CURRENT LITERATURE IN CLINICAL SCIENCE

ARE ICTAL FAST RIPPLES AN "ELECTRONIC SIGNATURE" FOR THE SEIZURE-ONSET ZONE?

High-Frequency Oscillations during Human Focal Seizures. Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. *Brain* 2006;129(Pt 6):1593–1608. Discrete high-frequency oscillations (HFOs) in the range of 100–500 Hz have previously been recorded in human epileptic brains using depth microelectrodes. We describe, for the first time, similar oscillations in a cohort of unselected focal epileptic patients implanted with EEG macroelectrodes. Spectral analysis and visual inspection techniques were used to study seizures from 10 consecutive patients undergoing presurgical evaluation for medically refractory focal epilepsy. Four of these patients had focal seizure onset in the mesial temporal lobe, and in all 12 of their seizures, well-localized, segmental, very high frequency band (VHF 250–500 Hz) oscillations were visually identified near the time of seizure onset from contacts in this zone. Increased high-frequency band (HF 100–200 Hz) activity compared with the background was distinguished both visually and with spectral analysis later in the seizures of 3/4 mesial temporal patients, involving contacts in the generator region and, in one patient, areas of contralateral perihippocampal propagation. Three patients with well-defined neocortical seizure-onset areas also demonstrated focal HF or VHF oscillations confined to the seizure-onset channels during their eight seizures. No discrete HF or VHF activity was present in the poorly localized seizures from the remaining three patients. These results show that discrete HFOs can be recorded from human focal epileptic brain using depth macroelectrodes, and that they occur mostly in regions of primary epileptogenesis and rarely in regions of secondary spread. Absent high-frequency activity seems to indicate poor localization, whereas the presence of focal HFOs near the time of seizure onset may signify proximity to the epileptogenic focus in mesial temporal lobe and neocortical seizures. We postulate that focal HFOs recorded with depth macroelectrodes reflect the partial synchronization of very local oscillations such as those previously studied using microelectrodes, and result from interconnected small neuronal ensembles. Our finding that localized HFOs occur in varying anatomical structures and pathological conditions perhaps indicates commonality to diverse epileptogenic etiologies.

COMMENTARY

When neurosurgical treatment of medically refractory focal epilepsy is considered, the site of seizure origination is often identified by concordance of localizing information from neuroimaging studies and noninvasive EEG recordings. In many cases, however, this information is inadequate, and invasive EEG recording of seizures, using intracranial subdural, depth, or epidural electrodes, is needed to identify the zone of seizure onset. Interpretation of invasive ictal recordings can be challenging, both because electrical abnormalities may be widespread and because surgically implanted electrodes may be placed in a location that does not adequately cover the seizure-onset zone. Interictal epileptiform discharges are seldom discretely localized to the region of seizure onset. When electrode arrays are not correctly placed, the electrode in which the ictal electrographic discharge first appears may only be a region of secondary propagation from an uncovered, and thereby unidentified, seizure-onset zone.

Epilepsy Currents, Vol. 7, No. 1 (January/February) 2007 pp. 7–9
Blackwell Publishing, Inc.

When interpreting invasive recordings, how can one be certain that the true region of seizure onset has been identified? When should the clinician suspect that only a region of secondary spread has been found? One criterion is the temporal relation between the initial behavioral seizure manifestations and the onset of the electrographic discharge. If signs or symptoms of the seizure begin before the electrical changes, surely only a region of secondary propagation has been identified. Another clue is the presence of high-frequency activity, typically in the gamma (30–80 Hz) frequency range, at the onset of the ictal electrographic discharge (1,2). Such activity, sometimes colloquially referred to as a "buzz," has long been recognized by electroencephalographers as a useful marker of the seizure-onset zone. Yet, this phenomenon has been poorly characterized and understood, which is in part because conventional EEG recordings typically are limited to a bandwidth of approximately 0.5 to 70 Hz.

Investigation of higher-frequency bands—consisting of "ripples" (high-frequency oscillations of 80–200 Hz) and "fast ripples" (very high-frequency oscillations of 250–500 Hz)—in human focal epilepsy is compelled by an impressive body of basic research. Ripples were first recorded in CA1 hippocampal

pyramidal cells and later in entorhinal cortex; they are most prominent during non-REM sleep and are thought to have a normal, functional role (3). Both ripples and fast ripples have been recorded in experimental hippocampal and neocortical focal seizures (4,5) and in human mesial temporal epilepsy (5). In human epileptic hippocampus and entorhinal cortex, two spectrally distinct oscillations have been recorded and interpreted as representing physiological ripples and pathological fast ripples associated with epileptogenesis (6). In rats made epileptic by intrahippocampal kainate injection, stable sites of interictal fast ripples are established in the hippocampus, and the number of electrodes from which fast ripples could be recorded correlate with how often spontaneous seizures occur (7). It has been proposed that high-frequency 200-Hz oscillations in the hippocampus result from axons of depolarized hippocampal pyramidal cells, which are electrically coupled by gap junctions that phasically excite interneurons at ripple frequencies (8). Another, perhaps, complimentary mechanism, which was proposed to explain observations of recordings of experimental neocortical seizures, is that ictal fast oscillations could be a reflection of synchronous action potentials that generate strong field potentials ("field ripples"), which help produce and synchronize action potentials in an autoregenerative fashion (4). Grenier et al. also have presented evidence that ripples occur at the transition to ictal events and are involved in the mechanism of seizure initiation (4).

The experimental data cited in the previous paragraph put fast ripples at the onset of seizures, both in time and in space. In this context, the work by Jirsch et al. begins to translate these basic science findings into a useful clinical tool for seizure localization. The authors describe the recording and analysis techniques for identifying and localizing ictal ripples and fast ripples during presurgical recordings with conventional depth electrodes in human focal epilepsy. Acquisition with a low-pass filter of 500 Hz and a sampling frequency of 2,000 Hz is key. Visual inspection of the recording (with appropriate expansion of the time base and high-pass filtering) is a more informative method of identifying high- and very-high-frequency oscillations than is spectral analysis.

The work by Jirsch and colleagues convincingly demonstrates, for the first time, that it is possible to detect and localize ictal 80–400 Hz activity in human intracranial recordings using conventional depth electrodes and that this activity is found at the seizure-onset zone, as determined by analysis of the EEG at conventional frequencies. However, it has not yet been proven that the boundaries of a fast ripple zone would correspond exactly to the margins of the seizure-onset zone that should be surgically resected. It also has not yet been demonstrated that fast ripples are a universal feature of seizure foci of all etiologies.

This important preliminary research by Jirsch et al. raises several issues for future research:

1. At this point, the results only have been validated by comparison with conventional clinical determination of the seizure-onset zone, not by the "gold standard" of surgical outcomes.
2. Only 10 patients have been studied, with focal cortical dysplasia, mesial temporal atrophy, destructive gliotic lesions, or cryptogenic epilepsy—a larger number of localization-related epilepsies of diverse etiologies needs to be investigated.
3. Depth electrodes have only limited spatial sampling along a single dimension. Mapping of neocortical seizure-onset zones in two dimensions with subdural grids may help to better define the borders of the ictal electrical changes and, thereby, confirm exact colocalization of the fast ripple and seizure-onset zones. Special recording arrays with smaller, more densely placed electrodes may be necessary to reliably detect and adequately localize fast oscillations.
4. The experimental literature indicates that fast ripples are also an interictal marker of the seizure-onset zone—brief bursts of fast oscillations without associated change in behavior occur frequently in animals with kainate-induced epilepsy. Jirsch et al. only looked at fast ripples that occurred during behavioral seizures and did not examine other portions of the recording for high-frequency oscillations. If this relationship between interictal fast ripples and the seizure-onset zone also exists in human epilepsy and is robust, this finding could lead to new approaches to identifying the surgical seizure focus without ictal recording, perhaps even noninvasively, by techniques such as magnetoencephalography.

Finally, the work by Jirsch et al. provides additional evidence that the conventional EEG recording bandwidth, determined by the technical limitations of midtwentieth century recording devices, discards very valuable information. Scalp ictal recordings typically contain their highest power at infraslow (<0.5 Hz) frequencies, which can be used for ictal localizations (9). The current work now demonstrates that for invasive monitoring, recording of frequency bands in the 80–500 Hz range may not only be a practical tool to identify the seizure focus for surgical resection, but also may give new insights into mechanisms of epileptogenesis.

by John W. Miller, MD, PhD

References

1. Allen PJ, Fish DR, Smith SJ. Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1992;82:155–159.
2. Fisher RS, Webber WR, Lesser RP, Arroyo S, Uematsu S. High-frequency EEG activity at the start of seizures. *J Clin Neurophysiol* 1992;9:441–448.

3. Busaki G, Horvath Z, Urioste R, Hetke J, Wise K. High-frequency network oscillation in the hippocampus. *Science* 1992;256:1025–1027.
4. Grenier F, Timofev I, Steriade M. Neocortical very fast oscillations (ripples, 80–200 Hz) during seizures: intracellular correlates. *J Neurophysiol* 2003;89:841–852.
5. Bragin A, Engel J Jr., Wilson CL, Fried I, Mathern GW. Hippocampal and entorhinal cortex high frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. *Epilepsia* 1999;40:127–137.
6. Staba RJ, Wilson CL, Bragin A, Fried I, Engel J Jr. Quantitative analysis of high-frequency oscillations (80-500 Hz) recoded in human epileptic hippocampus and entorhinal cortex. *J Neurophysiol* 2002;88:1743–1752.
7. Bragin A, Wilson CL, Engel J Jr. Spatial stability over time of brain areas generating fast ripples in the epileptic rat. *Epilepsia* 2003;44:1233–1237.
8. Traub RD, Bibbig. A model of high-frequency ripples in the hippocampus based on synaptic coupling plus axon-axon gap junctions between pyramidal neurons. *J Neuroscience* 2000;20:2086–2093.
9. Vanhatalo S, Holmes MD, Tallgren P, Voipio J, Kaila K, Miller JW. Very slow EEG responses indicate the laterality of temporal lobe seizures: a DC-EEG study. *Neurology* 2003;60:1098–1104.

Is Epilepsy Intractability Predetermined or Acquired?

How Long Does it Take for Epilepsy to Become Intractable? A Prospective Investigation Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, Smith S. *Ann Neurol* 2006;60:73–79. OBJECTIVE: To determine prospectively when in the course of epilepsy intractability becomes apparent. METHODS: Data are from a prospective cohort of 613 children followed for a median of 9.7 years. Epilepsy syndromes were grouped as focal, idiopathic, catastrophic, and other. Intractability was defined in two ways: (a) two drugs failed, 1 seizure/month, on average, for 18 months (stringent), and (b) failure of two drugs. Delayed intractability was defined as 3 or more years after epilepsy diagnosis. RESULTS: Eighty-three children (13.8%) met the stringent and 142 (23.2%) met the two-drug definition. Intractability depended on syndrome ($p < 0.0001$): 26 (31.3%) children meeting stringent and 39 (27.5%) meeting the two-drug definition had delayed intractability. Intractability was delayed more often in focal than catastrophic epilepsy (stringent: 46.2 vs 14.3%, $p = 0.003$; two-drug: 40.3 vs 2.2%, $p = 0.0001$). Early remission periods preceded delayed intractability in 65.4–74.3% of cases. After becoming intractable, 20.5% subsequently entered remission and 13.3% were seizure free at last contact. INTERPRETATION: Intractable epilepsy may be delayed, especially in focal epilepsy. It often is preceded by a quiescent period, followed by further remissions. These findings help explain why surgically treatable epilepsies may take 20 years or longer before referral to surgery.

COMMENTARY

Epilepsy appears intractable in more than 35% of newly treated patients (1). As expected, the prevalence of intractability is higher in referral centers (2), and patients with partial epilepsy are more likely to be intractable. It has long been debated whether intractability is already present when the condition first expresses itself or develops over time. Some investigators have suggested that the longer uncontrolled seizures continue, the more difficult they will be to control, perhaps implying that a delay in effective treatment may contribute to the intractability (3). However, other studies have indicated that intractable epilepsy can often be detected early after onset of seizures (1,4). In one study of newly treated epilepsy, overall, 64% of patients became seizure free, while only 11% of those in whom the first drug was ineffective and only 4% of those who failed two drugs became seizure free (1). Thus, poor response to the first and the second drug is a predictor of intractability. In addition, the pathology of hippocampal sclerosis was consistently predictive of intractability (2,5).

If the failure of two drugs predicts intractability, then one would expect that those patients who are candidates for epilepsy surgery could be identified and referred within 2–3 years, the time it would take to verify failure of at least two drugs. However, in a prior retrospective study examining the outcomes of resective epilepsy surgery, Berg and colleagues found that the mean duration of epilepsy before surgery was 22.1 years (6). Two factors for this delay were that as many as a quarter of patients reported variable periods of remission before deciding to pursue surgery and that the average time to failure of the second drug was 9 years. Early age at onset of epilepsy was the strongest predictor of delayed intractability. Because of these findings, it seemed appropriate to prospectively evaluate the latency to intractability in a cohort of children with epilepsy.

The prospective study by Berg and colleagues confirmed that delayed intractability is not uncommon, although early

Epilepsy Currents, Vol. 7, No. 1 (January/February) 2007 pp. 9–10
Blackwell Publishing, Inc.

intractability remained more likely. Approximately 30% of children with intractable epilepsy had delayed intractability. This phenomenon was more likely in focal than in other types of epilepsy. Temporal lobe epilepsy and hippocampal sclerosis were both associated with delayed intractability in the retrospective study (6). The current study found a greater likelihood of intractability in temporal lobe than in extratemporal epilepsy, which is in agreement with one referral center retrospective study (2). However, Berg et al. did not identify clear differences between temporal and extratemporal epilepsy with respect to delayed intractability. The study results did not include the prevalence of hippocampal sclerosis among patients with temporal lobe epilepsy, however, the authors indicated in the discussion that only one child had MRI evidence of hippocampal sclerosis at study entry. Although this finding may be a low estimate, it is nevertheless very likely that hippocampal sclerosis is much less prevalent in a population-based pediatric temporal lobe epilepsy group than it is in an adult temporal lobe epilepsy surgery group. Hippocampal sclerosis may still be specifically associated with delayed intractability.

Delayed intractability raises the possibility that epilepsy may be a progressive condition in some affected individuals. If accurate, the finding in turn may offer an opportunity for intervention, provided the underlying pathophysiology is understood. Assuming that the process of epileptogenesis is still ongoing in patients with delayed intractability, the development of antiepileptogenic drugs could be pursued to arrest this process. However, the mechanism of delayed medical intractability could be very different than progression of epileptogenesis. At the present time, two main mechanisms of drug resistance have been proposed: (a) increased expression of multidrug transporters (also called drug resistance proteins) that remove antiepileptic drugs from the epileptogenic zone and (b) reduced sensitivity of the drug target in the epileptogenic zone (7). Development of tolerance is another mechanism that now is receiving more attention (8).

Both drug transporter expression and certain drug targets can be modified by seizure activity in animal models. In particular, it has been demonstrated that some drug transporter proteins can be transiently overexpressed in rodent brain after experimentally induced seizures (7). It is not known what role the drug transporter proteins play in development of medically refractory human epilepsy. If human seizures can also induce drug resistance proteins, then induction of these proteins could potentially contribute to the occasional development of intractable epilepsy after antiepileptic drug withdrawal in previously seizure-free patients (9). With progress in the in vivo imaging of drug resistance proteins in the human brain, there is potential to learn if these proteins play a role in the delayed development of intractable epilepsy (10). If they do, strategies could be developed to reduce their impact, including the use of specific inhibitors.

Intractability is not always an irreversible phenomenon. Berg and colleagues reported that more than 20% of intractable patients went on to experience one or more remissions after meeting their stringent criteria of intractability and almost 50% had remissions following the less stringent criteria. Almost two-thirds of these patients were still in remission at the time of the last contact. The authors were not able to identify the factors responsible for late remissions and found no evidence that new antiepileptic drugs were responsible for better outcomes. However, that possibility cannot be excluded. The new antiepileptic drugs have been associated with seizure freedom for at least 6 months in up to 13% of previously highly refractory patients (11). A detailed analysis of the circumstances surrounding relapse and remission after apparent intractability would be of great interest. The prospective study of the current cohort is likely to continue to shed more light on the natural history of epilepsy intractability.

by Bassel W. Abou-Khalil, MD, PhD

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
2. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, Cavalcanti D, Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256–1262.
3. Reynolds EH, Elwes RD, Shorvon SD. Why does epilepsy become intractable? Prevention of chronic epilepsy. *Lancet* 1983;2:952–954.
4. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. *Neurology* 2001;56:1445–1452.
5. Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? *Epilepsia* 2001;42:357–362.
6. Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, Bazil C, Pacia SV, Spencer SS. How long does it take for partial epilepsy to become intractable? *Neurology* 2003;60:186–190.
7. Schmidt D, Loscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. *Epilepsia* 2005;46:858–877.
8. Loscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. *Epilepsia* 2006;47:1253–1284.
9. Schmidt D, Loscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurol Scand* 2005;111:291–300.
10. Elsinga PH, Hendrikse NH, Bart J, Vaalburg W, van Waarde A. PET Studies on P-glycoprotein function in the blood-brain barrier: how it affects uptake and binding of drugs within the CNS. *Curr Pharm Des* 2004;10:1493–1503.
11. Zaccara G, Messori A, Cincotta M, Burchini G. Comparison of the efficacy and tolerability of new antiepileptic drugs: what can we learn from long-term studies? *Acta Neurol Scand* 2006;114:157–168.

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 ^{1}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

Epilepsy Currents, Vol. 7, No. 1 (January/February) 2007 pp. 11–12
Blackwell Publishing, Inc.

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.

by Jorge G. Burneo, MD, MSPH

References

1. Lovblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR, Warach S. Clinical experience with diffusion-weighted MR in patients with acute stroke. *AJNR Am J Neuroradiol* 1998;19:1061–1066.
2. Kim JA, Chung JI, Yoon PH, Kim DI, Chung TS, Kim EJ, Jeong EK. Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: periictal diffusion-weighted imaging. *AJNR Am J Neuroradiol* 2001;22:1149–1160.
3. Hugg JW, Butterworth EJ, Kuzniecky RI. Diffusion mapping applied to mesial temporal lobe epilepsy: preliminary observations. *Neurology* 1999;53:173–176.
4. Diehl B, Najm I, Ruggieri P, Tkach J, Mohamed A, Morris H, Wyllie E, Fisher E, Duda J, Lieber M, Bingaman W, Luders HO. Postictal diffusion-weighted imaging for the localization of focal epileptic areas in temporal lobe epilepsy. *Epilepsia* 2001;42:21–28.
5. Kuzniecky R, Hetherington H, Pan J, Hugg J, Palmer C, Gilliam F, Faught E, Morawetz R. Proton spectroscopic imaging at 4.1 tesla in patients with malformations of cortical development and epilepsy. *Neurology* 1997;48:1018–1024.
6. Farina L, Bergqvist C, Zimmerman RA, Haselgrove J, Hunter JV, Bilaniuk LT. Acute diffusion abnormalities in the hippocampus of children with new-onset seizures: the development of mesial temporal sclerosis. *Neuroradiology* 2004;46:251–257.
7. Lewis DV, Barboriak DP, MacFall JR, Provenzale JM, Mitchell TV, VanLandingham KE. Do prolonged febrile seizures produce medial temporal sclerosis? Hypotheses, MRI evidence and unanswered questions. *Prog Brain Res* 2002;135:263–278.
8. Tasch E, Cendes F, Li LM, Dubeau F, Andermann F, Arnold DL. Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. *Ann Neurol* 1999;45:568–576.
9. Garcia PA, Laxer KD, van der Grond J, Hugg JW, Matson GB, Weiner MW. Correlation of seizure frequency with *N*-acetylaspartate levels determined by 1H magnetic resonance spectroscopic imaging. *Magn Reson Imaging* 1997;15:475–478.
10. Burneo JG, Knowlton RC, Faught E, Martin R, Sawrie S, Kuzniecky RI. Chronic temporal lobe epilepsy: spatial extent and degree of metabolic dysfunction studied with magnetic resonance spectroscopy (MRS). *Epilepsy Res* 2004;62:119–124.

New Evidence Supports Cognitive Decline in Temporal Lobe Epilepsy

Cognitive Prognosis in Chronic Temporal Lobe Epilepsy. Hermann BP, Seidenberg M, Dow C, Jones J, Rutecki P, Bhattacharya A, Bell B. *Ann Neurol* 2006;60:80–87. OBJECTIVE: First, to determine whether patients with chronic temporal lobe epilepsy have a different cognitive trajectory compared to control subjects over a prospective 4-year interval; second, to determine the proportion of patients who exhibit abnormal cognitive change and their profile of demographic, clinical epilepsy, and baseline quantitative magnetic resonance imaging characteristics; and third, to determine the most vulnerable cognitive domains. METHODS: Participants with chronic temporal lobe epilepsy ($N = 46$) attending a tertiary referral clinic and healthy control subjects ($N = 65$) underwent neuropsychological assessment and reevaluation 4 years later. Analysis of test–retest patterns identified individual patients with adverse cognition outcomes. RESULTS: The prospective cognitive trajectory of patients with chronic temporal lobe epilepsy differs from age- and sex-matched healthy control subjects. Lack of practice effects is common, but frank adverse cognitive outcomes are observed in a subset of patients (20%–25%), particularly in vulnerable cognitive domains that include memory. Cognitive declines are associated with a profile of abnormalities in baseline quantitative magnetic resonance volumetrics, lower baseline intellectual capacity, as well as longer duration of epilepsy and older chronological age. INTERPRETATION: Cognitive prognosis is poor for a subset of patients characterized by chronicity of epilepsy, older age, lower intellectual ability, and more baseline abnormalities in quantitative magnetic resonance volumetrics.

COMMENTARY

This recent report by Hermann et al. provides the most systematic evidence to date for the presence of evolving cognitive deficits in persons with epilepsy. Unlike previous investigations of cognitive change in patients with epilepsy,

Epilepsy Currents, Vol. 7, No. 1 (January/February) 2007 pp. 12–14
Blackwell Publishing, Inc.

subjects in this study were evaluated prospectively during an interval of 4 years. The study provided thorough documentation of seizure history and antiepileptic drug (AED) use in the epilepsy group as well as careful matching of demographic characteristics between the control and epilepsy groups. Some of the findings are subtle yet clearly supportive of previous cross-sectional results on cognition in epilepsy. The subtlest finding involves the fact that the epilepsy group fell short of predicted cognitive test scores upon retesting; the predicted scores were statistically derived from test–retest scores in the control group. That is, the practice effect, which typically results in an improved score when repeating a cognitive test (even over a 4-year span), was not found in the epilepsy group. Therefore, although the test scores for the epilepsy group generally demonstrated little cognitive decline over the study interval, retesting of normal controls revealed significantly improved scores. Overall, 57% of the control group's test results improved upon retest, while only 6% of the temporal lobe epilepsy group improved.

Using z-scores more than 2.0 standard deviations below expected, Hermann and colleagues identified a subset of patients with chronic temporal lobe epilepsy who had cognitive decline over time (approximately 25%–40% of the epilepsy group). The cognitive decline occurred most frequently in the domains of confrontational naming, delayed visual memory, delayed verbal memory, and motor speed. Within the epilepsy group, predictors of decline in performance on specific cognitive tests included lower IQ at baseline, longer duration of epilepsy, smaller baseline left hippocampus, decreased volume in other brain compartments on volumetric MRI, and older age at the time of the study. These factors are not unexpected, based on reports from cross-sectional studies of intellect and neuropsychological testing in adults with epilepsy.

The authors previously have reported on cross-sectional cohorts that demonstrated that longer duration of epilepsy is associated with cognitive deficits (1); they also have reported an association of cognitive deficits with smaller hippocampal volume as well as with reduced total brain volume (2,3). Multiple, previous investigators have validated these findings with reports of memory impairment associated with hippocampal atrophy (2–7). Another report links decreasing hippocampal volume with longer duration of epilepsy (8). Therefore, hippocampal atrophy may be a marker for cognitive impairment as well as a predictor of cognitive decline. Although the earlier cross-sectional study indicated that fewer years of formal education was a risk factor for cognitive decline within the epilepsy group, this prospective study did not corroborate that finding (1). The earlier study also reported that seizure onset before the age of 14 years was a risk factor for cognitive decline (2)—again, a factor that was not found in the current study; however, most of the subjects did have an early onset of epilepsy (mean age of onset 11.1 years, SD 7.3). Therefore, the investigators simply may not have had enough subjects with an age of onset above 14 years to make a meaningful comparison, using age 14 years as a cutoff point.

Antiepileptic drugs (AEDs) and recurrent seizures—the factors usually considered to be either confounders and/or contributors to cognitive dysfunction in epilepsy—are well accounted for in this study and did not emerge as risk factors. The only exception to this finding was AED polytherapy, which was associated with adverse change in confrontational naming and speeded fine motor dexterity. The mean number of secondary generalized seizures during the entire 4-year study was low, at 2.8. If AEDs and seizures are not predictors of cognitive decline, the epileptic process itself emerges as a major factor in producing cognitive decline. The fact that smaller brain compartments, particularly the hippocampi, are predictors of progressive cognitive dysfunction supports the hypothesis that brain injury and degeneration are aspects of the epileptic process. Further, if recurrent seizures are reasonably considered to be part of an epileptic process, hippocampal atrophy and T2 signal abnormalities may predict seizure recurrence over the long term, even among patients who have prolonged seizure-free periods off AEDs (9). In other words, this finding supports numerous previously published studies that mesial temporal sclerosis is a predictor of medical intractability.

The findings by Hermann et al. pull together several spheres of information to support the concept that epilepsy is an entity characterized by more than recurrent seizures and their sequelae. Therefore, when patients complain of cognitive difficulties and memory problems, it should be kept in mind that it is not always the AEDs, depressed mood, or even the seizures causing their complaints—it could be that they are experiencing progressive cognitive impairment that is an inherent part of the epileptic process.

by Cynthia L. Harden, MD

References

1. Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, Seidenber M, Hermann BP. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology* 2004;62:1736–1742.
2. Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Prog Brain Res* 2002;135:429–438.
3. Oyegbile TO, Bhattacharya A, Seidenberg M, Hermann BP. Quantitative MRI biomarkers of cognitive morbidity in temporal lobe epilepsy. *Epilepsia* 2006;47:143–152.
4. Griffith HR, Pyzalski RW, O'Leary D, Magnotta V, Bell B, Dow C, Hermann B, Seidenberg M. A controlled quantitative MRI volumetric investigation of hippocampal contributions to immediate and delayed memory performance. *J Clin Exp Neuropsychol* 2003;25:1117–1127.

5. Martin RC, Sawrie SM, Knowlton RC, Bilir E, Gilliam FG, Faught E, Morawetz RB, Kuzniecky R. Bilateral hippocampal atrophy: consequences to verbal memory following temporal lobectomy. *Neurology* 2001;57:597–604.
6. Baxendale SA, van Paesschen W, Thompson PJ, Connelly A, Duncan JS, Harkness WF, Shorvon SD. The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia* 1998;39:158–166.
7. Reminger SL, Kaszniak AW, Labiner DM, Littrell LD, David BT, Ryan L, Herring AM, Kaemingk KL. Bilateral hippocampal volume predicts verbal memory function in temporal lobe epilepsy. *Epilepsy Behav* 2004;5:687–695.
8. Theodore WH, Bhatia S, Hatta J, Fazilat S, De Carli C, Bookheimer SY, Gaillard WD. Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. *Neurology* 1999;52:32–36.
9. Cardoso TAM, Coan AC, Kobayashi E, Guerreiro CAM, LI LM, Cendes F. Hippocampal abnormalities and seizure recurrence after antiepileptic drug withdrawal. *Neurology* 2006;67:134–136.