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# MRI, $^1$H-MRS, and functional MRI during and after prolonged nonconvulsive seizure activity

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**Article abstract—***Background:* Various structural and functional changes, such as focal edema, blood flow, and metabolism, occur in the cerebral cortex after focal status epilepticus. These changes can be assessed noninvasively by means of MRI techniques, such as fluid-attenuated inversion recovery (FLAIR), EEG-triggered functional MRI (EEG-fMRI), and proton MR spectroscopy (MRS). *Methods:* The authors report on a 40-year-old patient with nonlesional partial epilepsy in the left posterior quadrant in whom these MRI techniques were applied in an active seizure focus and repeated during a follow-up of 1 year. *Results:* FLAIR imaging taken at the time of status epilepticus showed a signal hyperintensity in the occipital region. $^1$H-MRS of this cortical region showed elevated lactate, decreased *N*-acetylaspartate (NAA), and elevated choline (Cho). In the same region, EEG-fMRI revealed an area of signal enhancement. After seizure control, recovery of lactate and Cho was observed, whereas the NAA level remained reduced. The structural abnormality demonstrated on FLAIR disappeared within 3 months. *Conclusions:* Repetitive MRI with sensitive sequences during clinically critical periods may disclose the structural correlate in a previously nonlesional epilepsy case. Corresponding to the clinical evolution, reversible and irreversible focally abnormal metabolism can be determined with $^1$H-MRS, reflecting both increased neuronal activity and neuronal damage.

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During the last decade, new MRI methods were developed that are becoming available to improve the noninvasive localization of epileptogenic focus. These recent MRI techniques include the fluid attenuated inversion recovery sequence (FLAIR),[1] which improves the sensitivity of detecting structural changes associated with hippocampal sclerosis as well as in remote subcortical and cortical regions in epilepsy.[2-4]

Another new approach to localize the epileptic focus is the use of functional MRI (fMRI). Blood oxygen level dependent (BOLD) fMRI is able to detect blood flow changes related to neuronal activity and has been applied in epilepsy using the hemodynamic response concomitant to neuronal firing during seizure.[5-7] The aim is to record the EEG while the patient is in the magnet in order to trigger the fMRI acquisition with epileptic activity.[8] This method provides images of interictal dysfunction with a high spatial resolution, allowing a direct comparison with structural MRI.

Proton MR spectroscopy ($^1$H-MRS) has been an established tool in clinical epilepsy studies for almost a decade. It has been used mainly to detect and quantify *N*-acetylaspartate (NAA), which is considered a marker for neuronal integrity. A decrease of the NAA level indicates neuronal loss or dysfunction and has been observed in the hippocampus by many groups.[9-11] Other metabolic changes such as an increase of choline-containing compounds (Cho) and creatine + phosphocreatine (Cr) in the hippocampus have been reported and were attributed to reactive astrocytis.[10] In the neocortex involving epileptic activity, metabolite alterations including elevated glutamine/glutamate signal (glx) and lactate have been observed as well.[12-14]

Few studies have used the outlined techniques in combination to identify the epileptic focus in patient with the initial diagnosis of nonlesional extratemporal epilepsy. In fact, this patient group is the most difficult to treat surgically if this line of treatment

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needs to be pursued because of pharmacoresistance. Furthermore, few follow-up studies are available elucidating the temporal evolution of the anomalies in each of the described MRI-based techniques. Here we present a case in which repetitive FLAIR sequences, $^1$H-MRS, and EEG-fMRI acquisition allowed localization of the epileptic focus as well as the assessment and evolution of metabolic alterations during a 1-year follow-up.

**Patient and methods.** *Case report.* A 40-year-old right-handed man with a history of complex partial seizures since age 31 experienced a generalized tonic-clonic seizure followed by brief episodes of simple visual phenomena described as moving color dots in the right visual field. Rarely intermittent micropsia or palinopsia was reported as well. Postictally a right hemianopia was observed. The simple partial visual seizures became more and more frequent, finally evolving to a simple partial status epilepticus. He was admitted to our institution for an evaluation of his epilepsy at this time. His neurologic examination was unremarkable. During his first evaluation (36 months before the current study), he had frequent simple partial seizures associated with left temporo-occipital discharges as recorded on EEG. The anatomic spin echo MRI was normal, whereas PET showed posterior left temporo-occipital hypometabolism. Two ictal SPECT studies showed consistent hyperperfusion of the left posterior quadrant, whereas the interictal SPECT was normal. Thus a left occipital lobe epilepsy was diagnosed. During this first evaluation, two 8 mL single-voxel $^1$H-MRS examinations were also performed using long echo time spin echo sequence. The position of the voxels was based on seizure semiology, ictal and interictal EEG, and nuclear imaging findings. One voxel was located in the mesial occipital lobe and the other was on the lateral side of the occipital lobe. Homologous voxels in the right hemisphere served as control. No metabolic abnormality was detected from the two left-sided locations when compared to the controls.

Medication was changed from a phenobarbital and phenytoin bitherapy to valproate monotherapy, yielding good seizure control for 3 years. However, his habitual seizures recurred, up to the point that nonconvulsive status epilepticus was diagnosed, necessitating a further change in drug therapy. An increase of his daily valproate dosage together with the introduction of primidone caused a rapid control of his seizure disorder. Except for brief episodes of visual phenomenon in the right visual field without loss of contact (after visit 2, see below), his seizure disorder responded well to the new drug treatment for more than 1 year. During this 1-year follow-up period, the patient was monitored with five MRI and $^1$H-MRS examinations. We report findings about this period with the following naming convention: visit 1 corresponds to the nonconvulsive status epilepticus period; visit 2, 4 days after; visit 3, 30 days after; visit 4, 90 days after; and visit 5, 1 year after. fMRI triggered by recurrent simple partial seizures and interictal discharges was carried out at visit 2.

Informed consent was obtained according to our institution's ethical rules.

*MRI.* 1.5 tesla Eclipse system (Marconi Medical Systems, Cleveland, OH) with standard head coil was used. The MRI examination consisted of a FLAIR sequence (inversion time [TI]/echo time [TE]/repetition time [TR] 1700/83/7000 msec, echo train length 8, slice thickness 5 mm, field of view [FOV] 220 mm, acquisition matrix 192 $\times$ 256), a combined EEG-fMRI using single shot EPI (TE/TR 40/979 msec, flip angle 80°, FOV 250 mm, 11 contiguous 5 mm slices), and a single voxel $^1$H-MRS using STEAM sequence (TE/TR/mixing time [TM] 20/1500/13 msec, voxel volume 3.4 mL, number of averages 256).

*EEG-fMRI acquisition.* Sixteen gold-coated silver scalp electrodes (Neuroscan Inc., Sterling, VA) were applied with conductive paste according to standard positions of the 10/20 system. Data were recorded continuously on a 64-channel EEG machine (Deltamed SA, Paris, France) with a sampling rate of 128 Hz while the patient was positioned in the MRI machine.

fMRI data acquisition was triggered whenever an epileptic discharge was observed on the EEG recording or if the patient indicated the occurrence of a simple partial seizure ("activation" condition). In both cases, EEG rhyth-

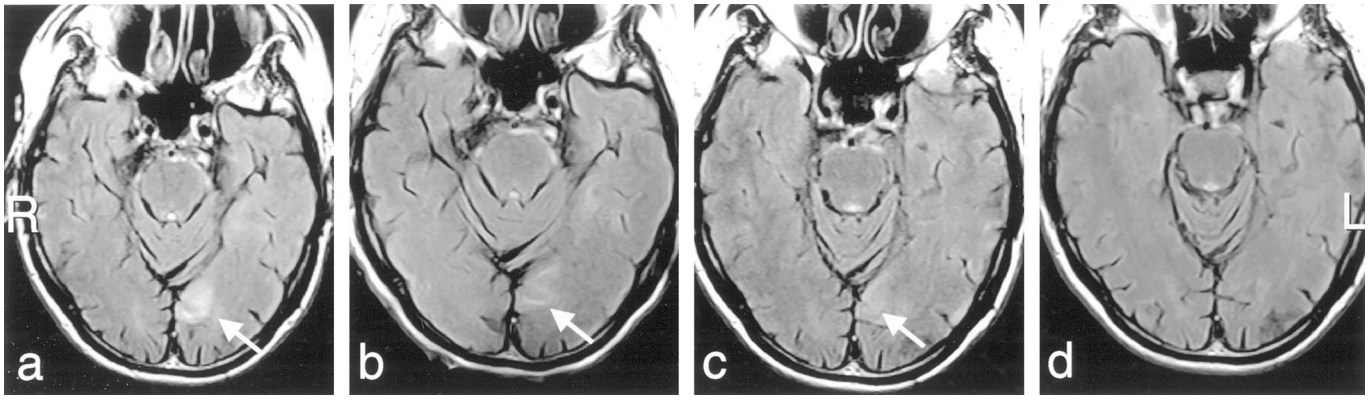


*Figure 1. Series of axial fluid-attenuated inversion recovery (FLAIR) images obtained during the status epilepticus (a; visit 1), 4 days later (b; visit 2), 30 days later (c; visit 3), and 90 days later (d; visit 4). During nonconvulsive status epilepticus, the FLAIR images showed diffuse hyperintensity (a, arrow) involving the gray and the white matter. The area of hyperintensity diminished in 4 days (b), now involving somewhat more the gray matter, and was still visible at day 30 (c). The FLAIR image obtained 90 days after seizure showed complete disappearance of the hyperintense signal (d) and remained normal up to 1 year after the status.*

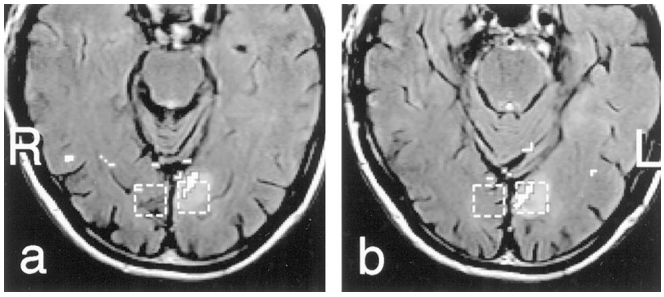


*Figure 2. Fluid-attenuated inversion recovery (FLAIR) image of two contiguous slices (a and b) obtained during the status epilepticus with the $^1$H-MR spectroscopy voxels of the areas studied shown in dotted lines. The blood oxygen level dependent signal enhancement is also superimposed on the image.*

mic or isolated spikes and sharp waves were maximal over the left temporo-occipital regions. A minimum of 15 seconds delay was given between each acquisition to avoid spin saturation effect. A second set of 40 images was acquired after injection of 1.5 mg clonazepam that eliminated most of the discharges on the EEG ("control" condition). For this data set, the delay between the two acquisitions was set to 15 seconds. After motion correction using the automatic image registration (AIR 3.08) algorithm,[15] the image time course was analyzed by computing the cross-correlation with a step function (activation/control).[16]

*$^1$H-MRS data reduction.* Processing of the spectra was done with SAGE spectroscopy analysis software (General Electric Medical Systems, Fremont, CA) and consisted of low frequency filtering, 1.5 Hz exponential apodization, zero filling, Fourier transform, and automatic zero order phase correction. The peak amplitudes were derived after fitting of the spectra using the Marquardt algorithm of the SAGE program. The different metabolites were assigned according to the literature[17-18] and the following abbreviations were used: lipids and/or macromolecules (lip); lactate (lact); NAA; Cr; Cho; myoinositol (mI). Reference-normalized concentrations were determined using water as internal standard assuming constant water concentration of 110 molar and were corrected for relative proton abundance, saturation effects, and tissue water content.[18-19] The effects of relaxation were not specifically determined, especially in the lesion, and therefore it was not possible to convert amplitudes to absolute concentrations. In this article, metabolite concentrations are referred to reference-normalized concentration measurements. Results were also expressed as ratios to the Cr peak. The contralateral spectrum was used as control.

**Results.** *Seizure.* At the time of the first visit, the patient experienced frequent simple partial seizures. The FLAIR image (T2-weighted) revealed a hyperintense signal without mass effect in the left occipital region; i.e., upper calcarine fissure (figure 1a), covering gray and white matter. The EEG signal recorded inside the magnet showed focal epileptogenic activity over the temporo-occipital regions and showed a similar topography as outside the magnet. EEG-fMRI showed a distinct region of activation in the left upper calcarine fissure, concordant with the hyperintense cortical region seen in the FLAIR image. The BOLD signal enhancement was around 6% with a statistical threshold set at $p < 0.05$ after Bonferroni correction. $^1$H-MRS voxels were targeted to investigate this distinct area. Figure 2 shows the BOLD localization on two contiguous slices of the seizure superimposed to the FLAIR image together with the 3.4 mL voxel locations represented in dotted lines. The corresponding spectra are shown on figure 3. The spectrum taken at the site of the lesion shows marked metabolite changes (figure 3b) when compared to the contralateral spectrum (figure 3a), including elevated lactate and reduced NAA (35%). An additional and previously unreported finding is a marked increase of Cho and a slight but significant decrease of mI.

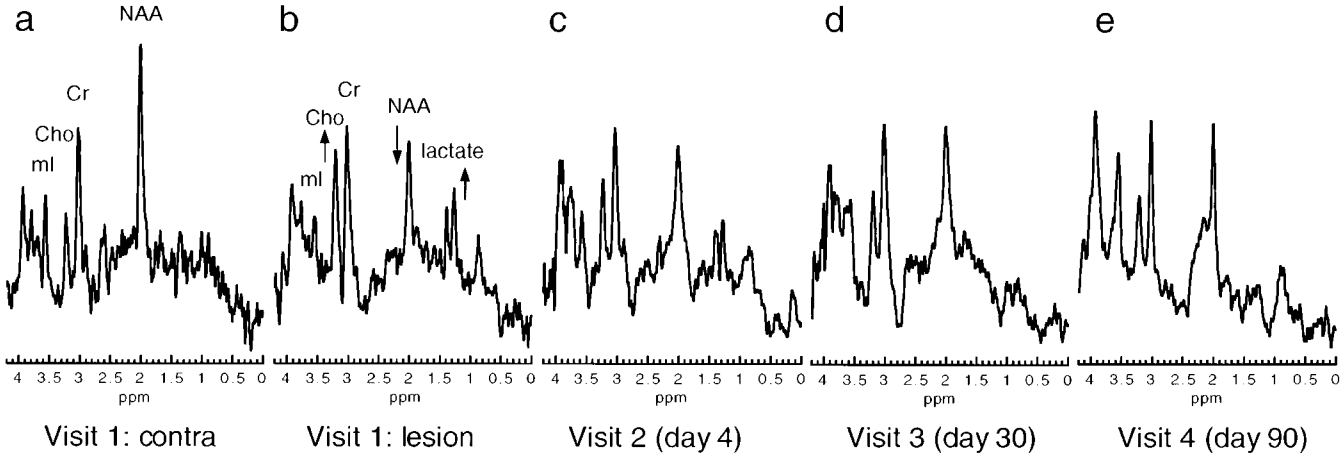


*Figure 3. Series of 3.4 mL STEAM (echo time 20 msec) spectra obtained during the status epilepticus (visit 1), as well as 4 days (visit 2), 30 days (visit 3), and 90 days after (visit 4). During the status epilepticus (b) the spectrum showed a marked depletion of* N*-acetylaspartate (NAA), an increase of lactate and choline-containing compounds (Cho), and a decrease of myoinositol (mI) compared to the control spectrum from the contralateral side (a). Lactate, Cho, and mI recovery is noticed 4 days after status epilepticus (c) and returned to normal at day 30 (d). NAA level remained low through the time study. The spectrum obtained after 1 year showed similar metabolite levels to the spectra obtained at day 90 (e).*

***Table*** *Metabolite ratios and concentrations*

| Metabolites | Control,* mean ± 2 SD | Visit 1, seizure | Visit 2, day 4 | Visit 3, day 30 | Visit 4, day 90 | Visit 5, day 360 |
|---|---|---|---|---|---|---|
| Ratios | | | | | | |
| mI/Cr | 0.52 ± 0.14 | 0.34 | 0.50 | 0.45 | 0.52 | 0.58 |
| Cho/Cr | 0.42 ± 0.11 | 0.91 | 0.68 | 0.64 | 0.54 | 0.43 |
| Glx/Cr | 0.47 ± 0.31 | 0.32 | 0.43 | 0.42 | 0.39 | 0.47 |
| NAA/Cr | 1.39 ± 0.16 | 0.86 | 0.76 | 0.89 | 0.90 | 0.86 |
| Lactate/Cr | 0.07 ± 0.19 | 0.98 | 0.41 | 0.00 | 0.15 | 0.29 |
| Concentrations† | | | | | | |
| mI | 4.07 ± 1.00 | 3.11 | 3.93 | 3.94 | 4.49 | 4.53 |
| Cho | 1.26 ± 0.30 | 2.76 | 1.89 | 1.88 | 1.59 | 1.12 |
| Cr | 8.06 ± 0.75 | 9.21 | 8.06 | 8.87 | 8.85 | 7.94 |
| Glx | 1.99 ± 1.43 | 1.54 | 1.81 | 1.95 | 1.82 | 1.95 |
| NAA | 10.76 ± 1.90 | 7.57 | 6.15 | 7.58 | 7.62 | 6.55 |
| Lactate | 0.49 ± 1.41 | 7.86 | 2.78 | 0.2 | 1.17 | 1.98 |

* N = 4 measurements in the homologous contralateral occipital cortex region.
† Reference-normalized concentrations to the water signal, after corrections for proton abundance and relaxation (T1 and T2). A water concentration of 110 M and a water content of 70% were assumed. The data are expressed in mM.

*Serial study.* Following the control of his seizure disorder, the patient had four consecutive MR examinations (visits 2 to 5). The FLAIR images obtained at day 4, day 30, day 90, and day 360 showed a progressive return to normal (figure 1, b through d). At visit 2 (day 4) there was still a marked hyperintense signal including gray and white matter in the left calcarine fissure (figure 1b). Thirty days later (visit 3), there was a marked reduction of hyperintense area involving only gray matter (figure 1c), whereas at day 90 (visit 4), no area of hyperintensity could be detected (figure 1d). One year later (visit 5), the FLAIR image remained normal.

The evolution of MRS spectra obtained at the same time points is shown in figure 3, c through e. The lactate level was reduced at day 4 (visit 2) and was undetectable at 30 days. Abnormal NAA values remained low even after 1 year. The Cho and the mI peaks progressively returned to normal within 30 days. These findings are summarized in the table, reporting the different metabolite ratios and concentrations corresponding to the different time points. Figure 4 represents the time course of the metabolites to Cr ratios.

**Discussion.** In the current report, a patient with occipital epilepsy and a previously unrevealing routine MRI showed a focal hyperintensity while experiencing frequent habitual seizures. Thus, optimal timing of follow-up imaging examinations, together with the use of more sensitive sequences, allowed the proper identification of the anatomic substrate of the epileptic focus.

Hyperintense signals in T2-weighted images after prolonged partial status epilepticus have been observed by different groups in both hippocampal and neocortical tissue.[20-24] The resolution of the signal changes within 3 months, as seen in our patient, has been also reported in several other studies.[21,22,25] The signal hyperintensity may or may not be associated with gadolinium contrast enhancement and does not exhibit mass effect.[23,24] Proposed mechanisms for these lesions include vasogenic edema reflecting altered permeability of the vessels in relation to seizures, which results in a breakdown of the blood–brain barrier and fluid accumulation in the white matter within the extracellular space. The implication of the gray matter may reflect a cytotoxic edema as well.[21] In our case, the changes seen in FLAIR

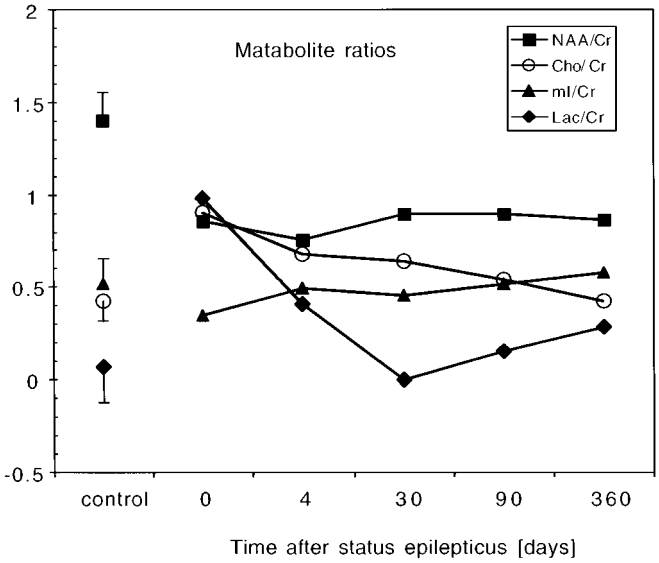


*Figure 4. Time series of metabolite to creatine + phosphocreatine (Cr) ratios. The left column represents the mean and 2 standard deviations of the metabolite levels of four control spectra obtained independently in the contralateral occipital cortex. The lactate, choline-containing compounds (Cho), and myoinositol (mI) levels recovered progressively within 30 days after the status epilepticus, whereas the* N*-acetylaspartate (NAA) level remained low.*

outlast the ictal activity, and disappeared between 1 and 3 months post status. Consequently, FLAIR imaging should still yield positive results if taken within 1 month after a period of significant seizure increase.

The EEG-fMRI results revealed a positive BOLD effect in the region that matches the localization of the hyperintense signal in the FLAIR image. This suggests an increase of the local blood flow as a consequence of increased epileptic activity, because the BOLD effect is primarily due to hemodynamic response as a result of neuronal activity. Note that the EEG-fMRI study was performed 4 days after the status epilepticus, whereas the EEG showed still important interictal abnormalities. As suggested by other reports, the so-obtained BOLD signal can be detected in the absence of T2 hyperintensity[5,6] and can be used to guide a more focused exploration of the suspicious brain region; for instance, the positioning of the spectroscopy voxel.

As outlined above, a decrease of NAA level indicates neuronal loss or dysfunction, whereas an increase of Cho and Cr reflects probably reactive astrocytosis. Metabolic changes assessed by $^{1}$H-MRS have been observed in adjacent temporal neocortex and in extratemporal epileptic areas.[10,12-14,26,27] Our results confirm the high sensitivity of $^{1}$H-MRS to detect epileptic activity in extratemporal cortex. Nevertheless, the main limitation of single voxel $^{1}$H-MRS used in this study is related to the choice of the voxel placement, which may be difficult in the absence of a lesion detected either by structural or functional MRI. A better anatomic coverage can be achieved by the use of chemical shift imaging as has been shown in temporal and extratemporal epilepsy.[12,28]

Few $^{1}$H-MRS longitudinal descriptions of spectral anomalies and their changes after prolonged seizure activity exist. In the current case, the lowest NAA level was observed at day 4 (see the table). The NAA time course showed a slight (10%) recovery, but remained low over the 1-year study period, which confirms a previous study's findings.[13] However, short-term NAA changes have been observed as well and reflect local metabolic dysfunctions rather than neuronal loss.[29] To our knowledge, it is not possible to differentiate the origin of low NAA values; it seems that only follow-up measurements provide a clue whether they represent a transient or persistent neuronal dysfunction.

We also measured high lactate levels up to 4 days after the initial event. This represents a highly localizing sign of epileptic activity and is consistent with the hypothesis that lactate is produced locally upon increased ictal metabolism, as suggested by previous observations.[26,29] Discrete lactate elevations have also been observed in the visual cortex of healthy subjects after visual stimulation,[30,31] and were attributed to astrocytic lactate production, which serves as an important energy source for neurons.[32,33] However, the presence of lactate is also closely temporally related to the incidence of increased epileptic discharges. During the acute phase (visits 1 and 2), the lactate peak was significantly elevated and disappeared between day 4 and day 30 (reduced already at day 4). Its reduction corresponded well with the significant clinical improvement as well as the decrease of the epileptic discharges. Lactate remained undetectable for the remaining 1-year follow-up period during which the patient had only rare simple partial seizures. Our findings are consistent with observations that found lactate only in patients with seizures occurring immediately before or during the $^{1}$H-MRS examination.[26] Transient lactate following seizures in rat models has been observed as well and suggests that lactate is related to excessive neuronal activity and not to neuronal damage.[29,34]

Elevated choline during the ictal phase has not been reported. Interestingly, although not reported, some published spectra showed clearly elevated choline (see, for instance, figure 3 in reference 34 and figure 2 in reference 28). Increased hippocampal choline has been observed in mesiotemporal epilepsy and has been attributed to gliosis.[10,35] Our data show a recovery of Cho that is too fast (in less than 30 days) to be associated with gliosis. The mobile choline-containing compounds include choline, acetylcholine, phosphocholine, and glycerophosphocholine. There is a distinct interaction between the different choline moieties.[36] Choline, for instance, is a biochemical precursor for both acetylcholine and phospholipids. Our $^{1}$H-MRS findings of increased Cho may reflect an increase in acetylcholine and choline, which was observed in rats during seizures induced by convulsant treatments.[37,38] Further studies are needed to investigate the choline changes as assessed by $^{1}$H-MRS in relation to seizure.


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