

# Subarachnoid Hemorrhage-Related Epilepsy



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**Abstract** Epilepsy is a significant worldwide public health problem that leads to reduced quality of life and negative psychosocial consequences and significantly increases mortality rates in those who are affected. The development of epilepsy from subarachnoid hemorrhage (SAH) has an important negative impact on long-term survival, functional status, and cognitive recovery in patients following aneurysmal rupture. Anticonvulsant medication (AED) administration to prevent the development of epilepsy following SAH is controversial, and studies to date have not shown effectiveness of AED use as prophylaxis. This paper reviews the pathophysiology of SAH in the development of epilepsy, the scope of the problem of epilepsy related to SAH, and the studies that have evaluated AED administration as prophylaxis for seizures and epilepsy.

## Introduction

Epilepsy affects many people worldwide representing 0.6% of the global burden of disease as measured by disability-adjusted life years [18]. In North America the prevalence rate is estimated to be 10/1000 [9]. However, in the severely under-resourced regions of the world such as sub-Saharan Africa, epilepsy prevalence is much higher. For example, epilepsy prevalence in East Africa has been estimated to be as high as 13% [13]. Worldwide including North America, poverty has been strongly linked with elevated epilepsy prevalence [4].

Most people with epilepsy (PWE) will have their seizures controlled with medication. However, a surprisingly large

population (about 30%) of PWE will be refractory to medication, so-called medically intractable epilepsy (MIE). MIE is defined by the International League Against Epilepsy as the failure of two or more antiepileptic medications (AEDs) to control the seizures [16]. Despite the currently approximately 20 medications available in the United States and Europe for epilepsy, only 2 need to be tried and failed to meet the definition of intractability. If two or more AEDs have failed to stop the epilepsy, the opportunity of any new medication or combination of medications to stop the epilepsy is less than 5% [15].

Individuals with MIE are found to have reduced health-related quality of life, and MIE is associated with significant negative psychological and social consequences including lower education levels, lower rates of employment, social isolation, and stigma [2, 5, 7].

MIE results over time in morbidity of cognitive decline due to recurrent seizures and significantly increases the mortality rate of individuals with epilepsy. The cognitive consequence of MIE is most commonly seen in patients with temporal lobe epilepsy that particularly negatively impacts memory function. A decline in declarative memory is thought to result from excitotoxic injury to the mesial temporal lobe structures, which often manifests neuroanatomically as an atrophic hippocampus [8]. Epilepsy is a dangerous disease that has a mortality rate 2.3 times that of age-matched controls in the general population. Most striking however are individuals with MIE who are exposed to a risk of death 4.69 times the general population [26]. The excess mortality is mostly due to sudden unexpected death in epilepsy (SUDEP), trauma, and other injuries.

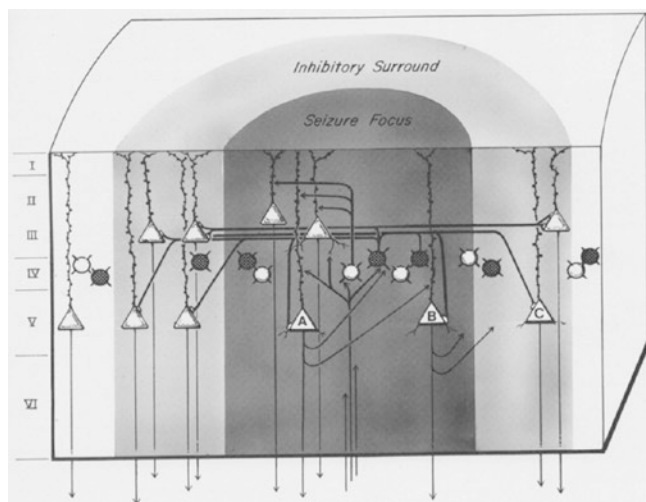
## The Epileptic Focus

A seizure results from paroxysmal depolarization, which is an exaggeration of the normal neuronal depolarization. This occurs when a predominance of glutaminergic excitation

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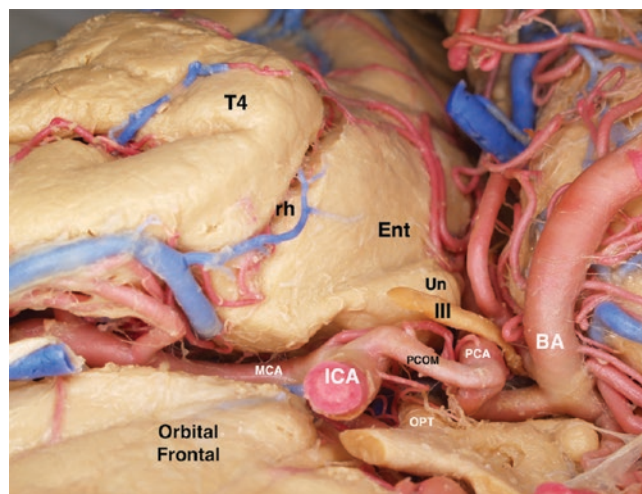
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**Fig. 1** The figure illustrates a conceptual framework for the initiation and propagation of a seizure. Cell A represents an epileptic pyramidal neuron; discharges will capture cell B via excitatory recurrent collateral connections. When many cells like A and B fire synchronously, an epileptic spike appears on EEG. Inhibitory interneurons (dark round cells) become activated and turn off cells A and B as well prevent spread of the seizure discharge to neurons in the surrounding cortex (cell C). Reprinted by permission of Oxford University Press, USA. From Lothman EW, Collins RC. *Seizures and Epilepsy*. In: *Neurobiology of Disease: Seizures and Epilepsy* edited by Pearlman and Collins (1990) Fig. 1 pp. 276–298

overcomes the surrounding GABAergic inhibition (Fig. 1). The limbic structures including basal forebrain and mesial temporal lobes are the most susceptible brain regions to epileptogenesis, and these supratentorial bases of the brain regions are most likely to be involved by an anterior circulation aneurysmal subarachnoid hemorrhage due to the close proximity to the circle of Willis (Fig. 2).

Different factors related to SAH can induce the changes required in the cortex that will lead to cortical hyperexcitability. One of the most important contributors to injury and neuronal hyper-excitability is the breakdown products of subarachnoid hemorrhage, predominantly Fe compounds derived from hemoglobin. Free iron is a potent oxidizer that damages cell membranes due to creation of reactive oxygen species, peroxidation damage to cell membrane lipids, production of free radicals, and injury to oxidant-sensitive cellular enzymes such as Na, K-ATPase [25]. Yip and Sastry studied the effects of hemoglobin and its degradation products (hemin and iron) on synaptic transmission in a rat model [31]. While hemoglobin did not appear to produce significant effects on synaptic transmission, both hemin and iron were shown to have significant effect on neuronal function by depressing the excitatory postsynaptic potential. In hemorrhagic stroke or intracerebral hemorrhage, iron released from the hemoglobin that has leaked out of the neurovascular space is a potent oxidative metabolite that produces free radicals which ultimately leads to neuronal cell death [23].



**Fig. 2** View of a fixed and injected brain from the orbital frontal surface looking posteriorly. The normal relationship of internal carotid artery and circle of Willis vascular structures that lie adjacent to the highly epileptogenic limbic brain structures of the mesial temporal and orbital frontal regions is visualized. *T4* fusiform gyrus of the temporal lobe, *rh* rhinal sulcus, *Ent* entorhinal sulcus (most anterior extent of the parahippocampus), *Un* uncus, *III* oculomotor cranial nerve, *ICA* internal carotid artery, *PCA* posterior cerebral artery, *PCOM* posterior communicating artery, *OPT* optic chiasm, *BA* basilar artery

Additionally, iron compounds, such as FeCl<sub>3</sub>, have been commonly used in animal models of epilepsy due to their highly epileptogenic effect when injected into the animal hippocampus and cortex [27, 30].

Brain injury of any type leads to an increase in permeability of the blood-brain barrier and neuroinflammatory responses [1]. Subarachnoid hemorrhage and blood breakdown products result in oxidative stress due to overproduction of reactive oxygen species, which in turn incite a neuroinflammatory reaction. Neuroinflammation results from a myriad of mediators released from the injured blood vessels and immune cells of the body that responds to injury. The resulting inflammatory process is a powerful epilepsy inducer that contributes to not only epileptogenesis but drug resistance as well in animal models [29]. And a number of anti-inflammatory drugs have been found to reduce experimental model epilepsy seizure frequency and/or seizure duration as well as mitigate experimental epileptogenesis [28]. Many human epilepsy syndromes are being recognized to be mediated by neuroinflammation resulting in an increase in immune-modulating therapies benefitting human epilepsy as well [14].

### Subarachnoid Hemorrhage-Related Epilepsy

The risk of developing epilepsy after SAH has been analyzed in two large population-based studies. The cumulative incidence of epilepsy in a Finnish population served by one ter-

tiary hospital was found to be 8% at 1 year after hemorrhage and increased to 12% after 5 years [11]. Olafsson et al. in an Iceland population-based study identified that 25% of individuals with ruptured aneurysmal SAH developed epilepsy [20]. The actuarial risk of epilepsy was 18% by the first year, 23% by the second year, and 25% by the fifth year in survivors of SAH. Aneurysm location most associated with the development of SAH-related chronic epilepsy is middle cerebral artery at the M1 branch and artery bifurcation [11]. Severe Hunt and Hess scores as well as intraventricular hemorrhage elevate the risk of having a seizure after SAH [21]. Also, the degree of neurological impairment and presence of an acute seizure soon after the time of SAH have been identified as factors increasing the risk of chronic epilepsy [20].

The development of epilepsy from subarachnoid hemorrhage has an important impact on the cognitive recovery and long-term survival of the patient after aneurysm rupture. In one population study of individuals admitted to an Eastern Finland hospital and alive at least 12 months after subarachnoid hemorrhage, Jukka Huttunen et al. analyzed epilepsy-related long-term mortality [12]. Using cox regression analysis of risk factors of mortality from ruptured intracranial aneurysms, the authors identified that acute seizures occurring within 1 week after admission had no significant relationship with death. However, death at over 12 months after subarachnoid hemorrhage was highly correlated with SAH-related chronic epilepsy.

Seizures following SAH more commonly occur acutely during hospitalization and may be identified in as many as 10–20% of patients who suffer from SAH and are mostly nonconvulsive [10]. Barret Rush et al. queried a nationwide inpatient database to evaluate the association between seizures and mortality in patients with aneurysmal subarachnoid hemorrhage [24]. The presence of seizures during the hospital stay among several other variables was identified to be a factor significantly associated with mortality, and in those patients who survived hospitalization, having a seizure increased the patients' hospital length of stay. The overall burden of number of seizures experienced in SAH-related nonconvulsive epilepsy was found by De Marchis et al. to be highly associated with functional and cognitive decline [6]. The authors identified in SAH patients who underwent continuous EEG monitoring during the hospital stay, the detection of any seizure on EEG was associated with more than threefold elevated odds of unfavorable outcome at 3 months in functional status and cognitive abilities.

## AED Prophylaxis

AED prophylaxis is a topic of both interest and controversy. Due to the high seizure risk observed following SAH and the unfavorable outcome associated with seizures, preven-

tion should be an important part of treatment to reduce disability and death. However, prophylactic anticonvulsant medications have performed poorly and not substantially reduced the incidence of early or late seizures and epilepsy after SAH [22].

Raper et al., after reviewing seizures following aneurysmal SAH, determined there was no significant difference in the incidence of early or late seizures in individuals who received AEDs compared to those who received no AEDs [22]. Similarly, Panczykowski et al. analyzed the use of prophylactic AED administration following spontaneous subarachnoid hemorrhage [21]. This study identified the risk of clinical or electrographic seizures was significantly associated with severe Hunt-Hess score and intraventricular hemorrhage. However, the incidence of seizures did not vary significantly based on the use of AED prophylaxis, and a propensity score-matched analysis suggested patients who received prophylactic AED had a similar likelihood of suffering seizures as those who did not. After adjustment for Hunt-Hess score, cisternal SAH burden, and intraventricular hemorrhage, the multivariable regression analysis did not reveal prophylactic AED therapy to be a significant predictor of seizure risk; likewise, timing of prophylactic AED administration and duration of treatment did not impact seizure risk.

Despite a lack of evidence of efficacy, anticonvulsants are often prescribed to patients as seizure prophylaxis. Of the anticonvulsant therapies available, phenytoin has historically been administered for seizure prophylaxis after SAH, though current practice is trending toward the use of levetiracetam. However, adverse effects of AEDs may outweigh benefit in preventing seizures. Naidech et al. studied the use of phenytoin in SAH patients [19]. The use of phenytoin was associated with poor functional and cognitive outcome in a dose-dependent manner following subarachnoid hemorrhage at 14 days. The higher phenytoin dose burden increased the odds of poor functional outcome at 14 days. The higher quartile of phenytoin dosage was also associated with worse cognitive status scores both at discharge and at 3 months.

The newer anticonvulsants have also been implicated in worse functional outcome when prescribed as seizure prophylaxis in SAH. Human et al. identified in a randomized open-label trial of levetiracetam use as prophylaxis in SAH patients that administration of medication during the entire hospitalization resulted in significantly reduced functional status compared to patients that stopped medication after 3 days from admission [10]. In an animal model of neuroinflammation type of epilepsy, exposure to levetiracetam increased the number of seizures and seizure burden of the epileptic mice that was cumulative over time [3].

## Conclusion

Epilepsy is a worldwide burden that results in reduced quality of life, is associated with negative psychosocial consequences, and significantly elevates mortality rates in those who are affected. The development of epilepsy from SAH plays an important role in the impact of long-term survival, functional status, and cognitive recovery in patients following aneurysmal rupture. Utilization of AEDs to prevent the development of epilepsy following SAH continues to remain a controversy, and studies to date have not shown effectiveness of AED use as prophylaxis. In fact, the weight of the evidence suggests harm from the administration of AEDs as prophylaxis. Despite clear guidelines existing for the use of AED to prevent early seizures in traumatic brain injury, evidence is lacking in SAH. The Epilepsy Group of the Cochrane Collaboration identified a lack of evidence to support or refute the use of AEDs for the prevention of SAH-related seizures and concluded that “well-designed randomized controlled trials are urgently needed to guide clinical practice [17].”

**Conflict of Interest** The authors affirm that they have no conflicts of interest related to this manuscript.

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