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Seizures in Acute Neurological Disorders

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Introduction

Seizures may herald, complicate, or become persistent sequellae of acute neurologic disorders such as acute cerebrovascular insult (stroke or hemorrhage), bacterial or viral meningoencephalitis, and head trauma. The occurrence of seizures in patients with primary neurological insults invariably adds an additional layer of complexity to patient management. For example, diminished arousal after generalized tonic-clonic seizures or status epilepticus (SE) may put a patient at risk for aspiration or hypoxia and may warrant airway protection via intubation and mechanical ventilation. Many patients will develop aspiration pneumonia. Phasic and substantial increases in intracranial pressure (ICP) during generalized tonic clonic seizures may lead to brain herniation in the setting of an existing mass lesion such as an acute stroke, hemorrhage, or brain tumor. Increased mean arterial blood pressure (MAP), hypoxemia, and metabolic or respiratory acidosis may accompany generalized tonic-clonic seizures and complicate the management of patients with acute stroke, sepsis, cardiac ischemia, or pulmonary edema. Finally, systemic toxicity of antiepileptic drugs (AEDs) may be encountered and cause medical complications such as cardiac dysrhythmia, hypotension, the Stevens–Johnson syndrome, other hypersensitivity reactions, and hepatic failure. Some of these complications may be life threatening even if the underlying neurologic event is not. It is important for the clinician, whether in the outpatient, hospital ward, or Emergency Department setting, to remember that a first-time seizure may herald a potentially significant and even disastrous neurologic event. This chapter will focus on the etiologic, diagnostic, and treatment implications of seizures in several acute neurologic disorders such as arterial

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and venous cerebral infarcts, intracerebral hemorrhage, including hypertensive, subdural, and subarachnoid hemorrhage, meningoencephalitis, and brain trauma.

Seizures in Cerebrovascular Disease

Acute Stroke

Cerebrovascular disease is a common cause of epilepsy in the elderly. Up to 10–15% of patients with acute stroke or transient ischemic attack (TIA) will present with a seizure, and in some studies, twice that number will suffer a seizure within the first 24–48 h after their initial infarct *(1)*. For example, in 71 young patients (aged 15–45 years) affected by a cerebral infarct, poststroke seizures occurred in 7 patients (10.8%) *(2)*. Seizures in the first 24–48 h are more common than later seizures or epilepsy and tend to be focal motor, brief, and isolated. Epilepsy usually does not follow early seizures, but the risk of subsequent poststroke epilepsy is increased. Late seizures occur months to years after a stroke and are probably the result of structural brain abnormalities leading to the development of an epileptic focus. Of course, the risk of seizures is increased markedly when the cerebrovascular event involves the cerebral cortex, and deep-seated hemispheric or infratentorial lesions rarely produce seizures or epilepsy. There may be a higher incidence of seizures in hemorrhagic stroke, although this remains to be proved. The risk is also increased in patients with other medical problems known to lower seizure threshold, such as renal failure. Venous thrombosis, e.g., cortical vein thrombosis and sagittal sinus thrombosis, carries an increased risk of seizure that may be higher than cerebral arterial thrombosis.

The most common types of seizures associated with cerebrovascular disease include focal motor and generalized tonic-clonic seizures. Focal motor seizures typically emanate from the cortical region that has sustained an ischemic insult. Complex partial seizures may present in the setting of acute stroke and, like focal seizures, typically are believed to emanate from the ischemic region. Whereas single seizures are the most common, recurrent seizures and SE may occur. Surprisingly, convulsive SE is relatively rare in acute stroke. These results have been reported in a large number of retrospective and prospective analyses worldwide. It has also been suggested that embolic infarction has a higher incidence of seizures than does thrombotic infarction, but definitive evidence is again lacking. Interestingly, the presence of seizures in an acute stroke does not seem to correlate with the size of the lesion, functional outcome, or mortality *(3)*.

Several studies have assessed the incidence and course of poststroke seizures. Ninety patients with seizures following acute stroke were studied retrospectively to investigate the common clinical features, prognosis, and

electroencephalographic findings *(4)*. Of 90 seizures, 33% appeared early (within 2 wk after the infarction), and 90% of the 30 early seizures appeared within 24 h after the infarction. Of 90 seizures, 56% were single, and SE occured in only 8%. Early-onset seizures were more likely to be partial (57% of 30 patients). Of 90 initial seizures, 39% recurred, and there was no significant difference in recurrence rate between early- or late-onset initial seizures. Seizures in 88% of the 90 patients were managed with monotherapy.

The incidence of early seizures in 1000 consecutive patients with stroke and transient ischemic attacks was evaluated propectively to determine whether seizure occurrence correlates with stroke type, pathogenesis, or outcome *(3)*. Seizures occurred in 44 patients (4.4%), including 24 patients (6.5%) of 370 patients with cortical infarction, and 4 (3.7%) of 109 with hemispheric transient ischemic attacks. Lobar or extensive hemorrhage, or subarachnoid hemorrhage, was also associated with seizures. Lacunar infarcts and deep hemorrhages were not associated with seizures in this series. Interestingly, in patients with cortical infarcts, there was no association between seizure occurrence and stroke pathogenesis. Seizures generally occurred within 48 h of stroke onset and were usually single, partial, and readily controlled. Seizures were not associated with a higher mortality or worse functional outcome.

The development of seizures was evaluated in 219 consecutive patients who had ischemic or hemorrhagic stroke *(5)*. Seizures developed in 13 of 183 patients with ischemic stroke and 9 of 36 patients with hemorrhagic stroke. Seizures were more common in those with cortical lesions and in a lesion occupying more than one lobe. The occurrence of seizures within 15 days of a first stroke or transient ischemic episode was evaluated prospectively in 1640 patients to study relation between seizures and type of stroke *(6)*. Seizures occurred in 90 patients (5.4%), with the most common setting being cardiogenic embolus followed by large vessel atheroma, TIA, subcortical infarcts, and lacunar infarcts. Other causes included supratentorial hematoma and subarachnoid hemorrhage. Seizures were the initial sign of stroke in 80 (89%) of 90 cases and were usually single and partial. Seizure symptoms were most often motor, sensory, or visual. The number and type of seizures, initial stroke severity, infarct size, mortality, and outcome were studied recently in 1197 patients with acute stroke *(7)*. Fifty patients (4.2%) had seizures within 14 days of a stroke. Using a multivariate analyses, only initial stroke severity was related to early seizure, whereas stroke type and lesion localization were not related. The occurrence of an early seizure did not influence the risk of death during hospital stay.

In a recent hospital-based study from South India, up to 40% of seizures presenting to the Emergency Department were related to cerebrovascular disease such as stroke and superior sagittal sinus thrombosis *(8)*. Similarly, in a

study of the north–central region of Saskatchewan, seizures were caused by stroke in 19 of 84 (23%) cases analyzed *(9)*. EEGs were abnormal in 61 of 84 (73%) cases, with epileptiform discharge in 33 of 84 (39%). Another study determined the profile of late-onset epileptic seizures following cerebral infarcts, as well as the predictive clinical and radiological factors associated with their development *(10)*. In this analysis 86 patients were evaluated who developed late seizures after cerebral infarction and 285 patients were evaluated who did not develop seizures for at least 1 y after their strokes. Simple partial (motor) seizures, with or without secondary generalization, accounted for 80% of the classifiable seizures. Factors that appeared to be predictive of seizure development were the presence of large cortical infarcts and the presence of apparently preserved cerebral tissue within the infarcted area. Seizures were rare in patients with lacunar infarction, but the presence of associated leukoaraiosis increased the risk. Motor and cognitive deficit, as well as epilepsy, are common in patients with periventricular leukomalacia (PVLM).

Interestingly, SE is an infrequent complication of acute stroke. Several studies have demonstrated an incidence of convulsive SE in acute stroke of approx. 3–5%. Both complex partial SE (*see* ref. 11) and convulsive SE may occur in the acute setting or will arise within the first 24–72 h. Clinically, nonconvulsive SE is heralded by persistant alteration in mental status or subtle motor manifestations. Continuous focal motor seizures (focal motor SE or epilepsia partialis continua) can be an especially disabling complication of acute stroke. A recent study demonstrated that the most common cause of focal SE was acute brain ischemia, which was especially difficult to control *(12)*. Of these patients, many had electrographic evidence of seizures with only subtle clinical manifestations. These investigators suggest that controlling focal SE may be especially problematic despite multiple anticonvulsant agents.

The rising use of cocaine in the 1980s and 1990s has been associated with a well-documented and significant risk of stroke or cerebral hemorrhage and concomitant seizures. Cocaine can provoke seizures, exacerbate preexisting epilepsy, or cause an ischemic or hemorrhagic stroke that leads to seizures *(13)*. Mitochondrial DNA mutations resulting in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) have been linked to seizures (for review, *see* ref. *14*). Silent infarcts have been reported in 17% of young patients with sickle cell disease and are associated with impaired performance on standardized psychometric tests as well as with epilepsy *(15)*. One interesting report suggested that stroke and seizure may be the initial presentation of HIV infection in children *(10)*. Sturge–Weber syndrome is characterized by the presence of a port-wine nevus, epilepsy, stroke-like episodes, headache, and developmental delay.

Evidence obtained using fluorodeoxyglucose (FDG)—positron emission tomography (PET) suggests that progressive hypo-perfusion and glucose hypometabolism are associated with neurologic deterioration in Sturge–Weber syndrome *(17)*. The family of vasculitides that affect the CNS, including giant cell arteritis, primary angiitis of the CNS, Takayasu's disease, periarteritis nodosa, Churg–Strauss syndrome, Wegener's granulomatosis, Behçet's disease, other collagen vascular diseases, and vasculitis secondary to the use of illicit drugs may present with symptoms and signs such as headache, encephalopathy, seizures, and stroke (*18*). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an increasingly recognized autosomal dominant disorder leading to cerebrovascular manifestations in early adulthood that may be associated with seizures in as many as 10–20% of cases *(19)*. Arteriovenous malformations may be complicated by acute stroke or hemorrhage and, therefore, can induce single and recurrent seizures. Patients with small arteriovenous malformations (AVMs) (<3 cm) were more likely to present with hemorrhage, whereas those with large AVMs were more likely to present with seizures *(20)*. In pregnant females, an especially disabling cause of seizures is eclampsia (for review, *see* ref. *21*). Eclampsia is a complex multisystem disorder with potentially severe, irreversible sequelae, including a progressive and often relentless arteriopathy that can result in acute stroke and vasospasm.

Acute Intracerebral Hemorrhage

Seizures may complicate intracerebral hemorrhage (ICH) in as many as 15–25% of cases. In one series *(22)*, seizures occurred in 15% of patients with ICH (early in 12% and delayed in 3%). Seizures were most frequent with lobar hemorrhages and uncommon with deep subcortical hemorrhages. Lobar hemorrhages in the frontal, parietal, or temporal, but not occipital, regions were more commonly associated with seizures. Seizures were most common if the hemorrhage was the result of an aneurysm, angioma, or neoplasm and less common if hypertensive or spontaneous. AVM may be a common cause of lobar hemorrhage with early seizures.

Among 1402 patients with ICH, early seizures occurred in 64 (4.6%) *(23)*. Seizure was the first manifestation of ICH in 19 patients (30%), and SE occurred in 11 patients (17%). SE was the initial presentation of ICH in 6 individuals (9%). The majority of seizures were simple partial (motor) seizures. Fifty-five cases of epileptic seizures associated with spontaneous ICH were reported *(24)*. Seizures appeared as the first symptom in 23 of 55 patients with ICH. Seizures occurred early (within 2 wk) in 18 patients and late (after 2 wk) in 14. Partial seizures were the most frequent type (63%) especially in the

setting of lobar hemorrhage. In a retrospective study in 1200 Chinese veterans with cerebrovascular disease, 32% experienced ICH; of these patients, 2.8% developed seizures *(25)*. A prospective analysis of 123 patients with hypertensive ICH revealed that 12% of these patients had seizures within the first 24 h of the ICH ictus *(26)*. The majority of seizure types were partial with fewer being generalized. SE occurred in only 10% of patients following ICH. Another study demonstrated that seizures occurred in 19 of 112 patients (17%) with nontraumatic, supratentorial ICH *(27)*. All seizures occurred at ICH onset. Seizures were significantly associated with extension of blood into the cerebral cortex. These investigators concluded that seizures in ICH occur most commonly at hemorrhage onset, patients without seizures at hemorrhage onset are at very low risk for subsequent seizures during their hospitalization, and hemorrhage involving the cerebral cortex, regardless of site of origin, predisposes to seizures. Cerebral amyloid angiopathy is a well-known cause of cerebral lobar hemorrhage and may be associated with subacute dementia, seizures, or an acute encephalopathy without lobar hemorrhage *(28)*.

The incidence of seizures in subarachnoid hemorrhage is approx. 10%. Seizures may also herald symptomatic but unruptured aneurysm *(29)*. An early retrospective series of 100 consecutive patients with subarachnoid hemorrhage caused by a ruptured aneurysm was performed to determine the incidence and the prognostic implications of seizures during the acute phase *(30)*. Seizures occurred in 26% of the patients, and the majority of seizures occurred near the onset of the initial hemorrhage. The occurrence of early seizures did not correlate with the location of the aneurysm or the prognosis. A proportion of seizures occurred immediately after rebleeding, with no greater morbidity or mortality compared to all patients who rebled. The occurrence of seizures was analyzed retrospectively in 131 consecutive cases of spontaneous subarachnoid hemorrhage *(31)*. Convulsions occurred in 31 patients (24%) and most often within 24 h of bleeding. Motor manifestations of partial seizures had no clear lateralizing value to aneurysm site. Early mortality, rebleeding, and intracerebral hematoma were similar in both seizure and nonseizure groups. Interestingly, late seizures were infrequent in survivors who had suffered seizures in the acute stage. In a prospective study of 253 patients with subarachnoid hemorrhage, 16 (6.3%) had seizures at the onset of bleeding *(32)*. None had a previous history of seizures or evidence of other metabolic derangement. Hemiparesis, Hunt's grade >3, a large amount of subarachnoid blood, and the presence of an aneurysm were significantly more frequent in patients with seizures at the onset of subarachnoid hemorrhage. Although rebleeding, mortality, or severe disability at discharge was more frequent in these patients, seizures were not a significant predictor of long-term prognosis.

Seizures in patients with acute epidural or subdural hematoma occur between 5% and 20% of cases *(33)*. In one study, the incidence of epilepsy in infants with extradural hematoma was 7.5% *(34)*. A large-scale analysis of seizures in acute epidural or subdural hematoma remains to be performed.

Seizures in CNS Infections

Seizures may occur in the setting of any CNS infection, including bacterial or viral meningitis, viral encephalitis, especially resulting from herpes simplex virus (HSV) infection, bacterial abscess, parasitic infection, e.g., toxoplasmosis, cysticercosis, or opportunistic infection, e.g., mucormycosis, and cryptococcosis. For example, the etiological spectrum of symptomatic localization-related epilepsies was generated from a study in South India *(35)*. Seizure occurred in close temporal association with an acute CNS insult in 53% of 991 patients. Infections of the CNS accounted for 77% of patients with symptomatic epilepsy.

In patients with HSV1 encephalitis (HSVE), the most common long-term symptoms are memory impairment (69%), personality and behavioral abnormalities (45%), and epilepsy (24%) *(36)*. Children and adults with HSVE may present with focal or complex partial seizures, can be initially afebrile, and can have a normal brain computerized tomography (CT) scan despite an abnormal EEG *(37)*. Rarely are acute encephalopathy and SE associated with human herpesvirus 6 infection *(38)*. Seizures are present frequently during acute La Crosse encephalitis, and recurrent seizures may occur in 6–13% of patients 1–8 y after infection *(39)*.

Seizures are the presenting sign in the majority of patients with neurocysticercosis (*see* ref. *40*). In one series *(41)*, seizures were present in 48 of 54 patients, representing the most common clinical presenting manifestation. CT scan of the brain revealed parenchymal brain cysticerci in 52 patients. In this report, all patients with seizures were treated with antiepileptic drugs with an excellent rate of seizure control.

Neurologic complications occur in approx. 30% of patients with infective endocarditis and represent a major factor associated with an increased mortality rate. Cerebral embolism is the most common complication and may account for all other sequellae, such as mycotic aneurysm, meningoencephalitis, and brain abscess, that may develop. Emboli are more common in patients with mitral valve infection and in those infected with more virulent organisms such as *Staphylococcus aureus*. Seizures are common in patients with infective endocarditis as well as in those who develop brain abscess. Focal seizures are associated more commonly with acute emboli, whereas generalized seizures are associated more commonly with systemic metabolic factors such as sepsis.

New-onset seizures are frequent manifestations of central nervous system (CNS) disorders in patients infected with HIV (ref. *42*). Seizures are more common in advanced stages of the disease, although they may occur early in the course of illness. In the majority of patients, seizures are of the generalized type. SE is also frequent. Associated metabolic abnormalities increase the risk for SE. Cerebral mass lesions, cryptococcal meningitis, and HIV encephalopathy are common causes of seizures. The prognosis of seizures in HIV-infected patients depends on the underlying cause, and seizures related to focal lesions may be more difficult to control.

Seizures in Acute Head Trauma

Seizures occur in the setting of acute head trauma and may persist as post-traumatic epilepsy. The risk of seizures is increased after traumatic brain injury, but the extent and duration of the increase in risk are unknown. One study examined the ictal phenomenology and outcome of convulsions occurring within seconds of impact following violent collision while playing rugby *(43)*. These investigators evaluated 22 cases of concussive convulsions documented on television videotape. Convulsions began within 2 s of impact and comprised an initial period of tonic stiffening followed by myoclonic jerks of all limbs lasting up to 150 s. Some asymmetry in the convulsive manifestations was common, and recovery of consciousness was rapid. No structural or permanent brain injury was present on clinical assessment, neuropsychological testing, or neuroimaging studies. Epilepsy did not develop in any player during the 3.5 y of follow-up.

Young children are more prone to early seizures, and adolescents and adults, to late seizures following brain trauma. The main risk factors for late seizures are early seizures and depressed skull fracture *(44)*. Severity of brain injury, as measured by a low Glasgow Coma Scale (GCS) score, prolonged unconsciousness, and posttraumatic amnesia (PTA) without local brain lesion, should not be considered risk factors for late post-traumatic seizures. Low GCS and a longer period of unconsciousness after head trauma, especially >12 h, have a higher likelihood of suffering convulsions after head injury *(45)*. A recent study identified the characteristics of brain injuries that are associated with the development of seizures in 4541 children and adults using a multivariate analysis. Significant risk factors for later seizures were brain contusion with subdural hematoma, skull fracture, loss of consciousness, or amnesia for more than 1 day, and an age of 65 years or older *(46)*.

One series reviewed the seizure incidence in 4232 adult patients with mild closed head injury who did not receive prophylactic anticonvulsant agents *(33)*. One hundred patients (2%) experienced seizures within 1 wk after head injury, whereas 43 of these (1% of the series) had seizures within 24 h after trauma. Most of the seizures (84%) that developed during the first week after

injury were generalized tonic-clonic. The incidence of generalized tonic-clonic seizures was higher than that of partial seizures within the first 24 h and within the first week following the trauma. No definite intracranial pathological findings were detected by CT in 53% of patients with early posttraumatic seizures. However, six patients had intracranial hemorrhage without intracranial parenchymal damage (three with epidural hematoma and three with subarachnoid hemorrhage). The most common positive CT scan findings in the early posttraumatic-seizure group were ICH (24%), followed by acute subdural hematoma with ICH (17%). Intracerebral parenchymal damage could be identified on CT scans in 41 (48.8%) of 84 patients with generalized tonic-clonic seizures and 5 (31%) of 16 patients with partial seizures with motor symptoms. The intracerebral parenchymal damage was detected most commonly in the frontal lobe (21%) and the temporal lobe (19%). Seven patients with early posttraumatic seizures received emergency craniotomy to remove an intracranial hematoma. This review suggested that early posttraumatic seizures after mild closed head injury have a high incidence (53%) in patients with normal CT scan findings. In another series, the incidence and clinical significance of early post-traumatic seizures after severe closed head injury were assessed prospectively in 3340 adult patients with severe closed head injuries, each of them having a GCS of 3–8 after trauma (*47*). Anticonvulsant agents were not given to these patients unless there was evidence of seizure. One hundred twenty-one patients (3.6%) experienced seizures within 1 wk after head injury, and 42 of these were within 24 h after trauma. The incidence of intracerebral parenchymal damage was higher among those patients who developed seizures in the first week (66.1%) than in those who did not (62.7%). Interestingly, the patients with early seizures had a lower mortality rate. In patients who survived the initial injury, the occurrence of early posttraumatic seizures did not appear to influence the neurological recovery at 6 mo after injury. These investigators concluded that the presence of intracerebral parenchymal damage on CT scan after severe closed head injury did not increase the risk of early posttraumatic seizures and that the occurrence of early seizures did not influence the neurological recovery in patients who survived the initial severe closed head injury.

Several studies have documented the incidence of convulsive and nonconvulsive SE (NCSE) by using continuous EEG monitoring in patients in the Neurointensive Care Unit (NICU) during the initial 14 days following brain trauma. NCSE occurs commonly in the setting of an acute brain injury (*see* ref. *48*). It may persist following cessation of generalized convulsive SE, and it is not uncommonly associated with acute cerebral ischemia. In the absence of EEG testing, NCSE is likely to be missed or delayed. Increasing evidence suggests that brain trauma and NCSE are synergistically detrimental and increase brain injury. In one series of 94 patients with moderate-to-severe

brain injuries, convulsive and nonconvulsive seizures occurred in 21 (22%), with many displaying SE *(49)*. In 52% of patients, the seizures were nonconvulsive and were diagnosed on the basis of EEG studies alone.

Mechanisims of Epileptogenesis

In most cases, seizures occurring in the setting of acute neurological disorders result from structural brain injury that affects the cerebral cortex. The degree to which there is overlap between the cellular and molecular pathogenesis of seizure genesis in acute ischemia versus acute hemorrhage remains to be defined. Current wisdom is that there is a disruption of the complex and delicate balance between neural excitation and inhibition in the cerebral cortex as a result of the acute insult. These changes likely affect the excitatory glutamatergic system as well as the inhibitory GABA-ergic system.

The rapid progress in recent years in the molecular and cellular pharmacology of excitatory amino acid receptors has shed light on the pathogenesis of hypoxic–ischemic (HI) injury to the brain. It has become clear that excitotoxic injury also complicates prolonged seizure activity in the brain and that the glutamate family of receptors contributes to epileptogenesis in humans. In experimental animals, ischemia potentiates seizures induced by a variety of measures, including picrotoxin and pentylenetetrazol *(50)*. Excessive activation of glutamate receptors may contribute to neuronal loss after a traumatic or ischemic CNS insult. Such injuries are often associated with hemorrhage and extravasation of hemoglobin, a pro-oxidant and putative neurotoxin. Hemoglobin potentiates the neurotoxicity of low concentrations of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) and kainate *(51)*.

After transient cerebral ischemia in fetal sheep, cortical seizures are accompanied by a progressive decrease in the concentration of oxidized cytochrome oxidase as measured by near-infrared (IR) spectroscopy *(52)*. These investigators suggest that nitric oxide and nitric oxide synthetase are important mediators of ischemia and epileptogenesis. Brain areas damaged by stroke and seizures express high levels of heat shock protein (HSP72). Overexpression of HSP72 improves neuron survival against focal cerebral ischemia and systemic kainic acid (KA) administration *(53)*. In recent study the effect of chemically induced seizures on cerebral HI damage in immature animals *(54)*. Cerebral HI injury was produced in 7- and 13-d postnatal rats by combined unilateral common carotid artery ligation and hypoxia. Seizures were induced chemically by the subcutaneous injection of KA or inhalation of flurothyl vapor. Histologic examination of brains of animals subjected to seizures prior to HI injury and their HI-only controls showed that seizures occurring before HI injury conferred protection against cerebral damage. These investigators concluded that there was no evidence that seizures in early postnatal development aggravate pre-existing cerebral HI damage.

Changes in gene transcription underscore the molecular pathogenesis of seizure initiation following brain ischemia. For example, differential alterations in expression of c-*fos*, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), TrkB, and TrkC mRNAs have been reported at different reperfusion times following unilateral middle cerebral artery occlusion *(55)*. These and other data suggest that HI injury can induce long-lasting changes in gene transcription that affect cell death and survival pathways. Altered expression of the immediate early genes c-*fos*, c-*jun*, and *jun B* and their cognate proteins has been demonstrated by immunocytochemistry following unilateral entorhinal cortex lesion in experimental animals *(56)*. Within the denervated fascia dentata, some of these changes may be linked to the reorganization processes following traumatic brain lesion. Alternatively, the alterations in immediate early gene expression reported in this study may be the result of changes in synaptic activity or postlesional seizures that occur in this lesioning paradigm. An increase in extracellular glutamate has been demonstrated after human traumatic brain injury, which may be secondary to reduced cerebral perfusion pressure and early posttraumatic seizures *(49)*.

The presence of an intracranial hematoma has a robust association with the development of posttraumatic epilepsy. Extravasation of blood is followed by hemolysis and deposition of heme-containing compounds into the neuropil, initiating a sequence of univalent redox reactions and generating various free radical species, including superoxides, hydroxyl radicals, peroxides, and perferryl ions. Free radicals initiate peroxidation reactions by hydrogen abstraction from methylene groups adjacent to double bonds of fatty acids and lipids within cellular membranes. Intrinsic enzymatic mechanisms for control of free radical reactions include activation of catalase, peroxidase, and superoxide dismutase. Steroids, proteins, and tocopherol also terminate peroxidative reactions. Tocopherol and selenium are effective in preventing tissue injury initiated by ferrous chloride and heme compounds. Treatment strategies for prevention or prophylaxis of post-traumatic epilepsy must await absolute knowledge of mechanisms. Antioxidants and chelators may be useful, given the speculation that peroxidative reactions may be an important component of brain injury responses. In addition, potential treatment strategies involving GABA agonists, NMDA receptor antagonists, and barbiturates need further scientific assessment.

Head trauma initiates a sequence of responses that includes altered blood flow and vasoregulation, disruption of the blood–brain barrier, increases in intracranial pressure, focal or diffuse ischemia, hemorrhage, inflammation, necrosis, and disruption of fiber tracts (*see* ref. 57). Head trauma with cerebral contusion or primary ICH causes extravasation of red blood cells, followed by hemolysis and deposition of iron-containing blood products within

the neuropil. Liberation of heme compounds is associated with deposition of hemosiderin and, with gliosis, neuronal loss and occasionally the development of seizures. Free radical reactions initiated by iron or heme deposited within the neuropil may be a fundamental reaction associated with brain injury responses, and possibly with posttraumatic epileptogenesis. Hemoglobin has been demonstrated to be neurotoxic when injected into the cerebral cortex in vivo. Exposure of neuronal cultures to hemoglobin for 24–28 h produced widespread and concentration-dependent neuronal death *(51)* that was blocked by the ferric iron chelator deferoxamine. Thus, hemoglobin may be neurotoxic, and its neurotoxicity may contribute to neuronal injury processes after trauma and ICH.

An increase in leukotriene-like immunoreactivity was identified by radioimmunoassay in the gerbil forebrain following ischemia and reperfusion, subarachnoid hemorrhage, or nonlethal concussive brain injury *(58)*. Cerebral vessels and circulating blood are capable of producing leukotrienes, which may have a role in the pathophysiology of cerebral edema formation, cerebral vasospasm, and seizure activity following ICH.

Epileptogenesis following neocortical trauma may result from two sources of disinhibition, including the physical removal of important superficial inhibitory circuits and glutamate-triggered increases in intracellular calcium *(59)*. Using a fluid percussion injury (FPI) model and patch-clamp recordings from hippocampal slices, D'Ambrosio et al. *(60)* found impaired glial physiology 2 d after FPI. A reduction in transient outward and inward K^+ currents was observed that resulted in an abnormal extracellular K^+ accumulation in the post-traumatic hippocampal slices, accompanied by the appearance of CA3 after-discharges. Traumatic brain injury (TBI) causes loss of K^+ conductance in hippocampal glia that results in the failure of glial K^+ homeostasis. Enhanced self-sustaining epileptogenic activity and disinhibition were observed in hippocampal slices from rats exposed to lateral FPI *(61)*.

One study evaluated the incidence of seizure activity following acute traumatic brain injury to the right parietal cortex in artificially ventilated rats *(62)*. Generalized seizure activity occurred within 1 min and was accompanied by a transient increase of aspartate, taurine, glutamate, and glycine. These investigators concluded that elevated levels of aspartate and glutamate may have a role in post-traumatic seizure activity. Following FPI, two typical responses to TBI were recorded *(63)*. Some animals developed seizures at various stages after TBI. When severe injury was induced, ischemic depolarization (ID) developed, whereas mild or moderate injury led to repetitive spreading depression (SD) cycles. Intracranial pressure (ICP) before injury was between 2 and 6 mmHg and increased to 20–22 mmHg 2–3 min after ID. Following severe head injury, ICP remained high and in some cases increased to critical values, causing death of these animals.

Complications of Seizures in Acute Neurological Disturbances

Seizures in the setting of acute neurological disorders such as acute stroke or hemorrhage can lead to numerous medical and neurologic complications. For example, increased ICP, hypoxemia, acidosis, and hypercarbia may contribute to worsening brain ischemia in stroke or subarachnoid hemorrhage. Hypoxia during a generalized tonic clonic seizure can in theory extend neuronal HI injury.

Patients may develop high ICP in the setting of prolonged seizures or SE. Increased ICP can occur during both complex partial and generalized tonic-clonic seizures. Previous work has demonstrated loss of vasomotor regulatory tone in the cerebrovascular bed in the setting of generalized tonic-clonic seizures. As such, the normal mechanisms that protect against increased ICP in the setting of rising MAP are lost. Changes in the pressure–volume compliance curve during generalized tonic-clonic seizures result in large and potentially life-threatening increases in ICP. These considerations are especially important in the setting of large cerebral infarctions or hemorrhages in which ICP is already precariously close to generating an incipient herniation syndrome. Experimental results in cats examined the relationship between prolonged convulsions and ICP *(64)*. Pentylenetetrazole- or bicuculline-induced convulsions resulted in a three- to fivefold increase in ICP attaining maximal pressures of 20–94 mmHg after 20–420 s of seizure activity. Interestingly, the ICP remained high for between 47 s and 10 min but then began to fall gradually, reaching pre-ictal levels after 2–30 min despite the continuation of convulsions. Changes in ICP were independent of changes in blood pressure. In one report, ICP and electroencephalographic activity were monitored in a patient with viral encephalitis and frequent partial motor seizures. Each ictal episode was associated with stable blood pressure and an increase in ICP *(65)*. The average seizure duration was approx. 1 min, and the average maximum increase of ICP above baseline during the seizures was 6.5 mmHg. These investigators used a simple mathematical model to predict the rate of ICP increase, the peak ICP, the phase difference between maximum spike frequency and maximum ICP, and the rate at which ICP returned to pre-ictal values after termination of the seizure. They concluded that the time course of the ICP appears to be determined by the frequency of spikes and the CSF pressure–volume dynamics existing at the time of the seizure.

Metabolic consequences of seizures are more likely to accompany SE and include hypoxia, hypercarbia, respiratory and metabolic (lactic) acidosis, rhabdomyolysis, and cardiac ischemia. In addition to absent respiratory effort during a convulsion, airway obstruction in even a single generalized tonic-clonic seizure can lead to diminished tissue oxygenation. Aspiration

pneumonia remains an important risk following either single or prolonged seizures and, if missed, can lead to sepsis, the acute respiratory distress syndrome (ARDS), and the need for prolonged mechanical ventilation. Rarely, neurogenic pulmonary edema may develop in the setting of SE. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion or neurogenic diabetes insipidus can follow convulsive SE. Elevated creatine kinase levels may herald rhabdomyolysis, which can lead to acute renal insufficiency.

Several side effects of AEDs may complicate the clinical picture in patients with seizures and acute neurological disorders. Hypotension in patients receiving intravenous phenytoin can exacerbate poor cerebral perfusion in the setting of acute stroke. Similarly, cardiac dysrhythmia following phenytoin (PHT) *(66)* may diminish cerebral perfusion and worsen brain ischemia. Significant sedation can accompany phenytoin, phenobarbital (PB), and carbamazepine (CBZ) administration, which can cloud interpretation of the mental status exam.

The incidence of head injuries and intracranial hematomas owing to falls caused by seizures is increased in epilepsy patients. In one series of 1760 adult head-injured patients, 582 head injuries (33.1%) were caused by falls and 22 (3.8%) of these were caused by seizures *(67)*. Based on the prevalence rates for epilepsy in the general population of 0.5–2%, the investigators concluded that epilepsy patients are several times more likely to suffer a head injury as the result of a fall.

Diagnostic Considerations

A first-time seizure may in fact be a manifestation of a new and potentially life-threatening neurologic event such as stroke, ICH, subarachnoid hemorrhage, or encephalitis. Seizures in the setting of acute TBI may herald substantial CNS injury. It is also important to remember that concomitant medical illnesses such as hypoxemia, hypoglycemia, hyponatremia, hypocalcemia, hepatic or renal failure, urinary tract infections, pneumonia, sepsis, and iatrogenic or illicit drug use may lower seizure threshold in any individual and especially those with CNS structural injury. In addition, recent expert opinion has suggested that seizures persisting for >5 min should be viewed as SE and treated as such *(68,69)*.

On first assessment of a patient with seizures and known or suspected neurologic disease, a calm and methodical approach is best adopted. If possible, a thorough history should be obtained from patient family members or friends regarding recent symptoms or complaints such as change in mental status, history of TIA or stroke, loss of vision, focal weakness or sensory loss, or change in gait. Use of prescription or illicit drugs should be determined. Initial assessment of vital signs and maintenance of airway, breathing, and circulatory sta-

bility ("ABCs") is paramount. Special attention should be given to the presence of cardiac dysrhythmias such as atrial fibrillation, which may predispose to embolic stroke. Once these parameters are ascertained, a rapid but complete neurologic exam should be performed. Salient features of the exam should include determination of mental status and, if indicated, gradation using the GCS. Evidence of localizing signs such as pupillary or eye movement abnormalities, hemiparesis, reflex asymmetry, or extensor plantar reflexes should be sought. If feasible, funduscopic exam may be revealing especially in the setting of increased intracranial pressure (papilledema), acute stroke (Hollenhorst plaques), or septic cardiac emboli (Roth spots). Evidence of CNS infection such as meningismus, headache, fever or supportive evidence such as rash should also be sought and an early decision regarding lumbar puncture should be made. Initial laboratory studies should include electrolytes, serum glucose, O_2 saturation and/or arterial blood gas, complete blood count with differential, toxicology profile, AED levels if detected in toxicology screen, and β-HCG (human chorionic gonadotropin) in female patients.

If there is strong suspicion of acute CNS lesion, a neuroimaging study such as CT or magnetic resonance imagery (MRI) is indicated. If infection is suspected, an initial dose of antibiotics or antiviral medications such as acyclovir may be given prior to imaging and CSF examination. As a general rule, it is better to control a patient's seizures with intravenous medications such as lorazepam or diazepam prior to initiation of a neuroimaging study. Patients who experience seizures in the MR or CT scanner are at risk for injury from fall, aspiration, asphyxiation, and post-ictal confusion or aggression. Additionally, in the absence of known hypersensitivity to benzodiazepines, there are currently no neurologic disorders including potentially life-threatening conditions such as SAH, epidural hemorrhage, meningitis, stroke, or increased ICP, in which rapid treatment of seizures with benzodiazepines is contraindicated. In short, cessation of seizures, even if only for a brief period while more clinical data are obtained, is the goal in the setting of acute neurologic disorders.

EEG Monitoring

A recent review outlines the role of continuous EEG (CEEG) monitoring in the NICU and Emergency Department *(70).* CEEG may serve as a neurophysiologic monitor that can detect brain abnormalities at a reversible stage and therefore guide timely and physiologically sound interventions *(71).* CEEG monitoring is of benefit in the early diagnosis and management of cerebral ischemia, acute cerebral infarction, and post-SAH vasospasm. In comatose patients, it can provide important diagnostic and prognostic information. More recently, it has been found advantageous for targeting management of acute severe head trauma patients.

EEG Findings in Acute Stroke

Evidence of focal slow activity may suggest an underlying structural brain lesion such as a cerebral infarct or hemorrhage. Periodic lateralized epileptiform discharges (PLEDs) are most commonly associated with acute vascular lesions and may persist for several months following a stroke. Focal high-voltage delta waves with polyspikes (FHDPS) may correlate with ictal events including focal clonic or myoclonic seizures in patients with MELAS *(72)*. In the subacute and chronic stages, focal spikes or sharp waves and 14- and 6-Hz positive bursts were recorded frequently in MELAS patients. Intracranial EEG in one reported patient with PVLM demonstrated multifocal epileptic discharges *(73)*. In one series, the most common electroencephalographic abnormality in patients with seizures and acute stroke was focal slowing *(4)*. Recurrent seizures occurred in all of the 4 patients with PLEDs and in 75% of the 8 patients with diffuse slowing.

EEG Findings in ICH

The EEG changes associated with ICH are typically focal and more pronounced than those seen in ischemic stroke. More overt EEG changes occur in the setting of lobar hemorrhage than thalamic or basal ganglia hemorrhage. Whereas spikes or sharp waves may develop, they are often not seen in the setting of acute ICH. In contrast, focal ipsilateral delta activity (intermittent or continuous) and loss of normal background cerebral activity, i.e., alpha and sleep spindles, may be observed in regions adjacent and ipsilateral to the ICH. ICH involving the third ventricle or those with extension into the ventricular system or thalamus bilaterally may cause clinical coma. In these patients, the EEG may reveal diffuse bilateral theta and delta with minimal spontaneous reactivity. Finally, cerebellar hemorrhage may occur with little change in the EEG as long as the patient remains awake. If brainstem compression occurs, loss of consciousness will be followed by diffuse delta and theta activity on the EEG. In the setting of subarachnoid hemorrhage, more diffuse abnormalities may be detected such as diffuse theta or delta. Marked suppression of the background amplitudes may also occur. If there is extension of the hemorrhage into the brain parenchyma, focal delta may be seen in this region.

EEG Findings in CNS Infection

In virtually all forms of viral encephalitis, the EEG is abnormal to some extent. Diffuse delta is seen most commonly but intermittent rhythmic delta may also be observed. The EEG in the acute stage of HSVE can show a variety of abnormalities, including unilateral or bilateral periodic sharp waves or

attenuation of amplitude, focal or generalized slow waves or epileptiform discharges, or electrographic seizures (for comprehensive review, *see* ref. *74*). No specific EEG patterns are pathognomonic for HSVE, but a focal or lateralized EEG abnormality in the presence of encephalitis is highly indicative of HSV infection. In the acute stage, EEG appears to be more sensitive than CT imaging or radioisotope brain scanning. The EEG findings tend to differ during the course of illness, and the periodic discharges occur only during the acute stage. The EEG findings in either the acute stage or on long-term follow-up do not predict the chance of survival or severity of disability, and EEG changes appear to lag behind the clinical changes. EEG results can become normal in both adults and neonates when the acute stage is over. In one study, the EEG abnormalities included frontotemporal delta slowing in five patients, periodic lateralized epileptiform discharge in three, and runs of spike and periodic activity in one patient each *(75)*. Periodic discharges are considered by many as a sine qua non of HSVE, although PLEDs may be seen in a variety of other disorders. The periodicity of PLEDs in HSVE and other viral encephalidities tends to be more rhythmic and montonous *(76)*.

In one series of 32 patients with tuberculous meningitis, the EEG was abnormal in 24 patients *(77)*. The EEG abnormalities included diffuse theta or delta slowing in 22 patients, frontal intermittent rhythmic delta activity (FIRDA) in 15, asymmetry in 5, and epileptiform discharges in 4 patients. The EEG findings correlated with the severity of meningitis, the degree of coma, and outcome at 3 mo as assessed by the Barthel index score.

EEG Findings in Brain Trauma

After initial loss of consciousness following brain injury, background EEG may show diffuse slowing. Epileptiform abnormalities such as sharp waves and spikes may be seen immediately and may be either focal or widespread. In the setting of mild brain trauma, the EEG may be normal or exhibit subtle slowing. Following severe brain trauma there may be a dramatic cessation of EEG activity. In one series of 76 patients, spontaneous EEG activity was initially absent from 33 patients who were subsequently shown to have no cerebral perfusion by angiography. EEG activity was recorded in 32 patients, but 20 of these died within the ensuing 2–4 d *(78)*. EEG and CT scans of 280 cases of minor head injury in children under 15 yr of age were studied *(79)*. Abnormality on initial EEG was shown in 42.5% patients. Those who lost consciousness had a higher incidence of abnormality than those who did not, and incidence was also higher between 4 and 13 yr of age. The most frequent abnormality was slow waves, seen predominantly in the occipital regions. The EEGs became or remained normal in 95% of patients.

Therapeutic Considerations

Recent evidence suggests that prophylactic AEDs are effective in reducing early seizures following brain trauma, but there is no evidence that treatment with such drugs reduces the occurrence of late seizures (i.e., epilepsy), or has any effect on death and neurological disability *(80)*. Whereas AED prophylaxis for posttraumatic seizures (PTS) is common, results of clinical trials raise questions regarding the benefits of such treatment. A subcommittee of the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation reviewed published literature (1998) regarding AED prophylaxis of PTS and suggested recommendations in the form of a practice parameter *(81)*. The treatment standard is that prophylactic use of PHT, CBZ, sodium valproate (VPA), or PB is not recommended for preventing late PTS, defined as seizures that occur after 1 wk of injury, in the patient in whom there has been no history of seizures following a nonpenetrating traumatic brain injury. However, it is recommended as a treatment option that PHT, PB, and CBZ may be used to prevent early PTS in patients at high risk for seizures following TBI. Finally, prophylactic use of PHT, CBZ, VPA, or PB is not recommended for preventing late PTS following penetrating TBI.

The long-term use of AEDs to prevent postoperative seizures in patients with cerebral aneurysms is common. However, in recent case series of aneurysm patients, there has been a low incidence of seizures. To investigate the incidence of seizures following aneurysm surgery, Baker et al. *(82)* categorized 387 of the 420 craniotomies for aneurysm surgery over a 4-yr period into those deemed to have low risk of seizure. Postoperative anticonvulsant medication in this group was restricted to an average of 3 d. A retrospective analysis of the incidence of early postoperative seizures and late postoperative seizures was performed in the populations of patients with ruptured and unruptured aneurysms with an average follow-up of 2.4 yr. The overall seizure rate in the study group was 5.4%. Patients with ruptured aneurysms had an early postoperative seizure rate of 1.5% and a long-term seizure rate of 3.0%. Early and long-term seizure rates for unruptured aneurysms were 2.6% and 4.4%, respectively. No patients who had early seizures went on to develop epilepsy, and all seizures were well controlled once AEDs were begun. These data support the idea that anticonvulsant medication may be safely restricted to the immediate perioperative period for most patients with aneurysms.

The prevalence of perioperative seizures following subdural hematoma was reviewed in 98 patients *(83)*. The onset of new seizures was found in 17 (18.5%) of 98 patients and was associated with increases in morbidity and mortality. Patients who received prophylactic AED demonstrated a significant decrease in the occurrence of seizures, and these investigators concluded that PHT prophylaxis in patients treated surgically for chronic subdural hematoma was beneficial.

Prophylactic treatment with AEDs is not clearly indicated for most types of strokes. In a study of ICH, Berger et al. *(27)* concluded that the prophylactic use of anticonvulsants in the acute management of ICH patients is unwarranted, especially in those patients in whom the ICH does not involve cortex. In patients with lobar ICH that affects cerebral cortex, AEDs may afford some prophylactic benefit especially in the setting of increased ICP.

In pre-eclampsia or eclampsia, recent multicenter studies show a benefit of magnesium sulfate over either PHT or diazepam in the prevention of seizures. In a prospective study of over 200 female patients, Lucas et al. *(84)* demonstrated that magnesium sulfate was superior to PHT for the prevention of eclampsia in hypertensive pregnant women. In a recent series of 50 eclamptic females randomized to either PHT or magnesium sulfate *(85),* women treated with PHT had a higher incidence of recurrent seizures (10 of 25–40%) than those treated with magnesium sulfate (2 of 25–8%). The majority of the women treated with PHT (6 of 10–60%) had single convulsion after initiation of anticonvulsant therapy and 1 woman in each group had recurrent convulsions. There was no significant difference in perinatal outcome in either group. Maternal morbidity was comparable in both groups, and there was no maternal death in either group. In addition to its anticonvulsant properties, magnesium sulfate may offer additional prophylaxis against stroke in eclampsia.

Summary

Seizures may herald an acute neurologic disturbance and therefore must be fully investigated. The assiduous clinician can glean from a thorough history and careful neurologic exam a rapid assessment of potentially life-threatening disorders and be able to institute appropriate diagnostic tests and therapeutic maneuvers.

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