Seizures and Encephalopathy

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ABSTRACT

There is a complex relationship between seizures and encephalopathy. Seizures alone without any underlying neurologic or medical illness can be the sole cause of encephalopathy. Often these patients have a history of epilepsy, in which case accurate diagnosis is straightforward. Acute neurologic conditions often contribute to encephalopathy, but also increase the risk of seizures—many of which are subclinical. In these scenarios, it can be difficult to determine whether the encephalopathy is caused by seizures, the underlying neurologic disorder, or both. In addition, systemic diseases are commonly associated with encephalopathy; they may also increase the risk of seizures, although less commonly than acute neurologic conditions, and therefore may go unrecognized. This review will examine common and uncommon causes of seizures in encephalopathic patients, typical clinical presentations as well as diagnosis and treatment.

KEYWORDS: Seizure, encephalopathy, nonconvulsive status epilepticus, electroencephalogram, EEG monitoring

There are various ways that seizures contribute to encephalopathy. Altered mentation is typical during the ictal or postictal phase and can occur in the setting of either isolated seizures or status epilepticus (SE). Convulsive seizures rarely go undetected, particularly in hospitalized patients already undergoing evaluation for encephalopathy or other medical conditions. However, nonconvulsive seizures (NCS) have an extremely broad range of clinical presentation and require a high index of suspicion for timely detection and treatment. Nonconvulsive seizures occur most commonly following an episode of generalized convulsive status epilepticus and have been documented to occur in up to 48% of these patients.¹ However, increased use of continuous electroencephalogram monitoring (cEEG) has revealed that nonconvulsive seizures occur in a wide variety of patient populations with no known history of clinical seizures.

In the spectrum of how seizures contribute to encephalopathy, nonconvulsive status epilepticus (NCSE) is the most dangerous with significant contribution to morbidity and mortality, particularly if undetected and treatment is delayed. There is no universally accepted definition of NCSE. Synonyms include the terms non- tonic-clonic SE, spike-wave stupor, dialeptic SE, and subtle SE. In addition, clinical classification is quite complex and includes a heterogeneous group of disorders that each have different outcomes and management strategies. EEG findings can be just as varied, ranging from continuous ictal discharges, either focal or generalized, to periodic patterns of undetermined significance. In addition, there is no consensus on minimum duration of seizure activity to qualify for an episode of nonconvulsive status, with proposed times ranging from 5 to 30 minutes. Response to treatment with antiepileptic medications has been proposed as a means of defining which clinical and EEG patterns represent ictal phenomenon, but treatment response can be variable and does not always occur immediately following infusion of medication.

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Acute and Subacute Encephalopathies; Guest Editor, Martin A. Samuels, M.D.

Semin Neurol 2011;31:194–201. Copyright © 2011 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.


ISSN 0271-8235.
Studies evaluating the incidence of NCS and NCSE are largely based on inpatient series of patients with severe encephalopathy or coma. Privitera et al prospectively evaluated 198 patients with encephalopathy of unknown cause and found either NCS or NCSE in 74 (37%). Furthermore, clinical signs and history were not predictive of which patients experienced seizures. A more recent study by Towne and colleagues evaluated 236 critically ill patients in coma with no clinical signs of seizure activity. Routine EEG identified 19 (8%) in NCSE.3 The most common etiology was hypoxia, but over one third did not have any obvious underlying neurologic disorder. Studies utilizing cEEG in patients at high risk for seizures admitted to neurocritical care units identified NCS or NCSE in 19–34% (Table 1).4–6 Subclinical seizures are most common after resolution of generalized convulsive status epilepticus (GCSE). In the study by Delorenzo et al following resolution of GCSE, 48% of patients were found to have ongoing NCS.1 However, many patients with no prior history of clinical seizures are also found to have NCS when undergoing cEEG.2–7 In the series by Oddo et al, 201 patients admitted to the medical intensive care unit (ICU) without any known neurologic injury underwent EEG monitoring for changes in mental status.10 Electrographic seizures were detected in 21 (10%), and two thirds of these seizures were not associated with any clinical correlate.

**CAUSES OF SEIZURES AND ENCEPHALOPATHY**

Common Causes

Acute cerebrovascular disease is a common precipitant of seizures. Seizures are a well-recognized complication of subarachnoid hemorrhage (SAH) with prior studies demonstrating clinical seizures in 4–9% of patients during hospitalization.11 However, more recent studies of patients undergoing cEEG have shown that electrographic seizures are even more common in this patient population, especially in patients who are comatose. In a series of 108 patients with SAH, 19% were found to have electrographic seizures, most of which were purely subclinical.4 In addition, 70% of the patients with seizures were in NCSE. Nonconvulsive status epilepticus has also been shown to be an independent predictor of poor outcome in patients with SAH.9

Intracerebral hemorrhage (ICH) has also been associated with a high rate of acute clinical seizures ranging from 3–19% of patients.11 Two studies have evaluated the incidence of seizures in patients with ICH undergoing cEEG.8,12 Vespa et al found that 28% (18/63) of patients with ICH experienced nonconvulsive seizures, which were associated with an increase in midline shift, higher NIH stroke scale scores, and worse outcome compared with ICH patients without seizures.12 In a series of 102 patients with ICH, seizures were detected in 31% and over half were purely electrographic.8 Perhaps more importantly, seizures were associated with an increase in the volume of hemorrhage and a trend toward worse outcomes.

Ischemic stroke is a common cause of both acute and chronic seizures, and the leading cause of epilepsy in the elderly population. Seizure rates in hospitalized patients average from 5–17%.7 Although clinical seizures have been associated with increased morbidity and mortality in the acute setting, studies of the effect of nonconvulsive seizures in patients with ischemic stroke are lacking. However, as with SAH and ICH, cEEG monitoring has shown that the incidence of seizures in this patient population is underestimated when relying on reports of clinical seizures alone.7

Seizures are a common complication following cardiac arrest and can have a variety of clinical presentations from myoclonus to generalized convulsions. Clinical seizures in these patients are generally regarded as an effect of the anoxic encephalopathy rather than a contributing cause, and their presence can be a useful marker for prognosis. American Academy of Neurology (AAN) practice guidelines support a poor prognosis for patients with myoclonic status epilepticus within the first day of
cardiac arrest (level B). Less is known about the implications of nonconvulsive seizures following anoxic brain injury, although cEEG studies have shown that they are quite common, seen in up to 20% of patients in one series. With increasing utilization of therapeutic hypothermia following cardiac arrest, even more questions have arisen regarding the incidence and implications of seizures in association with anoxic brain injury, which merit much further investigation.

Many studies have evaluated the incidence of clinical seizures (both acute and chronic) following traumatic brain injury (TBI), where the focus has largely been on strategies for prevention. However, only recently has the incidence and acute effects of subclinical seizures been recognized. In a series of 96 patients, Vespa found electrographic seizures in 22% of patients with moderate or severe TBI, half of which were exclusively nonconvulsive seizures. Seizures following TBI have also been associated with increased intracranial pressure, abnormal neuronal metabolism (transient elevation in lactate/pyruvate ratio on cerebral microdialysis), and hippocampal atrophy.

Clinical seizures are commonly associated with acute central nervous system (CNS) infections, particularly viral infections. In fact, prior studies have shown that approximately half of all patients with confirmed herpes encephalitis experience seizures. Although the incidence of nonconvulsive seizures in patients with CNS infection is less well studied, guidelines have recommended EEG monitoring for patients with meningitis and clinical seizures or fluctuating level of consciousness. Recently, Carrera et al identified 42 patients with CNS infection that underwent EEG monitoring. The majority had viral infections (64%). Electrographic seizures were seen in 14 (33%) with only 5 (36%) associated with a clinical correlate. Electrographic seizures were also independently associated with poor outcome, such as severe disability, vegetative state, or death.

Brain tumors are also a common cause of seizures, and patients often undergo neurosurgical procedures that leave them at even higher risk for seizures. The postoperative period is a particularly vulnerable time when seizure risk is high. Electrographic seizures can go completely undetected during this period and contribute to prolonged encephalopathy and increased mortality. There have been few studies evaluating the incidence of subclinical seizures in patients with brain tumors with or without recent surgical resection. However, cEEG should be strongly considered for brain tumor patients with unexplained or prolonged encephalopathy, especially following any neurosurgical procedure.

Sepsis is associated with several serious systemic complications, which include effects on the nervous system. Although the presence of encephalopathy as well as polyneuropathy is quite prevalent in this patient population, seizures have not traditionally been considered to be a significant issue until recently. A retrospective study of septic patients undergoing EEG monitoring in a medical intensive care unit found electrographic seizures in 16% (most of which were subclinical) and noted periodic epileptiform discharges in another 16% of patients. Risk factors for seizures included older age, renal failure, and shock. Seizures, as well as periodic epileptiform discharges, were independently associated with poor outcome. Although sepsis-related seizures are still poorly understood, these findings underscore the importance of monitoring for seizures in septic patients.

**Uncommon Causes**

Limbic encephalitis is clinically defined by a combination of encephalopathy, seizures, and psychiatric disease, which may or may not be associated with an underlying malignancy. Diagnostic studies including magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and EEG are abnormal in over half of patients. Antineuronal antibodies are invaluable in directing the search for occult malignancy and guiding treatment, although up to 30% of patients with limbic encephalitis have negative antibody studies. Seizures often precede the onset of other symptoms, and therefore maintaining a high index of suspicion provides for the opportunity for early diagnosis and treatment.

Paraneoplastic limbic encephalitis is one of the most common paraneoplastic syndromes. Clinical seizures are seen in approximately two-thirds of patients, which are usually complex partial seizures of temporal lobe onset. However, patients may have very brief, subtle seizures that can be difficult to distinguish from concomitant encephalopathy and often go unrecognized. The most common cancers associated with paraneoplastic limbic encephalitis include small cell lung, testicular, and breast. Tumor detection often lags behind onset of seizures and other clinical symptoms for months to years.

Limbic encephalitis with antibodies against NMDA receptors is being increasingly recognized as a paraneoplastic syndrome seen most commonly in young women who present with prominent psychiatric symptoms, dyskinesias, and both clinical and subclinical seizures. In a series of 100 patients, 60% were found to have an underlying tumor, most commonly ovarian teratoma. Early recognition is important, as many patients respond to immunomodulation with corticosteroids or IVIg in addition to tumor resection.

Patients with antibodies against voltage-gated potassium channels (VGKC) present with clinical and radiographic findings that are indistinguishable from paraneoplastic limbic encephalitis. However, although limbic encephalitis with VGKC antibodies may be
associated with thymoma or lung cancer, most cases are not paraneoplastic. Patients may initially present with idiopathic intractable epilepsy without other features of limbic encephalitis. Early diagnosis is also important in this patient population because patients may be refractory to antiepileptic agents, but have a dramatic response to corticosteroid treatment.

There are several other causes of autoimmune encephalopathy in which seizures play a significant role that are not associated with underlying malignancy or limbic encephalitis. Steroid-responsive encephalopathy, previously known as Hashimoto’s thyroiditis, presents with a multitude of neuropsychiatric features, but without evidence of thyroid dysfunction despite the presence of antithyroid antibodies. Seizures and myoclonic jerks are a prominent feature of clinical presentation in addition to fluctuating mental status and tremor, which may be difficult to distinguish from seizures without the use of EEG monitoring. Other systemic autoimmune diseases associated with seizures that usually respond to steroid therapy include systemic lupus erythematosus, Sjögren’s syndrome, Wegener’s granulomatosis, and neurosarcoidosis.

Posterior reversible encephalopathy syndrome (PRES) is characterized by altered mental status, seizures, and visual changes accompanied by classic neuroimaging changes in the parietal and occipital lobes. It is associated with a variety of underlying clinical conditions that may cause seizures and encephalopathy in isolation as well. Seizures in the setting of PRES often present in clusters or as status epilepticus.

Treatment of the underlying cause is paramount and rapid initiation of antiepileptic medications to prevent further neuronal injury from seizures is vital.

Subacute encephalopathy with seizures in chronic alcoholism (SESA) is a clinical syndrome first described by Niedermeyer in 1981 who reported alcoholic patients presenting with confusion, seizures, and focal neurologic deficits. The occurrence of SESA is likely underestimated, as many patients may be misdiagnosed with alcohol withdrawal seizures. Nonconvulsive status epilepticus can account for the encephalopathy and focal neurologic deficits seen in patients presenting with the clinical syndrome of SESA. Therefore, a high degree of suspicion is warranted, and continuous EEG monitoring recommended for alcoholic patients with encephalopathy and focal neurologic deficits. An accurate diagnosis is critical because these patients require long-term treatment with antiepileptic medications to prevent recurrence.

There are a variety of other systemic diseases that can contribute to both encephalopathy and seizures, including hepatic failure, uremia, human immunodeficiency virus (HIV) infection, and drug intoxication (both prescription as well as recreational). Patients recently undergoing cardiothoracic surgery have also been identified as a population in whom encephalopathy and seizures often coexist.

Finally, the term epileptic encephalopathy refers to a group of epilepsy syndromes with onset in infancy or childhood in which refractory seizures contribute to progressive cognitive decline. These include more common epilepsies, such as West’s syndrome and Lennox-Gastaut’s syndrome as well as more rare diseases, such as Ohtahara’s syndrome, Dravet’s syndrome, myoclonic astatic epilepsy, and Landau-Kleffner’s syndrome. Each of these syndromes is distinguished by particular seizure types, EEG findings, and other clinical factors.

**CLINICAL PRESENTATION**

Patients with seizures as a cause or consequence of encephalopathy present with a wide variety of neurologic symptoms from mild reduction or alteration of consciousness to coma. Findings on neurologic exam are often nonfocal, nonspecific, and not predictive of the presence of seizures. Patients may or may not have subtle motor findings accompanying the presentation of encephalopathy. Signs range from very focal findings, such as nystagmus, eye flutter, blinking, and eye deviation to more widespread signs, such as myoclonus, tremulousness, and autonomic instability. Subtle SE is a term that has been used for encephalopathy accompanied by myoclonic jerks in association with electrographic discharges, and can be difficult to differentiate from nonepileptic myoclonus that often accompanies a toxic or metabolic encephalopathy without epileptiform abnormalities on EEG.

Negative phenomena, such as neglect syndrome, apraxia, aphasia, amnesia, homonymous hemianopia, and hemiparesis, are rarely associated with seizures, but often lead to misdiagnosis. Patients with ictal aphasia or ictal amnesia often undergo evaluation for toxic, metabolic, or infectious causes of encephalopathy and neuroimaging to evaluate for stroke without consideration of the possibility of seizures.

Seizures in the elderly population deserve special consideration. Not only does clinical presentation differ from younger adults but underlying etiologies as well as diagnosis and treatment vary. Distinguishing seizures from paroxysmal nonepileptic events can be a particular challenge as presentation is often atypical. Inattention, memory lapses, and confusion can be attributed to “senior moments” or early signs of dementia; as such, the clinician must maintain a high index of suspicion for seizures in older patients. Prolonged postictal state is also common and often regarded as a nonspecific delirium,
particularly if no one witnessed or recognized a seizure as the precipitating event. Not only are isolated seizures common in the elderly, but there is also an increased incidence of SE in the elderly population (both NCSE and GCSE), which is of longer duration and higher mortality.39 Finally, Litt et al found the elderly to have an increased risk of death when SE was treated aggressively with benzodiazepines.30 Therefore, careful consideration of risks versus benefits of treatment is necessary.

The presentation and prognosis of NCSE is primarily based on underlying seizure type, EEG findings, and comorbidities. Absence SE, often referred to as spike-wave stupor, presents with various degrees of altered consciousness, which can be associated with blinking or myoclonus, and often the diagnosis is not at all obvious. At times, these symptoms culminate in a convulsive seizure at which time diagnosis is certain. Absence SE may be precipitated by sleep deprivation, noncompliance with antiepileptic medications, or stress, but also occur de novo in the patient with no history of epilepsy or precipitating factors. The duration can last from hours to several days, and diagnosis is only confirmed by typical 3 Hz generalized spike wave discharges on EEG. Fortunately, absence SE usually responds very well to treatment with no associated long-term sequelae, morbidity, or cognitive decline.31–34

Complex partial SE consists of recurrent discrete seizures or continuous focal seizures, usually in patients with a prior history of epilepsy. Clinical manifestations include a decrease in responsiveness and fluctuating, often bizarre behaviors with repetitive motor or verbal actions. EEG shows seizures confined to one region or hemisphere. Response to treatment is variable and can be refractory to first- or second-line treatment choices. There have been very few studies evaluating morbidity in pure complex partial SE, but limited studies have shown that outcome is not as benign as absence status with many patients experiencing recurrent episodes and some suffering long-term cognitive sequelae, typically memory disturbances.35–37 Our knowledge of the frequency and degree of cognitive sequelae is also limited because many patients do not undergo complete neuro-psychologic testing following the episode of SE. Outcomes are also noted to be worse when associated with an underlying structural lesion.

Nonconvulsive seizures in patients with serious neurologic or medical disease have been more thoroughly studied. As with GCSE, prognosis is primarily determined by the underlying illness and time to resolution of seizures. In a series of 101 patients with NCSE, Shneker et al found that 27% with severe medical illness died compared with 3% with NCSE attributable to a history of epilepsy.38 Other studies have shown mortality from 27% to 100% in patients with NCSE and severe illness with the highest rates seen in anoxic brain injury and SAH.39 It can be difficult to separate mortality attributed to seizures from mortality associated with the underlying disease to determine whether the presence of NCS worsens prognosis. Young et al looked at outcome in patients with NCSE independent of etiology and found the most important predictors of outcome following NCS or NCSE to be time to diagnosis and total duration of SE. For patients not diagnosed until after 24 hours of symptom onset, mortality was 75%, twice that of patients diagnosed within 30 minutes of onset.40 Duration of seizure activity following initial diagnosis has an even larger impact on mortality, with 85% mortality for seizures continuing greater than 20 hours compared with 10% mortality when there is resolution of seizures within 10 hours of diagnosis.40 These findings emphasize the importance of rapid initiation of treatment with appropriate agents.

**DIAGNOSIS AND TREATMENT**

The key to accurate diagnosis of seizures in encephalopathic patients is to have a high index of suspicion for seizures as a potential cause of ongoing altered mental status. The next step in confirming the presence of seizures is diagnostic testing with EEG. Routine 30-minute EEG has been the gold standard for "ruling out" seizures as a cause of encephalopathy. However, given that seizures and interictal epileptiform activity is often intermittent, a brief EEG recording may lead to a missed diagnosis. Therefore, continuous EEG monitoring, for a minimum of 24 to 48 hours, should be considered for encephalopathic patients with no other reasonable etiology. Using continuous EEG monitoring, Claassen et al found that seizures were detected within the first 24 hours in 88% of patients who would eventually have seizures on EEG monitoring and in an additional 5% of patients within 48 hours.4

Although seizures can often be readily identified on EEG, there are many periodic and rhythmic patterns seen in encephalopathic patients where the diagnosis is not quite as clear. Periodic epileptiform discharges are common findings in confused or comatose patients, but their clinical significance has long been debated. Periodic lateralized epileptiform discharges (PLEDs) are commonly associated with acute structural lesions, as well as CNS infections (particularly herpes encephalitis), whether or not the patient has a history of seizures. Clinical seizures have been documented in 58 to 100% of patients with PLEDs,41 but there is much controversy over whether the presence of PLEDs represents ongoing ictal activity. Although there is evidence of functional imaging changes on PET and SPECT concurrent with PLEDs,42 most consider PLEDs to be an “interictal” finding, with the exception of patients who exhibit focal motor movements time locked with the discharges.
Therefore, the finding of PLEDs should always raise high suspicion for seizures and prophylactic treatment with an antiepileptic drug seriously considered.

Generalized periodic discharges (GPEDs) are seen in a broader range of neurologic and systemic diseases, including anoxic brain injury, toxic metabolic disturbances, CNS infection, and stroke. Although data are more limited, seizures have been associated with GPEDs in 32 to 90% of patients. One of the first patterns described in association with toxic-metabolic derangements was that of triphasic waves in hepatic encephalopathy. Triphasic waves consist of an initial negative phase followed by a larger positive phase and a final negative phase. Recently, the clinical significance of triphasic waves has become quite controversial. Triphasic waves can have a very similar appearance to GPEDs (many consider them a subtype of GPEDs) and at times can be indistinguishable from NCSE. In addition, triphasic waves have been associated with a variety of conditions outside of toxic or metabolic conditions, including anoxic encephalopathy and seizures. Finally, there are many EEG patterns that do not meet clear criteria for electrographic seizures, but have characteristics of rhythmicity or subtle evolvement that are worrisome for possible ictal activity (Fig. 1). These patterns create significant frustration for the electroencephalographer and have been termed the ictal-interictal continuum. These patterns must be interpreted with extreme caution and with careful attention to the clinical scenario and associated exam findings. As the field of ICU EEG monitoring grows and more multicenter data are collected, the clinical significance of all of these rhythmic and periodic patterns should become clearer.

The most important principle in treating seizures is to initiate treatment rapidly, especially in patients with recurrent seizures or SE. Faster treatment is not only associated with greater success in resolving seizures, but also reduces the risk of secondary neuronal injury and improves outcome. Treating the underlying cause of seizures is also paramount to reducing the risk of subsequent seizures. In patients with reversible systemic disease as the cause of seizures, long-term antiepileptic medications treatment may not be needed.

There are well-established protocols for the treatment of GCSE, although treatment guidelines for NCSE are lacking and there is much debate about how aggressively to treat NCS and NCSE. Given the morbidity and mortality associated with NCS and NCSE, especially in comatose patients, swift intervention is recommended, but with careful consideration of the side effects of treatment, especially aggressive treatment with anesthetic agents. Finally, for those patterns that fall along the ictal-interictal continuum, a trial of a

Figure 1  Electroencephalogram pattern of uncertain significance (the ictal-interictal continuum).
short-acting benzodiazepine or parenteral antiepileptic drug is recommended while closely monitoring both the patient and the EEG for improvement. Resolution of the EEG pattern and concurrent improvement in the clinical examination provides strong evidence that the pattern in question represents an ictal pattern. It is important to recognize that many periodic or rhythmic EEG patterns may resolve temporarily with administration of a benzodiazepine; therefore, concurrent clinical improvement of the patient is required for a definitive diagnosis of seizure.

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