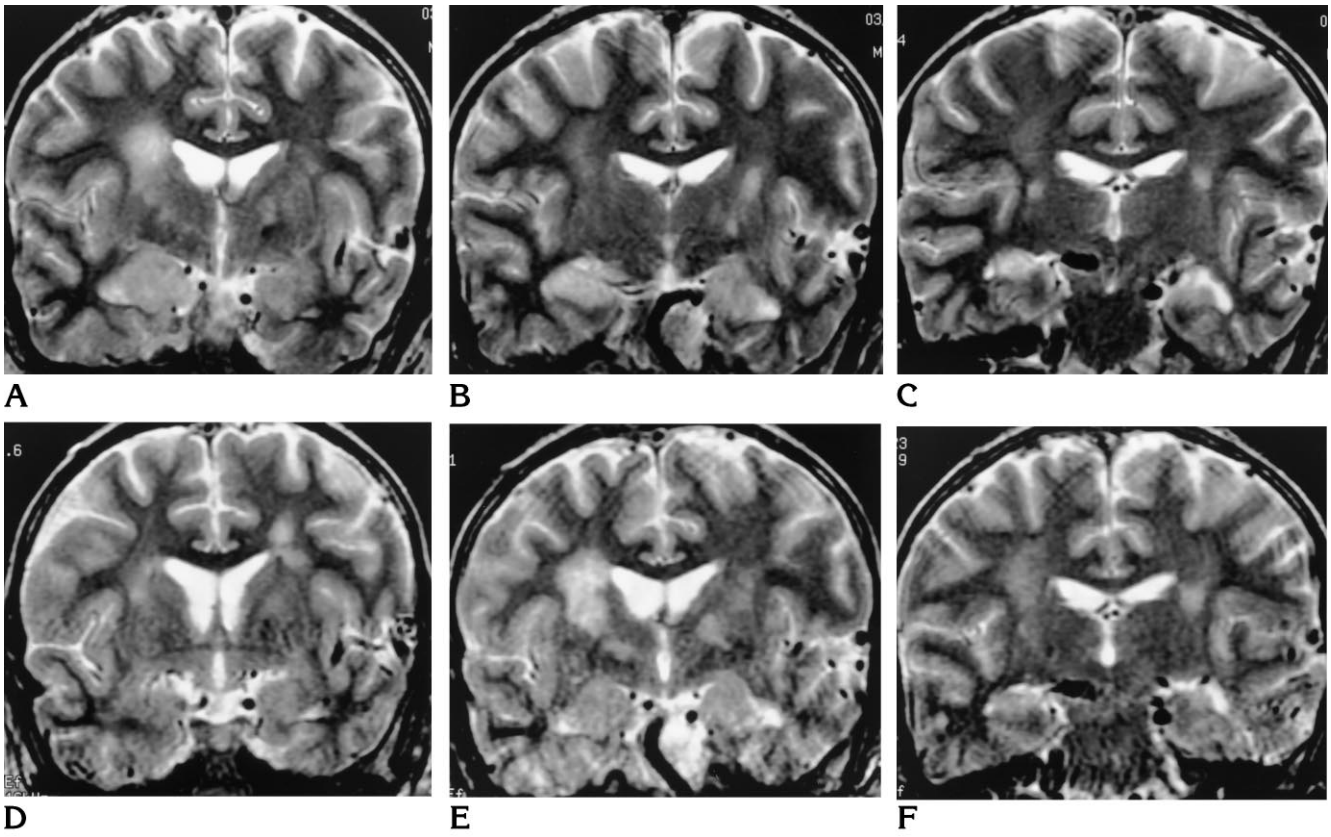

Fig 2. Twelve-year-old patient with status epilepticus and known left occipital lobe arteriovenous malformation.

A, Coronal T2-weighted fast spin-echo MR image (3500/85) of the anterior temporal lobe shows increased signal intensity of the right medial temporal lobe in the region of the amygdala. An increase in the size of the right amygdala is apparent, as compared with the left. Also noted is increased signal of the right periventricular white matter.

B, Coronal T2-weighted fast spin-echo MR image (3500/85) at the level of the basilar artery shows abnormally increased signal intensity localized to the anterior right hippocampus. No signal abnormality of the right temporal lobe neocortex or of the left hippocampus is present. Small foci of increased signal are identified within the left basal ganglia.

C, Coronal T2-weighted fast spin-echo MR image (3500/85) 1 cm posterior to image in *B* shows abnormally increased signal intensity of the posterior right hippocampus. Also noted are small foci of increased signal intensity within both basal ganglia posteriorly.

D–F, Coronal T2-weighted fast spin-echo MR images (2500/102), obtained 9 days later at the levels of the temporal lobe corresponding to those in *A–C*, show interval resolution of the signal abnormality of the right amygdala and hippocampus. Persistent white matter hyperintensity of the right frontal lobe is unchanged but appears on different images because of differences in angulation. Increased signal intensity of the left periventricular white matter is also seen, but was identified on the prior MR study (image not shown here) and is not changed.

TABLE 3: Pertinent historical data

Patient	Follow-up Clinical Data and Outcome
1	Chronic partial epilepsy of L temporal lobe; mild developmental delay in language
2	Chronic partial epilepsy, nonlocalizing on EEG; seizures controlled by medications
3	Chronic partial epilepsy, nonlocalizing on EEG; severe cerebral palsy and mental retardation without improvement
4	Development of progressive myoclonic epilepsy documented by closed-circuit television EEG; continued regression of motor and cognitive skills
5	L parietooccipital arteriovenous malformation treated by embolization and surgical resection; no further seizures
6	Chronic partial epilepsy of L temporal lobe treated by temporal lobectomy (see “Results” for further details)

gest that a principal component of the reversible signal abnormality on the initial MR study was reversible cytotoxic edema. The astrocytosis on the cortical specimens from the temporal lobectomy was obtained during a period of recurrent, chronic, intractable seizure activity without prolonged seizures, which suggests that the cytotoxic edema stemming from the acute phase of reactive astrocytosis is at least partially responsible for the reversible signal abnormalities on T2-weighted images.

Astrocytic reaction has been described as a common response to many different kinds of central nervous system injury, including ischemia, trauma, metabolic insults, and status epilepticus (3). This change in behavior includes swelling and proliferation of astrocytes (15). It is hypothesized that reactive astrocytes play a significant role in cellular and tissue repair by detoxifying various noxious substances (such as ammonia, glutamate, free radicals, xenobiotics, and metals) and by promoting such cellular responses to injury as production of trophic factors, restoration of extracellular ionic milieu, and clearance of extracellular debris (16). There is excessive release of glutamate during an episode of status epilepticus, and preliminary experimental results with proton MR spectroscopy in patients with recent status epilepticus corroborate this observation (17) (L. P. Mark, R. W. Prost, V. Haughton, et al, "An MR Spectroscopic Study of Glutamate in Patients with Temporal Lobe Seizures," presented at the annual meeting of the American Society of Neuroradiology, Chicago, Ill, April 1995). An astrocytic response to excessive glutamate release could serve to dampen its excitotoxic effects, but could also result in morphologic changes of the astrocyte, such as swelling. Using the kainic acid–treated rat model of sustained seizures, some researchers have obtained evidence from diffusion-weighted MR images of the brain that shows a decrease in apparent diffusion coefficient changes in the amygdala and piriform cortex at 1 and 24 hours after sustained seizures (18). This change in apparent diffusion coefficient could be explained by the development of cytotoxic edema after prolonged seizures.

Alternatively, the reversible signal abnormality in patient 6 could be attributed to an unusual encephalitis not detected on the initial temporal lobe biopsy and indistinguishable from gliosis in the specimens from the temporal lobe resection. However, the absence of fever and the excellent recovery from this episode make this possibility less likely. In particular, herpes encephalitis, which is the most common form of encephalitis to affect the temporal lobe and is associated with significant morbidity, would be considered unlikely on clinical grounds.

An interesting finding is that there was no qualitative evidence of mesial temporal sclerosis on the histopathologic specimens. The pathologic findings of the hippocampus from patient 6 showed mild diffuse neuronal loss, but not of the specific pattern of neuronal loss in the CA1 subfield and the end-folium, which is considered to be the sine qua non of classic mesial temporal sclerosis according to Margerison and Corsellis (19) and Bruton (20). In addition, the follow-up MR study showed no evidence of mesial temporal sclerosis, although the follow-up STIR MR sequence did show increased signal intensity within the cortex of the affected temporal lobe, consistent with the residual astrocytosis within the anterior temporal lobe cortex.

None of the other cases showed obvious findings of mesial temporal sclerosis on the follow-up MR studies. It is conceivable that temporal lobe MR imaging can miss a case of mesial temporal sclerosis, but studies performed at our institution during that time have shown 88% sensitivity to signal abnormality and 83% sensitivity to volume loss in cases of pathologically proved mesial temporal sclerosis (S. Chan, unpublished data, 1994). Tien et al (5) reported findings in four patients with status epilepticus in whom complex partial seizures later developed with evidence of mesial temporal sclerosis on fast spin-echo MR images. The difference between our results and theirs is explainable by the possibility that only a minority of the patients who suffer from status epilepticus actually go on to have classic mesial temporal sclerosis. It is also possible that mesial temporal sclerosis may sometimes require years to become evident radiologically. Several studies have shown that infants with one or more prolonged febrile convulsions before the age of 1 year are particularly prone to the development of complex partial seizures (21) and severe hippocampal neuronal loss (22) after a prolonged convulsion. A larger, long-term study involving patients of various ages with prolonged seizure activity would be necessary to address this question.

All our patients had at least one seizure before the episode of prolonged or multiple con-

secutive seizure(s) that led to the MR study. Therefore, we cannot determine in these patients whether the prolonged duration of seizure activity was responsible for either establishing or worsening an epileptogenic focus. Two of our patients underwent surgical treatment. The first patient (patient 6) has been discussed. The second patient underwent several embolization procedures followed by resection of an arteriovenous malformation of the occipital lobe. Although this patient experienced no further seizures after definitive treatment, other patients may have recurrent seizures postoperatively as a result of residual vascular malformation or hemorrhage. Also, secondary epileptogenic foci have been identified by EEG in patients with arteriovenous malformations, raising the possibility of a "kindled" seizure focus even after definitive treatment in those patients with recurrent seizures (23).

In summary, prolonged seizure activity, particularly that affecting the medial temporal lobe structures, can result in identifiable signal abnormalities on MR images. The specific vulnerability of the medial temporal lobe suggests a mechanism of pathogenesis for the development of mesial temporal sclerosis after prolonged febrile convulsions. However, our evidence suggests that only a subset of patients with status epilepticus actually go on to have classical mesial temporal sclerosis, and that further work needs to be performed to determine all the risk factors, such as age, involved in the pathogenesis of mesial temporal sclerosis.

References

1. Corsellis JAN, Bruton CJ. Neuropathology of status epilepticus in humans. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. *Advances in Neurology: Status Epilepticus.* New York: Raven Press; 1983;34:129–139
2. Fowler M. Brain damage after febrile convulsions. *Arch Dis Child* 1957;32:67–76
3. Meldrum BS, Bruton CJ. Epilepsy. In: Adams JH, Duchen LW, eds. *Greenfield's Neuropathology*. 5th ed. New York, NY: Oxford University Press; 1992:1246–1283
4. Leppik IE. Status epilepticus. *Neurology* 1990;40(suppl 2):4–9
5. Tien RD, Felsberg GJ. The hippocampus in status epilepticus: demonstration of signal intensity and morphologic changes with sequential fast spin-echo MR imaging. *Radiology* 1995;194:249–256
6. Kramer RE, Luders H, Lesser RP, et al. Transient focal abnormalities of neuroimaging studies during focal status epilepticus. *Epilepsia* 1987;28:528–532
7. Riela AR, Sires BP, Penry JK. Transient magnetic resonance imaging abnormalities during partial status epilepticus. *J Child Neurol* 1991;6:143–145
8. Callahan DJ, Noetzel MJ. Prolonged absence status epilepticus associated with carbamazepine therapy, increased intracranial pressure, and transient MRI abnormalities. *Neurology* 1992;42:2198–2201
9. Cox JE, Mathews VP, Santos CC, Elster AD. Seizure-induced transient hippocampal abnormalities on MR: correlation with positron emission tomography and electroencephalography. *AJNR Am J Neuroradiol* 1995;16:1736–1738
10. Schwartz RB, Jones KM, Kalina RL, et al. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. *AJR Am J Roentgenol* 1992;159:379–383
11. Weingarten K, Barbut D, Fillipi C, Zimmerman RD. Acute hypertensive encephalopathy: findings on spin-echo and gradient-echo MR imaging. *AJR Am J Roentgenol* 1994;162:665–670
12. Sanders TG, Clayman DA, Sanchez-Ramos L, Vines FS, Russo L. Brain in eclampsia: MR imaging with clinical correlation. *Radiology* 1991;180:475–478
13. Truwit CL, Denaro CP, Lake JR, et al. MR imaging of reversible cyclosporin A-induced neurotoxicity. *AJNR Am J Neuroradiol* 1991;12:651–659
14. Allard JC, Tilak S, Carter AP. CT and MR of MELAS syndrome. *AJNR Am J Neuroradiol* 1988;9:1234–1238
15. Norenberg MD. Astrocyte responses to CNS injury. *J Neuropath Exp Neurol* 1994;53:213–220
16. Norenberg MD, Hertz L, Schousboe A, eds. *The Biochemical Pathology of Astrocytes.* New York, NY: Alan R Liss; 1988
17. Fazekas F, Kapeller P, Schmidt R, et al. Magnetic resonance imaging and spectroscopy findings after focal status epilepticus. *Epilepsia* 1995;36:946–949
18. Nakasu Y, Nakasu S, Morikawa S, Uemura S, Inubushi T, Handa J. Diffusion-weighted MR in experimental sustained seizures elicited with kainic acid. *AJNR Am J Neuroradiol* 1995;16:1185–1192
19. Margerison JH, Corsellis JAN. Epilepsy and the temporal lobes. *Brain* 1966;89:499–530
20. Bruton CJ. *The Neuropathology of Temporal Lobe Epilepsy*. New York, NY: Oxford University Press; 1988
21. Davidson S, Falconer MA. Outcome of surgery in 40 children with temporal lobe epilepsy. *Lancet* 1975;1:1260–1263
22. Sagar HJ, Oxbury JM. Hippocampal neuron loss in temporal lobe epilepsy: correlation with early childhood convulsions. *Ann Neurol* 1987;22:334–340
23. Yeh HS, Privitera MD. Secondary epileptogenesis in cerebral arteriovenous malformations. *Arch Neurol* 1991;48:1122–1124