

Seizures and Epilepsy following Subarachnoid Hemorrhage: A Review on Incidence, Risk Factors, Outcome and Treatment

Crises convulsivas e epilepsia após hemorragia subaracnoide: uma revisão sobre incidência, fatores de risco, desfecho e tratamento

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Abstract

The mortality rates of subarachnoid hemorrhage (SAH) average 51%, and survivors frequently experience acute and long-term neurological conditions, including seizures and epilepsy. The incidence of post SAH-related seizures and epilepsy, its risk factors, outcomes and management are controversial. The present paper aims to discuss these aspects, to provide the pros and cons of different management options of this condition. A review on PubMed was performed encompassing the incidence of seizures and epilepsy following SAH, the risk factors for its occurrence, its related outcomes, and treatment. The incidence of seizures and epilepsy following SAH varies widely in the literature (from 6 to 26%). Some possible risk factors were identified, such as middle cerebral artery (MCA) aneurysm, Hunt and Hess grade III, aneurysm clipping, thick subarachnoid clot, intracerebral hemorrhage, rebleeding, ischemic brain infarction, Fisher grade III or IV, acute hydrocephalus, hypertension history and poor World Federation of Neurosurgical Societies (WFNS) grade. Nevertheless, these relations are frequently uncertain. Also, it appears that the outcome of patients who suffered SAH is worsened by seizures. Given these uncertainties, the need for antiepileptic drug (AED) prophylaxis, the choice of the best drug and dose, as well as the duration of the treatment are controversial topics. However, some recommendations based on low quality evidence are reasonable to be adopted. These include considering AED prophylaxis when a seizure occur after SAH, considering routine long-term AED prophylaxis in specific populations, considering electroencephalogram (EEG) monitoring, and avoiding phenytoin prescription. That is, an individualized approach appears to be the best option, since there is no high-quality evidence.

Keywords

- ▶ subarachnoid hemorrhage
- ▶ epilepsy
- ▶ incidence
- ▶ risk factors
- ▶ anticonvulsants
- ▶ prognosis

Resumo

As taxas de mortalidade da hemorragia subaracnoide (HSA) são de 51%, e os sobreviventes frequentemente sofrem condições neurológicas agudas e em longo prazo, incluindo convulsões e epilepsia. A incidência de convulsões e epilepsia após

HSA, seus fatores de risco, desfecho e tratamento são controversos. O presente artigo pretende discutir esses aspectos para fornecer os prós e os contras de diferentes opções de manejo dessa condição. Realizou-se uma revisão no PubMed, englobando a incidência de convulsões e epilepsia após HSA, os fatores de risco para a sua ocorrência, seu desfecho e tratamento. A incidência de convulsões e epilepsia após HSA varia amplamente na literatura (de 6 a 26%). Alguns possíveis fatores de risco foram identificados, como aneurisma da artéria cerebral média (ACM), Hunt e Hess grau III, clipagem do aneurisma, coágulo subaracnoide espesso, hemorragia intracerebral, ressangramento, isquemia cerebral, Fisher grau III ou IV, hidrocefalia aguda, história de hipertensão e uma pontuação desfavorável na escala da Federação Mundial de Sociedades de Neurocirurgia (WFNS, na sigla em inglês). Entretanto, essas relações frequentemente são incertas. Além disso, os pacientes que apresentam convulsões após HSA parecem ter pior desfecho. Devido a essas incertezas, a necessidade de profilaxia com anticonvulsivantes, a escolha do melhor fármaco e posologia, e a duração do tratamento são controversos. Contudo, algumas recomendações baseadas em evidências de baixa qualidade podem ser adotadas. Elas incluem considerar profilaxia com anticonvulsivantes para convulsões pós HSA, considerar profilaxia rotineira em longo prazo em populações específicas após HSA, considerar monitoramento com eletroencefalograma (EEG), e evitar a prescrição de fenitoína. Ou seja, uma abordagem individual parece a melhor opção até que haja evidências de alta qualidade.

Palavras-chave

- ▶ hemorragia subaracnoidea
- ▶ epilepsia
- ▶ incidência
- ▶ fatores de risco
- ▶ anticonvulsivantes
- ▶ prognóstico

Introduction

Mortality rates due to subarachnoid hemorrhage (SAH) seem to be decreasing in some countries; yet, it averages 51%.¹⁻⁵ However, survivors often develop acute and long-term severe neurological conditions. These conditions include neurocognitive dysfunction, seizures and epilepsy, as well as various other focal neurological deficits.^{1,6,7}

The incidence of seizures and further epilepsy development following SAH vary widely in literature.⁸⁻¹⁶ More recent data suggest that this figure is decreasing over the years, which may be explained by the recent improvement in SAH management.^{7,17-24} Although the exact incidence remains unclear, several factors were described to be associated with a greater risk of seizures and epilepsy development after SAH.^{7,10,17,25-29} Moreover, the outcomes appear to be worsened by seizures after SAH – with some controversies.^{8,10,14,15,18,30}

Since there is a high variability regarding the incidence, the risk factors and outcome of seizures and epilepsy after SAH, the need for antiepileptic drug (AED) prophylaxis, the choice of the best drug and dose, as well as the duration of the treatment remain unclear. Therefore, this paper aims to discuss aspects related to the incidence, risk factors, outcome, and treatment of seizures and epilepsy after SAH, to provide the pros and cons of different management options.

Materials and Methods

A literature review was performed on PubMed during the period of February 2018, encompassing aspects related to the incidence of seizures and epilepsy following SAH, the risk factors for their occurrence after SAH, the related outcomes, and the treatment of this condition.

Key Concepts

The International League Against Epilepsy (ILAE) provides 3 conditions in which epilepsy can be defined: 1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years; or 3) diagnosis of an epilepsy syndrome.³¹

A seizure is defined by a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.³¹ In addition, these seizures can be classified as provoked or unprovoked. Provoked seizures, also called 'reactive seizures' or 'acute symptomatic seizures,' are defined as seizures caused by an acute condition, including SAH. Conversely, unprovoked seizures are those of unknown etiology or those that occur in relation to an existing prior brain lesion or progressive nervous system disorder.³¹

A SAH can provoke seizures as well as cause a brain lesion that will then lead to unprovoked seizures. Therefore, it is possible for a patient who suffered SAH to develop late epilepsy (that is, epilepsy), with one of the criteria for epilepsy diagnosis occurring after one week of the onset of the acute event.¹⁰

Incidence

The incidence of seizures following SAH varies widely in the literature, reaching values between 6% and 26%.⁸⁻¹⁶ Although more recent studies show a decrease in the incidence of clinical seizures, the spreading of continuous electroencefalogram (EEG) monitoring allows the recognition of nonconvulsive status epilepticus (NCSE) as well as subclinical seizures.^{8-10,14-16} It is also important to state that

the majority of studies was retrospective and there is the possibility that some seizures were not registered.²⁸ In addition, partial seizures were sometimes excluded and, frequently, seizures are not witnessed by a health professional.^{7,10} The onset of seizure-like behavior was reported to be frequent, accounting for a big part of post SAH seizures.^{8,10,32,33} However, it is not known if these are truly epileptic in origin or if they represent just a posturing at the time of the aneurysmal rupture.^{32,33}

The occurrence of seizures after the onset of SAH is, in general, less common than the onset seizures.²⁹ Among post-treatment seizures, a systematic review demonstrated that early posttreatment events (those occurring during the initial hospital stay after intervention) were observed in 2.3% of patients who suffered SAH, while late seizures (occurring after discharge from the hospital) were observed in 5.5%, with an average latency of 7.45 months.²⁸ In addition, Claassen et al¹⁸ showed that 11% of the patients who suffered SAH had at least one unprovoked seizure in one year as survivors. Yet, seizures may occur years after the initial SAH episode.^{34,35} Actually, late seizures can be related to rebleeding of the aneurysm, gliosis, and development of meningocerebral cicatrix.^{13,34}

Since the conditions to make the diagnosis of epilepsy were updated in 2014, its precise incidence following SAH may be difficult to assess in older studies.³¹ Actually, the incidence of late epilepsy following SAH remains uncertain, ranging from 3 to 35%.^{7,17-24} However, it appears to be decreasing over the years, which may be explained by improvements in the management of SAH.³⁶ For instance, Buczacki et al⁷ conducted a large retrospective study, in which only 23 (4.9%) out of 472 patients developed late epilepsy after the clipping of ruptured aneurysms. Similarly, the international subarachnoid aneurism trial (ISAT) trial data showed that 25 (4%) out of 612 patients developed late epilepsy after 12 months of follow-up.³⁷

Risk Factors

Several factors were associated with a high risk of seizures and late epilepsy following SAH (→ **Table 1**).^{7,10,17,25-29} A systematic review of the literature showed that the occurrence of seizures was strongly related to aneurysm in the middle cerebral artery (MCA), Hunt and Hess (HH) grade III and clipping microsurgical repair.²⁹ Other reported risk factors include thick subarachnoid clot, intracerebral hemorrhage, rebleeding prior to operation, infarction, Fisher grade III or IV, poor World Federation of Neurosurgical Societies (WFNS) grade, acute hydrocephalus, and past medical history of hypertension.^{7,10,17,25-28} In addition, seizures at the onset of aneurysm rupture were related to increased epilepsy incidence,^{14,18} but this remains controversial.¹⁰ Moreover, acute symptomatic seizures have a lower risk for further unprovoked seizure than remote symptomatic seizures.³⁸ A detailed discussion about each possible risk factor is provided subsequently.

Aneurysm Location

Raper et al²⁹ performed a systematic review and found that, among patients who had seizures after SAH, there was a strong relationship to its location in the MCA. Indeed, 39% of them had

Table 1 List of possible risk factors for the development of seizures and epilepsy after subarachnoid hemorrhage

• MCA aneurysm
• Hunt and Hess grade III
• Clipping microsurgical repair
• Thick subarachnoid clot
• Intracerebral hemorrhage
• Rebleeding prior to operation
• Infarction
• Fisher grade III or IV
• Acute hydrocephalus
• History of hypertension
• Poor WFNS grade
• Onset seizure

Abbreviations: MCA, middle cerebral artery; WFNS, World Federation of Neurosurgical Societies.

an MCA aneurysm, compared with 29.3% in the anterior communicating artery, 13.8% in the internal carotid artery, 8.9% in the posterior communicating artery, 6.5% in the anterior cerebral artery, and 2.4% in the basilar apex locations.

Clinical and Radiological Scales

Clinical classifications, such as the HH and the WFNS scores, have been shown to be related to seizure occurrence after SAH.^{7,29} A great number (41.7%) of seizure events was observed among patients with a HH grade III. Conversely, this figure was much lower for grades I (25%), II (18.3%), IV (11.7%) and V (3.3%).²⁹ In addition, a study reported that a poor WFNS grade (excluding grade 5) after SAH was related to an increased risk of late epilepsy development.⁷ In fact, this occurred in 1.4% of grade I patients, 3.8% of grade II, 9.6% of grade III, and 12.5% of grade IV. The Fisher radiological scale was also related to seizure incidence after SAH.¹⁰ Actually, worse grades (Fisher III and IV) had a stronger relationship with late epilepsy than better grades (Fisher I and II), with an odds ratio of 1.81 and confidence interval (CI) between 1.07 and 2.15.

Type of Treatment

There is a very strong correlation between the type of treatment (such as surgical clipping or endovascular coiling) and the occurrence of further seizures. Raper et al,²⁹ in their systematic review, showed that 18.4% of patients who had post SAH seizures underwent endovascular coiling of the aneurysm. Conversely, 81.6% underwent surgical clipping.

Onset Seizures

The presence of seizures at the onset of aneurysm rupture were related to increased epilepsy incidence,¹⁴ but this remains controversial.¹⁰ Butzkueven et al¹⁴ showed that onset seizures and late seizures within the first 6 weeks were independently related (odds ratio [OR] = 27; $p < 0.01$). Conversely, onset seizures were not predictors of late epilepsy in the study of Choi et al.¹⁰ In addition, acute symptomatic seizures have a

lower risk of further unprovoked seizure occurrence than remote symptomatic seizures.³⁸

Other Associated Comorbidities

Various other associated comorbidities were described to be related to an increased seizure incidence following SAH. These include history of hypertension, presence of a thick subarachnoid clot, intracerebral hemorrhage, rebleeding prior to operation, ischemic brain infarction, and acute hydrocephalus.^{17,25–28}

Outcome

The impact of seizures after SAH on the outcome of the patient is not so clear, although they appear to be an independent risk factor to a poor outcome.^{14,18} Some evidence pointed that seizures following SAH are independent predictors of a poor prognosis.¹⁴ Indeed, Butzkueven et al¹⁴ showed that, besides the already mentioned increased risk for late epilepsy development, disability after weeks of the SAH episode (according to the Glasgow Outcome Scale) was independently related to the presence of onset seizure. Another study demonstrated that epilepsy after SAH was related to a poor functional recovery (using the modified Rankin Scale), to an increased instrumental disability (using the Lawton Instrumental Activities of Daily Living scale), to a reduced quality of life (using the Sickness Impact Profile), and to increased anxiety (using the Spielberger Anxiety Inventory).¹⁸ Moreover, NCSE was also strongly related to a poor outcome.^{15,30} Conversely, other studies found no differences in the outcomes of patients who suffered SAH and had a seizure.^{8,10}

Treatment

Neither primary nor secondary prevention treatments are supported or refuted for seizures related to SAH, according to

a 2013 Cochrane Review.³⁹ This was explained by an absence of prospective randomized clinical trials or other high-quality studies encompassing this matter. Due to this lack, there is a lot of controversy regarding the need for AED prophylaxis, choice of the best drug and dose, as well as duration of the treatment. Indeed, the prophylactic use of AED after SAH varies dramatically (from 7 to 93%) among physicians from different countries.⁴⁰

Some guidelines and recommendations for the management of SAH (including seizure management) were published recently. In 2011, the recommendations from the Multidisciplinary Consensus Conference of the Neurocritical Care Society (NCS) were published,³³ whereas in 2012 the American Heart Association (AHA)/American Stroke Association (ASA) recommendations³² on this subject were published. None of these societies support or refute strongly one or another approach based on high-quality evidence regarding the treatment of seizures after SAH, although some provided points are of important value for the clinical decision. ► **Table 2** shows the recommendations by both entities.

When to Use Antiepileptic Drugs

First of all, it is important to emphasize that there is no consensus regarding the benefits of primary and secondary prophylaxis with AEDs after SAH.³⁹ Actually, there are even studies that showed a worse prognosis among patients who used AEDs after SAH, mainly phenytoin.^{41,42} Therefore, the choice to use or not to use remains more empirical than evidence-based. In the next paragraph, the separated treatment recommendations for primary and secondary seizure prevention related to SAH are provided.

Primary Prevention

As shown in ► **Table 2**, both the NCS and the AHA/ASA agree regarding routine prophylaxis for seizures after SAH.

Table 2 Management of seizures after SAH according to the Neurocritical Care Society recommendations and the AHA/ASA guideline

Neurocritical Care Society recommendations (2011) ³³
• Routine use of anticonvulsant prophylaxis with phenytoin is not recommended after SAH (low-quality evidence—strong recommendation)
• Routine use of other anticonvulsants for prophylaxis may be considered (very low-quality evidence—weak recommendation).
• If anticonvulsant prophylaxis is used, a short course (3–7 days) is recommended (low-quality evidence—weak recommendation).
• In patients who suffer a seizure after presentation, anticonvulsants should be continued for a duration defined by local practice (low-quality evidence—weak recommendation).
• Continuous EEG monitoring should be considered in patients with poor-grade SAH who fail to improve or who have neurological deterioration of undetermined etiology (low-quality evidence—strong recommendation).
AHA/ASA guideline (2012) ³²
• The use of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period (Class IIb; Level of Evidence B).
• The routine long-term use of anticonvulsants is not recommended (Class III; Level of Evidence B), but may be considered for patients with known risk factors for delayed seizure disorder, such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or aneurysm at the middle cerebral artery (Class IIb; Level of Evidence B).

Abbreviations: AHA, American Heart Association; ASA, American Stroke Association; EEG, electroencephalogram; SAH, subarachnoid hemorrhage.

Indeed, their statements say that routine prophylaxis with AEDs may be considered right after SAH. Neither of the recommendations supports a long-term prophylaxis with AEDs.^{32,33} However, the AHA/ASA guideline states that this prophylaxis may be considered in some risk populations.³² These include those with intracerebral hemorrhage, intractable hypertension, infarction, or aneurysm at the MCA. It is also reported that, once the AED treatment is initiated, three days of prophylaxis should be preferred, since the percentages of early and late seizures were similar when compared with a long-term course of AEDs.⁴³

Secondary Prevention

In patients who suffer a seizure after presentation, the NCS recommendations state that AED treatment should be continued, and the AHA/ASA guideline supports the consideration of AED treatment.^{32,33} Since there is an absence of poststroke absolute predictors for further epilepsy development, many physicians empirically treat seizures in the setting of a stroke history in the past 2 to 3 years.⁴⁴ The American Academy of Neurology (AAN), together with the American Epilepsy Society (AES), made an evidence-based guideline for the management, in general, of first unprovoked seizures.⁴⁵ These recommendations are shown in **Table 3**.

For acute symptomatic seizures, the decision to start or not AED treatment depends on the severity of the underlying illness, the duration of the seizure, and the risks associated with a recurrent seizure. When the cause is severe SAH, therapy is generally initiated, since a seizure may worsen the prognosis of the patient.^{14,18} Thus, an individualized approach seems the most convenient.

Conversely, the literature strongly supports the initiation of AED treatment after the second unprovoked seizure. Indeed, Hauser et al⁴⁶ showed that 73% of those with 2 or 3 unprovoked seizures had further seizures within 4 years, whereas the risk of a second unprovoked seizure after 5 years of the first seizure was 33%. Given the high seizure incidence after the second seizure, AED treatment should be initiated after the second seizure.^{46,47}

The Antiepileptic Drug Choice

No AED was reported clearly to be the most effective in a few randomized clinical trials in the literature, and the choice of a specific AED depends mainly on its pharmacokinetic properties, collateral effects, cost, tolerance, seizure type, and on the characteristics of the patient.^{48–52} As a general rule, newer AEDs are more tolerated than others – with some exceptions.⁴⁸ In a single study, it was shown that phenytoin may worsen the neurological outcome in patients who suffered SAH.⁴¹ Due to this, the statement of the NCS recommends against the use of phenytoin for seizure prophylaxis in the setting of SAH.³³ However, it is unclear if AEDs other than phenytoin have also a deleterious effect, so their prescription must be made with caution.

Electroencephalogram Monitoring

In poor-grade patients who suffered SAH, NCSE and subclinical seizures can be detected with EEG monitoring in many cases. Given that NCSE is strongly related to poor outcomes after SAH,^{24,37} it is reasonable to consider both EEG monitoring in poor-grade patients and AED treatment, although the literature lacks information regarding the efficacy of AED therapy in this setting. Indeed, there is a statement of the NCS recommending a specific approach in terms of continuous EEG monitoring (**Table 2**).³³

Conclusion

The lack of consensus in the literature regarding the incidence, risk factors, outcomes and treatment of SAH-related seizures and epilepsy makes difficult to the physician to determine the need for AED prophylaxis, the choice of the best drug and dose, as well as the duration of treatment. So far, recommendations are in general based on low quality evidence, but they suggest some relevant points, such as considering AED prophylaxis when a seizure occurs after SAH, considering routine long-term AED prophylaxis in specific populations, considering continuous EEG monitoring, and avoiding phenytoin prescription.^{32,33} In other words, it is reasonable to individualize the approach for

Table 3 Recommendations from the 2015 AAN/AES guideline for the management of first unprovoked seizure in adults⁴⁵

<ul style="list-style-type: none"> • Adults presenting with an unprovoked first seizure should be informed that the chance of a recurrent seizure is greatest within the first 2 years after the first seizure (21–45%) (Level A).
<ul style="list-style-type: none"> • Clinicians should also advise these patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as stroke or trauma (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain imaging abnormality (Level B), or a nocturnal seizure (Level B).
<ul style="list-style-type: none"> • Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of seizure recurrence in the 2 years subsequent to the first seizure (Level B), it may not improve the quality of life (Level C).
<ul style="list-style-type: none"> • Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission (Level B).
<ul style="list-style-type: none"> • Patients should be advised that their risk for adverse effects with the use of AEDs ranges from 7 to 31% (Level B), and that these adverse effects are predominantly mild and reversible.

Abbreviations: AAN, American Academy of Neurology; AED, antiepileptic drugs; AES, American Epilepsy Society; EEG, electroencephalogram.

each patient. Randomized controlled studies are urgently needed to guide the best clinical decision regarding seizures and epilepsy following SAH.

Conflict of Interests

The authors have no conflicts of interests to declare.

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