Super Refractory Status Epilepticus

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Joseph Zachariah, Jeff Britton, and Sara Hocker

Contents

J. Zachariah, DO • J. Britton, MD • S. Hocker, MD (✉)
Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55902, USA
e-mail: Zachariah.Joseph@mayo.edu; Britton.Jeffrey@mayo.edu; hocker.sara@mayo.edu

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Introduction

Earlier definitions of status epilepticus (SE) were based on the duration of seizures, but newer definitions rely more on a pragmatic staging based on treatment failures (Table 1). Refractory status epilepticus (RSE) is defined as SE that continues despite administration of both benzodiazepines and an appropriately dosed second-line antiseizure drug. Depending on the semiology of the seizures and comorbidities of the patient, this stage may be treated with further antiseizure drugs or anesthesia. When seizures recur upon weaning the anesthetic agent, typically after 24 h of seizure suppression, or in the rare cases where seizure control cannot be achieved with anesthesia, status epilepticus is considered to be super refractory (SRSE). The incidence of status epilepticus has been increasing, from 3.5 to 12.5/100,000 population between 1979 and 2010. During this time hospital mortality has not changed [1].

Approximately 30–50 % of status epilepticus episodes progress to RSE [2, 3] and ~15 % of these progress to SRSE [2]. Peak incidence of SE is in a bimodal distribution with ages less than 1 and greater than 60 years. RSE does not discriminate between basic patient demographics such as age, sex, or gender. New-onset RSE without an obvious cause after initial investigations has been termed NORSE or new-onset refractory status epilepticus. This may represent a unique group of patients who are more likely to have an antibody-mediated cause.

As with seizures and status epilepticus, RSE may be simplistically categorized as convulsive or nonconvulsive and focal or generalized. These delineations have treatment implications. Convulsive seizures are easily recognized and must be controlled emergently. At the refractory stage of convulsive SE, the standard treatment is anesthesia which is highly effective at achieving seizure suppression. The semiology of nonconvulsive status epilepticus is highly varied and thus may be diagnosed after some delay when seizures are identified on the electroencephalogram (EEG) with limited or fluctuating clinical correlates. Patients may have subtle behavioral changes, confusion, or automatisms as well as an altered level of consciousness. Patients in NCSE may exhibit subtle rhythmic jerks, eye fluttering, or gaze deviation. The optimal treatment of refractory nonconvulsive status epilepticus is not well established. Compared with focal status epilepticus, generalized status epilepticus may warrant more aggressive treatment. Yet, paradoxically, both focal motor seizures and nonconvulsive status epilepticus predict development of refractoriness [3].

Table 1 Stages of status epilepticus

Stage 1: early SE	Seizure lasting 5 min *or* two or more seizures without recovery of consciousness between
Stage 2: established SE	Ongoing SE after appropriately dosed benzodiazepine
Stage 3: refractory SE	Ongoing SE after failure of benzodiazepines and an appropriately dosed second-line antiseizure drug (typically fosphenytoin, valproic acid, phenobarbital, lacosamide, or levetiracetam) or SE requiring an anesthetic agent for control
Stage 4: SRSE	Ongoing SE despite use of an anesthetic drug *or* recurrence of SE upon weaning of anesthesia

SE status epilepticus

Forty percent of generalized convulsive SE evolves into nonconvulsive status epilepticus by the time anesthetic agents are initiated [4]. Nonconvulsive seizures after control of convulsions should be suspected in patients who do not regain consciousness within 15–30 min of the cessation of convulsions. While certain variables may suggest a prolonged postictal period, such as high doses of benzodiazepines or barbiturates or underlying cognitive impairment or structural brain disease in the setting of prolonged convulsions, these are unreliable, and only EEG can ensure adequate seizure control in this setting.

Seizures become refractory when there is excessive excitatory stimulation with glutamate via N-methyl-D-aspartate (NMDA) receptors and insufficient inhibition via Ð-aminobutyric acid (GABA). Receptor trafficking with an increase in glutamatergic receptors and a reduction in GABA receptors is thought to contribute to pharmacoresistance and perpetuation of seizures. Additionally, mitochondrial failure, electrolyte disturbances due to compromise of the blood–brain barrier, and changes in gene expression may all play a role in the development of refractoriness.

Etiology

While the epidemiology of SRSE is not well described, it is likely to be very similar to that of RSE. Between 38 and 60% of episodes of refractory status epilepticus occur in patients with epilepsy [4, 5], among whom precipitating factors include low antiseizure drug levels, changes in drug regimen, drug intoxication or withdrawal, systemic infection, metabolic derangement, or progression of the underlying disease responsible for their epilepsy. RSE which develops in the absence of underlying epilepsy is most commonly due to acute encephalitis, stroke, brain tumor, traumatic brain injury, or drug or alcohol withdrawal. Myoclonic status resulting from hypoxic ischemic injury will be discussed in Chap. 18. A more comprehensive list of etiologies is shown in Table 2. Identification of the etiology is important for both treatment and prediction of outcome.

Table 2 Etiologies

Structural
Traumatic brain injury
Hemorrhagic or ischemic stroke
Venous sinus thrombosis
Hypoxic ischemic brain injury
Polymicrogyria
Heterotopias
Schizencephalies
Cortical dysplasias
Autoimmune conditions
N-methyl-D-aspartate (NMDA) encephalitis

(continued)

Table 2 (continued)

Glutamic acid decarboxylase (GAD) antibody
Voltage-gated potassium channel (VGKC) antibody
Voltage-gated calcium channel (VGCC) antibody
$GABA_A$ receptor, $GABA_B$ receptor antibody
Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antibody
Leucine-rich glioma inactivated protein 1 (LGI1) antibody
Contactin-associated protein-like 2 (Caspr2) antibody
Dipeptidyl-peptidase-like protein-6 (DPPX) antibody
Metabotropic glutamate receptor 5 (mGluR5) antibody
Hashimoto encephalopathy
CNS lupus
Central nervous system infections
Viral encephalitis
Meningitis
Abscess
Empyema
HIV
Creutzfeldt–Jakob disease
Cat-scratch disease
Progressive multifocal leukoencephalopathy
CNS tumors
Primary CNS tumors
Metastatic CNS tumors
Hereditary diseases
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
Myoclonic encephalopathy with ragged red fibers
Neuropathy, ataxia, and retinitis pigmentosa
Leigh syndrome
Mitochondrial spinocerebellar ataxia and epilepsy (MSCAE)
Occipital lobe epilepsy
Alper's disease
Maple syrup urine disease
Porphyria
Wilson's disease
Leukodystrophies
Systemic conditions
Sepsis
Electrolyte or glucose derangements
Hyperammonemia
Organ failures
Acid–base derangements
Drug intoxication or withdrawal
Alcohol

Table 2 (continued)

Cocaine
Ecstasy
LSD
Amphetamines
Medication effects
Cephalosporins
Supratherapeutic AED levels
Tigabine
Valproic acid
Carbamazepine
Chemotherapeutic agents
Ifosfamide
Cisplatin
Calcineurin inhibitors (posterior reversible encephalopathy syndrome or tacrolimus toxicity)
Epilepsy (patients with a history of seizures)
Any factor listed above
Or
AED noncompliance
Subtherapeutic AED levels
Inappropriate AED choice
Progression of underlying neurologic disease
Cryptogenic

CNS central nervous system, *AED* antiepileptic drug

Structural Injury

Cerebrovascular disease makes up the most common etiology of SE in Western countries [6]. Acute and remote strokes and hemorrhages account for almost 50 % of the cases of SE and 30–35 % of cases of RSE [3, 7]. In contrast, SRSE due to stroke or hemorrhage was found in only 3–7 % of cases from India and China, respectively [8, 9]. Traumatic brain injury is also a common cause of SE that is refractory to treatment [10]. Six percent of RSE cases were related to traumatic injuries [5]. Apart from acute structural damage, developmental malformations such as polymicrogyria, heterotopias, schizencephalies, and cortical dysplasias can also lead to refractory seizures.

Iatrogenic Causes

Antibiotics such as fluoroquinolones and cephalosporins have long been known to cause neurological problems. The theory behind these effects lies in the molecular similarity between cephalosporins and bicuculline, a GABA receptor antagonist

[11]. Supratherapeutic doses of tiagabine, valproic acid, and carbamazepine as well as chemotherapeutic agents such as ifosfamide, cisplatin, and tacrolimus have been reported to paradoxically cause seizures likely through systemic effects (see Chap. 23).

Infectious Etiologies

The most common cause of SRSE in developing countries is encephalitis, accounting for 67–69 % of the cases in two SRSE studies from India and China, respectively [8, 9]. In contrast, a study from Berlin with 36 cases of RSE revealed 22 % with an etiology of encephalitis [7]. Each of these studies labeled patients as presumed encephalitis based on the definition from the California Encephalitis Project, encephalopathy plus one or more of the following: fever, CSF pleocytosis, focal neurological deficit, or EEG or MRI changes suggestive of encephalitis. A responsible infectious agent was identified in less than 30 % of the patients in these studies. Other potential infectious etiologies include meningitis, brain abscess, and empyema.

Hereditary Diseases

Several mitochondrial diseases have been related with SE such as mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonic encephalopathy with ragged red fibers (MERRF); neuropathy, ataxia, and retinitis pigmentosa (NARP); Leigh syndrome; mitochondrial spinocerebellar ataxia and epilepsy (MSCAE); occipital lobe epilepsy; and Alper's disease. Once mitochondrial patients have SRSE, it is usually related to the progression of disease, and the prognosis is typically poor. Along with mitochondrial diseases, inborn errors of metabolism such as maple syrup urine disease, porphyria, Wilson's disease, and several of the leukodystrophies have been associated with seizures.

Systemic Conditions

Systemic conditions such as sepsis, hyperammonemia, organ failures, electrolyte or acid–base derangements, and hypo- or hyperglycemia can result in SRSE. The elderly have a higher incidence of SRSE of metabolic etiology than younger adults (26 % vs 2 %) [8]. Treatment for SRSE on the other hand can complicate treatment of the underlying systemic cause.

Autoimmune, Paraneoplastic, and Neoplastic Conditions

Autoimmune refractory epilepsies usually associated with limbic encephalitis include anti-neuronal antibodies to glutamic acid decarboxylase (GAD),

voltage-gated potassium channels (VGKC), voltage-gated calcium channels (VGCC), and NMDA receptors. These patients have CSF pleocytosis and MRI features suggestive of limbic encephalitis such as mesial temporal or hippocampal signal changes. Patients in whom autoimmune limbic encephalitis is suspected may benefit from a trial of immunosuppression. The remaining list of known antibodies are as follows: $GABA_A$ receptor, $GABA_B$ receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, leucine-rich glioma inactivated protein 1 (LGI1), contactin-associated protein-like 2 (Caspr2), dipeptidyl-peptidase-like protein-6 (DPPX), and metabotropic glutamate receptor 5 (mGluR5).

Intracranial tumors whether primary brain tumor or metastatic cancer can undoubtedly lead to refractory seizures. Tumors in the limbic areas and frontal and temporal lobes have a higher epileptogenicity. The pathophysiology of seizure propagation is more than local irritation. The mechanisms resulting in seizure generation are thought to be the results of primary injury by tumor microinvasion into surrounding tissue or due to ischemia as a result of direct compression. The secondary mechanisms of seizure propagation include loss of the integrity of the blood–brain barrier, high extracellular glutamate, reduced GABAergic neurotransmission, and electrolyte alterations in extracellular peritumoral space [12].

Several paraneoplastic etiologies of SRSE have been discovered; the most well known of which is anti-NMDA receptor encephalitis. NMDA encephalitis more commonly affects women and half of women with this entity have an ovarian teratoma. Resection of the tumor is generally related to favorable outcomes. Patients present with a constellation of neuropsychiatric symptoms ranging from anxiety, psychosis, and mutism to memory impairment, insomnia, and seizures. Treatment consists of aggressive immunosuppression and treatment of any associated malignancy.

Epilepsy

Between 38 and 60 % of RSE patients have a prior history of epilepsy [4, 5]. Risk factors for the generation of SRSE in these cases include subtherapeutic AED levels, progression of primary CNS disease, or the addition of any of the other acute causes that may affect patients without epilepsy. Inadequate AED coverage is the cause of up to 10–31 % of SE admissions [3, 13]. A 30-patient SRSE study reports 13 % of cases to be due to inadequate AED levels [8]. SE in the setting of low AED levels has the lowest mortality rate of 4 % [6].

Drug and Alcohol Use

It is common knowledge that alcohol intoxication as well as withdrawal can cause seizures and is the etiology in 8–10 % of RSE cases [7, 8]. Super refractory SE

due to alcohol intoxication or withdrawal has not been reported in the literature. Drug intoxication with ecstasy and amphetamines can lead to seizures as well, but cocaine intoxication can theoretically lead to vasculitis and thus refractory seizures.

Cryptogenic

Preliminary data from the global audit of SRSE suggests that cryptogenic etiologies are the most commonly listed cause of SRSE (https://www.status-epilepticus.net/). New etiologies of autoimmune states are discovered on a regular basis. Anti-NMDA receptor encephalitis, currently the main cause of autoimmune encephalitis-related refractory epilepsy, was discovered only as recently as 2007. The latest discovery is of a $GABA_A$ antibody [14]. As new discoveries continue to occur, the percentage of the cryptogenic cases will continue to decline.

Diagnostic Evaluation

After achieving seizure control, evaluation begins with a focused history and examination. Important historical features include circumstances at seizure onset (prodromal illness, motor vehicle accident, or party suggesting substance abuse), medical history (epilepsy, neoplasms, autoimmune conditions), and active medications (cephalosporins, fluoroquinolones). The patient should be examined for signs of trauma, meningismus, and focal neurological deficits. In nearly all episodes of status epilepticus, a comprehensive laboratory evaluation including antiseizure drug levels, serum electrolytes, glucose level, urine and serum toxicology screens, troponin, lactate and creatine kinase levels, and a head computed tomography (CT) scan is warranted. Because cardiopulmonary complications are commonly associated with status epilepticus, a screening chest X-ray and electrocardiogram would aid in evaluation for aspiration, ischemic changes or development of a prolonged QTc, or other stress-related changes. When laboratory evaluation and neuroimaging do not yield an etiology for SRSE, workup continues with CSF analysis for infection and autoimmune and paraneoplastic conditions. This basic workup will identify the most common causes of SE. In addition to this evaluation, mitochondrial studies are occasionally conducted in younger patients. A stepwise approach to the evaluation of RSE etiology is presented in Table 3.

The ability to perform continuous EEG (cEEG) monitoring is a cornerstone of SRSE treatment as anesthetic agents are titrated against the EEG. Occasionally, the EEG can provide clues to the etiology of the seizures. Periodic lateralized epileptiform discharges (PLEDs) will point the practitioner to a focal intracranial lesion, while the so-called extreme delta brush suggests possible autoimmune encephalopathy, specifically anti-NMDA receptor encephalitis. PLEDs or generalized periodic epileptiform discharges (GPEDs) are a frequent finding after prolonged and untreated seizures.

Table 3 Diagnostic evaluation

First line:
Blood glucose
Electrolyte panel
Complete blood count
Liver function test
Serum ammonia
Serum and urine toxicology screen
Alcohol level
Troponin
Creatine kinase
Lactate
CT head
Chest X-ray
EKG
Second line:
Continuous EEG monitoring
CSF analysis:
Cell count and differential
Protein and glucose
Bacterial, viral, and fungal gram stain, cultures, and smear
Viral and fungal serologies (in appropriate situations)
MRI brain with and without contrast
Third line:
Serum and CSF paraneoplastic panel
Thyroperoxidase antibody
CSF cytology
N-methyl-D-aspartate receptor antibodies
Voltage-gated potassium channel antibodies
Glutamic acid decarboxylase 65 antibodies
Fourth line:
CT chest/abdomen/pelvis
CT body positron emission tomography
Testicular and pelvic ultrasounds (male and female)
Exploratory surgery for ovarian teratoma

CT computed tomography, *EEG* electroencephalogram, *CSF* cerebral spinal fluid, *MRI* magnetic resonance imaging

Treatment

Excessive glutamatergic activity from seizures is thought to trigger a cascade of electrolyte imbalances, oxidative stress, and mitochondrial dysfunction. These processes result in neuronal cell damage within a few hours of the seizure, which is the

principle that drives urgent treatment. Rapid identification and treatment of the underlying etiology is critical to resolution of SRSE; however, as previously discussed, a substantial portion of patients may undergo an exhaustive diagnostic search with no identified etiology.

Widely accepted treatment recommendations for SRSE are based on small, retrospective case series and general consensus. However, anesthetic drugs used for long-term suppression of seizures in this setting can also have detrimental effects, leading some experts to reexamine their protocols. The first-line treatment for status epilepticus is benzodiazepine administration. Proven second-line therapies include fosphenytoin, valproic acid, or phenobarbital. Less established options include levetiracetam and lacosamide. Anesthetics should be considered once second-line medications fail [5]. Clinicians should progress through this protocol rapidly in convulsive status epilepticus where it is not advisable to await completion of the second-line agent to begin intubation, initiation of mechanical ventilation, and induction of an anesthetic drug. In nonconvulsive seizure types, it is often reasonable to await true failure of the second-line agent or even trial a third- or fourth-line non-anesthetic antiseizure drug prior to committing the patient to anesthesia. Any patient requiring an anesthetic drug for seizure control requires continuous EEG monitoring and admission to an intensive care unit. Table 4 provides the overall treatment algorithm, mechanism of action, recommended dosing, and adverse effects of commonly used anesthetic agents for SRSE.

ICU

The basis for intensive care monitoring is to meet the medical and nursing needs of these complex patients. These needs include mechanical ventilation and aggressive pulmonary hygiene, hemodynamic and cEEG monitoring, and meticulous nursing care to avoid the myriad complications that can occur in an immobilized sedated patient.

Anesthetics

Anesthetic infusions commonly used in SRSE include benzodiazepines, propofol, barbiturates, and ketamine. Benzodiazepines bind and enhance the $GABA_A$ receptor. The benzodiazepine of choice in inducing anesthesia is midazolam with the benefit of a rapid offset and lack of accumulation. Cardiovascular depression, eventual tolerance from downregulation of GABA receptors, and unclear clearance in patients with renal failure are its main disadvantages. Benzodiazepines such as lorazepam or diazepam are delivered in propylene glycol solutions, and prolonged infusions can result in propylene glycol toxicity, which consists of elevated anion gap, hyperosmolarity, and severe metabolic acidosis.

Propofol is considered to be a modulator of the $GABA_A$ receptor. A major advantage of propofol is its rapid clearance despite prolonged use as well as the welcomed absence of significant drug–drug interactions. Propofol has a faster offset and less

Table 4 Treatment algorithm for SE and SRSE

First line: early status epilepticus			
Benzodiazepines	**Loading dose**		
Lorazepam-	0.1 mg/kg IV, in divided doses		
Midazolam	10 mg IM		
Diazepam	0.2 mg/kg PR		
Second line: established status epilepticus			
Antiepileptics	**Loading dose**		**Maintenance**
Fosphenytoin	20 mg/kg at 150 mg/min		5 mg/kg/d in divided doses
Levetiracetam	1–3 g IV		Up to 4 g total daily
Valproic acid	20–40 mg/kg at 3–6 mg/kg/min		Up to 7.5–15 mg/kg in divided doses
Third line: refractory status epilepticus			
Anesthetics agents	**Loading dose**		**Maintenance**
Midazolam	0.2 mg/kg		0.05–2 mg/kg/h
Propofol	1–2 mg/kg		30–200 mcg/kg/h
Pentobarbital	5–15 mg/kg		0.5–5 mg/kg/h
Ketamine	0.5–4.5 mg/kg		<5 mg/kg/h
Fourth line: super refractory status epilepticus			
If seizures are uncontrolled:			
Consider either switching to an alternative anesthetic agent or combining a second agent with the first if seizures occur upon weaning attempt:			
Resume anesthetic infusion at prior dose ± additional bolus depending on seizure semiology and urgency to treat			
Consider alternative anesthetic agents or adjunctive therapies			
Adjunctive therapies: (limited evidence for all)			
Treatment	**Dose**	**Adverse events**	**Contraindications**
Hypothermia	32–36 degrees	Acid–base and electrolyte imbalance, coagulation disorder, arrhythmia, ileus	Coagulation disorders
Magnesium	Infusions of 2–6 g/h to maintain serum level >3.5 mmol/l	Hypotension, arrhythmia, weakness	Myasthenia gravis, kidney failure
Ketogenic diet	3:1 or 4:1 ketogenic ratio to attain ketosis	Acidosis, hypoglycemia	β-Oxidation or pyruvate carboxylase deficiency
Surgical resection	Focal or lobar resection, subpial transection, corpus callosotomy	Any complication of surgery	Lack of an identifiable surgical focus
Electroconvulsive therapy	5–8 daily sessions	Arrhythmias, increased ICP, requirement of holding AEDs for treatment	Intracranial tumors, recent stroke, myocardial infarction

(continued)

Table 4 (continued)

Adjunctive therapies: (limited evidence for all)			
Treatment	**Dose**	**Adverse events**	**Contraindications**
Vagal nerve stimulator	0.25–1.75 mA	Asystole, cough, bradycardia	Prior neck surgery
Immunosuppression	Prednisolone 1 g daily ×3 days followed by 1 mg/kg/day	Ileus, psychiatric disorders	Infections
	Immunoglobulins 2 g/kg administered over 5 days	Coagulation disorders	History of clotting, IgA deficiency (leads to anaphylaxis)
	Plasma exchange – 5-day course	Active infection, severe thrombocytopenia, hypotension	Hypocalcemia, anaphylactoid reactions, hypotension

cardiorespiratory depression compared to barbiturates and benzodiazepines. However, prolonged use of propofol at high doses can lead to propofol infusion syndrome (PRIS) which is a rare but frequently fatal constellation of hypoxia, severe metabolic acidosis, rhabdomyolysis, renal failure, and cardiovascular collapse. Other disadvantages include drug-induced involuntary movements that can closely mimic seizures.

Barbiturates enhance the action of the $GABA_A$ receptor and have been historically favored for use in RSE due to their high efficacy. They have the added properties of producing a degree of hypothermia and immunosuppression. They are currently preferred as a second- or third-line anesthetic agent due to the prolonged half-life, numerous drug interactions, and serious common systemic adverse effects including infections, ileus, hypotension, and cardiovascular depression.

Ketamine acts by NMDA receptor antagonism, which decreases the excitability of the brain. It has been gaining favor as a third- and fourth-line agent in SRSE. As the other anesthetics primarily act on GABA receptors and as GABA receptors are downregulated with time, a novel mechanism of action is theoretically attractive. The adverse effect of hypertension is generally welcomed as cardiovascular depression is common with the other anesthetic agents.

Infusion rates of anesthetics should be used at the minimum dose that controls clinical and electrographic seizures. The drug is titrated against the EEG background, and weaning often commences 24 h after achieving seizure control with careful monitoring of the continuous EEG. There is no consensus regarding the rate of weaning anesthetics but it is generally done over 12–24 h. Further discussion on weaning of anesthetics can be found in Chap. 29.

Immunosuppression

Immunosuppression is used in antibody-mediated, vasculitic, and some other inflammatory etiologies, and it is often used empirically in cryptogenic cases of

SRSE as many of these are thought to be antibody mediated. Options for immunosuppression include steroids, IVIG, or plasma exchange and later transition to a steroid-sparing agent such as rituximab or cyclophosphamide.

Polypharmacy

The desire to frequently alter the patient's AED regimen should be avoided. Rapid weaning of medications can lead to unpredictable AED levels considering inter-AED drug–drug interactions which can in turn lead to more seizures. There is no evidence favoring specific polytherapy, and so any decision to change ongoing regimens should be undertaken with caution and implemented slowly. The use of multiple agents with differing mechanisms of action, described as rational polypharmacy, has been suggested to be useful in animal models in SE [15].

Alternative Therapies

Alternative therapies with varying degrees of success include hypothermia, ketogenic diet, resective surgery for lesional epilepsy, and electrical stimulation therapies such as deep brain stimulation, vagal nerve stimulation, or electroconvulsive therapy. These interventions will be discussed in Chap. 30.

Complications

In addition to the treatment-related adverse events mentioned above, patients admitted for SRSE will be subject to various neurological and systemic complications as a consequence of the seizure itself. MRI can demonstrate irreversible changes of laminar necrosis as well as mesial temporal sclerosis after prolonged seizures. Reversible changes include signal changes in the thalamus, basal ganglia, and contralateral cerebellum. The contralateral cerebellum is involved through pathways of crossed cerebellar diaschisis otherwise known as the corticopontocerebellar pathway. Laminar necrosis is theorized to occur due to cytotoxic edema from excessive excitatory amino acid release [16]. Serial imaging can reveal cerebral atrophy that results from prolonged seizures [2] and is likely the result of excitotoxic injury to the neurons. The significance of these radiographic changes is not well established. Epileptogenesis is not infrequent in patients who recover from SRSE. Sixty-nine percent of patients who recover go on to suffer medically refractory seizures [17] likely as a result of structural damage and glial scarring. SRSE affects nearly every organ system. Systemic complications include cardiac arrhythmias, hypotension, venous thromboembolism, infections, and critical illness neuropathy and myopathy, among others. While these complications are common to any patient that remains in the intensive care setting for weeks to months, they appear to be more common in the setting of RSE even after adjusting for length of stay [3].

Outcome

The heterogeneous etiologies of SRSE, numerous treatment options, and various serious adverse effects of treatment make accurate prognostication challenging. Type and duration of status, premorbid APACHE 2 scores, anesthetic choice, and even age have not been shown to reliably influence prognosis [10]. Although age is a well-known predictor in SE, it is not shown to be a strong predictor in RSE or SRSE. The variation in mortality estimates in various studies likely stem from the studies' length of follow-up, the use of anesthetics, the ratio of convulsive vs NCSE, and the variable exclusion of myoclonic status due to hypoxic ischemic injury. Although studies examining outcomes have been largely underpowered, etiology has consistently impacted prognosis. As previously mentioned, SRSE due to AED noncompliance in patients with pre-existing epilepsy has the lowest mortality at 4 %. Patients with NMDA encephalitis produce NMDA antibodies which are not destructive to the CNS. Therefore, these patients may have a favorable outcome despite months of SRSE. On the other hand, SRSE as a result of glioblastoma multiforme or progression of mitochondrial disease portend a poor prognosis.

Convulsive SE is thought to foreshadow a worse prognosis than NCSE [10]. This has been postulated to be due to more excitotoxic injury to the brain as well as increased systemic complications due to the massive sympathetic outpouring during the convulsions. Prolonged convulsive seizures are undoubtedly taxing to the body with excessive lactic acidosis, rhabdomyolysis and secondary renal failure, aspiration pneumonia, as well as cardiopulmonary stress.

Although the mortality in SRSE is generally high, some patients may have good functional recovery after weeks to even months of general anesthesia for SRSE. Sixty percent of patients survive SRSE. Among those who survive, 60 % stabilize or improve their functional status over time [10]. A significant minority of survivors (22 %) are able to achieve independence [17], and 10 % return to their premorbid functional status [17]. The high mortality rates in SRSE patients are largely driven by either changes in the goals of care or complications of treatment and critical illness. Therefore, the relationship between duration of SRSE and outcome might be a result of accumulating systemic complications rather than the seizure itself. [5] Transition to palliative care is usually guided by family members or medical staff after bearing witness to weeks or months of refractory seizures and when treatment options have been exhausted.

Representative Cases

Case 1

A 47-year-old woman presented with status epilepticus in the setting of progressive encephalopathy following a flu-like illness. Her symptoms began with headache, malaise, and poor oral intake. CSF analysis showed no white blood cells, glucose 71 mg/dL, protein 28 mg/dL, and negative polymerase chain reaction (PCR) titers for influenza A and B, herpes simplex virus, Epstein–Barr virus, and varicella-zoster virus.

The next day she experienced two witnessed generalized tonic–clonic seizures. She was loaded with fosphenytoin and underwent a noncontrast CT scan of the head followed by an MRI of the brain, blood and urine cultures, and repeat CSF analysis, all of which were normal. She experienced a flurry of recurrent seizures necessitating admission to the intensive care unit where she was noted to have myoclonic pelvic jerking and twitching of the eyelids which abated with repeated doses of midazolam. Brief 40 s seizures were noted on EEG monitoring, though there was no correlate with her pelvic jerking and facial twitching. Midazolam was replaced with a pentobarbital load and infusion when seizures broke through 2 mg/kg/h of midazolam.

A repeat CSF analysis remained unremarkable for basic chemistry as well as *Borrelia burgdorferi* IGM, IGG, *Rickettsia rickettsii*, *Anaplasma phagocytophilum*, and *Leptospira* serologies. Autoimmune encephalitis and paraneoplastic antibody panels including voltage-gated potassium channel and anti-NMDA receptor antibodies were negative. A repeat contrasted brain MRI/MRA demonstrated nonenhancing symmetric T2 hyperintensity in the mesial temporal lobes, amygdala, and subinsular region, suggestive of paraneoplastic limbic encephalitis, and a 5-day course of methylprednisolone was completed and followed with weekly pulse steroids. A CT of the chest abdomen and pelvis, transvaginal ultrasound, and finally a CT positron emission tomography scan of the body showed no masses or areas of increased metabolic uptake concerning for malignancy.

As she continued to have seizures, plasmapheresis was performed in addition to increasing her antiepileptic coverage, which included valproic acid, levetiracetam, and phenobarbital infusion. Despite these measures, intermittent breakthrough seizures continued. She was started on isoflurane in an attempt to reduce her dose of phenobarbital and achieve better seizure control. Felbamate and lacosamide were trialed but subsequently discontinued due to skin rashes. Adjunctive hypothermia and ketamine infusions did not improve seizure control. She ultimately required neuromuscular blockade to improve synchrony with the mechanical ventilator and reduce her myoclonic jerking. Continued aggressive attempts at immunosuppression including weekly rituximab failed to reduce her seizure frequency. Repeat brain MRI performed approximately 3 months after presentation revealed global cerebral atrophy with hyperintensities in bilateral hippocampi suggestive of significant neuronal cell loss secondary to damage from ongoing seizure activity (see Fig. 7).

Systemic complications during her admission included a ventilator-associated pneumonia, lower extremity deep venous thrombosis, bacteremia and sepsis requiring vasopressors, urinary tract infection, lacosamide-associated rash, ventricular bigeminy secondary to a central line, heparin-induced thrombocytopenia, stress-induced cardiomyopathy, critical illness polyneuropathy, and ileus. Three months after presentation, her family decided to transition to comfort care and then she died shortly thereafter. Autopsy revealed widespread variable microglial activation, focal marked neuronal loss and gliosis, mild perivascular chronic inflammation, acute hypoxic encephalopathy, and generalized cerebral edema with a final diagnosis of probable autoimmune limbic encephalitis. An antibody was never identified.

The continuous cEEG findings are shown in Figs. 1, 2, 3, 4, 5, and 6. Examples of the patient's cEEG on Hospital Day 1 upon transfer to our institution are shown in Fig. 1. The EEG showed multifocal lateralized periodic

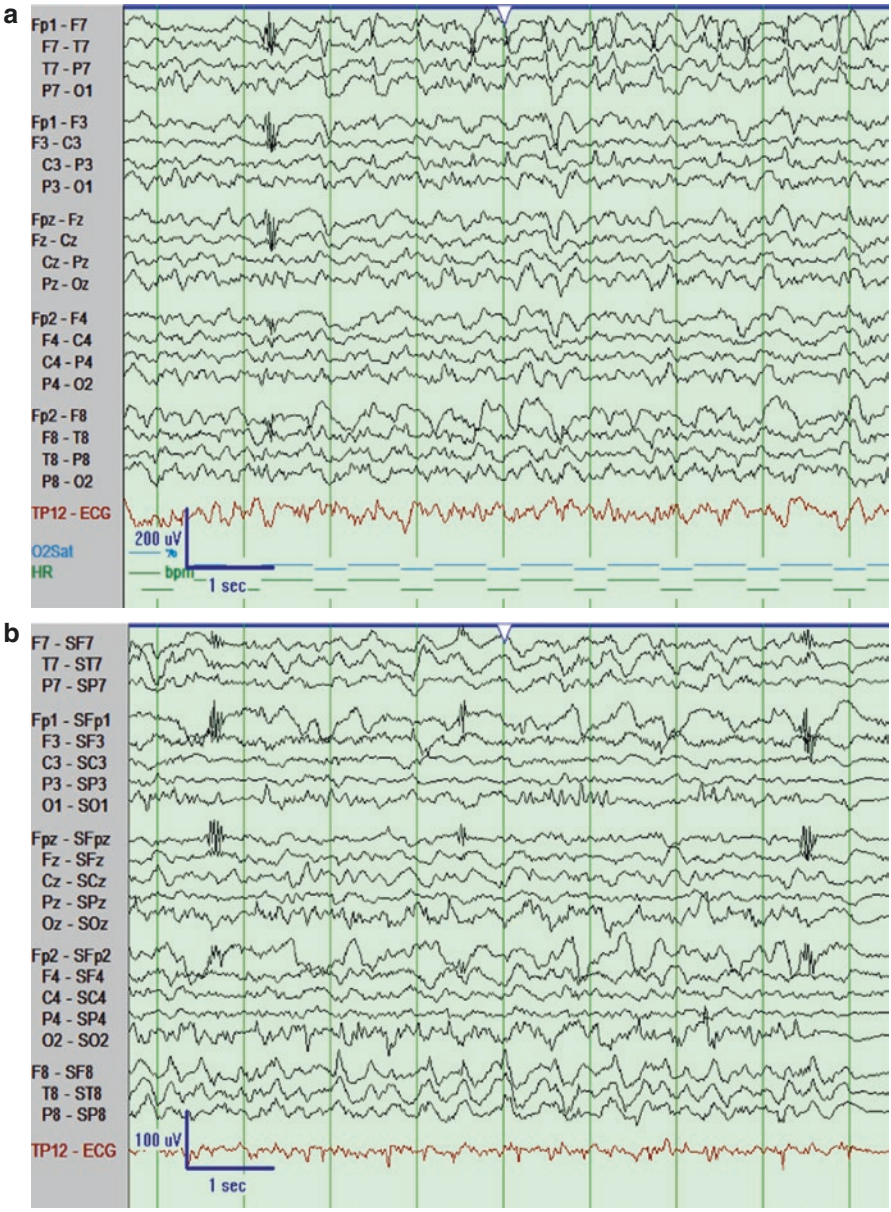


Fig. 1 EEG on Hospital Day 1 showing multifocal epileptiform abnormalities and electrographic seizures. (**a**) Lateralized periodic discharges noted left frontal (F3). (**b**) Seizure discharge noted consisting of rhythmic sharp activity at F8 (longitudinal Laplacian montage). (**c**) Bursts of rhythmic high-frequency activity left occipital region (O1). (**d**) Electrographic seizure activity consisting of rhythmic spikes left frontotemporal region (F7)

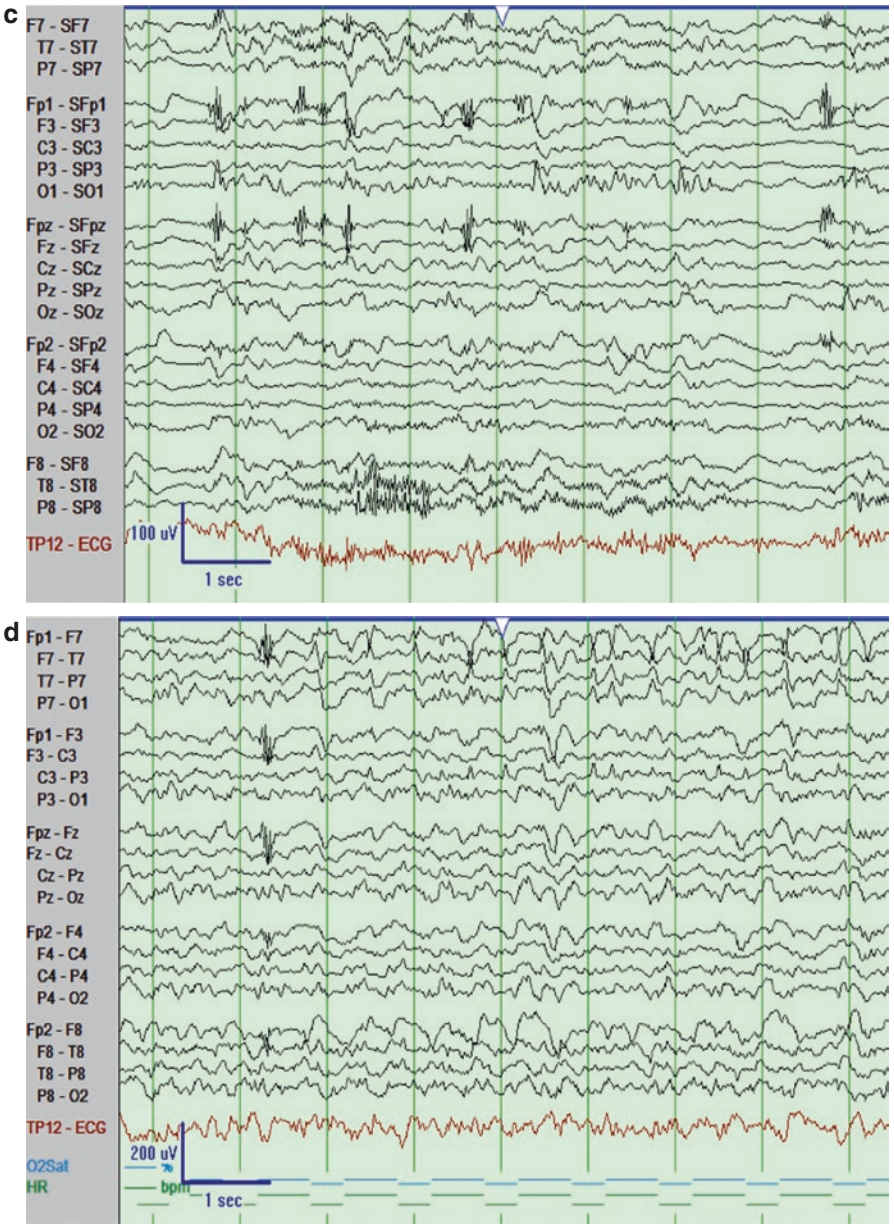


Fig. 1 (continued)

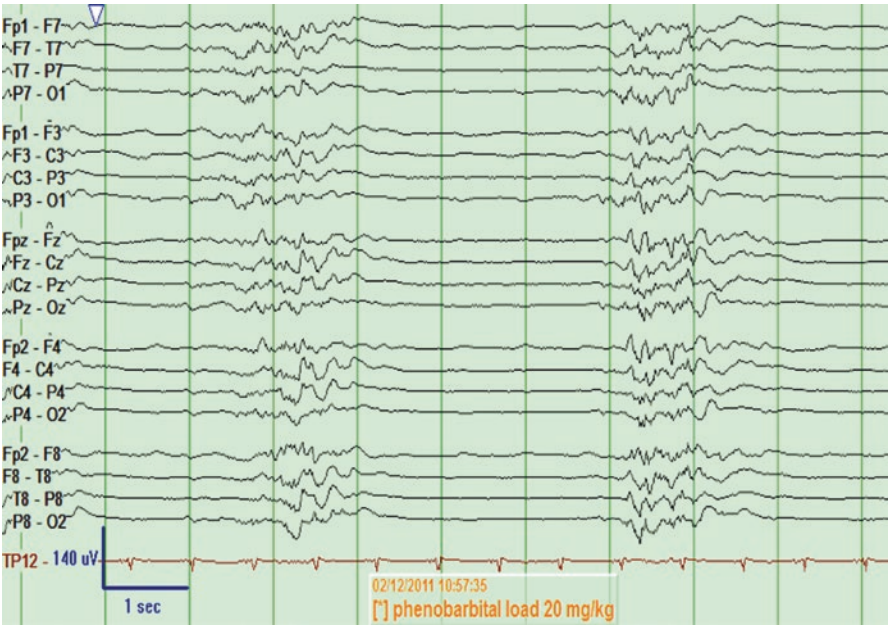


Fig. 2 Burst–suppression pattern following administration of 20 mg/kg phenobarbital on Hospital Day 2

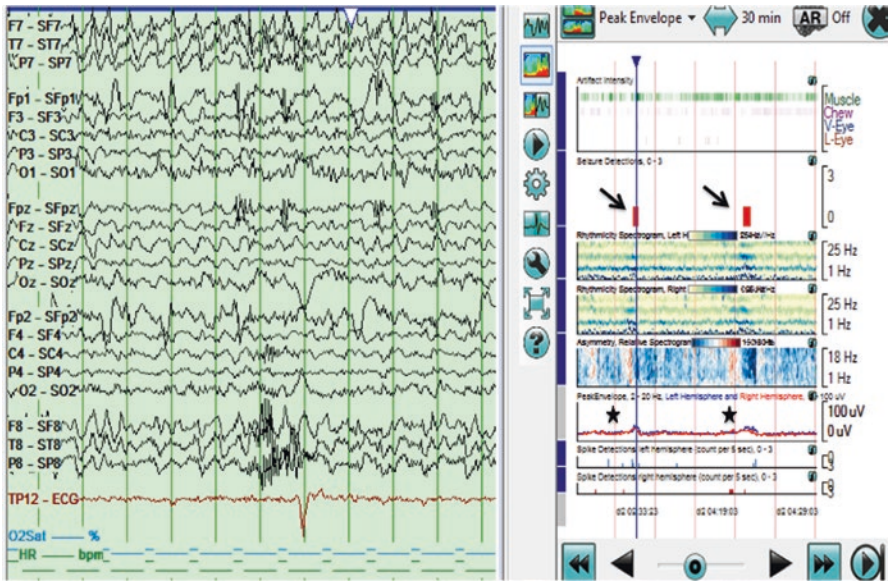


Fig. 3 Routine EEG with compressed sweep of 15 mm/s showing electrographic seizures predominantly involving left temporal derivations. Quantitative EEG trending software display shows seizure detection marked by red bar in seizure detection tool (*arrows*) and by transient rises on the peak envelope tool, which reflects detection of increases in amplitude during seizures (indicated by *stars*)

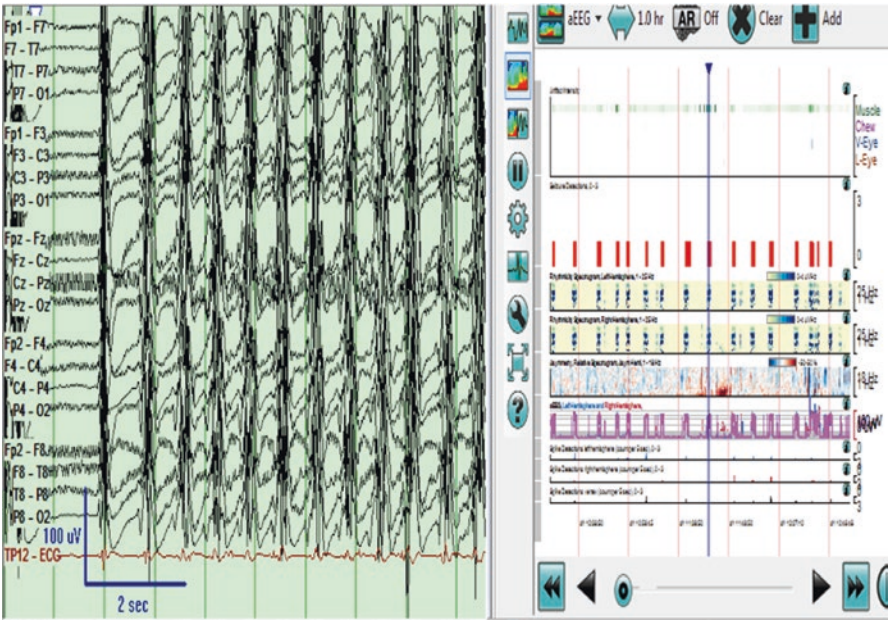


Fig. 4 EEG from Hospital Day 10 during attempt to reduce sedation showing onset of generalized electrographic seizure discharge on raw EEG. Quantitative EEG trending software shows 16 seizure detections in a 1-h period

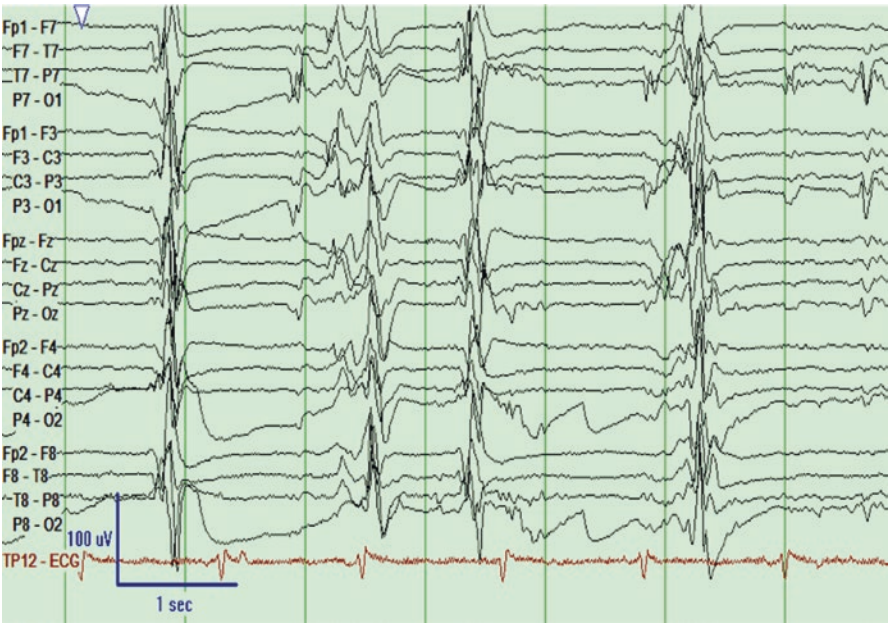


Fig. 5 EEG Hospital Day 35 showing intermittent generalized and left posterior temporal sharp complexes. Electrographic seizures suppressed

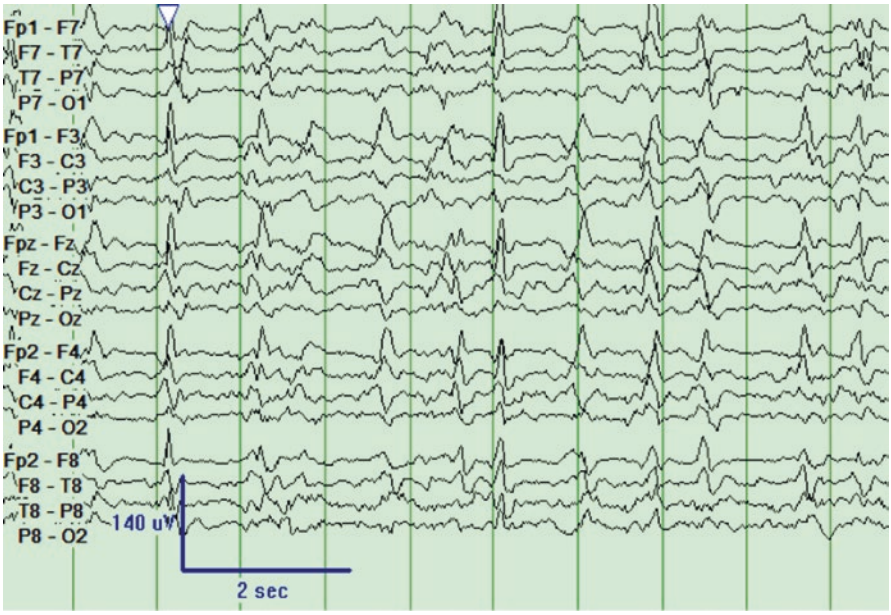


Fig. 6 EEG on Hospital Day 58 shows generalized periodic discharges (GPDs)

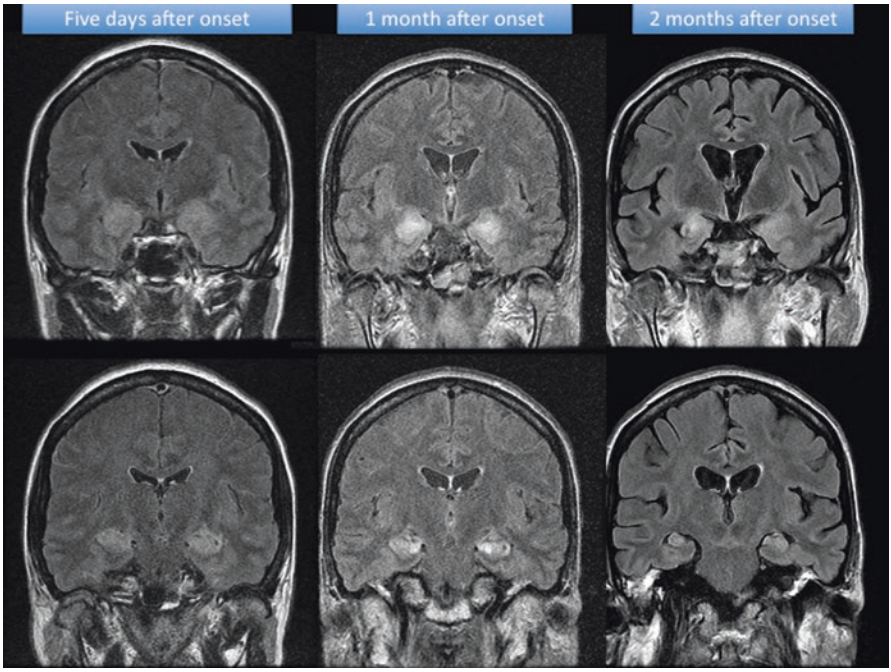


Fig. 7 Serial FLAIR-weighted coronal MRI images of the brain showing high signal involving the medial temporal structures initially. Progressive atrophy is apparent at 1 month and 2 months after onset of status epilepticus

discharges localized independently in the left frontal, right and left frontotemporal, and occipital head regions. These findings were consistent with a widespread encephalopathic etiology. The patient exhibited a number of clinical features such as pelvic thrusting that were not directly correlated in time with the discharges. This electromechanical dissociation suggested a subcortical as opposed to cerebral origin for these clinical features. Given the continued electrographic seizures and clinical events, phenobarbital was administered, leading to a discontinuous, and in her case, burst–suppression pattern (Fig. 2). Despite treatment with several anticonvulsants and phenobarbital administration, seizures continued to occur. A left temporal seizure discharge is noted in Fig. 3. Quantitative EEG trending software facilitates following efficacy of therapy. The quantitative EEG in this patient (Fig. 3) indicated that seizures were continuing to occur at a rate of 4 per hour. During the patient's treatment, sedation was decreased periodically in order to determine if seizure potential had ceased. An example of the patient's cEEG from Hospital Day 10 shows continued seizures (Fig. 4). The seizures at this point were more widespread when compared to the distribution of the discharges at admission, suggesting the development of synchrony between the multifocal regions previously generating the seizures at admission. Quantitative EEG showed seizures occurring at a rate of 16 per hour at that point in the patient's care. The cEEG on Hospital Days 35 (Fig. 5) and 58 (Fig. 6) showed continued generalized and lateralized periodic discharges. Anesthetic therapies were required to prevent seizure recurrence.

Case 2

A 22-year-old woman with a history of right-sided focal seizures presented with worsening seizures. Her seizures began at age 15 with right-sided focal seizures with an EEG demonstrating interictal epileptiform discharges arising from the left occipital region. MRI at the time was unremarkable. These seizures were originally controlled on phenobarbital and valproic acid with occasional breakthrough seizures a few times per year characterized by flashing lights.

She developed gradually progressive gait ataxia, tremor, dysarthria, and diplopia. MRI showed significant cerebral and cerebellar atrophy. She also developed persistent twitching of the left head, shoulder, arm, and leg which started to become painful. Lacosamide was added to her regimen of phenobarbital and valproic acid without benefit. As the focal motor seizures became more prominent and painful and EEG monitoring showed persistent right posterior lateralized periodic discharges, she was intubated and started on a midazolam infusion. As her movements were controlled, phenobarbital was increased and midazolam slowly weaned. Her jerking movements resurfaced, and the midazolam infusion resumed in addition to phenobarbital and lacosamide.

Valproic acid was discontinued because of a recently discovered family history of mitochondrial disease and was replaced with levetiracetam. EEG continued to demonstrate right-sided PLEDs, and clonazepam was started with the goal of liberating her from the midazolam infusion. Continuous EEG started to show

stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) in addition to PLEDs, while her clonic activity became progressively multifocal. This prompted initiation of ketamine. Her EEG then returned to baseline PLEDs and her ketamine was discontinued. A ketogenic diet was initiated although she never achieved ketosis due to the many medications and their carbohydrate contents. Intravenous methylprednisolone was attempted but did not impact favorably on her EEG. A repeat MRI of the brain performed after 3 weeks of SRSE revealed diffuse cortical atrophy, bilateral mesial temporal sclerosis, and FLAIR signal hyperintensities in bithalamic nuclei. Muscle biopsy showed cytochrome C-negative muscle cells, suggesting mitochondrial cytopathy. A chromosomal array showed 530 kilobase duplication at 10q26.3. Further DNA testing was sent and pending when she underwent single-photon emission computed tomography (SPECT) imaging to evaluate for a possible resectable seizure focus, but the results were inconclusive, and she was not deemed a candidate for surgical or DBS intervention.

Her hospital course was complicated by a urinary tract infection, ventilator-acquired pneumonia, acute respiratory distress syndrome (ARDS), anemia requiring transfusion, thrombocytopenia, pressure ulcers, *C. difficile* colitis, and adynamic ileus. Despite aggressive therapy, she had persistent myoclonic activity and dyscognitive features with abnormal mental status despite complete liberation from anesthetic agents for 10 days. After extensive discussions, her family decided to pursue comfort measures upon which she passed away with hospice care.

The cEEG findings in this patient are shown in Figs. 8, 9, 10, 11, 12, and 13. The cEEG at admission showed polyphasic lateralized periodic discharges over the right posterior head region (Fig. 8). The patient showed intermittent left upper extremity jerks, which were not in synchrony with the discharges. Rhythmic right upper extremity jerks were also noted. The lateralized periodic discharges were polyphasic in morphology, suggesting some degree of asynchrony of the underlying epilepsy network generator. The cEEG also showed rhythmic activity during stimulation and cares (Fig. 9). These discharges had the characteristics of SIRPIDs (stimulus-induced rhythmic, periodic, or ictal discharges) and had no clear clinical correlate. Further maturation of the lateralized periodic discharges occurred by Hospital Day 3. This was suggested by the conversion of polyphasic to bi- and triphasic morphology (Fig. 10). These periodic discharges would emerge and resolve in a periodic manner as shown on the quantitative EEG trend display (Fig. 11). These continued as did the patient's multifocal clonic activity, prompting sedation with several agents including ketamine. The periodic discharges would resolve following administration of sedative agents (Fig. 12a) and convert to a discontinuous (Fig. 12b) and sometimes a burst–suppression pattern. The patient's status epilepticus did not resolve despite several interventions. Lightening of anesthetic treatment would result in reemergence of the periodic discharges. Over time, the individual complexes became longer in duration compared to baseline as shown in Fig. 13.

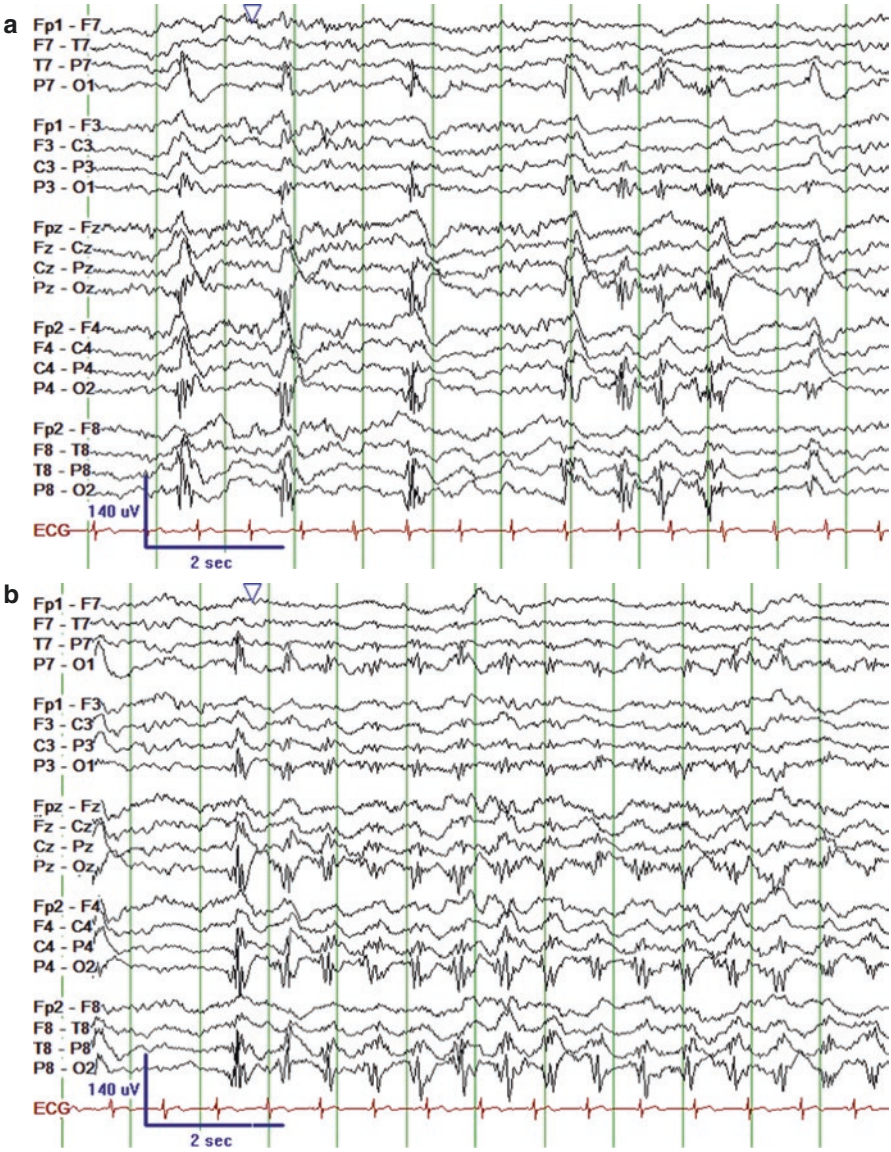


Fig. 8 EEG on admission in Case 2 with focal status epilepticus. (**a**) EEG shows quasiperiodic polyphasic right posterior lateralized discharges. (**b**) EEG shown with compressed sweep of 15 mm/s showing train of polyphasic lateralized discharges which were maximal over the posterior head region

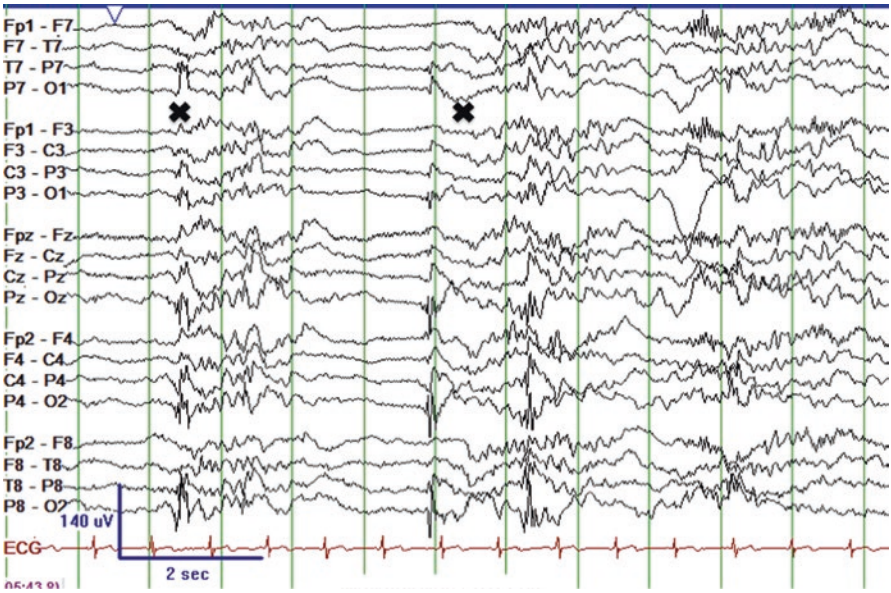


Fig. 9 During cares, the lateralized periodic discharges become associated with bursts of rhythmic theta (marked by Xs)

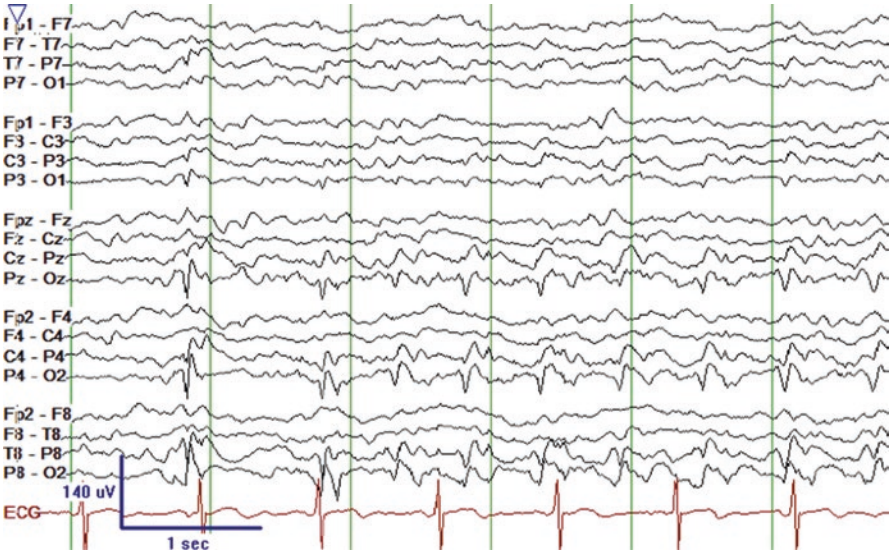


Fig. 10 EEG on Hospital Day 3. Right occipital lateralized periodic discharges have become bi- and triphasic, as opposed to polyphasic, suggesting greater synchrony within the neural network underlying it

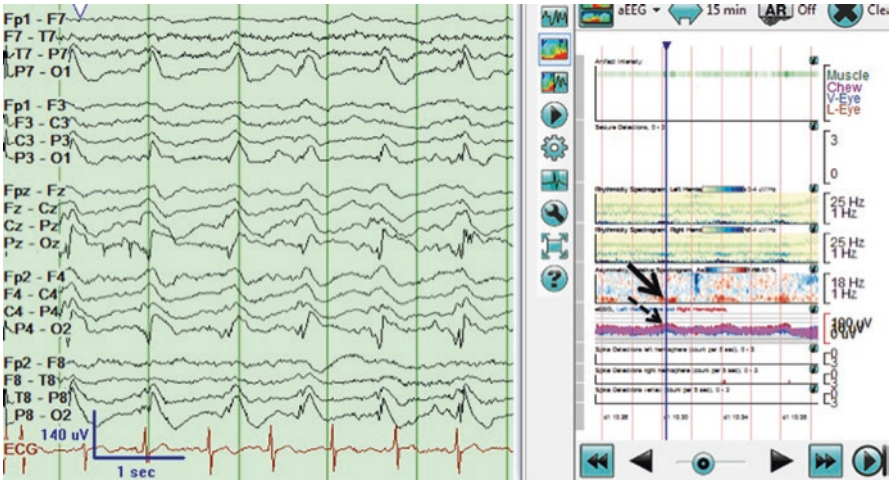


Fig. 11 Lateralized periodic discharges primarily involving the right occipital regions. Quantitative EEG trends show transient deflections in the rhythmicity spectrogram (*solid arrow*) and amplitude-integrated EEG tool (*dashed arrow*)

Case 3

A 53-year-old man who fell down the stairs secondary to alcohol intoxication was found by his wife the next morning and noted to be confused and poorly responsive. A CT head showed a large subdural hematoma with the right frontal and temporoparietal intraparenchymal hemorrhages. Following successful drainage of the subdural hematoma, the patient was noted to be intermittently mute. In addition, nursing staff noted the patient to exhibit intermittent jerking of the left face, thumb, and fingers. An emergency EEG showed polyphasic periodic lateralized epileptiform discharges ("poly-PLEDs") over the right posterior temporal–occipital region. Poly-PLEDs are typically present in acute or subacute conditions as opposed to chronic focal cerebral lesions. Over time, the area of cerebral damage gives rise to more synchronous discharges, and poly-PLEDs may evolve to less complex biphasic or triphasic PLEDs. This EEG was also notable for the presence of iterative discharges seen in the same derivations as the poly-PLEDs. PLEDs occurring in association with iterative discharges are referred to as "PLEDs plus." Clinical seizures occur at a higher prevalence in patients with PLED plus compared to those with PLEDs alone. Prolonged EEG monitoring should be considered in patients with PLEDs plus, given the risk of subclinical electrographic seizures in these cases. In addition to poly-PLEDs and PLEDs plus, frequent electrographic and clinical seizures were present in this patient, justifying a diagnosis of focal NCSE. He was conscious in between seizures and had not required ventilator support. Non-sedating therapies for status epilepticus were utilized initially including levetiracetam, phenytoin, lacosamide, and low-dose lorazepam, which were unsuccessful. An IV

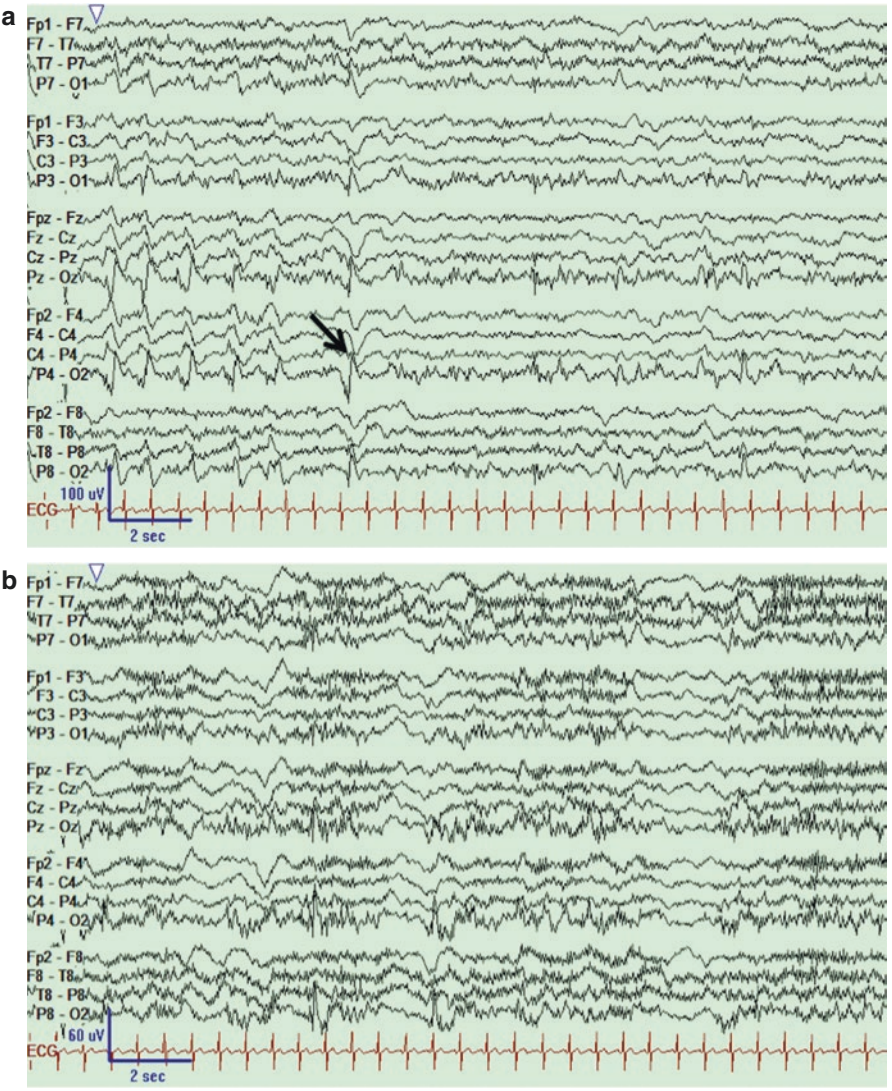


Fig. 12 cEEG during induction of sedation with ketamine. (**a**) The EEG initially shows attenuation of right occipital lateralized periodic discharges (*arrow*). (**b**) The EEG progresses to a discontinuous pattern following ketamine infusion

infusion of phenobarbital at a subanesthetic dosage of 5 mg/kg resulted in definitive suppression of seizures in this case.

The cEEG findings in this patient are shown in Figs. 14, 15, 16, and 17. The CT head in this patient showed a moderate-sized right subdural hematoma and bleeding in the right cerebral parenchyma (Fig. 14). An emergency EEG showed intermittent lateralized periodic discharges localized to the right

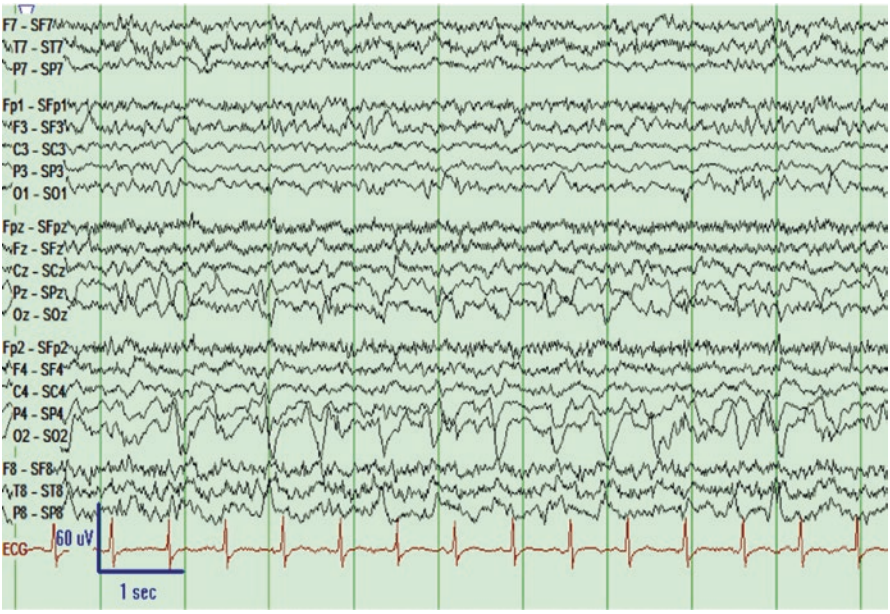


Fig. 13 EEG with reduction of sedation shows resumption of right occipital lateralized periodic discharges

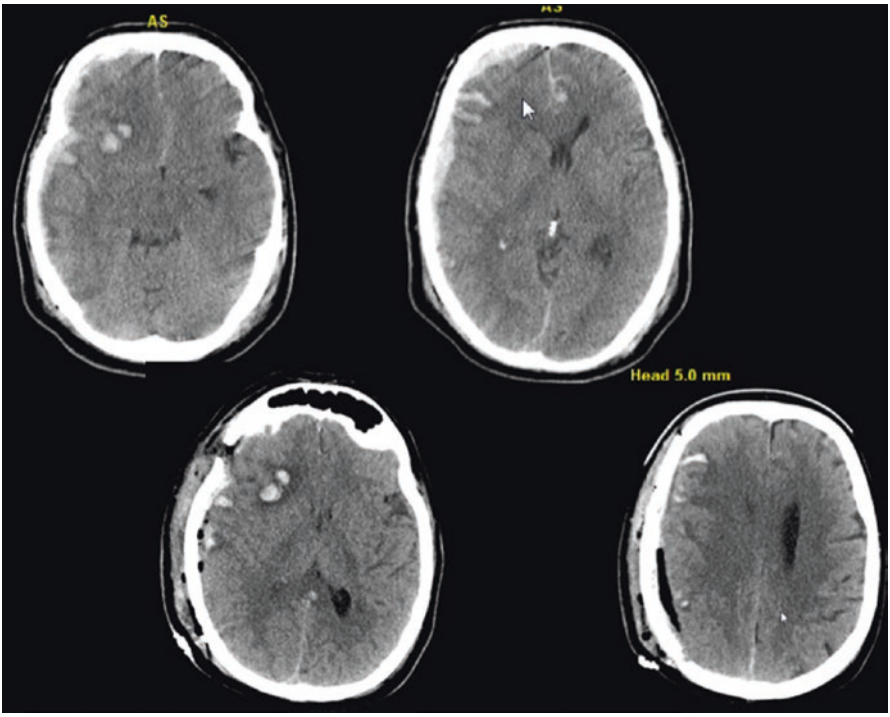


Fig. 14 CT head imaging showing a right hemispheric subdural hematoma and right frontotemporal parenchymal contusion

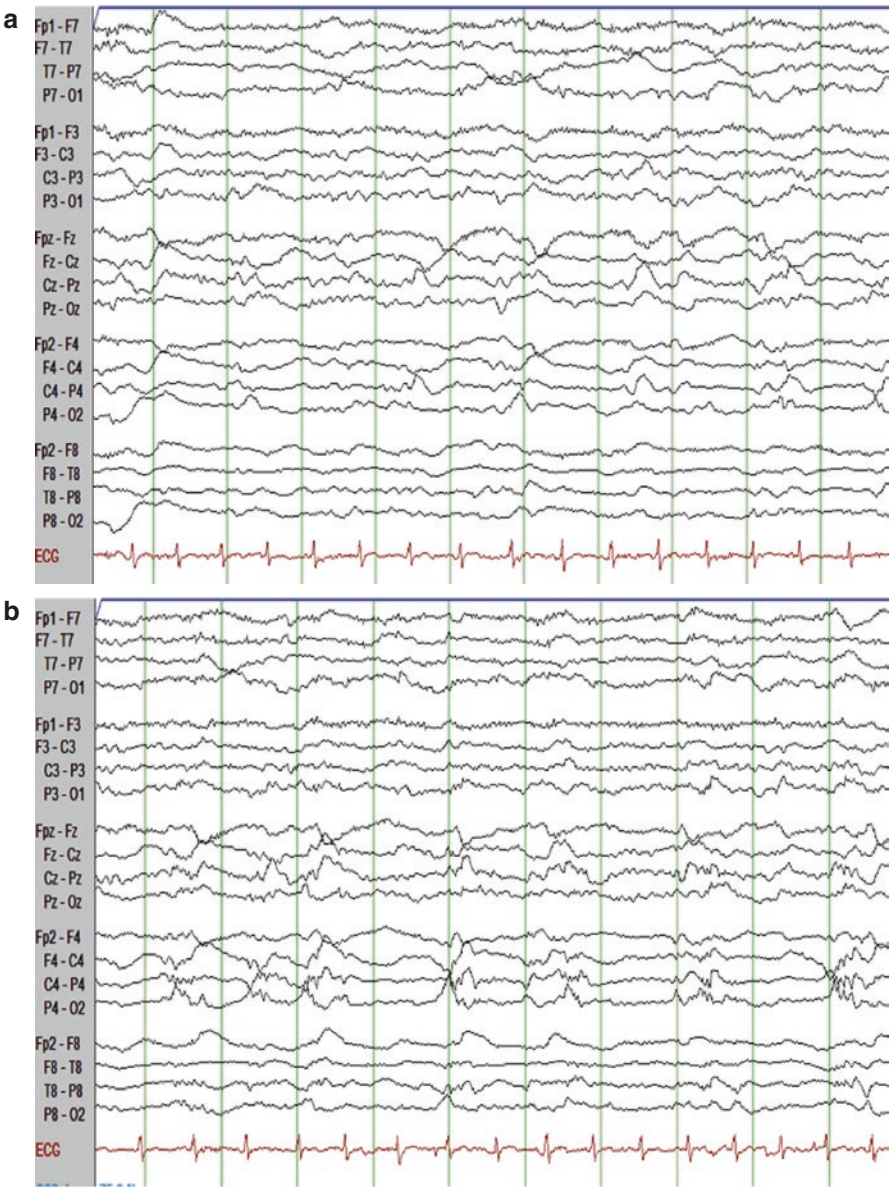


Fig. 15 Emergency EEG in Case 3. (**a**) Subtle onset of intermittent lateralized periodic discharges in the Cz-Pz and C4–P4 derivations. (**b**) Further evolution of periodic discharge in right centroparietal region. The morphology of the periodic discharges has evolved from subtle rounded complexes to polyphasic potential which show phase reversal at C4–P4

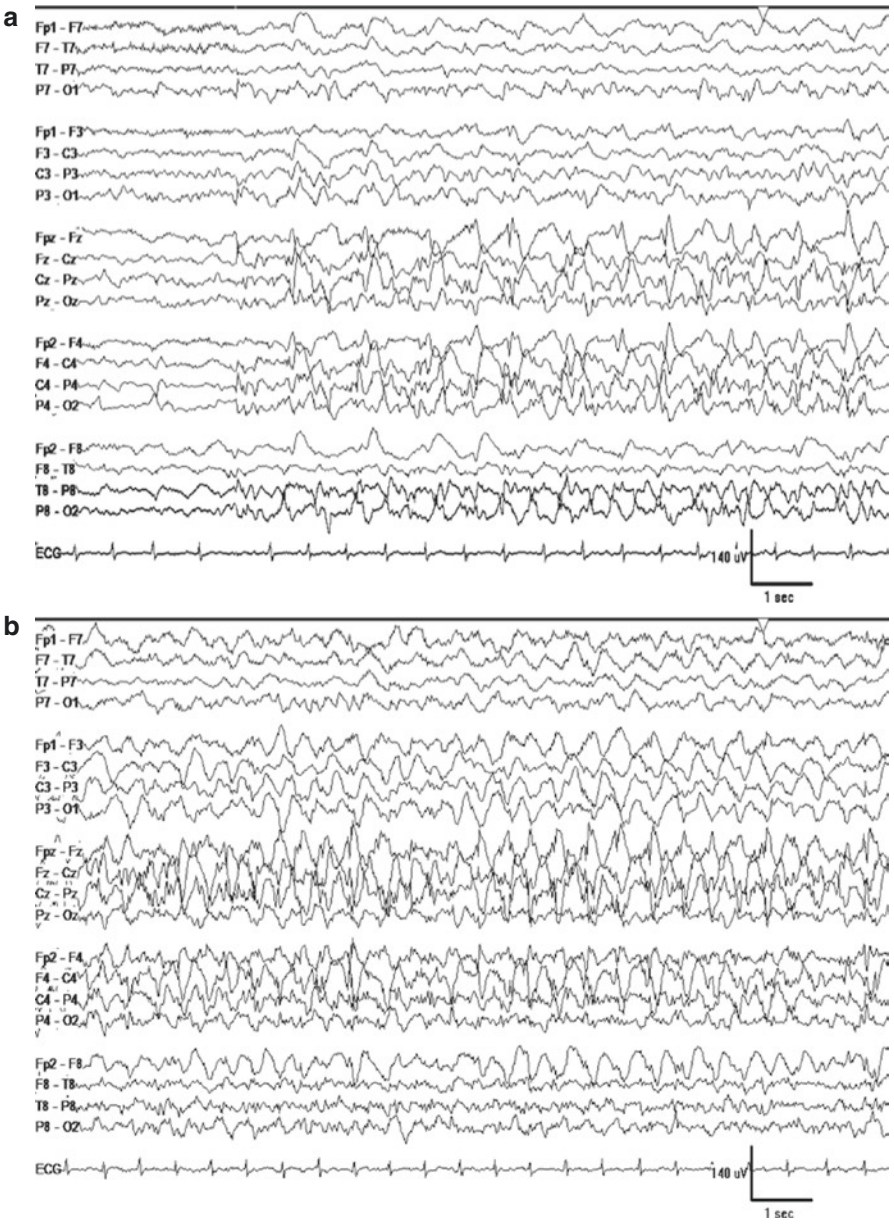


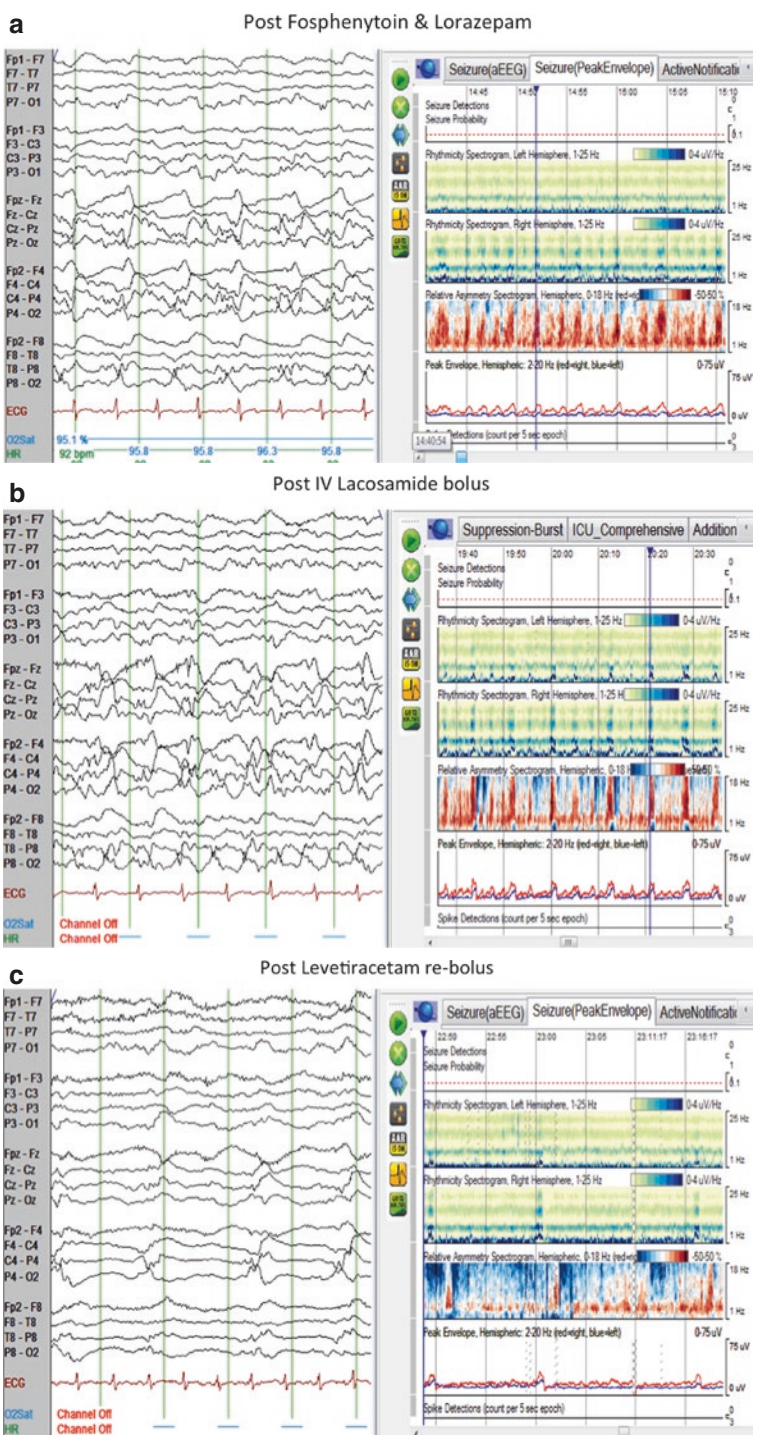
Fig. 16 Recorded seizures on cEEG in Case 3. (**a**) Onset of seizure discharge that consists of onset of rhythmic activity showing phase reversal at P8 with a field also involving the right and midline frontoparietal regions. (**b**) Continued seizure discharges manifested by rhythmic activity involving right and midline centroparietal derivations with spread to the left parasagittal regions

centroparietal region (Fig. 15), which was anatomically concordant with the imaging findings. The features of the EEG were concerning for the potential for seizures, and cEEG was recommended. cEEG showed frequent seizure discharges (Fig. 16), some of which were subclinical and some of which were associated with focal motor seizures involving the left face and upper extremity. Several seizures were noted per hour. Trials of several non-anesthetic medications were administered in order to try to avoid the need to intubate the patient who was relatively easy to arouse, somewhat conversant between seizures, and breathing spontaneously. cEEG and quantitative EEG trend software were utilized to monitor seizure frequency following each intervention (Fig. 17). The seizures were eventually controlled following phenobarbital administration at a dose of 5 mg/kg.

Areas of Need/Future Directions

Progress in SRSE research is slow because of the rarity of the disease. A multinational database of RSE and SRSE patients is currently being compiled at https://www.status-epilepticus.net/. There are a few ongoing studies of hypothermia and ketogenic diet in SE and RSE, respectively (ClinicalTrials.gov, study NCT01359332 and NCT01796574). An American multicenter pilot study of compound SAGE-547, an allosteric modulator of $GABA_A$ receptors, is ongoing and scheduled to complete in June 2015 (ClinicalTrials.gov, study NCT02052739). Work is needed in many areas including (1) identification of the causes of cryptogenic status epilepticus, (2) use of rational polypharmacy, (3) optimal patient and drug selection for the use of anesthetic agents, (4) elucidation of the prognostic implications of brain atrophy development, and (5)

Fig. 17 Utilization of cEEG and quantitative EEG in monitoring the effects of therapeutic intervention. (**a**) Lorazepam and fosphenytoin previously led to a temporary suppression of seizure activity; however, seizures returned as shown in this figure. Quantitative EEG trend shows a seizure rate of 21 seizures per 30 min epoch. (**b**) Quantitative EEG shows modest reduction of seizure rate from 21 to approximately 13 seizures per 30 min epoch following the administration of IV lacosamide. (**c**) cEEG and quantitative EEG show further reduction in seizure rate to three seizures per 30 min epoch following administration of levetiracetam. The seizure rate ultimately returned to near baseline within a few hours. Phenobarbital subsequently led to termination of the patient's seizures


a
Post Fosphenytoin & Lorazepam
b
Post IV Lacosamide bolus
c
Post Levetiracetam re-bolus
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fpz - Fz
Fz - Cz
Cz - Pz
Pz - Oz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECG
O2Sat
HR
Channel Off
Seizure(aEEG)
Seizure(PeakEnvelope)
Suppression-Burst
ICU_Comprehensive
Addition
Seizure Detections
Seizure Probability
Rhythmicity Spectrogram, Left Hemisphere, 1-25 Hz
Rhythmicity Spectrogram, Right Hemisphere, 1-25 Hz
Peak Envelope, Hemispheric: 2-20 Hz (red-right, blue-left)
Spike Detections (count per 5 sec epoch)

understanding of the role of inflammation in the development of seizure refractoriness.

Conclusion

SRSE is defined as the persistence or recurrence of seizures despite 24 h of general anesthesia. Risk factors for refractoriness include traumatic brain injury, stroke, encephalitis, brain tumors, AED noncompliance in patients with epilepsy, and drug intoxication or withdrawal. Apart from etiology, there are no reliable predictors of outcome. In addition to the established treatment, there are several alternative or adjunctive treatment options that have anecdotal success but remain poorly studied. Mortality is generally due to transition to palliative care or complications related to treatment. Prognosis can be favorable in up to 20 % of patients despite weeks or months of seizures.

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