Treatment of Status Epilepticus

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ABSTRACT

Status epilepticus (SE) is a neurological emergency that requires prompt diagnosis and treatment, as delay is associated with a higher likelihood of poor response to treatment and worse outcome. Lorazepam has been well established as a first-line therapy. Subsequent steps are less established, and there are many reasonable options, including intravenous fosphenytoin, valproate, midazolam, propofol, and phenobarbital. If intravenous access is not immediately available, rectal diazepam or nasal or buccal midazolam should be given; this can also be used as out-of-hospital treatment to prevent or treat SE. For refractory SE, continuous intravenous midazolam and propofol, separately or in combination, are rapidly effective, with pentobarbital remaining the gold standard for prolonged cases. If a patient does not awaken after treatment, urgent electroencephalogram (EEG) should be obtained to rule out nonconvulsive seizure activity. In refractory SE, continuous EEG monitoring is required to recognize recurrence of seizure activity, as most seizures will be nonconvulsive.

KEYWORDS: Status epilepticus, seizure, nonconvulsive status epilepticus, epilepsy, continuous EEG monitoring

Status epilepticus (SE) is a medical and neurological emergency. Overall, mortality is ~17 to 26%.[1–3] An additional 10 to 23% of patients who survive SE are left with new or disabling neurological deficits.[2,4]

DEFINITION

Traditionally, SE is defined as continuous or repetitive seizure activity persisting for at least 30 minutes without recovery of consciousness between attacks. More recently, authors have suggested that seizures exceeding 5 to 11 minutes should be considered SE.[5,6] For all practical purposes, a patient should be considered to be in SE if a seizure persists for more than 5 minutes, as very few single seizures will last this long.

PRESENTATION AND DIAGNOSIS

Several types of SE exist. Clinically, the most important distinction to make is between convulsive and nonconvulsive SE (NCSE), based on whether or not rhythmic jerking of the extremities is observed. Typically, patients who present with generalized convulsive SE (GCSE) are expected to awaken gradually after the motor features of seizures disappear. If the level of consciousness does not improve by 20 minutes after cessation of movements, or the mental status remains abnormal 30 to 60 minutes after the convulsions cease, NCSE must be considered and urgent electroencephalogram (EEG) is advised. In a study by DeLorenzo and colleagues,[7] 14% of patients treated successfully for convulsive SE were in NCSE when EEG was begun; of the patients who underwent continuous EEG monitoring (cEEG) after

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convulsive SE was controlled, 48% had nonconvulsive seizures.

There is no clear consensus on the further classification of NCSE. Many authors have classified NCSE into generalized or partial onset, and into simple and complex, based on whether or not there is alteration of consciousness. In clinical practice, however, it is often not possible to differentiate between these classifications even with the help of EEG. In the intensive care unit (ICU), the majority of seizures are nonconvulsive and will be missed without cEEG (Case 1).[8] Nonconvulsive seizures are more common than previously recognized; nonconvulsive seizures have been reported in 34% of neurological ICU patients,[9] 16% of severe head trauma patients,[10] and 8% of comatose patients that have no clinical evidence of seizures.[11] Nonconvulsive seizures have also been reported in 18 to 28% of patients with intracerebral hemorrhage (ICH)[12,13]; such posthemorrhagic seizures are associated with neurologic worsening on the National Institutes of Health Stroke Scale (14.8 vs. 18.6, $p < 0.05$), and with an increase in midline shift ($+2.7$ mm vs. -2.4 mm, $p < 0.03$).[13] In a series of 102 ICH patients who underwent cEEG at our center, electrographic seizures were associated with an increase in ICH volume of 30% or more between admission and 24-hour follow-up computed tomographic (CT) scan (33% vs. 15%; odds ratio 9.5; 95% confidence interval, 1.7 to 53.8).[12] Moreover, the many possible presentations of NCSE outside of the ICU setting (Table 1) may also be a cause of delay in diagnosis. Since an increasing duration of seizure activity is associated with worse outcomes,[14] it is crucial to recognize and treat NCSE early.

Table 1 Semiological Spectrum of Nonconvulsive Seizures and Nonconvulsive Status Epilepticus

Negative Symptoms	Positive Symptoms
Anorexia	Agitation/aggression
Aphasia/mutism	Automatisms
Amnesia	Blinking
Catatonia	Crying
Coma	Delirium
Confusion	Delusions
Lethargy	Echolalia
Staring	Facial twitching
	Laughter
	Nausea/vomiting
	Nystagmus/eye deviation
	Perseveration
	Psychosis
	Tremulousness

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Table 2 Criteria for Nonconvulsive Seizure*

Any pattern lasting at least 10 seconds satisfying any one of the following three primary criteria:

Primary criteria

- Repetitive generalized or focal spikes, sharp waves, spike-and-slow wave, or sharp-and-slow wave complexes at ≥ 3/sec
- Repetitive generalized or focal spikes, sharp waves, spike-and-slow wave, or sharp-and-slow wave complexes at < 3/sec and the secondary criterion
- Sequential rhythmic, periodic, or quasiperiodic waves at ≥ 1/sec and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/sec; e.g., 2 to 3/sec), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not enough to satisfy evolution in morphology.

Secondary criterion

- Significant improvement in clinical state or appearance of previously absent normal EEG patterns (such as posterior dominant ''alpha'' rhythm) temporally coupled to acute administration of a rapidly acting AED. Resolution of the epileptiform discharges leaving diffuse slowing without clinical improvement and without appearance of previously absent normal EEG patterns would not satisfy the secondary criterion.

*Satisfying these criteria is adequate for confirming nonconvulsive seizure activity. However, failing to meet these criteria does *not* rule out nonconvulsive seizure activity; clinical judgment and correlation are required in this situation.
Reproduced with permission from Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. J Clin Neurophysiol 2005;22:79–91, who modified the criteria of Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology 1996;47:83–89.
AED, antiepileptic drug.

See Table 2 for the criteria for diagnosing definite nonconvulsive seizures. A suggested method for performing a benzodiazepine trial to diagnose NCSE is presented in Table 3. A common mistake is to give too high a dose of benzodiazepine; this results in marked sedation, which has no diagnostic utility even if the EEG pattern rapidly resolves. Small incremental doses may allow observation of a clinical improvement without marked sedation.

TREATMENT

Rapidity of treatment is key in the treatment of SE. There are animal and human data to suggest that therapeutic interventions are most effective when initiated early, and that efficacy decreases significantly with increasing seizure duration.[15,16] For all practical purposes, treatment should be started after 5 minutes of continuous seizure activity.

Table 3 Benzodiazepine Trial for the Diagnosis of Nonconvulsive Status Epilepticus

Applies to: patients with rhythmic or periodic focal or generalized epileptiform discharges on EEG with neurological impairment

Monitoring: EEG, pulse oximetry, blood pressure, ECG, respiratory rate with dedicated nurse

Antiepileptic drug trial:

- Sequential small doses of rapidly acting short-duration benzodiazepine such as midazolam at 1 mg/dose
- Between doses, repeated clinical and EEG assessment
- Trial is stopped after any of the following:
  - Persistent resolution of the EEG pattern (and exam repeated)
  - Definite clinical improvement
  - Respiratory depression, hypotension, or other adverse effect
  - A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher may be needed if on chronic benzodiazepines)
- Test is considered positive if there is resolution of the potentially ictal EEG pattern *and* either an improvement in the clinical state or the appearance of previously absent normal EEG patterns (e.g., posterior dominant ''alpha'' rhythm) occurs; if EEG improves but patient does not, the result is equivocal

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EEG, electroencephalogram; ECG, electrocardiogram.

Initial Management

A sample protocol for the treatment of SE (as used in our center) is given in Table 4. Initial steps involve basic life support: administering oxygen, monitoring vital signs, and assessing and maintaining the airway. Intravenous (IV) access should be established quickly, but rectal, buccal, or nasal benzodiazepines should be given if there is any delay in obtaining IV access (see the following section on alternative modes of administration). Laboratory studies should be sent (Table 4). A fingerstick blood glucose level should be obtained and 100 mg of thiamine and 50 mL of 50% glucose should be administered if glucose level is low or unknown. For seizures due to a metabolic derangement, correcting the metabolic problem is often more effective than antiepileptic drugs (AEDs). Fever, hypoxia, and hypotension should also be treated concurrently, as these can exacerbate seizures and the associated neuronal injury.

Other components of management include determining whether there is a history of alcohol or drug use, previous epilepsy, possible acute neurological insult, obtaining a description of the seizure at onset if witnessed, and brain imaging once the patient is stable and seizures are controlled. Patients should not be pharmacologically paralyzed unless cEEG is absolutely necessary or being recorded. Use of medications that can lower the seizure threshold (Table 5) should be identified and minimized.

Pharmacotherapy for SE

First-line medications control SE in 80% of patients when initiated within 30 minutes, but in only 40% if started after 2 hours of onset.[15]

Benzodiazepines are the preferred initial therapy. Most experts recommend IV lorazepam (0.1 mg/kg) as the first-line therapy. Patients who respond to first-line agents will usually require maintenance therapy with a second-line agent. Additional treatment must be provided quickly when patients continue to seize. The longer SE persists, the higher the risk for developing refractory SE. There is a lack of prospective data for second-line agents, but phenytoin (PHT) or fosphenytoin is used most frequently.[17]

Comparison of Initial Treatment Options of SE

Only a few prospective randomized trials have compared initial treatment strategies for SE. The largest prospective study was the Veterans Affairs (VA) Status Epilepticus Cooperative study,[18] which was a randomized, double-blind, multicenter trial that compared four IV treatments: lorazepam 0.1 mg/kg, diazepam 0.15 mg/kg plus PHT 18 mg/kg, phenobarbital 15 mg/kg, and PHT 18 mg/kg alone. In generalized convulsive SE, lorazepam was found to be most effective (65% for lorazepam alone vs. 58% for phenobarbital, 56% for diazepam plus PHT, and 44% for PHT alone). The differences only reached significance between lorazepam and PHT alone. For subtle SE, no statistical difference was found between the groups and response was poor (only 8 to 24% responded to first treatment, vs. 44 to 65% for overt SE). All four treatment arms had similar complication rates. No class I randomized controlled trials have been conducted for second- or third-line therapy for SE.

PHT or fosphenytoin is frequently recommended as a second-line agent. Seizure activity is often very difficult to control once patients fail to respond to two AEDs. In the VA Cooperative Study,[18] of the 38% of patients with "overt" SE and the 82% of patients with "subtle" SE that continued to seize after receiving two AEDs, only 2% and 5%, respectively, stopped seizing after receiving a third agent. Once lorazepam failed, few patients responded to PHT as a second-line agent ($\sim$5%); for this reason, some experts advocate progressing directly to continuous IV (cIV) anesthetic drips once lorazepam has failed (Table 4; also reviewed in Hirsch and Arif[19]).

Although currently not approved by the Food and Drug Administration (FDA) for use in SE, there is growing evidence to support the efficacy of IV valproate (VPA) for SE. In a recent unblinded study from India,

Table 4 Status Epilepticus Adult Treatment Protocol: Columbia University Comprehensive Epilepsy Center, 2008

Time (min)	Action
0–5	Diagnose; give O_2; ABCs; obtain IV access; begin ECG monitoring; draw blood for chem-7, magnesium, calcium, phosphate, CBC, LFTs, AED levels, ABG, troponin; toxicology screen (urine and blood)
6–10	Thiamine 100 mg IV; 50 mL of D50 IV unless adequate glucose known Lorazepam 4 mg IV over 2 minutes; if still seizing, repeat × 1 in 5 minutes If no rapid IV access give diazepam 20 mg PR or midazolam 10 mg intranasally, buccally, or IM*
10–20	If seizures persist, begin fosphenytoin 20 mg/kg IV at 150 mg/min, with blood pressure and ECG monitoring. *This step can be skipped initially, especially if proceeding to midazolam or propofol, or performed simultaneously with the next step; if done simultaneously, administration rate should be slowed; using IV valproate instead of fosphenytoin is a justifiable option as well, particularly in those allergic to phenytoin or with hypotension.*
10–60	If seizures persist, give one of the following four options (intubation often necessary except for valproate): 1. cIV midazolam: load: 0.2 mg/kg; repeat 0.2–0.4 mg/kg boluses every 5 minutes until seizures stop, up to a maximum total loading dose of 2 mg/kg. Initial cIV rate: 0.1 mg/kg/h. cIV dose range: 0.05–2.9 mg/kg/h. If still seizing, add or switch to propofol or pentobarbital. *or* 2. cIV propofol: load: 1–2 mg/kg; repeat 1–2 mg/kg boluses every 3–5 minutes until seizures stop, up to maximum total loading dose of 10 mg/kg. Initial cIV rate: 2 mg/kg/h. cIV dose range: 1–15 mg/kg/h†. If still seizing, add or switch to midazolam or pentobarbital. *or* 3. IV valproate: 40 mg/kg over ~10 minutes. If still seizing, additional 20 mg/kg over ~5 minutes. If still seizing, add or switch to cIV midazolam or propofol. *or* 4. IV phenobarbital: 20 mg/kg IV at 50–100 mg/min. If still seizing, add or switch to cIV midazolam, propofol, or pentobarbital.
> 60	cIV pentobarbital: load: 5 mg/kg at up to 50 mg/min; repeat 5 mg/kg boluses until seizures stop. Initial cIV rate: 1 mg/kg/h. cIV dose range: 0.5–10 mg/kg/h; traditionally titrated to suppression-burst on EEG but titrating to seizure suppression is reasonable as well.
	Begin EEG monitoring as soon as possible if patient does not rapidly awaken, or if any cIV treatment is used.

*The IV solution of diazepam can be given rectally if Diastat is not available; the IV solution of midazolam can be given by any of these routes.
†Prolonged use of propofol at > 5 mg/kg/h increases the risk of the propofol infusion syndrome; see text.
cIV, continuous intravenous; ABCs, stabilize airway, breathing, and circulation; ECG, electrocardiogram; CBC, complete blood count; LFTs, liver function tests; AED, antiepileptic drug; ABG, arterial blood gases; PR, per rectum; IM, intramuscularly.

Misra and colleagues randomized 68 patients with untreated convulsive SE to IV VPA (30 mg/kg) or PHT (18 mg/kg); seizures were aborted in 66% in the VPA group versus 42% in the PHT group. If the first agent failed, patients were given the other agent. As the second agent, VPA was effective in 79% and PHT was effective in 25%. Tolerability between the two groups did not differ.[20] Several other case series suggest good efficacy for IV VPA in the treatment of different types of SE, including partial-onset, nonconvulsive, absence, and myoclonic status.[21–23] Another recent study randomized

Table 5 Commonly Used Drugs That Can Lower the Seizure Threshold

Antibiotics, especially in the elderly or those with renal impairment
Imipenem
Penicillins
Cephalosporins
Isoniazid (treat overdose with pyridoxine)
Metronidazole
Antihistamines, including over-the-counter diphenhydramine (Benadryl)
Antipsychotics, especially clozapine and low potency phenothiazines (e.g., chlorpromazine)
Antidepressants
Maprotiline (Ludiomil)
Bupropion (Wellbutrin)
Tricyclics, especially clomipramine; possibly least with desipramine
Baclofen
Fentanyl
Flumazenil (benzodiazepine antagonist)
Ketamine
Lidocaine
Lithium (especially in overdosage)
Meperidine (Demerol)
Propoxyphene (Darvon)
Theophylline

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100 age- and sex-matched patients with benzodiazepine-refractory SE to IV VPA ($n = 50$) or IV PHT ($n = 50$).[24] Treatment was considered successful if all motor or EEG seizure activity ceased within 20 minutes after the beginning of the drug infusion and no seizure activity recurred during the next 12 hours. Intravenous VPA was successful in 88% and IV PHT in 84% ($p > 0.05$) of patients with SE, with a significantly better response in patients with SE < 2 hours in duration ($p < 0.05$). Of the patients who failed PHT and were crossed over to VPA, seizure activity ceased in 57% (4/7); of the 5 patients who failed VPA and were crossed over to PHT, 40% (2/5) stopped seizing (not significant). There were no differences in secondary outcomes between the two groups (recurrence of seizures within the 12-hour study period or outcome at 7 days), although VPA was slightly better tolerated ($p > 0.05$). Mild elevation of liver enzymes was found in 8% (4/50) treated with IV VPA; 12% (6/50) treated with IV PHT developed hypotension, and 4% (2/50) developed respiratory depression.

Alternative Modes of Administering Treatment for SE and Seizure Clusters (Not IV or Oral)

Due to the clear importance of rapid treatment, recent studies have investigated out-of-hospital treatment of SE. Alldredge and associates showed that benzodiazepines were safe and effective when administered by paramedics for out-of-hospital SE in adults.[25] In this study, 59% of patients with SE treated with IV lorazepam (2 mg, repeated as needed) in the field were no longer seizing upon arrival at the emergency department (vs. 43% with IV diazepam 5 mg [repeated as needed] and 21% with placebo). Importantly, the rate of respiratory depression or circulatory complications was *lower* in the two benzodiazepine groups (10 to 11%) compared with the placebo group (22.5%). This and other studies confirm that *not* giving benzodiazepines is more risky than giving them for prolonged convulsive seizures. If widely practiced (as is occurring in many countries), this type of rapid prehospital treatment could have a major impact on the prevention of refractory SE.

Investigated alternative modes of administration (primarily of benzodiazepines, especially midazolam) include buccal, intranasal, intramuscular, and rectal. Good efficacy and rapid seizure control have been demonstrated for all of these.[26,27] Currently, the only FDA-approved version of these options is a rectal diazepam gel (Diastat, Xcel Pharmaceuticals, San Diego, CA) available in prefilled syringes. However, buccal or intranasal benzodiazepines (primarily midazolam) are easier to administer, more socially acceptable than the rectal route, and allow patients to treat themselves during prolonged auras, simple partial seizures, or clusters with recovery between seizures. Several prospective, randomized studies have shown that buccal or nasal midazolam is equal or superior to IV or rectal benzodiazepines, primarily due to the more rapid administration.[27–29] Thus, buccal or nasal midazolam—or another rapid-acting benzodiazepine—should become the outpatient treatment of choice as soon as a practical form becomes widely available; a buccal midazolam preparation is already available in several countries, but not the United States.

Refractory SE

Most authors define refractory SE as generalized convulsive or NCSE that continues clinically or electrographically despite first- and second-line therapy (Case 2). The likelihood of developing refractory SE increases if SE is not treated early on. After failure of benzodiazepines and PHT/fosphenytoin, the traditional treatment algorithm suggests loading with phenobarbital, followed by continuous IV pentobarbital if that fails. We and others usually choose to proceed directly to rapid-acting, highly potent drips (midazolam or propofol) rather than to phenobarbital once a patient has failed first- (and possibly second-) line drugs.

In a systematic review of the literature on treatment of refractory SE, Claassen et al found no difference in mortality (48%) comparing 193 refractory SE patients treated with cIV propofol, cIV midazolam, or cIV pentobarbital.[30] This review also did not demonstrate any differences between propofol and midazolam for clinical endpoints such as acute treatment failure, breakthrough seizures, or post-treatment seizures. By contrast, pentobarbital had a lower frequency of acute treatment failure and breakthrough seizures, but this was confounded by the fact that pentobarbital was more often infused with a titration goal of EEG background suppression and the lack of cEEG in most pentobarbital-treated patients. In our experience and others',[7,31] most breakthrough seizures in these patients are nonconvulsive (89% in our midazolam series[31]) and will be unnoticed without cEEG. Hypotension also occurred more often with pentobarbital (titrated to EEG background suppression) than with propofol or midazolam (usually titrated to suppression of seizures).[30]

A recent series from Europe showed good outcomes when propofol was used in combination with IV clonazepam[32]: of 31 episodes of SE, 67% were successfully treated with no major drug-related adverse events and a favorable mortality rate of only 22%. The mean propofol infusion rate in this study was 4.8 mg/kg/h (range, 2.1 to 13, with a goal to achieve suppression-burst), and the median duration of treatment was 3 days (range, 1 to 9). It may be that the concomitant IV benzodiazepines allowed use of a lower and safer dose of propofol; that is, the benzodiazepine infusion was used as a propofol "dose-sparing" technique. Other treatments that have been used for refractory SE include

very-high-dose phenobarbital (primarily in children, with serum levels 100 to 300 mg/mL), thiopental, lorazepam or diazepam as a continuous infusion, lidocaine, etomidate, isoflurane or other inhalational anesthetics, paraldehyde, electroconvulsive therapy, transcranial magnetic stimulation, or neurosurgery. See Robakis and Hirsch[33] for a detailed discussion of treatment of prolonged highly refractory SE.

Use of Other Standard Antiepileptic Drugs

AEDs that are only available in an oral form can be given via nasogastric tube or percutaneous endoscopic gastrostomy in SE patients, though not for initial treatment. Levetiracetam,[34] topiramate,[35] gabapentin, oxcarbazepine, carbamazepine, and pregabalin have been used for this purpose, particularly for prolonged SE refractory to traditional first- and second-line agents, and to wean off anesthetic-dose drips. These medications may be helpful for preventing breakthrough and withdrawal seizures, particularly just prior to tapering cIV AEDs. There is some preliminary evidence that topiramate[36] and levetiracetam[37] may have neuroprotective or antiepileptogenic properties as well.

Levetiracetam has recently become available in an IV formulation; although not FDA-approved for use in SE, it is being tested in clinical trials already and results should be available soon. It is currently approved for up to 1500 mg IV given over 15 minutes as replacement for oral dosing (1:1 ratio), but there are data showing safety and tolerability in normal volunteers at higher and faster rates of up to 2500 mg in 5 minutes or 4000 mg over 15 minutes.[38] Reports of the efficacy of IV levetiracetam in NCSE are beginning to emerge.[39] Knake et al retrospectively reviewed the use of IV levetiracetam in 18 episodes (16 patients) of SE (mean loading dose 944 mg, maintenance dose 2166 mg/24 h).[40] All patients received at least a benzodiazepine (lorazepam in 94%) before IV levetiracetam was given. SE was controlled in all patients by administration of a combination of different AEDs. In 16 episodes, IV levetiracetam was the last drug administered: only 2 patients required further treatment with other AEDs. Tracheal intubation was avoided in 17/18 episodes (94%). All patients tolerated intravenous levetiracetam without any severe adverse events.

SE in Pediatric Patients

Convulsive SE is the most common medical neurological emergency in childhood.[41] Etiology of SE in children differs from that in adults, with prolonged febrile seizures being the most common cause of SE; this is generally associated with low morbidity and mortality.[42,43] The distribution of etiology is reported to be highly age-dependent. Acute symptomatic etiologies or febrile seizures are more common in children younger than 2 years ($> 80\%$), whereas cryptogenic and remote symptomatic causes are more common in older children ($p < 0.001$).[44]

There is accumulating evidence to demonstrate that nonconvulsive seizure (NCSz) and NCSE occur frequently in critically ill children. A retrospective study at our center examined a population of 117 critically ill children who underwent cEEG[45]; seizures were recorded in 51 (44%) of 117 patients. The vast majority of these patients (75%) had purely NCSz, which would not have been diagnosed without cEEG. Those with clinical seizures (not necessarily prolonged) prior to cEEG were more likely to have NCSz on cEEG (83%) than those without prior seizures (17%).

The general principles of management and the initial agents used in the pediatric population remain the same as for adults (Table 4). The initial drug of choice is IV lorazepam when an IV is available, at 0.05 to 0.1 mg/kg, and may be repeated once after 5 minutes if necessary.[46] If IV access cannot be established or the child is in an out-of-hospital setting, rectal diazepam at 0.2 to 0.5 mg/kg should be given, or nasal/buccal benzodiazepines as discussed above. Unlike adults, cIV propofol may be a poor option due to the seemingly higher risk of multiorgan failure and the propofol infusion syndrome,[47] though proper dosing may allow safe use in children.[48] Intravenous VPA should be used cautiously if at all in children under age 2 or children with possible metabolic disorders at any age due to the risk of fulminant hepatitis. A recent retrospective multicenter study from Japan studied the efficacy and safety of midazolam in 358 children with SE.[49] Midazolam was administered as a bolus dose (0.25 ± 0.21 mg/kg), followed if necessary by continuous infusion (0.26 ± 0.25 mg/kg/h). Of the 286 cases given bolus midazolam, the seizures stopped in 162/286 (56.6%). Of these 162 cases, 28 were seizure-free with no further need for continuous midazolam infusion, 119 remained symptom-free with continuous midazolam infusion, and 15 cases showed seizure relapse. The incidence of adverse events was 19.2% in the group receiving the bolus only, 28.2% in the group given continuous infusion not more than 0.4 mg/kg/h, and 58.6% in those who received > 0.4 mg/kg/h. Respiratory distress was seen in 86 (24%) cases; only 71 (19.8%) required tracheal intubation.

As in adults, it is important in the pediatric population to exclude NCSE by performing a prolonged EEG if a patient does not wake up after the clinical control of convulsive seizures or SE. In fact, prolonged EEG monitoring may be warranted in pediatric patients even after brief convulsive seizures. A recent study of 19 pediatric patients with NCSE reported that although most children (17/19) with NCSE had clinical (usually convulsive) seizures prior to onset of NCSE, in the majority of cases (12/19) these seizures were brief, isolated convulsions.[50]

SE that is not controlled by first-line treatment (refractory SE) may require prolonged treatment with other agents in many cases, and knowledge of the prognosis is important in making therapeutic decisions in these patients. Although the prognosis of SE in general is better in children than adults, mortality of refractory SE in children seems more similar to that in adults (16 to 43.5%).[51–53] Etiology is a very important determinant of outcome, and acute symptomatic refractory SE carries a higher mortality and morbidity. Sahin and colleagues[54] studied the long-term outcome in seven previously normal children with refractory SE and presumed encephalitis. High-dose pentobarbital or midazolam or both was administered to achieve a suppression-burst pattern on EEG, aiming for an interburst interval of >5 seconds. Duration of treatment ranged from 11 to 146 days. All seven patients developed intractable epilepsy on long-term follow-up, as well as severe learning problems and attention disorders. It is unclear whether the poor outcome results from severe brain injury caused by the acute insult alone or if prolonged refractory SE contributes to neurologic morbidity. However, these results do suggest that refractory SE may need to be treated more aggressively. After discharge, a latent period was seen before seizure recurrence in five of the patients, with a mean time to seizure recurrence of 5.3 months; this raises the question of whether different agents, such as those providing neuroprotection during refractory SE or antiepileptogenesis after refractory SE, would help prevent this evolution into refractory chronic epilepsy.

Tapering Off Continuous Infusions

In all patients treated with continuous infusions of an AED, these should be continued for 12 to 24 hours after seizures are stopped before a gradual taper is started. Our practice is to taper off continuous infusions over ~24 hours. If seizures recurred with a prior taper, it may be necessary to treat longer and taper more slowly the next time while maintaining high therapeutic levels of other AEDs. Maintaining patients on phenobarbital may increase the chances of weaning off of pentobarbital without seizure recurrence.[55]

Recurrence of SE

Hesdorffer and colleagues recently studied the risk of recurrence of SE in a population-based sample.[56] Among the 183 episodes of first afebrile SE, the risk of recurrent SE was 31.7% over a 10-year follow-up period. The risk of recurrence was ~25% for those with acute symptomatic SE, remote symptomatic SE, and idiopathic cryptogenic SE. Recurrence was 100% for those with SE associated with a progressive symptomatic disease. Female gender and progressive symptomatic etiology increased the risk for recurrent SE. Both partial SE and good therapeutic response to the initial AED therapy were associated with a decreased risk of recurrent SE.

How Aggressively Should SE Be Treated?

There are no studies demonstrating a convincing difference in outcome based on the goal of treatment (seizure suppression vs. burst suppression vs. flat line) independent of etiology. Krishnamurthy and Drislane reported persistent seizure control after pentobarbital taper in 3/3 patients who never reached suppression-burst, 6/12 who reached suppression-burst but never a flat record, and 17/20 who reached a flat record (complete suppression). Recurrence of electrographic status predicted clinical relapse as well. Isolated epileptiform discharges during pentobarbital treatment did not correlate with outcome.[57] The same authors also found that clinical relapse after pentobarbital withdrawal predicted higher mortality (mortality of 8/9 vs. 9/26, $p < 0.005$).[34] Thus, these retrospective, uncontrolled data (the only kind of data available for this question) suggest possible benefit from a period of intense EEG suppression. The most recent attempt to answer this by Rossetti and colleagues, who reviewed 49 episodes of refractory SE, concluded that outcome was independent of the agent of choice and the extent of EEG suppression.[58] Similarly, it is still debatable how aggressively to treat NCSE.[59,60] While nonconvulsive seizures have definite potential for neuronal injury, aggressive treatment also carries significant risk. Only a randomized trial can truly address this issue. One retrospective study in the critically ill elderly found that aggressive treatment with IV benzodiazepines was associated with worse outcome despite similar severity of illness.[61] When comparing outcome via conservative non-ICU treatment due to advance directives to outcome with ICU care, aggressive ICU management prolonged stay by 17 days with no difference in outcome.

FUTURE DIRECTIONS IN THE MANAGEMENT OF SE

A randomized trial is needed to determine the best treatment for SE that does not stop with lorazepam. Although IV lorazepam is an excellent and proven first-line treatment, the steps after this are less clear. The exact roles of IV VPA and levetiracetam are still unclear (particularly the latter), but they are useful additions to the armamentarium of drugs used to treat SE. Buccal/nasal midazolam has great promise for out-of-hospital treatment that may greatly decrease delays in diagnosis and treatment, thus preventing refractory SE and possibly improving outcomes. Randomized trials are also needed to help decide the goal or depth of treatment: cessation of seizures versus suppression of background.

Animal studies of prolonged status will also be helpful in this regard.

The next important focus for research in treating SE is likely to be neuroprotection, and animal research will probably be most important in the coming decade. There is preliminary evidence that some of the newer AEDs have neuroprotective and antiepileptogenic properties (i.e., they may prevent neuronal injury and future epilepsy). Other potential neuroprotective agents or methods that may be worthy of study in SE include hypothermia, glutamate receptor antagonists, calcium channel blockers, antioxidants, and erythropoietin.

Development of a reliable neuronal injury marker will also be helpful in determining which patients and EEG patterns require treatment, and may have a role as a surrogate marker for outcome. The work of DeGiorgio[62] and others suggests that neuron-specific enolase, or NSE, may be an appropriate marker for this. After isolated seizures, NSE is usually normal or elevated for a few hours only. However, after SE it is often elevated for days. NSE correlates with the duration of SE and the outcome. It is most elevated in patients with subtle or nonconvulsive seizures. It is also elevated in patients with SE but without any acute brain injury, further evidence that seizures themselves, including nonconvulsive ones, can cause neuronal injury.

Education about the prevalence of subclinical seizures and NCSE is immensely important. Diagnosis is often delayed, and this delay has been found to correlate with a worse prognosis.[14] Education and training regarding the pitfalls of EEG interpretation will also be important; the review of simultaneous video is quite helpful when attempting to distinguish between ictal patterns and artifact or encephalopathic patterns.

Whether or not further brain injury is occurring during NCSE or periodic discharges can be studied in many ways, perhaps most effectively with animal models. In humans, there are now many potential markers of neuronal injury and noninvasive methods of studying the underlying pathophysiology during and after SE: magnetic resonance imaging (MRI) with diffusion weighted imaging (often shows focal bright signal representing restricted diffusion during and after SE), functional MRI, serum and cerebrospinal fluid (CSF) markers such as NSE discussed above, positron emission tomography, single photon emission computed tomography, MR spectroscopy (e.g., for lactate), and other more invasive monitoring techniques such as brain-tissue oxygen and cerebral microdialysis (for parenchymal interstitial fluid lactate, pyruvate, glutamate, glycerol, neurotransmitters, and more). It is hoped that all these techniques, combined with clinical trials and experience, will enable more definitive evidence-based and physiology-based recommendations and improved outcomes in management of patients with SE.

CONCLUSION

SE is a neurological emergency. Rapid diagnosis and treatment are much more important than the choice of agent used. Out-of-hospital treatment of prolonged seizures or clusters is now available and should be utilized. Widespread use of benzodiazepines by caregivers or paramedics, including buccal, nasal, and rectal administration, could significantly improve prevention of refractory SE.

NCSE remains an underdiagnosed entity; it should be promptly considered in anyone with unexplained impairment or fluctuation of mental status/behavior, especially if there is a history of seizures or epilepsy risk factors, in children, in coma, and after convulsive SE if the patient does not rapidly awaken.

Further research is needed to determine how aggressively to treat critically ill patients with NCSE, which agent to use, when to stop treatment, and how to interpret periodic discharges and other equivocal EEG patterns.

As the population ages, it is likely that we will be seeing more patients with SE, especially the nonconvulsive and refractory forms. Technology is now available to study in detail cerebral blood flow, brain metabolism, intracranial pressure, EEG, neuronal injury markers, and other parameters in these patients. Active research in these areas, as well as in neuroprotection and antiepileptogenesis, will continue to keep SE an evolving, highly active topic in the coming years. We hope the lessons learned will translate into more effective treatment and improved outcomes.

CASE STUDIES

Case 1: Poststroke NCSE

A 67-year-old man with hypertension and atrial fibrillation on chronic warfarin presented with dizziness, left hemiparesis, and lethargy. Initial head CT was negative and international normalized ratio was subtherapeutic. In the emergency room, the neurology consultant noted rhythmic facial twitching and the patient was loaded with fosphenytoin 18 mg/kg. No further twitching was seen, and initial overnight EEG showed right hemisphere slowing and occasional isolated epileptiform discharges on the right, but no seizures. Fosphenytoin was discontinued after several days and levetiracetam was started instead to minimize drug interactions and potential long-term adverse effects. Repeat head CT (Fig. 1) showed hemorrhagic conversion of a moderate to large right middle cerebral artery infarct and a smaller left medial parietal hemorrhagic infarct. The patient was stable, but developed medical complications including pneumonia, renal insufficiency, and a deep vein thrombosis. On day 14 of his hospital stay he had a witnessed convulsion, followed by continued impaired mental

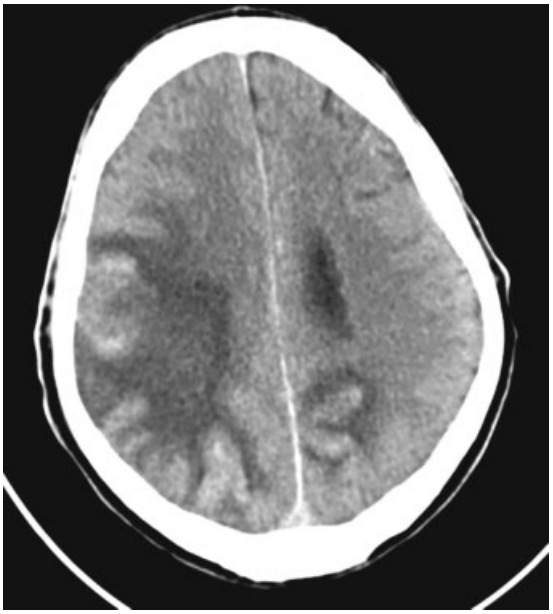

Figure 1 Case 1: Head computed tomography image showing bilateral hemorrhagic infarcts, much larger on the right (left side of figure).

status and leg twitching. He was given 4 mg of lorazepam and was reloaded with fosphenytoin 18 mg/kg. All motor activity ceased after ~15 minutes, as fosphenytoin was being administered. Urgent EEG was arranged and showed nearly continuous seizures from the left posterior quadrant (see EEG, Figs. 2, 3, and 4) lasting up to 4 minutes each with only a minute or so between seizures. There was no detectable clinical correlate to any of these electrographic seizures.

Levetiracetam was increased to 1500 mg twice a day and PHT (100 mg) was given three times a day per feeding tube. However, levels were low and erratic with enteric administration so fosphenytoin was resumed IV at 200 mg twice a day instead, maintaining total PHT serum levels at ~8 to 12 μg/mL, which corresponded to a measured free PHT of 2.0 to 3.0 μg/mL. Seizures rapidly decreased to a few isolated nonconvulsive seizures per day that resolved over a few days as the patient's medical condition improved and PHT levels were maximized. Due to occasional agitation, levetiracetam was changed to gabapentin, rapidly increased to 900 mg three times a day. His mental status improved gradually, he resumed speaking and following simple commands, but he was left with significant neurological impairment. He was discharged to a nursing home.

COMMENT

This case shows NCSE after an isolated but prolonged convulsive seizure in an acutely ill inpatient in the poststroke setting. Medication management was complicated by the desire to avoid drug interactions in a complex medical patient (by avoiding the strong P450 enzyme-inducer PHT), probable poor gastrointestional absorption (preventing confidence in enteral medications, especially ones without readily available serum levels), and agitation (which can occur from some antiepileptic medications, particularly levetiracetam). EEG monitoring played an important role in following this patient's nonconvulsive seizures as they could not otherwise be identified. Seizures increase metabolic demand and cerebral blood flow

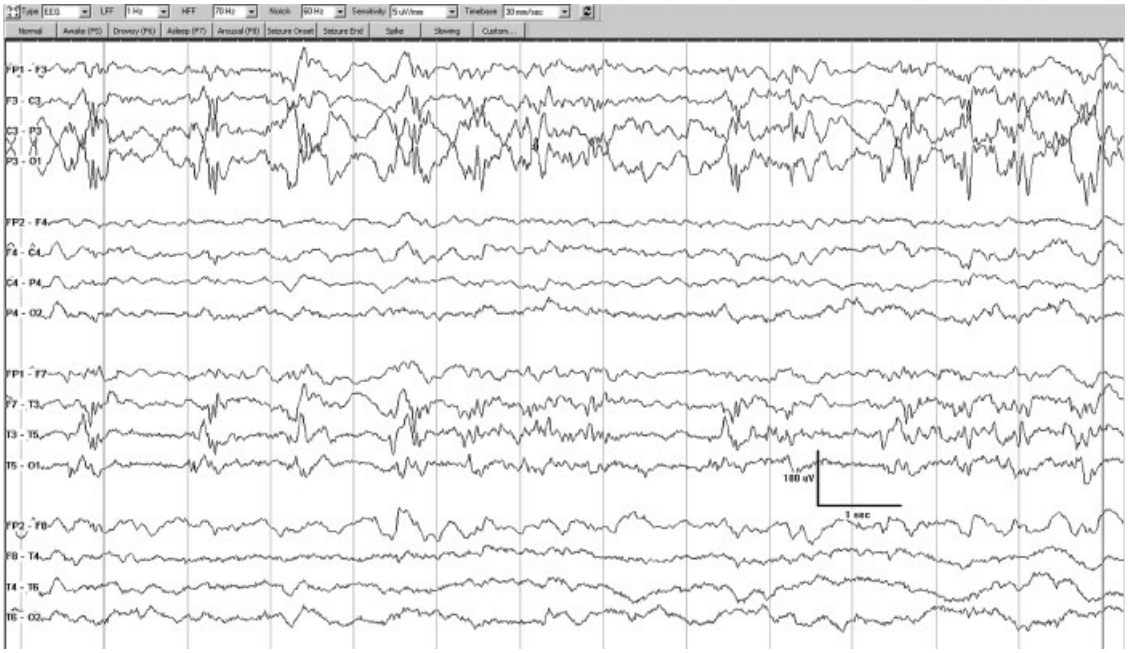

Figure 2 Case 1: Start of typical seizure from left posterior quadrant.

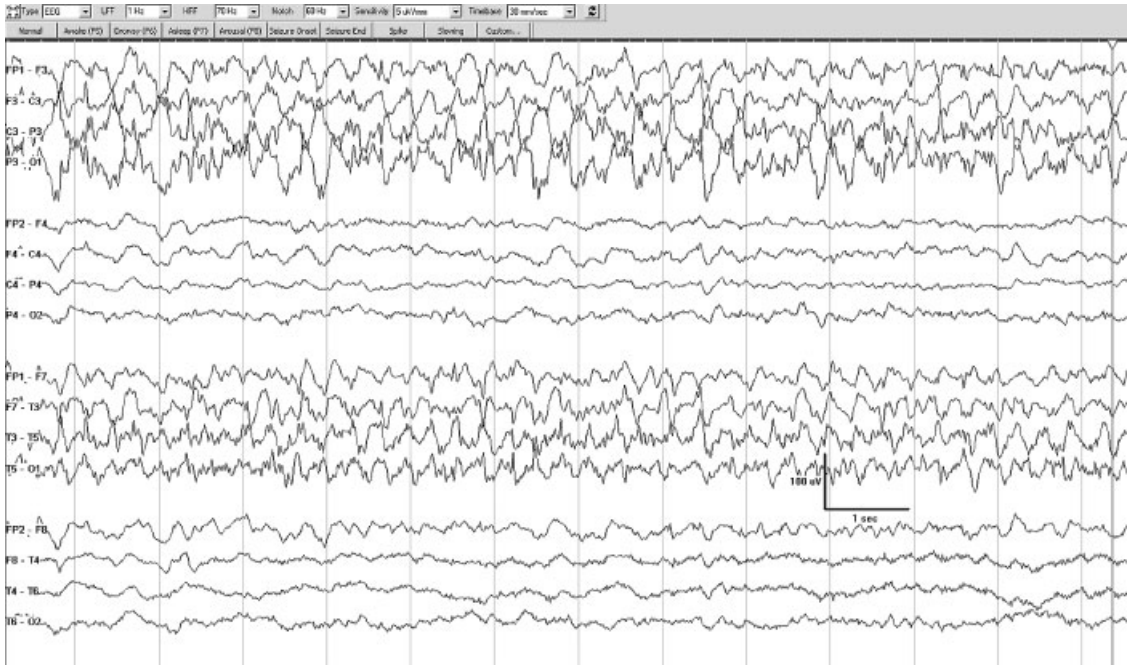

Figure 3 Case 1 continued: Middle of seizure, almost 2 minutes after EEG in Fig. 2, now involving entire left hemisphere.

and release glutamate, all of which are likely to exacerbate neuronal injury in the acute stroke setting such as this. As is typical in critically ill patients, the occasional clinical seizure was just the tip of the iceberg. It is interesting that his seizures seemed to arise from the smaller left parietal hemorrhagic infarct rather than the large one on the right.

Case 2: Refractory SE Requiring 1 Month of Iatrogenic Coma but with Good Outcome

A 63-year-old healthy woman presented with viral symptoms for a few days including fever, followed by a convulsion. She was loaded with fosphenytoin in the emergency room but her mental status remained impaired and intermittent focal seizures continued, consisting of

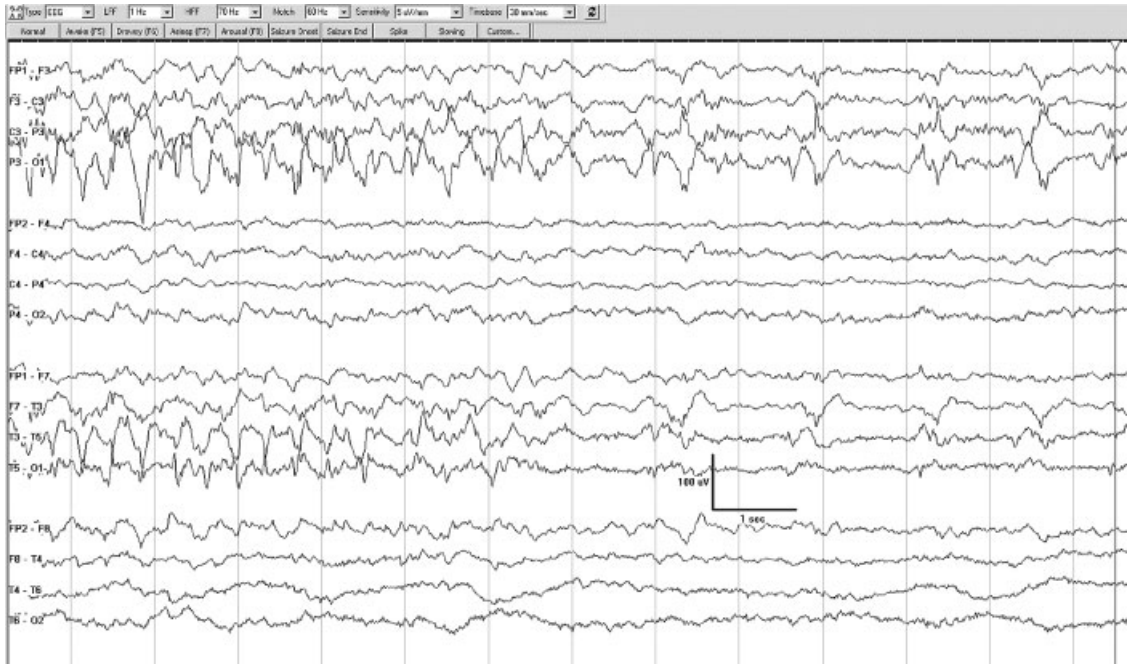

Figure 4 Case 1 continued: End of seizure, 1 minute after EEG in Fig. 3. After seizure offset, seizure activity is replaced by periodic lateralized epileptiform discharges recurring at just under 1 per second, also maximal in the left posterior quadrant.

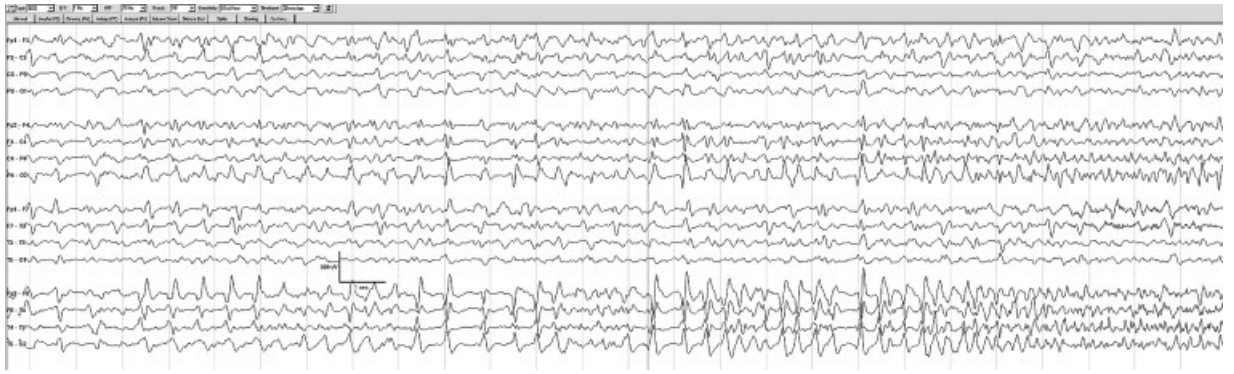

Figure 5 Case 2: Onset of typical nonconvulsive seizure from the right temporal region with spread to the right parasagittal region.

eye deviation and facial twitching. Lorazepam was given several times. Lumbar punctures showed 13 to 22 white blood cells per mm^3 (mostly lymphocytes), mildly elevated protein concentration, and normal glucose concentration. Brain MRI was normal as were all blood tests. CSF, herpes simplex virus, polymerase chain reaction, and other encephalitis tests were negative. EEG monitoring showed NCSE (see EEG, Figs. 5 and 6). The patient was treated with many agents, including ceftriaxone, acyclovir, midazolam infusion, propofol infusion (while following creatine phosphokinase, pH, and triglycerides), IV VPA, levetiracetam, topiramate (after off propofol), oxcarbazepine (while following sodium closely), and prolonged pentobarbital coma for 4 weeks. Every 1 to 4 days, an attempt to wean her off of pentobarbital was made, but seizures recurred each time for several weeks. Phenobarbital was maintained to attempt to minimize withdrawal seizures as pentobarbital was tapered, and this was eventually successful after just over 1 month in iatrogenic coma. No organism was ever identified for her presumed encephalitis.

The patient gradually awoke. Intermittent isolated seizures were tolerated. Over the subsequent 2 months, she gradually returned to baseline mental status except for mild-moderate memory dysfunction. Her critical illness myopathy improved and resolved completely after ~6 months. Subsequent MRIs showed mild bilateral hippocampal atrophy and increased signal suggesting hippocampal sclerosis. She returned to work part time and functioned well. One year later, she underwent epilepsy monitoring for refractory seizures, averaging a couple per week. Bilateral independent temporal lobe seizures were identified as well as occipital simple partial seizures. She received a vagus nerve stimulator, which helped modestly. She has since retired and now travels the world with her husband. She continues to have about 1 complex partial seizure per week.

COMMENT

This case reminds us that the prognosis in refractory SE, although poor overall, is not that bad for those with no severe brain injury. It is not unusual to require a few weeks or more of iatrogenic coma for encephalitis-related SE and still have good functional outcome, though most are left with epilepsy that can be severe. It is possible that earlier identification and treatment of NCSE could improve outcome even more, and perhaps prevent the permanent hippocampal injury and related seizures that many of these patients, including this one, develop.

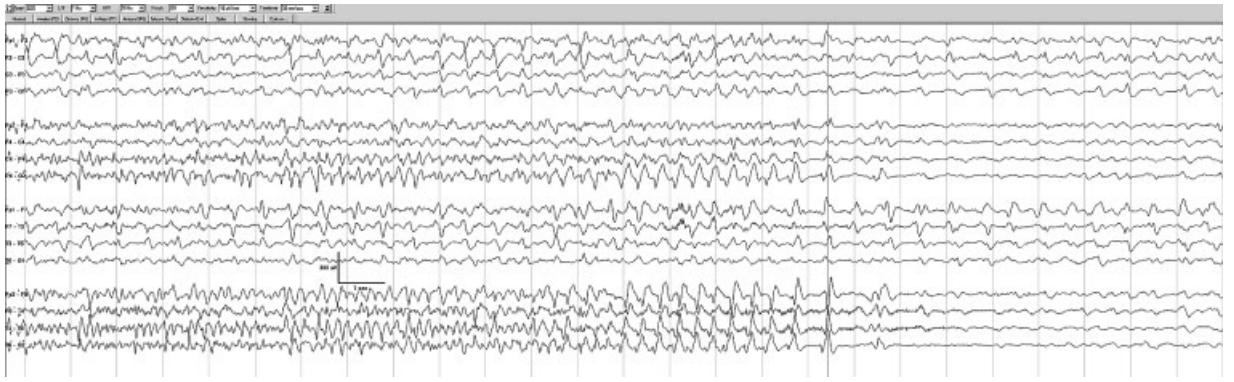

Figure 6 Case 2 continued: Continuation of seizure, remaining maximal on the right but spreading to the left, then ending at the end of this EEG segment. Left sided periodic discharges continued.

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