

Acute Symptomatic Seizures and Provoked Seizures: to Treat or Not to Treat?

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Abstract

Purpose of review Acute symptomatic and provoked seizures by definition occur in close proximity to an event and are considered to be situational. The treatment implications and likelihood of recurrence of acute symptomatic and provoked seizures differ from unprovoked seizures. In this article, the authors review the literature on acute symptomatic and provoked seizures with regard to therapeutic approach and risk of recurrence.

Recent findings In the acute period, patients who suffer from acute symptomatic and provoked seizures have higher rates of morbidity and mortality. Patients with acute symptomatic seizures in the setting of certain conditions including subdural hemorrhage, traumatic penetrating injuries, cortical strokes, neurocysticercosis, venous sinus thrombosis, and viral encephalitis have a higher rate of seizure recurrence although the rate of recurrence of seizures is less than that of patients with unprovoked seizures.

Summary In patients with acute symptomatic and provoked seizures, short-term treatment with anti-seizure medications is appropriate given the higher morbidity and mortality in the acute phase of illness. In patients with acute symptomatic seizures with persistent epileptiform activity on EEG and structural changes on imaging, longer-term treatment (i.e., a few months as opposed to 1 week) with anti-seizure medications can be considered due to high risk of seizure recurrence. If a patient subsequently has an unprovoked seizure, there is yet a higher risk of recurrence of seizures and likelihood of the development of epilepsy. In these patients, long-term seizure treatment can be considered, keeping in mind that although anti-seizure treatment may reduce risk of seizure recurrence in the short-term, it does not appear to influence long-term seizure remission rates.

Introduction

Acute symptomatic and provoked seizures refer to seizures that occur within the first 7 days of an event. These terms are often used interchangeably. However, provoked seizures are classified as resulting from transient derangements that involve metabolic, toxic, or medication side-effects, whereas acute symptomatic seizures are caused by an acute event such as stroke, traumatic brain injury (TBI), or CNS infection (Table 1; Fig. 1) [3•, 44]. In either case, seizures are thought to be a manifestation of the insult. For the purposes of this review, provoked seizures and acute symptomatic seizures will be referred to as symptomatic seizures unless otherwise specified.

A single seizure is not that uncommon, occurring in 10% of people during their lifetime [3•]. Having a single seizure does not mean one will develop epilepsy; the risk of a second unprovoked seizure is approximately 33% [4]. Symptomatic seizures by nature have an identifiable

cause. A seizure that occurs >1 week after an event, such as a stroke, is considered a remote symptomatic seizure (Table 1). Sometimes remote symptomatic seizures are referred to as unprovoked seizures. Both acute symptomatic seizures and remote symptomatic seizures often have the same underlying structural commonalities; it is the time window that defines these two conditions. This distinction between provoked seizures and acute symptomatic seizures versus remote symptomatic (unprovoked seizures) is of clinical significance. For provoked and acute symptomatic seizures, treatment is directed at the underlying cause whereas patients with remote symptomatic seizures are more likely to develop epilepsy. When a patient presents with a first-time seizure, the clinician must determine what type of event occurred. Studies show that 25–30% of first-time seizures are symptomatic seizures [1, 4–8]. Depending upon the etiology, there are differing risks of developing epilepsy as described below.

Populations at risk

Symptomatic seizures are more common in the extremes of age and are more common in males [2]. In a large epidemiological study, CNS infections and TBI were major causes of seizures from ages 1 to 14. In young adult males, alcohol withdrawal and head trauma were predominant causes. In middle age, alcohol withdrawal was a major cause in both sexes with cerebrovascular causes predominating in the elderly [2]. Lifetime risk of a symptomatic seizure was approximately 5% in males and 2.5% in females up to the age of 80 [2].

Table 1. Definition of terms

Epilepsy	At least two unprovoked seizures more than 24 h apart or one unprovoked seizure with a probability of a subsequent seizure recurrence risk of approximately 60% (similar to 10-year recurrence risk after two unprovoked seizures) [1].
Acute symptomatic seizure	Caused by acute illness (stroke, CNS infection, TBI): seizure within 7 days of an insult
Remote symptomatic seizure (unprovoked seizure)	Pre-existing brain injury: seizure greater than 7 days after insult
Provoked seizure	Caused by transient reversible alterations without structural change (toxin, metabolic factors, medication); occurs at time of insult or within 7 days

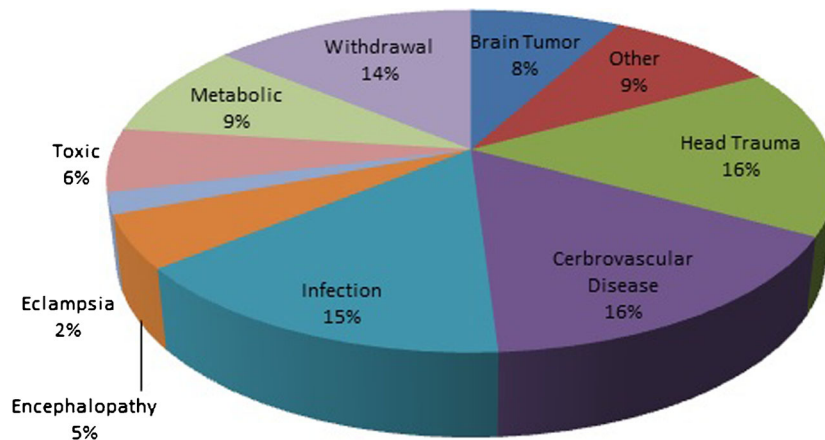


Fig. 1. Etiologies of acute symptomatic seizures [2] (copyright 2005 by ILAE. Adapted with permission).

Risk of subsequent seizures

A large retrospective study compared patients with seizures occurring in association with a CNS infection, stroke, or TBI within 7 days to patients with similar lesions but an unprovoked/remote symptomatic seizure. Patients with acute symptomatic seizures were 80% less likely to develop an unprovoked seizure over a 10-year time frame (18.7% versus 64.85) as compared to patients in the unprovoked remote symptomatic group (Fig. 2) [9].

In patients with acute symptomatic seizures, the risk of subsequent unprovoked seizure may vary with regard to initial insult. One retrospective study found a 30.8% risk of having an unprovoked seizure at 10-year follow-up in patients with hypoxic-ischemic brain injury with a risk of 10.8% for metabolic etiologies and 23.9% for structural etiologies including neoplasm, CNS infec-

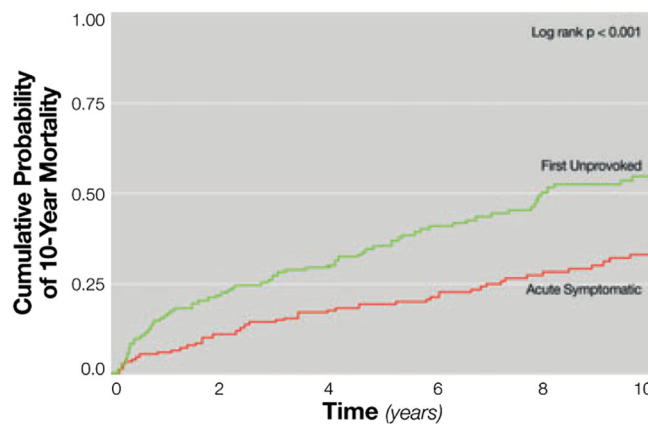


Fig. 2. Risk of unprovoked seizure after a first acute symptomatic seizure as compared to a first unprovoked seizure [9] (copyright 2009 by ILAE. Reprinted with permission).

tion, TBI, and stroke [10]. Interestingly, the risk a subsequent unprovoked seizure was significantly higher in patients who presented with status epilepticus (SE) due to a provoked or acute symptomatic cause (41% risk with SE versus 13% without SE).

Mortality in symptomatic seizures

In the acute phase, patients who suffer symptomatic seizures have a higher mortality, although long-term mortality rates are similar to those with unprovoked seizures. One-month mortality after an acute symptomatic seizure is upwards of 20%, with cerebrovascular disease and hypoxic-ischemic brain injury as the most common etiologies [11]. A large retrospective study found that patients with acute symptomatic seizures had a 1-month mortality 8.9 times higher than individuals with a first-time unprovoked seizure with similar static brain lesions [9]. The 10-year mortality rate was the same in both groups. Thirty-day mortality was 21.4% in patients with acute symptomatic seizures as compared to 3.4% in patients who had the same insults but had seizures greater than 1 week after the insult (unprovoked remote symptomatic seizures) [9].

After a first unprovoked seizure, the risk of developing epilepsy is 21–45% within the first 2 years and especially in the first year [8•]. Unprovoked seizures, particularly those due to “remote symptomatic etiology,” confer a much greater risk of developing epilepsy [4–7]. There are different treatment implications for patients with symptomatic seizures as compared to unprovoked, remote symptomatic seizures given the differences in likelihood of progressing to epilepsy as well risk of mortality in the acute phase of illness. There is a paucity prospective and randomized controlled trials of patients with acute symptomatic seizures, and therefore, no systematic approach exists to guide medical decision making in this complex patient population.

Specialized populations

Hospitalized patients

Symptomatic seizures were retrospectively investigated in hospitalized patients admitted for non-seizure reasons. This group consisted of both people who had a history of epilepsy (admitted for non-seizure reasons) and those who had never had a seizure before. In the hospital setting, symptomatic seizures were more likely to occur in patients who did not have a pre-morbid seizure history (64 vs 36%). Symptomatic seizures were more likely to recur in this seizure-naïve population. Additionally, patients who had a symptomatic seizure in the hospital who did not have a history of epilepsy were more likely to be discharged to a hospice or die [12].

ICU populations

Critically ill patients with non-neurologic conditions including sepsis, intoxication, withdrawal, and metabolic dysfunction have high rates of seizures, up to 10%, with the majority of seizures being non-motor (non-convulsive) and associated with increased morbidity and mortality [13]. The etiology of seizures in these non-neurologic populations is hypothesized to be related to blood-brain barrier dysfunction and alterations in cytokine and excitatory

neurotransmitter function. In patients with neurologic conditions including TBI, ischemic stroke, CNS infection, intracerebral hemorrhage (ICH), and brain tumor, 19% of patients had seizures with over 92% of these seizures being non-motor. Although the timing of the seizures was not elucidated in these studies (acute symptomatic versus remote symptomatic), existing studies highlight the high incidence of seizures, particularly non-motor seizures in acutely ill populations and the association of seizures with worse outcomes [14].

Symptomatic seizure: etiologies

Cerebrovascular disease

Cerebrovascular disease is a leading cause of epilepsy in adults, particularly among the elderly. In a prospective study in which patients had daily EEGs for 7 days following an acute anterior circulation stroke, 14.6% of patients had seizures, with 22.7% of these seizures being solely electrographic (non-motor). In this sample, 15.2% of all patients with an acute stroke developed epilepsy in the following year. Of these patients, 30.4% had an acute symptomatic seizure at presentation [15•].

Other studies posit that approximately 2–4% of patients with stroke suffer from post-stroke epilepsy [16]. A prospective multi-center study found that seizures were more typical in hemorrhagic strokes. For patients with ischemic strokes, cortical location was predictive of seizures. Although 8.9% of patients developed seizures, only 2.5% of patients went on to develop epilepsy. Late-onset seizures (defined as greater than 2 weeks after an insult, i.e., remote symptomatic seizures) were predictive of a subsequent diagnosis of epilepsy. The authors proposed that this increased risk for subsequent seizures may be due to the differing pathophysiology implicated in acute versus remote symptomatic strokes. They proposed that acute symptomatic seizures are caused by biochemical dysfunction in setting of hypoxia and release of excitotoxic neurotransmitters, whereas late-onset seizures are due to structural changes with gliosis and the development of a meningocerebral cicatrix. These structural changes may be epileptogenic, resulting in increased risk of subsequent seizures [17].

Intracerebral hemorrhage

A prospective trial of ICH in 522 patients noted that 14% of patients developed acute symptomatic seizures (defined as within 7 days of ICH), with a higher percentage of seizures in lobar ICH as compared to deep or posterior fossa ICH [51]. Only 2% of patients had more than one seizure during hospitalization. Interestingly, acute symptomatic seizures were not predictive of mortality at 7 days or functional outcome at 6 months [18].

Subarachnoid hemorrhage

Seizures are common in patients who suffer from subarachnoid hemorrhage, with seizures at onset noted in approximately 4 to 16% of patients [19]. In a retrospective study by Lin et al. 2003, 7.8% of patients had a seizure within 12 h of onset of the hemorrhage. The incidence of remote symptomatic seizures was 6.9%, with most occurring up to 8 months after the index event. The presence of

seizures at onset, pre-operative, or post-operative seizures was not predictive of remote symptomatic seizures. Persistent neurologic deficits and loss of consciousness of greater than 1 h at onset of ictus were predictive of remote symptomatic seizures [20].

Subdural hematoma

Post-traumatic epileptic seizures in patients with acute subdural hematoma is reported to be approximately 24%, with late seizures (defined as greater than 1 week after an event, i.e., remote symptomatic) having higher rates of recurrence than early seizures. Compared to other traumatic brain injuries (TBI), subdural hematomas are thought to be more likely to produce acute symptomatic and remote symptomatic seizures. Risk factors for acute symptomatic seizures included post-operative GCS score <8 within 24 h after evacuation, delay in operation for greater than 24 h, and the need for a craniotomy. With regard to pathophysiology, the hematoma is thought to be irritative and highly epileptogenic due to blood and degradation products. Remote symptomatic seizures were predicted by the need for a craniotomy although it is unclear if it is the procedure itself (thought to cause sudden decompression predisposing to parenchymal injury) that is related to risk of remote symptomatic seizures or whether craniotomy is more of a marker of the severity of injury. Forty-three percent of patients with acute subdural hematomas had remote symptomatic seizures [21•].

Hypoxic-ischemic brain injury

Approximately 1/3 of patients with hypoxic-ischemic brain injury develop seizures, which begin typically within 24 h after the onset of injury. Seizures are thought to be a consequence of an excitotoxic process on cortical neurons [22]. Seizures do not typically predict poor neurologic or functional outcome or predict development of post-hypoxic epilepsy. However, patients with SE do suffer worse neurologic and functional outcomes; it is not clear if it is the presence of SE that causes worsening outcomes or if the presence of SE points rather to the severity of an underlying injury [22, 23].

Venous sinus thrombosis

Venous sinus thrombosis is rare, accounting for less than 1% of cerebrovascular disease [50]. In a retrospective analysis of 69 patients with venous sinus thrombosis, 46% of patients had seizures, with 59% of these seizures occurring within 1 week. Focal neurologic deficits and thrombosis of the superior sagittal sinus were independent risk factors for seizures. No correlation was found between symptomatic seizures and functional outcome or mortality at 90 days [24]. A prospective trial found 34% of patients with cerebral vein thrombosis had acute symptomatic seizures (defined as within 2 weeks of onset) with 9.5% of all patients subsequently developing late seizures [25]. Most of these seizures occurred within 1 year. Remote symptomatic seizures were predicted by the presence of hemorrhage at onset and the presence of acute symptomatic seizures. Long-term functional outcome was not related to the presence of acute symptomatic or remote symptomatic seizures; however, mortality was higher in patients suffering from acute symptomatic seizures in the short term [26].

CNS infection

In developing countries, the leading cause for acute symptomatic seizures is infection in both pediatric and adult populations [45, 47, 48]. In a retrospective study in Korea of patients greater than 16 years of age with CNS infections, 23% suffered acute symptomatic seizures. Of these patients, viral encephalitis was a more frequent etiology than bacterial meningitis. Furthermore, the presence of viral encephalitis and a GCS ≤ 12 were significant independent predictors of acute symptomatic seizures. Interestingly, at 18-month follow-up, patients who did not suffer from an acute symptomatic seizure during their infection were seizure free, whereas 41% of patients who had an acute symptomatic seizure during their illness progressed to remote symptomatic epilepsy. This study posited that in viral encephalitis, there is more brain parenchymal involvement which may be implicated in the higher rates of seizures in this population (73% with viral encephalitis versus 17% with bacterial meningitis) [27].

Neurocysticercosis

Neurocysticercosis (NCC) is a CNS infection caused by *Taenia Solium*, a parasitic helminth worm. Infection accounts for upwards of 30% of epileptic seizures in Central and South America [26]. Seizures are the most common clinical manifestation of the disease [24, 49]. The mechanism of epileptogenicity is thought to be related to different stages of the cysticerci in brain parenchyma. A meta-analysis noted recurrence of seizures was reduced in 14% of patients who received cysticidal therapy as compared to 37% without treatment [28].

A study by Del Brutto 1994 noted that in patients treated with Albendazole who had seizures but were subsequently tapered off anti-seizure medications after 2 years of seizure freedom, recurrent seizures occurred in 50% after a seizure free period of approximately 3 months. The presence of residual calcifications was predictive of relapse. Parenchymal brain calcifications are thought to represent active epileptogenic foci and can be present independent of whether a patient received cysticidal therapy or not [29]. This author proposes that cysticidal therapy should be continued since there is an 80% reduction in cysts, thus reducing risk of seizures. Approximately 20% of residual cysts post-treatment can result in highly epileptogenic calcific lesions [30].

Studies have shown transient inflammation and edema around calcific lesions are associated with seizures. Given existing data regarding the epileptogenicity of residual calcifications, seizures may be viewed as remote symptomatic and individuals possessing such lesions have an enduring predisposition to seize. Given high relapse rates following discontinuation of anti-seizure medications, patients with numerous calcific lesions may warrant lifetime anti-seizure medication.

Trauma

Post-traumatic epilepsy accounts for up to 20% of symptomatic epilepsy. Risk factors for developing post-traumatic epilepsy include severity of trauma, penetrating injury, prolonged loss of consciousness and post-traumatic amnesia, ICH, subdural hemorrhage requiring surgical evacuation, and early post-traumatic seizures [52–54]. Approximately 80% of individuals experience a first seizure within 1 year post-injury. Early seizures, defined as within 2 weeks of injury, are

more common in children than in adults, although children are less likely to go on to develop post-traumatic epilepsy [31]. Interestingly, remote symptomatic seizures are correlated with higher rates of seizure recurrence than early symptomatic seizures. Mechanisms for the development of remote symptomatic epilepsy are thought to be related to iron deposition from extravasated blood triggering free radicals with resultant tissue damage and a release of excitotoxic neurotransmitters. Penetrating injuries produce a cerebral cicatrix that is also associated with increased risk of post-traumatic seizures [32].

A prospective study of patients with head injury found that early seizures, defined as within 10 days post-trauma, were present in 8% of patients and post-traumatic epilepsy was noted in 13.1% of the total population. In this sample, early seizures were followed by a seizure free period of at least 1 month. The authors suggested a different epileptogenic process may be related to early versus late seizures [33]. Post-traumatic epilepsy was predicted by low GCS score, early seizures (within 1 week of injury) and the presence of frontal or temporal lobe damage. Interestingly, an epileptiform EEG, as demonstrated by slow waves and/or epileptiform activity, was predictive of patients who went on to develop subsequent seizures over the year.

Brain Trauma Foundation Guidelines recommend prophylactic anti-seizure medications for 7 days after an injury [34], in part due to a randomized study in TBI which found Phenytoin superior to placebo in preventing early symptomatic seizures [25]. However, another study found that Phenytoin could delay functional recovery after brain injury [35]. Levetiracetam has been found to be equally effective in reducing post-traumatic seizures with a better side-effect profile as compared to phenytoin [21•].

Most practitioners choose to start prophylactic anticonvulsants for 1 week after a head injury due to concern for further damage to a compromised brain following increased metabolic demands, raised intracranial pressure, and neurotransmitter toxicity with seizure. Some authors propose perhaps continuing anti-seizure medications for greater than 1 week in patients with penetrating injuries, a subdural requiring evacuation, a persistently epileptiform EEG, early seizures, and multiple contusions [32, 33].

Eclampsia

Eclampsia is defined as convulsions or coma present prior, during, or after pregnancy. Incidence is 5/10,000 pregnancies in the Western world. Seizures occurring up to 48 h after birth are still considered part of eclampsia. Women typically present with hypertension, proteinuria and have headaches and blurred vision [36].

A small prospective study found seizures preceded labor in 41% of cases, occurred during labor in 5% of patients and followed delivery in 54% of patients. Thirty-three percent of seizures occurred >48 h post-partum. Interestingly, 38% of patients had multiple seizures, 15% of patients had focal onset seizures, and 1 patient had status epilepticus. Of the subset of patients followed for up to six months, 1 patient developed recurrent seizures and was treated with phenytoin [37].

Treatment for eclampsia involves IV magnesium, blood pressure control, and rapid delivery. IV magnesium is continued for at least 24 h after the last seizure and/or for at least 24 h post-delivery. Some patients are managed

subsequently with oral agents such as labetalol or nifedipine for blood pressure control. Of patients with eclampsia who receive imaging, MRI abnormalities are commonly seen in parietal and occipital white matter. These changes are thought to be related to reversible vasogenic edema in the setting of transient cerebral dysregulation. Long-term anti-seizure medications are not warranted in the majority of patients [36].

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) involves a constellation of symptoms including visual loss, altered mental status, headache, and seizures. Seizures are a frequent manifestation, occurring >90% of the time. Seizures are typically of generalized onset but may be focal to bilateral tonic-clonic. MRI is the preferred imaging modality, typically showing hyperintense, symmetric lesions in the parieto-occipital regions. The underlying pathophysiology of this condition is complex, although it is thought to involve transient leakage of the blood-brain barrier, with consequent vasogenic edema. The posterior regions are thought to be more vulnerable to these changes due to decreased sympathetic innervation to these blood vessels and therefore more impaired autoregulation. PRES is associated with various conditions, including renal dysfunction, immunosuppressant use, autoimmune disease, transplantation, pre-eclampsia/eclampsia, and rapid increases in blood pressure. Treatment is directed at the underlying etiology although anti-seizure medications are used in the short term. There are no guidelines regarding duration of anti-seizure medications and patients often do not go on to develop epilepsy. Typically, patients have improvement within 1 week with MRI abnormalities resolving after approximately 6 weeks. Treatment duration could be guided by resolution of EEG or radiographic abnormalities with some authors proposing 3 months of treatment [38].

Alcohol

Alcohol-related provoked seizures account for up to 1/3 of admissions for seizures, with more than 90% of alcohol withdrawal seizures occurring within 6–48 h of a last drink. Alcohol withdrawal seizures occur with abrupt cessation of heavy alcohol use, although the blood alcohol level does not need to reach zero to trigger a seizure. The rapid decline of alcohol may be a more significant precipitant of a seizure. Long-term heavy use results in an upregulation of NMDA receptors and a decrease in sensitivity of GABA-A receptors (main inhibitory neurotransmitter in the CNS). Seizures can present as focal onset or generalized onset motor seizures. Animal models have suggested a possible genetic predisposition to alcohol withdrawal seizures, although few human studies have shown this. After a first alcohol-related seizure, imaging should be obtained, as patients who abuse alcohol often have a higher rate of intracranial lesions, including subdural hematomas, subarachnoid bleeds, and brain contusions. Heavy alcohol use is related to a reduction in white matter volume and a decrease in density of Purkinje cells, although it is not known whether alcohol toxicity is directly implicated in seizure genesis. For patients with severe alcohol withdrawal, seizure prophylaxis is recommended

with benzodiazepines. A meta-analysis of randomized placebo-controlled trials for secondary prevention of seizures found phenytoin to be ineffective [39].

Recurrent withdrawal seizure risk during the same withdrawal period can be 13–24%, with Lorazepam reducing recurrence risk by a significant amount. In patients with acute symptomatic seizures related to alcohol withdrawal, the most effective treatment is alcohol cessation. Secondary prevention with anti-seizure medication is not indicated unless patients have seizures that are unrelated to alcohol intake. Prophylactic administration of anti-seizure medication is often difficult due to issues of drug-alcohol interactions and poor compliance with medications [40]. Complicating the picture is the high rate of head trauma, which may lead to post-traumatic epilepsy. However, in patients with a second seizure not clearly related to alcohol withdrawal with epileptiform activity on EEG, treatment with anti-seizure medication may be warranted.

Electrolyte disturbances

Electrolyte disturbances create alterations in ion gradients, which lead to hyperexcitability and seizures. These derangements are thought to impact function as opposed to structural integrity. Therefore, seizures are thought to be provoked. Anti-seizure treatment is usually not required and treatment of the underlying disorder is sufficient to stop seizures. Typically, seizures are of generalized onset although they can be of focal onset. Rapid changes in electrolytes, particularly with hypocalcemia, hypomagnesia and hyponatremia, are more likely to result in acute symptomatic seizures.

Table 2. Management guidelines

Etiology of seizure	Type of seizure	Short-term AED treatment	Long-term AED treatment
Alcohol	Provoked	Yes: benzodiazepines	No
Metabolic	Provoked	Maybe: if underlying derangement requires prolonged treatment	No
Ischemic stroke	Acute symptomatic	Yes: a short course may be necessary due to higher mortality rates in the short term	Yes, if patient develops remote symptomatic seizure in setting of underlying lesion (i.e., a cortical lesion with gliosis) resulting in an enduring predisposition to seize
Hemorrhagic stroke	Acute symptomatic	Yes: a short course may be necessary due to higher mortality rate in the short term	Yes, if patient develops remote symptomatic seizure in setting of underlying lesion (i.e., a cortical lesion with gliosis) resulting in an enduring predisposition to seize
Subdural	Acute symptomatic	Yes: a short course may be necessary due to higher mortality rate in the short term	Yes, if patient develops remote symptomatic seizure in setting of underlying lesion (i.e., a cortical lesion with gliosis)

Table 2. (Continued)

Etiology of seizure	Type of seizure	Short-term AED treatment	Long-term AED treatment
Subarachnoid	Acute symptomatic	Yes: a short course may be necessary due to higher mortality rate in the short term	resulting in an enduring predisposition to seize Yes, if patient develops remote symptomatic seizure in setting of underlying lesion (i.e., a cortical lesion with gliosis) resulting in an enduring predisposition to seize
Cerebral venous sinus thrombosis	Acute symptomatic	Yes: up to 6 months–1 year of anti-seizure medication treatment may be necessary due to higher mortality rate in the short term and increased risk of unprovoked seizures with hemorrhagic infarcts, superior sagittal thrombosis and history of acute symptomatic seizures	Yes, if patient develops remote symptomatic seizure in setting of underlying lesion (i.e., a cortical lesion with gliosis) resulting in an enduring predisposition to seize
PRES	Acute symptomatic	Yes: a short course may be necessary; treat the underlying condition simultaneously, remove offending agents, lower blood pressure	No
Eclampsia	Acute symptomatic	Maybe, also IV magnesium delivery, blood pressure control	No
Trauma	Acute symptomatic	Yes: 1 week of anticonvulsants. Consider longer (1–3 months of treatment) in patients with acute symptomatic seizures, moderate-severe depressed skull fracture, penetrating injury, subdural requiring evacuation, multiple contusions, epileptiform EEG, prolonged period of LOC or amnesia	Yes, if patient develops remote symptomatic seizure in setting of underlying lesion (i.e., a cortical lesion with gliosis) resulting in an enduring predisposition to seize
CNS infection	Acute symptomatic	Yes: a short course is necessary due to high mortality in short term. Could consider 1–3 months of treatment in patients with viral encephalitis—these patients with early seizures have a higher likelihood of developing epilepsy	Yes, if patient has remote symptomatic seizure or unprovoked seizure with structural lesion resulting in an enduring predisposition to seize (i.e., a patient with treated neurocysticercosis with residual calcifications or patient with history of viral encephalitis with gliosis on imaging)

Correction of sodium abnormalities must be gradual to prevent osmotic demyelination in cases of rapid correction of hyponatremia and cerebral edema in settings of rapid correction of hypernatremia. Hypernatremia is less likely to result in seizures and is more likely to be a consequence of seizures, particularly in generalized onset seizures due to osmotically active lactate driving water into cells. Hypocalcemia results in seizures, particularly with rapid changes in calcium levels and often requires rapid correction with IV calcium. Hypercalcemia rarely is associated with seizures due to decreased excitability of neuronal membranes. Hypomagnesemia, particularly at levels of <1 mEq/L, is associated with CNS hyperirritability with treatment typically involving IV magnesium with adjustment for renal dysfunction and concurrent repletion of potassium. Hyperglycemia and more frequently hypoglycemia can result in generalized seizures and less commonly seizures of focal onset [41]. Treatment includes rapid correction with intravenous 10% Dextrose and insulin and hydration in cases of hyperglycemia. Long-term treatment or use of anti-seizure medication is less effective, particularly when the underlying derangement has not been corrected.

Conclusion

Patients with acute symptomatic seizures and provoked seizures consist of a heterogeneous population, requiring individualized treatment on a case-by-case basis. Although patients who suffer acute symptomatic seizures and provoked seizures have less risk of developing epilepsy than those with an unprovoked or remote symptomatic seizure, the risk is still greater than the general population. In acute symptomatic seizures, this risk may in part be mediated by the presence and location of structural lesions. Patients with provoked seizures due to metabolic etiologies (i.e., hyponatremia, hypoglycemia) may be least likely to develop epilepsy due to the inherent reversibility of these conditions. The percentage of people who go on to develop epilepsy after a symptomatic seizure is not great enough to justify long-term prophylactic anti-seizure medication. In light of data from AAN guidelines and early prospective studies in unprovoked seizures, early versus late treatment of seizures does not alter the long-term risk of developing epilepsy. In other words, anti-seizure medication is not anti-epileptogenic [16, 17].

We propose treating acute symptomatic seizures and provoked seizures with anti-seizure medication throughout the acute phase given the high seizure recurrence rate during this phase of the illness and high rates of SE, as well as high morbidity and mortality [46]. Specifically, for toxic and metabolic derangements that are reversible, 1 week of treatment with anti-seizure medications may suffice. For patients with cerebral venous sinus thrombosis, history of moderate to severe head trauma and early seizures, penetrating injuries, viral encephalitis, acute subdural hematoma requiring evacuation, and the presence of persistent epileptiform abnormalities on EEG, 1–6 months of treatment may be warranted (Table 2). For patients with intractable, end-stage diseases such as inoperable CNS tumors and persistent metabolic derangements that could lead to further seizures, longer-term anti-seizure treatment could be considered, keeping in mind that early treatment of seizures does not appear to alter the long-term course of epilepsy [42, 43]. If a patient with a symptomatic seizure

goes on to develop an unprovoked seizure, the risk of recurrent seizures increases to approximately 60%. In these patients, long-term treatment with anti-seizure medications and a diagnosis of epilepsy should be considered.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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