TO STOP OR NOT TO STOP THE AED?

Consequences of Antiepileptic Drug Withdrawal: A Randomized, Double-Blind Study (Akershus Study). Lossius MI, Hessen E, Mowinckel P, Stavem K, Erikssen J, Gulbrandsen P, Gjerstad L. *Epilepsia* 2008;49:455–463. OBJECTIVE: Despite side effects associated with the use of antiepileptic drugs (AEDs), withdrawal of AEDs remains controversial, even after prolonged seizure freedom. The main objective of this study was to assess the effects of AED withdrawal on cognitive functions, seizure relapse, health-related quality of life (HRQOL), and EEG results. Additionally, potential predictors for freedom from seizures after AED withdrawal were studied. METHODS: Patients, seizure-free for more than 2 years on AED monotherapy, were recruited for a controlled, prospective, randomized, double-blinded withdrawal study lasting for 12 months, or until seizure relapse. Patients were randomized to AED withdrawal (n = 79) and nonwithdrawal (n = 81) groups. The examination program included clinical neurological examinations, neuropsychological testing, EEG-recordings, cerebral MRI, and assessments of HRQOL. Follow-up data on seizure relapse were also collected beyond the 12-month study period (median 47 months). RESULTS: Seizure relapse at 12 months occurred in 15% of the withdrawal group and 7% of the nonwithdrawal group (RR 2.46; 95% CI: 0.85–7.08; p = 0.095). After withdrawal, seizure relapse rates were 27% after a median of 41 months off medication. A normal result to all 15 neuropsychological tests increased significantly from 11% to 28% postwithdrawal. We found no significant effects of withdrawal on quality of life and EEG. Predictors for remaining seizure-free after AED-withdrawal over 1 year were normal neurological examination and use of carbamazepine prior to withdrawal. CONCLUSION: Seizure-free epilepsy patients on AED monotherapy who taper their medication may improve neuropsychological performance with a relative risk of seizure relapse of 2.46, compared to those continuing therapy.

COMMENTARY

Approximately two-thirds of patients with new-onset epilepsy become seizure-free when treated with antiepileptic drugs (AEDs) (1). In a portion of these patients who maintain prolonged remission, it is possible to withdraw AED therapy. The study by Lossius et al. adds additional information to help clinicians inform patients of the risks and benefits, when trying to make the decision as to whether to withdraw AEDs. Even when prior studies have been prospective and randomized, they have been open label. Lossius et al. conducted a well-controlled prospective, randomized, double-blind investigation assessing not only the effects of AED withdrawal on the risk of seizure relapse but also on possible changes in cognitive functions.

A critical review of 28 studies encompassing 4,571 patients noted that the risk of seizure relapsed after AED withdrawal ranged from 4 to 34% at 1 year and 9 to 39% at 2 years (2). The findings of Lossius et al. are similar to the largest single study of AED withdrawal, which was conducted by the Medical Research Council (MRC) from 1984 to 1988 (3). Lossius and colleagues found that the risk of seizure relapse in patients who withdrew AEDs was about double the risk of patients who continued AEDs at the end of 1 year (i.e., 15% vs 7% at the end of the double-blind period). In comparison, the MRC study, which included 1,031 patients, found that the risk of seizure recurrence was doubled at the end of 2 years (i.e., 41% vs 22%) (3). Since patients who were not in the AED withdrawal group in the first year of the Lossius et al. study were offered withdrawal after the 1 year double-blind period, data on recurrence with continued AED therapy are not available from their report after the first year; however, the AED withdrawal group can be compared to the MRC study. In fact, seizure recurrence at the end of 2 years in the AED withdrawal groups is remarkably similar (i.e., 19% in the present study vs 22% in MRC study). Further, a meta-analysis published in 1994 found that the risk of seizure relapse after AED withdrawal was 29 percent at 2 years (95% confidence intervals [CI], 24%, 34%) (4). In both studies and both reviews cited above, the large majority of seizure relapses occurred in the first 12 months, with the risk of seizure relapse thereafter being very similar, especially after 2 years, for the withdrawal and continued AED treatment groups.

Various factors may affect the risk of seizure relapse, although there is some controversy as to the importance of specific issues. Average risks may not be relevant to an individual patient, as epilepsy is a heterogeneous disorder (5). Thus, some patients will require AEDs for continued control of seizures, whereas prolonged AED treatment for others may be unnecessary. For example, up to 90% of patients with juvenile myoclonic epilepsy will relapse if AEDs are withdrawn, but children with

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benign rolandic epilepsy usually remit permanently. A multivariate analysis of the MRC study found that the risk of seizures with AED withdrawal increased with specific factors including: age >16 years, seizures only on awakening, myoclonic seizures, more than one AED, seizures after the start of AED therapy, and shorter seizure-free periods on AEDs (5). Other factors that have been found to increase the risk of seizure relapse include syndrome (e.g., juvenile myoclonic epilepsy), mental retardation, and abnormal neurological exam (2). Lossius et al. found that risk was reduced in patients with a normal neurological exam and in those withdrawing from carbamazepine. Interestingly, a similar finding for carbamazepine was seen in the MRC study, although the reason for the finding remains obscure (6). The lack of AED dose and blood level data in these studies may create variance in the results. Investigations have yielded mixed results on the risks related to age of onset and to duration of epilepsy. The role of EEG also has been inconclusive; however, many studies have lumped abnormal EEG findings, so distinct factors cannot be identified. One might expect that well-formed spike wave complexes, especially occurring in runs, would suggest a higher risk than poorly formed sharps or slowing. Unfortunately, EEG in the present study was only assessed for change and was not included in the analysis of possible predictors of seizure relapse. Hippocampal atrophy and sclerosis on MRI have been shown to increase the risk of relapse (7), but other types of MRI abnormalities have not been adequately studied. In addition, the certainty of the original diagnosis is another factor that might impact the risk of seizure relapse. Lossius et al. found that the presence of an MRI abnormality did not predict seizure relapse, but they did not analyze types of MRI abnormalities separately.

How long should a patient be seizure free before considering AED withdrawal? A Cochrane review concluded that there is evidence to support waiting ≥2 years with children; however, the optimal time period remains uncertain in adults (8). Note that most adult studies have been conducted in patients who are ≥2 years seizure free. The MRC study did find that a shorter duration of the seizure-free period increased risk of seizure relapse after AED withdrawal (3).

Does the rate at which the AED is tapered affect risk of relapse? A recent Cochrane review did not come to any reliable conclusion on the optimal taper rate (9). Of course, some AEDs (e.g., phenobarbital) require slow taper to avoid withdrawal seizures. Further, many physicians choose to taper slowly, based on the concept that if relapse occurs during the taper, the seizure may be less severe than after full withdrawal.

The risks associated with AED withdrawal (e.g., injury or loss of driving privileges) need to be balanced against the risks and cost of long-term AED therapy. Risks associate with long-term AED use include cognitive and behavioral side effects, osteopenia/osteoporosis, connective tissue abnormalities, weight gain, drug interactions (e.g., altered effectiveness of other drugs affected by AEDs), anatomical and behavioral teratogenesis in the children of women with epilepsy, and other untoward side effects. The study by Lossius et al. investigation found that AED withdrawal resulted in a modest improvement in cognitive functions. The magnitude of the cognitive effect was similar to prior studies (10) that examined the older AEDs employed in the Lossius et al. study. Although modest, these effects can be clinically significant (10). Given that several of the newer AEDs possess fewer cognitive effects (10), the benefit may not exist on withdrawal.

The decision to withdraw an AED in a patient who is seizure-free is ultimately one that has to be individualized and undertaken with the patient fully informed of the risks and benefits. The decision needs to take into account the known risk factors, the possible benefits of withdrawal, the certainty/uncertainty of our present data, and the individual patient's psychosocial factors. Additional blinded, randomized, controlled trials are needed to identify the optimal timing of AED withdrawal, further delineate the risk factors, and determine the risk/benefit ratios for the newer AEDs.

by Kimford J. Meador, MD

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The Real Truth Behind Seizure Count

Epilepsy: Accuracy of Patient Seizure Counts. Hoppe C, Poepel A, Elger CE. *Arch Neurol* 2007;64(11):1595–1599. OBJECTIVE: To evaluate the effects of a daily patient reminder on seizure documentation accuracy. DESIGN: Randomized controlled trial. SETTING: Monitoring unit of an academic department of epileptology. PATIENTS: Consecutive sample of 91 adult inpatients with focal epilepsies undergoing video-electroencephalographic monitoring. INTERVENTION: While all patients were asked to document seizures at the beginning of the monitoring period, patients from the experimental group were reminded each day to document seizures. MAIN OUTCOME MEASURE: Documentation accuracy (percentage of documented seizures). RESULTS: A total of 582 partial seizures were recorded. Patients failed to document 55.5% of all recorded seizures, 73.2% of complex partial seizures, 26.2% of simple partial seizures, 41.7% of secondarily generalized tonic-clonic seizures, 85.8% of all seizures during sleeping, and 32.0% of all seizures during the awake state. The group medians of individual documentation accuracies for overall seizures, simple partial seizures, complex partial seizures, and secondarily generalized tonic-clonic seizures were 33.3%, 66.7%, 0%, and 83.3%, respectively. Neither the patient reminder nor cognitive performance affected documentation accuracy. A left-sided electroencephalographic focus or lesion, but not the site (frontal or temporal), contributed to documentation failure. CONCLUSIONS: Patient seizure counts do not provide valid information. Documentation failures result from postictal seizure unawareness, which cannot be avoided by reminders. Unchanged documentation accuracy is a prerequisite for the use of patient seizure counts in clinical trials and has to be demonstrated in a subsample of patients undergoing electroencephalographic monitoring.

COMMENTARY

Trusting patients' count of seizures is a practice in which many clinicians engage, and sometimes it is the only way antiepileptic regimens are planned for a particular individual. Review of calendars, notebooks, agendas, and all sorts of visual aids for that purpose are part of a routine visit to the epilepsy clinic. But, the implications go beyond this clinical practice, because large-scale clinical trials (including those testing for new antiepileptic medications), population-based questionnaires, and other epidemiological studies also use patient feedback and reporting to determine optimal therapy regimens. The article by Hoppe et al. confirms, although with a larger patient population, what has been described before: a great number of patients underreport the occurrence of seizures (1,2). Although, this study was restricted to adult patients with partial seizures, underreporting also was seen in secondarily generalized seizures. What is unknown from the report by Hoppe and colleagues is whether underreporting also occurs with primarily generalized seizures. Their study indicates that underreporting does not take place because patients lack reminders to count seizures—in fact, their embedded, randomized, controlled trial show no improvement with reminders. Rather, their investigation revealed that underreporting was related to the patient's lack of awareness of the event.

Lack of awareness of a seizure was seen mainly in patients with an epileptogenic focus on the left hemisphere, which can be used as a localizing sign, particularly for temporal lobe onset (2,3). Their finding confirms previous information indicating that "consciousness can be disturbed much easier by the ictal activity in left temporal seizures" (4). Thus, the dominant hemisphere may be important in generating a state of alertness. Patients with left hemispheric seizures, particularly of left temporal lobe origin, experienced a significantly longer state of postictal confusion, which is something that cannot be explained by postictal aphasia alone. The question of whether patients forget their seizures or fail to recognize them is yet to be answered (5).

A technique that may allow greater accuracy in seizure counting is ambulatory EEG (6). This device is superior to the standard, sleep-deprived, 20 to 30 minute EEG recording for capturing seizures (7), although no comparative studies with prolonged video-EEG have been performed. Even though it is an expensive tool, inpatient seizure monitoring offers the advantage of video recording events and close surveillance of the technical quality of the EEG recording. Yet, the potential advantages of long-term ambulatory recordings in the patients' familiar environments are compelling as well. Many specific clinical questions, such as frequency of absence seizures or occurrence of unwitnessed nocturnal seizures, may be most easily answered with ambulatory EEG. Video capabilities can be adapted and incorporated into ambulatory EEG; in this way, the limitation of visual clinical correlation of electrographic and patient-identified events can be eliminated. Still, rigorous cost-effectiveness analysis should be applied to ambulatory EEG using adequate methodology and high-quality clinical data.

An interesting finding from the Hoppe et al. study is the possible interaction between seizure awareness and the specific

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antiepileptic medication used. In particular, patients on levetiracetam had better documentation accuracy than those on other medications—a finding that could be due to a sampling problem; however, changes in the semiology of seizures after the introduction of a new antiepileptic medication are sometimes seen in the outpatient setting as well. For some drugs, the changes are positive, particularly if the new semiology incorporates an aura not previously perceived prior to a seizure. In contrast, the disappearance of an aura may endanger somebody who previously had used them as a warning. The mechanisms underlying differences in documentation accuracy on various medications are not clear; larger studies, including a larger sample of patients each on a different antiepileptic medication, are needed.

Finally, it is important to take into account that this study was performed in an artificial environment. It is true that patients are unaware of most of their seizures, but there are always clues that a seizure just happened: a crowd of people suddenly showing up, friends or family members caring for the patient, paramedics arriving or taking the person to the hospital, among others. Furthermore, in the Hoppe et al. study, the majority of seizures not reported by patients happened during sleep—a time during which ambulatory EEG may be useful. However, in regard to daytime seizures, the question asked by clinicians should continue to be: "How many seizures have you had since the last time I saw you?"

by Jorge G. Burneo, MD, MSPH

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Seizure Aggravation—Evidence That Oxcarbazepine Requires Monitoring

Aggravation of Seizures and/or EEG Features in Children Treated with Oxcarbazepine Monotherapy. Vendrame M, Khurana DS, Cruz M, Melvin J, Valencia I, Legido A, Kothare SV. *Epilepsia* 2007;48(11):2116–2120. Epub 2007 Jul 21. PURPOSE: Exacerbation of epilepsy may occur following initiation of therapy with antiepileptic drugs (AEDs). The aim of this study is to analyze the clinical and EEG characteristics of a group of pediatric patients with worsening of seizures and/or EEG deterioration while on oxcarbazepine (OXC). METHODS: A retrospective analysis of a clinical database was performed to identify patients with epilepsy treated with OXC over the past 3 years. History, neurological examination, and EEG findings were reviewed to identify any who had developed exacerbation of seizures or new abnormalities on EEG. RESULTS: Of 290 patients on OXC, we identified 12 patients with new onset seizures, all with initial normal neurological exam and normal EEG, who developed either worsening of preexisting seizures, new seizure types, and/or EEG deterioration following introduction of OXC monotherapy. EEG changes were primarily characterized by new onset of generalized epileptiform activity not reported on the initial baseline EEG. Following substitution of OXC with a broad spectrum AED, significant improvement of seizure control and improvement in the EEG was observed. CONCLUSIONS: These findings suggest that OXC can aggravate seizures and/or worsen EEG features in children. Following initiation of therapy with OXC, monitoring of patients with follow-up EEGs may be important, especially in patients who do not show adequate response to therapy.

COMMENTARY

In the article by Vendrame and colleagues, oxcarbazepine is implicated in causing seizure aggravation and eliciting

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new seizure types in children ages 4 to 16 years. The most frequent transformation on the EEG in this case series was the appearance of generalized spike and slow wave complexes. Oxcarbazepine is a keto-analog to carbamazepine; therefore, it is not surprising that oxcarbazepine, like carbamazepine, can elicit new seizure types. In carbamazepine case studies, new seizure types have been reported especially in children with partial onset seizures or in seizures that at least initially appear to be partial onset (1). An important point of interest to clinicians is that the Verdrame et al. study investigates oxcarbazepine—the only drug that currently has a Level A classification from the International League Against Epilepsy Guidelines for use in children with partial onset seizures (2,3). These findings now may make the Guideline recommendations questionable. Yet, the frequency of seizure aggravation in this population was only 12 of 290 patients or 4.14 percent. Among the carbamazepine population in similar studies, seizure aggravation is found in up to 44 percent of patients <6 years of age (1).

The weakness of the Verdrame et al. study is that it is retrospective, and therefore the population studied cannot be reliably controlled for all factors. Still, it is a large study, and the patient histories seem to be well documented. Any patient complaining of worsening of seizures or having behavioral changes were reassessed by EEG. If EEG deterioration was seen, the patient was taken off oxcarbazepine and given another drug, most often valproate. The authors assert that the children's parents all kept seizure calendars as well as records of behavioral changes and school performance. If this assertion is correct, then this retrospective analysis could actually be of value for determining the risk of seizure exacerbation with oxcarbazepine, although seizure type or syndrome is never as well defined as in prospective trial. When a pattern of adverse events is detected outside of clinical trials, reports are almost always retrospective. Idiosyncratic side effects are frequently identified in postmarketing studies, as was the case with visual field deficits associated with vigabatrin (4). Therefore, retrospective studies reporting seizure aggravation are an important and valid initial step in determining novel adverse events.

The authors speculate on possible reasons for the seizure aggravation, pointing to the proposed mechanism of action of oxcarbazepine as a sodium-channel blocker and how that mechanism might elicit different seizure types. A recent report by Liu et al. concerning carbamazepine points to the possibility that seizure aggravation of carbamazepine, especially in absence seizures, could be caused by stimulation of a subtype of $GABA_A$ receptors in the ventrobasal nucleus of the thalamus (5). Liu and colleagues studied the effect of carbamazepine on $GABA_A$ stimulation by eliciting absence seizures in the GAERS rat model. Since, as mentioned, oxcarbazepine is a keto-analogue of carbamazepine, this interesting new mechanism may well apply to oxcarbazepine as well.

Seizure aggravation is a problem encountered mainly in GABAergic (e.g., tiagabine, gabapentin, and vigabatrin) and sodium channel blocking drugs (e.g., phenytoin, carbamazepine, and lamotrigine), although anecdotal reports of seizure provocation have been cited for almost all antiepileptic drugs (AEDs) (6). Particularly in patients with idiopathic epilepsies, seizure aggravation is not an uncommon problem, while adult patients with partial onset seizures seem to be more immune to this effect (7). However, children are different in this regard because they have a higher incidence of idiopathic epilepsy syndromes than adults and should be followed with greater care to avoid seizure aggravation, as it may occur when least expected (8).

How can the clinician be sure whether the drug used by a specific patient has elicited a new seizure type or instead has caused an increase in seizures or EEG change? It is possible that a change of seizure type or an increase of seizures could happen anyway—thus, the only way to explicitly demonstrate a correlation is to retest the patient after the drug is first withdrawn and the situation normalized. A retest is, however, not ethically possible so physicians have to rely on evidence of a temporal relationship between the drug use and the appearance of new seizure types.

What are the implications of these findings? It is important for all neurologists to be aware that patients, especially children, can develop a new seizure type or new cognitive and behavioral changes after administration of an untried AED. Changes in these variables might be due to the new AED or to a pharmacodynamic interaction with other AEDs. It is valuable when doctors vigilantly report occurrences in seizure aggravation to health authorities like the Food and Drug Administration and MedWatch in the United States, as patterns of adverse effects can then be detected.

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Seizure Remission in Adults with Intractable Epilepsy: Not Just a Pipe Dream

Likelihood of Seizure Remission in an Adult Population with Refractory Epilepsy. Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. *Ann Neurol* 2007;62(4):382–389. OBJECTIVE: We aimed to determine the likelihood of remission and its clinical predictors in adult patients meeting a strict definition of refractory epilepsy. We also wanted to investigate the influence of treatment regimen on remission. METHODS: A total of 246 patients with treatment refractory epilepsy (having at least 1 seizure per month and having not responded positively to at least 2 antiepileptic drugs) were identified in 2000 and followed for 3 years. We used Kaplan-Meier methods to estimate the rate of achieving a 6-month terminal seizure remission and Cox regression analysis to evaluate clinical predictors for seizure remission. RESULTS: The estimated 6-month terminal seizure remission rate was 19% (95% confidence interval, 14–26%) for all cases and 14% (95% confidence interval, 10–21%) when limited to those treated only with medication. Negative predictors for remission included a history of status epilepticus, younger age at intractability, number of failed drug therapies, and presence of mental retardation. No specific drug was significantly associated with remission, and frequently, no clear intervention led to terminal remission. INTERPRETATION: Fifteen percent (approximately 5% per year) of a drug refractory epilepsy population obtained a 6-month terminal seizure remission. Our results signify that no matter how many antiepileptic drug therapies have failed, there is always hope of a meaningful seizure remission in this population. Furthermore, we have elucidated four clinical predictors that can aid the epileptologist in prognostication.

COMMENTARY

Although an abundance of new anticonvulsants have been developed over the past decade, roughly a third of people with epilepsy still have medically intractable seizures (1). Poorly controlled seizures are associated with increased mortality and significant physical and psychosocial morbidity (2). While individuals occasionally demonstrate an exceptional response to the addition of one of the newer medications, there is little evidence that these agents have had a significant impact on seizure control for newly diagnosed patients (1) or patients who have not responded to other medications (3). In 2000, Kwan and Brodie reported that medical intractability often may be predicted early in treatment. In their study of newly diagnosed epilepsy, patients failing to respond to the first medication only had an 11 percent chance of responding to a second medication (1). Thus, clinicians have inferred that aggressive medication changes are likely to be futile in patients who have continued to have seizures despite several anticonvulsant trials.

Based on a series of patients with previously uncontrolled seizures, Callaghan and colleagues report that nearly 5 percent of patients per year will enter seizure remission, usually as a result of medication changes. While this finding is clearly less than optimal, the authors note that their data provide realistic hope that persistent medical attention may eventually improve a patient's seizure control. Their assertion is particularly important since most of these patients are not candidates for improving seizure control with surgery.

The authors contrast their findings with those of Kwan and Brodie; however, it is helpful to remember that the studies differ significantly in design and intent. The current study included patients who met strict criteria for poor seizure control (i.e., more than one seizure per month for 3 months, after trying at least two medications). Patients were treated aggressively, followed for roughly 3 years, and were considered in remission if they experienced a 6-month period without seizures. In contrast, Kwan and Brodie studied patients with newly diagnosed epilepsy, following them for as long as 16 years, and considered seizure free if they had not had seizures during the year prior to their last follow-up visit (1). Thus, Callaghan et al. scrutinized previously intractable cases for improvement, while Kwan and Brodie emphasized imperfect seizure control in patients who

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started treatment with a clean slate. These studies should be regarded as complimentary rather than discordant.

Callaghan and colleagues used Kaplan–Meier methods to estimate the cumulative seizure remission rate. They wisely performed a separate analysis censoring surgery, since many patients became seizure free as a result of their operations. The estimated remission rates are likely to be accurate for the population studied, although it is not clear whether the results would apply to patients who were not in long-term care at an institution. Furthermore, a prospective study of patients with refractory epilepsy might yield less favorable results than were found in the retrospective study by Callaghan et al.

A modest proportion of the patients entering seizure-free intervals did so without an obvious temporal relationship to anticonvulsant manipulation. This outcome suggests that the natural history of refractory epilepsy for some patients may include good periods rather than relentless seizures. Berg and colleagues have shown that children with refractory epilepsy often have periods of remission before becoming refractory and that a significant subset enter remission again later (4). Taken together, these observations support a concept of seizure control as a moving target, necessitating careful consideration of methods for analysis. The methods used in the Callaghan et al. study distinguish patients who sometimes do well from those who do not.

The authors also attempt to define predictors of intractability; however, none of the factors analyzed remained significant in multivariate analysis. They make the point that the factors that were significant in their univariate analysis are likely to be true predictors, given that they have been replicated in other studies (5,6) or make intuitive sense. These factors include mental retardation, status epilepticus, number of medications failed, and duration of intractability. MRI and EEG abnormalities did not predict intractability. Given the uncertainty of the independent predictive value of the defined risk factors, they cannot be used at this time to confidently stratify risk in individuals, though they may still be useful as rough indicators of intractability.

The most important consequence of this study is to serve as a reminder that counseling patients on seizure control prognosis is a tricky business that necessitates more than cursory explanations. Pertinent to the discussion is the fact that a large number of patients will have variable seizure control throughout life and that treatment success (both medical and surgical) will be superimposed on that background. Indeed, a recent long-term study of seizure surgery outcomes indicates that freedom from seizures may vary significantly over time. While some patients who were seizure-free at 2 years, developed recurrent seizures, 20 percent of the people who were still having seizures 2 years after surgery were seizure-free 8 years later (7). Callaghan and colleagues' study is a reminder that no matter how things are going, improvement may be just around the corner for those patients with seemingly persistent seizures.

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Nonconvulsive Seizures in Traumatic Brain Injury: What You Don't See Can Hurt You

Nonconvulsive Electrographic Seizures after Traumatic Brain Injury Result in a Delayed, Prolonged Increase in Intracranial Pressure and Metabolic Crisis. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, Glenn TC, Martin N, Hovda D. *Crit Care Med* 2007; [Epub ahead of print]. OBJECTIVE: To determine whether nonconvulsive electrographic post-traumatic seizures result in increases in intracranial pressure and microdialysis lactate/pyruvate ratio. DESIGN: Prospective monitoring with retrospective data analysis. SETTING: Single center academic neurologic intensive care unit. PATIENTS: Twenty moderate to severe traumatic brain injury patients (Glasgow Coma Score 3–13). MEASUREMENTS AND MAIN RESULTS: Continuous electroencephalography and cerebral microdialysis were performed for 7 days after injury. Ten patients had seizures and were compared with a matched cohort of traumatic brain injury patients without seizures. The seizures were repetitive and constituted status epilepticus in seven of ten patients. Using a within-subject design, post-traumatic seizures resulted in episodic increases in intracranial pressure (22.4 ± 7 vs. 12.8 ± 4.3 mm Hg; $p < .001$) and an episodic increase in lactate/pyruvate ratio (49.4 ± 16 vs. 23.8 ± 7.6; $p < .001$) in the seizure group. Using a between-subjects comparison, the seizure group demonstrated a higher mean intracranial pressure (17.6 ± 6.5 vs. 12.2 ± 4.2 mm Hg; $p < .001$), a higher mean lactate/pyruvate ratio (38.6 ± 18 vs. 27 ± 9; $p < .001$) compared with nonseizure patients. The intracranial pressure and lactate/pyruvate ratio remained elevated beyond postinjury hour 100 in the seizure group but not the nonseizure group ($p < .02$). CONCLUSION: Post-traumatic seizures result in episodic as well as long-lasting increases in intracranial pressure and microdialysis lactate/pyruvate ratio. These data suggest that post-traumatic seizures represent a therapeutic target for patients with traumatic brain injury.

COMMENTARY

Nonconvulsive seizures are common in critically ill patients. In fact, multiple studies have demonstrated that the majority of seizures occurring in these patients are nonconvulsive and can only be recognized via EEG monitoring (1). Are they harmful? Although no class I or II trials have been performed to date, there is substantial evidence that they may be harmful, particularly in the injured brain. Vespa and colleagues continue to contribute meaningfully to this literature in the current report.

In the current article, the authors compared ten patients with traumatic brain injury and seizures to ten other traumatic brain injury patients without seizures; the two groups were matched for head CT findings, age, and Glasgow coma score. All seizures happened to be nonconvulsive, and all patients received prophylactic phenytoin for 7 days. Rigorous neurological/neurosurgical intensive care unit (NICU) treatment was applied, with careful management of intracranial pressure [goal <20], cerebral perfusion pressure [kept at >60], jugular venous O_2 saturation [kept at 60–70%], and temperature [kept at 37–37.6°C]), with sedation maintained with propofol. EEG was recorded with 12 electrodes, continuously displayed at the bedside, and reviewed a minimum of three times daily. Total power trending software also was used and displayed at the bedside to aid in recognition of possible seizures, though raw EEG tracings always were reviewed for definitive diagnosis. Intracranial pressure and intracerebral microdialysis (a measure of metabolites in the parenchymal interstitial fluid) data were obtained hourly as part of routine clinical care at the center.

The results demonstrated that nonconvulsive seizures (often associated with periodic discharges as well) corresponded with higher intracranial pressure and higher brain lactate/pyruvate ratio (LPR; see following description for significance), often reaching abnormal levels (i.e., >20 mm Hg and >40, respectively). The timing of these elevations correlated with the presence of seizures, based on averaging the hourly samples over 12-hour epochs. Interestingly, there was a bimodal peak occurrence of seizures at 29- and 140-hours postinjury. Ictal intracranial pressure (during the 12-hour period beginning with seizure onset) was an average of 12 mm Hg higher than pre-ictal, and ictal LPR was double that of pre-ictal LPR on average. Elevated glutamate also was seen around the time of seizures, averaging 13.1 in the 12-hour designated ictal period versus 2.6 interictally ($p < 0.001$). Mortality and Glasgow Outcome Score outcomes did not differ significantly between the seizure and nonseizure groups.

These results add to the growing evidence that seizures, including nonconvulsive ones, are harmful to humans. Prior evidence includes the following:

- The delay to diagnosis and duration of nonconvulsive status epilepticus are each independent predictors of worse outcome (2).

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- The presence of either nonconvulsive seizures or periodic discharges is an independent predictor of worse outcome in multiple patient populations (1).
- In patients with epilepsy but without acute brain injury, prolonged nonconvulsive seizures can lead to permanent neurological injury, albeit rarely (3).
- Neuron-specific enolase, a marker of neuronal injury, can be elevated after nonconvulsive status epilepticus, even without acute brain injury (4).
- In patients with intracerebral hemorrhage, nonconvulsive seizures were associated with increased mass effect and shift on imaging, worsening neurological examination, and a trend toward worse outcome in one study (5), and expanding hemorrhages, with a trend toward worse outcome in another (6).
- Seizure activity can cause elevations in glutamate that reach neurotoxic levels (7) and delayed elevations in glycerol, suggesting membrane breakdown (8).
- Seizures are associated with peri-injury depolarizations (similar or identical to cortical spreading depression), another likely contributor to secondary neuronal injury after an acute brain insult (9).

The evidence of the damaging effects of nonconvulsive seizures in animal studies includes the following:

- Seizures are associated with increases in blood flow, metabolism, excitatory amino acid levels, and lactate.
- In a controlled, rat middle cerebral artery occlusion model, nonconvulsive seizures were associated with larger infarcts and a tripling of mortality (10).
- In a rat low-dose pilocarpine model, nonconvulsive status epilepticus was found to result in long-term motor deficits and impaired social behavior (11).

In contrast, the aggressive treatment often required to stop nonconvulsive seizures in critically ill patients is also potentially harmful (12), leaving room for ongoing controversy and appropriate variations in approach to management.

Elevated intracranial pressure remains a major issue in the management of patients with traumatic brain injury. In many academic NICUs, invasive multimodality monitoring of patients with a variety of acute brain injuries is a common practice, including monitoring intracranial pressure, brain tissue oxygen tension, cerebral blood flow, brain temperature, jugular venous oxygen saturation, and multiple metabolic parameters via cerebral microdialysis. These invasively obtained data are interpreted in conjunction with the usual vital signs, EEG (especially in the past couple years), and physical examination. Cerebral microdialysis was approved for clinical use by the United States Food and Drug Administration in 2002, and an international consensus statement supporting its use was published in 2004 (13). The most reliable measure of neuronal stress appears to be the LPR—a measure of the redox state of the brain. There are two types of elevation in LPR: ischemic (type I, with prominent elevation in lactate) and nonischemic (type II, with drop in pyruvate). The type II changes often have remained unexplained, but to date, most studies in published literature on cerebral microdialysis did not obtain concomitant EEG recordings.

The limitations of the study by Vespa and colleagues include the relatively small number of patients, the widely spaced sampling (hourly), the lack of clear definition of an electrographic seizure (not a trivial issue), the lack of any sample EEG tracings, and the nonrandomized nature of this retrospective study. Reporting on the relative utility of the quantitative EEG and bedside review (i.e., how often seizures were detected via these techniques) would have been quite useful. Data on the effect of treatment on intracranial pressure and LPR also would have been valuable—do they normalize when seizures stop? If so, how quickly? Finally, as the authors point out, intracranial recordings may show much more extensive epileptic activity than seen on scalp EEG. In fact, a recent report, using miniature intracranial transcortical depth electrode recordings in NICU patients requiring invasive monitoring, provides preliminary evidence to support this theory (14).

Despite these limitations, this is the largest and best investigation into the acute physiologic effects of nonconvulsive seizures in acute brain injury. The authors' conclusions that these data "confirm a long-held, but previously unsupported, premise that electrographic seizures are deleterious for traumatic brain injury patients" and their suggestion "that seizures can potentiate the metabolic distress of the brain injured patient and hence may lead to permanent cellular injury" are both justified and important. In addition to further studies to confirm and expand upon this one, a logical next step would be to investigate whether intervening in a timely fashion can prevent these adverse physiologic effects and ultimately improve outcome.

by Lawrence J. Hirsch, MD

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The Masquerades of Temporal Lobe Epilepsy in Childhood

Age-Dependent Seizure Semiology in Temporal Lobe Epilepsy. Fogarasi A, Tuxhorn I, Janszky J, Janszky I, Rásonyi G, Kelemen A, Halász P. *Epilepsia* 2007;48(9):1697–1702. Epub 2007 May 23. OBJECTIVE: To examine the effects of age on different aspects of temporal lobe seizure semiology. METHODS: We performed a video analysis of 605 archived seizures from 155 consecutive patients (age 10 months to 49 years) selected by seizure freedom after temporal lobectomy. Eighty patients had hippocampal sclerosis (HS). Beside semiological seizure classification, we assessed age dependency of several axes of seizure semiology: (1) aura, (2) number of different lateralizing signs, occurrence of ictal (3) emotional signs, (4) autonomic symptoms, (5) automatisms, and (6) secondary generalization as well as (7) the ratio of motor seizure components. RESULTS: From the 155 patients, 117 reported aura, 39 had ictal emotional signs, 51 had autonomic symptoms, 130 presented automatisms, while 18 patients showed secondary generalization at least once during their seizures. Altogether 369 (median: 2/patient) different lateralizing signs were recorded. Frequency of HS ($p < 0.001$), ictal automatisms ($p < 0.001$), secondary generalization ($p = 0.014$), number of different lateralizing signs ($p < 0.001$) increased while the ratio of motor seizure component ($p = 0.007$) decreased by age. Auras, emotional symptoms, and autonomic signs occurred independently of patients' ages. Hippocampal sclerosis adjusted linear models revealed that the frequency of automatisms and secondarily generalized seizures as well as the number of different lateralizing signs are HS-independent significant variables. CONCLUSION: Our findings support that brain maturation significantly influences the evolution of some important aspects (motor seizures, lateralizing signs) of temporal lobe seizure semiology. Conversely, other aspects (aura, emotional, and autonomic signs) are independent of the maturation process. This is the first report investigating age dependency of epileptic seizure semiology comparing all age groups.

COMMENTARY

Although over 70 percent of temporal lobe seizure disorders begin in childhood, early recognition is often impeded by a nonspecific semiology, multifocal-interictal and widespread-ictal EEG phenomena, and an initial lack of characteristic MRI features (1–3). Previous studies had disclosed a higher incidence of motor features in children with temporal lobe epilepsy (TLE) than that reported in adults (4,5). This current, retrospective, cross-sectional study by Fogarasi and colleagues confirms these findings in a larger cohort and adds the unique feature of video

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ictal analysis of children and adults with TLE. Unfortunately, only a longitudinal study will be able to determine whether and when the childhood semiology pattern found in these studies evolves to the more familiar adult pattern.

Several factors may contribute to the authors' finding of a greater incidence of motor phenomena in childhood than adult TLE. Lateral neocortical TLE occurs more commonly in children, whereas 90 percent of adult TLE originates mesially (2,6). Although the abundant mesial lateral temporal, reciprocal connections produce an ictal semiology principally shared by adults and children (7), clonic motor features and early ictal arm dystonia suggest a lateral temporal seizure origin (7,8). Prominent lateral temporal efferent fibers to the prefrontal cortex provide direct entry into the premotor cortex (9,10), while hippocampal efferent fibers through the subiculum project principally to the orbitofrontal and mesial frontal cortices (11). The greater incidence of extratemporal interictal spike foci in childhood TLE (3) may facilitate seizure propagation because such multiple foci may impair confinement of an epileptic discharge to a single region (12). Two additional factors that are characteristic of the immature brain with epilepsy may also promote ictal spread: 1) greater gap junction communication in immature brain (13) and 2) failure of the normal cortical pruning in the presence of epileptogenesis (14).

If the authors had categorized automatisms into oroalimentary and manual/gestural types they may have confirmed a predominance of the former in children less than 5 to 6 years of age and the latter in older subjects, as found in previous studies (15). The increasing incidence of secondarily generalized tonic–clonic seizures occurring with age found in the current article seems at variance with the higher motor seizure component ratio seen in young children. The possible effect of antiepileptic drug type and quantity on these findings is not stated.

The many factors involved in effectiveness of epilepsy surgery diminish somewhat the validity of postoperative seizure freedom in confirming seizure origin. Residual antiepileptic drugs, multiple seizure types, and limitation of surgical resection to spare significant functions are some of these factors. Additionally, a minimum follow-up period of 1 year (such as occurred in this study) is too short for a seizure localizing confirmatory role: seizures restarted 11 to 28 months after temporal lobectomy in 4 of 15 children in one study (16).

In summary, data from this study combined with earlier relevant works provide a valuable guide to the pediatric epileptologist. In a child with unexpectedly intractable focal seizures with prominent motor phenomena, multifocal EEG epileptiform activity, and a nondiagnostic MRI, TLE manifestations of a more mature brain may evolve as the brain matures. Valuable ictal lateralizing signs also may emerge over time, as Fogarasi and colleague's group ascertained. These ictal semiological changes transpiring with increased age in childhood onset TLE thus far have received scant attention in major textbooks.

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