Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage

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Object. The reported incidence, timing, and predictive factors of perioperative seizures and epilepsy after subarachnoid hemorrhage (SAH) have differed considerably because of a lack of uniform definitions and variable follow-up periods. In this study the authors evaluate the incidence, temporal course, and predictive factors of perioperative seizures and epilepsy during long-term follow up of patients with SAH who underwent surgical treatment.

Methods. Two hundred seventeen patients who survived more than 2 years after surgery for ruptured intracranial aneurysms were enrolled and retrospectively studied. Episodes were categorized into onset seizures (≤ 12 hours of initial hemorrhage), preoperative seizures, postoperative seizures, and late epilepsy, according to their timing.

The mean follow-up time was 78.7 months (range 24–157 months). Forty-six patients (21.2%) had at least one seizure post-SAH. Seventeen patients (7.8%) had onset seizures, five (2.3%) had preoperative seizures, four (1.8%) had postoperative seizures, 21 (9.7%) had at least one seizure episode after the 1st week postoperatively, and late epilepsy developed in 15 (6.9%). One (3.8%) of 26 patients with perioperative seizures (onset, preoperative, or postoperative seizure) had late epilepsy at follow up. The mean latency between the operation and the onset of late epilepsy was 8.3 months (range 0.3–19 months). Younger age (< 40 years old), loss of consciousness of more than 1 hour at ictus, and Fisher Grade 3 or greater on computerized tomography scans proved to be significantly related to onset seizures. Onset seizure was also a significant predictor of persistent neurological deficits (Glasgow Outcome Scale Scores 2–4) at follow up. Factors associated with the development of late epilepsy were loss of consciousness of more than 1 hour at ictus and persistent postoperative neurological deficit.

Conclusions. Although up to one fifth of patients experienced seizure(s) after SAH, more than half had seizure(s) during the perioperative period. The frequency of late epilepsy in patients with perioperative seizures (7.8%) was not significantly higher than those without such seizures (6.8%). Perioperative seizures did not recur frequently and were not a significant predictor for late epilepsy.

KEY WORDS • seizure • epilepsy • subarachnoid hemorrhage • ruptured aneurysm • epilepsy surgery

Epilepsy is a well-recognized complication that occurs after many neurological disorders and major intracranial surgery.17,18,26,31,32 Postoperative epilepsy in patients who undergo surgery for ruptured intracranial aneurysms may manifest in a delayed fashion, with a latency of up to 54 months after the operation (although most seizures occur within 2 years postsurgery).17,18,26,31,32,36,37,39–41 The reported risk of epilepsy after surgery for ruptured intracranial aneurysms has varied between 1 and 27.5%, and appears to be related to the SAH itself, the effects of craniotomy, or both.7,8,19,21,26,27,36,39,40,44 Comparisons of these findings are rather difficult because of different criteria for patient selection, variable follow-up times, and considerably different timing and methods of surgery among different studies. Additionally, there are few data pertaining to the precise definition of epilepsy and the inclusion of single and early seizures. The relationship between early-onset seizures and late epilepsy has traditionally been controversial and incompletely characterized.3,6,13,14,19,28–30,32,33,35 Our retrospective study includes 217 patients who harbored ruptured intracranial aneurysms for which surgical treatment was undertaken. Ascertainment of the true incidence of seizures and epilepsy over a relatively long period (> 2 years) was attempted in conjunction with the elucidation of particular predictive factors that may increase the risk of postoperative late epilepsy.

Abbreviations used in this paper: ACA = anterior cerebral artery; ACoA = anterior communicating artery; CI = confidence interval; CT = computerized tomography; EEG = electroencephalography; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICH = intracerebral hematoma; MCA = middle cerebral artery; OphA = ophthalmic artery; OR = odds ratio; PCoA = posterior communicating artery; SAH = subarachnoid hemorrhage; VP = ventriculoperitoneal.

Clinical Material and Methods

Patient Population

A total of 274 patients who underwent surgery for ruptured intracranial aneurysms at Kaohsiung Medical Univer-
Perioperative seizures and epilepsy after aneurysmal SAH

ity Hospital between 1987 and 1998 were identified. Fifty-seven patients were excluded because they died within 1 year of surgery. The remaining 217 patients received a diagnosis of SAH according to CT scan or lumbar puncture findings. Intracranial aneurysms were confirmed on cerebral angiography in all patients. The study population was composed of a preponderance of women (61%). The mean age of the patients was 49.3 ± 14.5 years (range 22–78 years). More than half (53%) were between the ages of 40 and 59 years, 29% were older than 59 years, with the remaining 18% younger than 40 years. No patient had preexisting epilepsy. The patients were followed from the date of the initial SAH for a total of 1423 person-years (mean 6.6 years, range 2–13.1 years).

This series is composed of 217 consecutive patients who underwent surgery for ruptured intracranial aneurysms at Kaohsiung Medical University Hospital between 1987 and 1998 and who survived for at least 1 year postoperatively. Data derived from the hospital records included the admission GCS score, history of cardiovascular disease and hypertension, duration of loss of consciousness at ictus (di- chotomized as ≥ 1 hour compared with < 1 hour), location of ruptured aneurysm, and Fisher SAH grade. Special note was made of factors such as rebleeding, acute and chronic hydrocephalus that required VP shunt placement, vasospasm, timing of surgery, and intraoperative aneurysm rupture. The criteria for classifying a patient as suffering from hypertension included a current regimen of antihypertension medication, previous antihypertension therapy that continued for longer than 1 year before its cessation, or documented hypertensive blood pressure levels (> 140/90 mm Hg) for more than 1 year before the SAH. Rebleeding was defined as sudden deterioration of the clinical state accompanied by new or increased blood on cerebral CT scans. Hydrocephalus was defined as deterioration of the level of consciousness or cognition with no identifiable cause other than new hydrocephalus on CT scans (bicaudate index > 95th percentile for age). Vasospasm was defined as development of focal neurological signs or deterioration in conscious state with either an unchanged CT scan or evidence of cerebral infarction with no other discernible cause.

A seizure, for the purposes of this study, was defined as repetitive, rhythmic jerking, with or without preceding tonic spasms, that was focal or generalized in nature, with or without loss of consciousness. Only seizures observed by the medical staff, or by relatives or ambulance personnel when seizures occurred outside the hospital were included. Seizures were divided into those occurring within 12 hours of the initial hemorrhage, which were called onset seizures; those occurring between 12 hours postictus and before surgery, which were called preoperative seizures; and those occurring within 1 week postoperatively, which were called postoperative seizures. Late epilepsy was defined as a disorder in which at least two spontaneous seizures occurred after the 1st week and were separated temporally by a minimum interval of 24 hours.

All patients were symptomatically treated with tranquilizers, analgesics, laxatives, and bed rest. Nimodipine therapy was initiated intraoperatively and continued for 2 weeks after the operation in the last 41 patients in this series. Prophylactic anticonvulsant medication was routinely used in all patients after admission to our hospital, and it was continued until the first outpatient visit 2 to 3 weeks postsur-

gery, at which time it was tapered if no late seizures had occurred. Routine treatment with phenytoin was continued unless it was not tolerated. In that instance, the anticonvulsant drug was changed to carbamazepine or valproic acid. Doses of anticonvulsant medications were chosen and adjusted to maintain therapeutic levels. No universal protocol was followed in terms of frequency of anticonvulsant monitoring, and in patients without seizures the levels of anticonvulsant drugs were checked less frequently.

A total of 217 patients underwent craniotomy to treat 225 aneurysms, of which 217 lesions were occluded with clips and eight underwent wrapping. The peritrochlear approach was used in all patients, except for aneurysms of the basilar tip, which were approached via the subtemporal route. The patients were followed until their death or the first half of 2000, and outcome was assessed using the five-point GOS. Follow-up information was obtained from the hospital records and from direct contact with patients and/or their relatives. The follow-up period ranged from 24 to 157 months (mean 78.7 months) postsurgery. A total of four patients died during the follow-up period: two died of pneumonia 2 years postsurgery; one died of cerebral infarction 3 years postsurgery; and another died of hypertensive intracerebral hemorrhage 7 years postsurgery. None of the aforementioned patients had experienced seizures or epilepsy after their SAH.

Statistical Analysis

All statistical analyses were performed using commercially available software (version 10.1; SPSS, Inc., Chicago, IL). The chi-square test (with correction for continuity or Fisher exact test when appropriate) and the OR with the respective 95% CI were used for statistical analyses. Statistical significance was represented by a probability value less than 0.05.

Results

A total of 46 patients experienced one or more seizures after SAH (Fig. 1). Seventeen patients (7.8%) with onset seizures were identified within 12 hours of the initial hemorrhage; 16 of them experienced tonic–clonic seizures, whereas the other one had a focal motor seizure. All but one of these episodes occurred within 1 hour post-SAH; the remaining onset seizures occurred 4 hours posthemorrhage. Recurrent seizures developed in only one of these individuals who experienced late epilepsy 24 months postsurgery. Additionally, none (2.3%) suffered a preoperative seizure (> 12 hours after the initial hemorrhage but before surgery). Of these patients, none experienced postoperative seizures or late epilepsy. Preoperative seizures occurred at a mean of 3 ± 0.8 days after onset of SAH. Postoperative seizures were found in four (1.8%) of 217 patients. None of these patients had an onset seizure or preoperative seizure, and none experienced late epilepsy. The mean time of postoperative seizure occurrence was 5.5 ± 3.9 days after surgery. Twenty-one patients (9.7%) had at least one episode of seizure 1 week after surgery; in 15 (71%) of these individuals late epilepsy developed. The mean latency between the operation and seizure onset was 8.3 months (range 0.3–19 months). The seizures occurred within 3 months in three patients, between 3 and 12 months in seven patients, and
between 13 and 19 months in the remaining five patients. Eleven patients in whom late epilepsy developed experienced tonic–clonic seizures, one had complex partial sei- zures progressing to generalized tonic–clonic seizures, and the remaining three had focal motor seizures.

Patient characteristics and neuroimaging data are illustrated in Tables 1 and 2. Hypertension was documented in 77 patients (35%). Based on admission GCS scores, 69% had a score of 15, 23% had a score of 8 to 14, and in 9% the score was less than 8. Thirty-three percent were classified as Fisher Grade 1 or 2, and 67% as Grade 3 or 4. Ninety-nine patients (46%) were found to have lost consciousness for more than 1 hour after onset of SAH.

The most common location of aneurysms in this study was the ACoA (51%), followed by the PCoA (30%). Approximately 8% of patients in this cohort had multiple aneurysms. Symptomatic vasospasm and preoperative rebleeding occurred in 21 and 5% of patients in this series, respectively. Acute hydrocephalus developed in 34 patients (16%) and nine of them received external ventricular drainage. Forty patients (18%) eventually required VP shunt placement to treat chronic hydrocephalus. Aneurysm surgery was performed as soon as the patient’s condition and operating room facilities permitted (20% were surgically treated within 3 days, 46% within 4–14 days, and 34% > 2 weeks after the initial hemorrhage). At follow up, 128 patients (59%) exhibited good recovery (GOS Score 1), 43 (20%) had moderate disability (GOS Score 2), 32 (15%) had severe disability (GOS Score 3), 10 (5%) were in a vegetative state (GOS Score 4), and four (2%) died (GOS Score 5). In total 85 patients (39%) were considered to have neurological deficits (GOS Scores 2–4) at follow up.

The relationship between onset seizures and certain characteristics recorded at the onset is depicted in Table 1. Results of a statistical analysis demonstrated that onset seizure was independent of factors such as sex, admission GCS score, history of hypertension, and the location and number of aneurysms. We did find that patients with onset seizures were more likely to be younger (OR 6.6, 95% CI 2.4–18.6; p = 0.001), to experience loss of consciousness for more than 1 hour postictus (OR 4.3, 95% CI 1.4–13.7; p = 0.008), and to demonstrate a Fisher SAH grade greater than 2 (p = 0.003). Fifty-three percent of patients with onset seizures were between 20 and 39 years of age, 29% were between 40 and 59, and 18% were older than 59 years of age. Nevertheless, more than half (55%) of patients without onset seizures were between the ages of 40 and 59 years (OR 0.3, 95% CI 0.1–0.8; p = 0.042), and only 15% were younger than 40 years of age. Loss of consciousness more than 1 hour postictus was more frequent in patients with onset seizures (76%) than in those without (43%). None of the 70 patients with Fisher SAH grades less than 3 had onset seizures, and in all 17 patients with onset seizures the Fisher grade was greater than 2 (Grades 3 and 4). There was a trend, which did not reach statistical significance, toward higher representation of OphA aneurysms in the group experiencing an onset seizure (40%). Seventeen patients had multiple aneurysms, which did not result in an increased risk of onset seizure (p = 0.089). Onset seizures also were not predictive of preoperative seizure, postoperative seizure, or late epilepsy. Nevertheless, onset seizure was a predictor for persistent neurological deficits (GOS Scores 2–4; OR 4.2, 95% CI 1.4–12.3; p = 0.006). Among 17 patients with onset seizures, 71% had neurological deficits, whereas 62% of patients without onset seizures demonstrated good recovery (OR 0.3, 95% CI 0.1–0.8; p = 0.001).

The relationship between patients with late epilepsy and other variables is illustrated in Table 2. There were two significant predictive risk factors for late epilepsy. The first was GOS Scores 2 to 4, which correlated with development of late epilepsy (OR 7.1, 95% CI 1.9–25.6; p = 0.001). Indeed, late epilepsy was more frequently seen in patients with significant adverse neurological sequelae (GOS Scores 2–4: 12 [14%] of 85) compared with patients with good recovery (GOS Score 1: 3 [2%] of 128) (OR 0.2, 95% CI 0.0–0.6; p = 0.001). The second risk factor was loss of consciousness for longer than 1 hour in initial hemorrhage; these patients exhibited a greater incidence of late epilepsy (OR 3.6, 95% CI 1.1–11.6; p = 0.026). Other complications seen after SAH, such as rebleeding, vasospasm, and acute hydrocephalus were not related to the development of late epilepsy. The occurrence of seizures during the perioperative period did not predict late epilepsy; this condition developed in only one (3.8%) of 26 patients who sustained a perioperative seizure. Other clinical characteristics and radiological data were not significantly related to late epilepsy. Three patients received anticonvulsant therapy at the time of the late seizure. Late epilepsy was adequately controlled by anticonvulsant therapy in 12 patients, and the remaining three needed protracted adjustments to therapeutic regimens (over the span of > 1 year) to control epilepsy. These patients required scalp EEG monitoring only (no in-

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**Fig. 1.** Chart showing 46 patients with at least one episode of seizure after SAH.

![Diagram](image.png)
TABLE 1
Characteristics of 217 patients with SAH according to presence or absence of onset seizures

<table>
<thead>
<tr>
<th>SAH (%)</th>
<th>Characteristic</th>
<th>No. of Patients (%) W/ Onset Sz</th>
<th>W/O Onset Sz</th>
<th>p Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>85 (39)</td>
<td>7 (41)</td>
<td>78 (39)</td>
<td>0.860 (1.0–4.3)</td>
</tr>
<tr>
<td>age group in yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>38 (18)</td>
<td>9 (53)</td>
<td>29 (15)</td>
<td>0.001 (2.4–18.6)</td>
</tr>
<tr>
<td>40–59</td>
<td>115 (53)</td>
<td>2 (12)</td>
<td>110 (55)</td>
<td>0.042 (0.3–1.0)</td>
</tr>
<tr>
<td>60–79</td>
<td>64 (29)</td>
<td>3 (18)</td>
<td>61 (31)</td>
<td>0.265 (0.5–1.7)</td>
</tr>
<tr>
<td>hypertension</td>
<td>77 (35)</td>
<td>6 (35)</td>
<td>71 (36)</td>
<td>0.986 (0.4–2.8)</td>
</tr>
<tr>
<td>LOC at ictus &gt;1 hr</td>
<td>99 (46)</td>
<td>13 (76)</td>
<td>86 (43)</td>
<td>0.008 (1.4–13.7)</td>
</tr>
<tr>
<td>GOS score</td>
<td>147 (67)</td>
<td>17 (100)</td>
<td>130 (65)</td>
<td>0.000 (0.3–6.7)</td>
</tr>
<tr>
<td>Fisher SAH Grade</td>
<td>3 or 4</td>
<td>147 (67)</td>
<td>130 (65)</td>
<td>0.000 (0.3–6.7)</td>
</tr>
<tr>
<td>location of ruptured aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACoA</td>
<td>110 (51)</td>
<td>10 (59)</td>
<td>100 (50)</td>
<td>0.485 (1.0–3.9)</td>
</tr>
<tr>
<td>PCAoA</td>
<td>65 (30)</td>
<td>3 (18)</td>
<td>62 (31)</td>
<td>0.249 (0.5–1.7)</td>
</tr>
<tr>
<td>MCA</td>
<td>20 (9)</td>
<td>2 (12)</td>
<td>18 (9)</td>
<td>1.000 (1.3–6.4)</td>
</tr>
<tr>
<td>ICA</td>
<td>13 (6)</td>
<td>0 (0)</td>
<td>13 (7)</td>
<td>0.606 NA</td>
</tr>
<tr>
<td>BA</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>1.000 NA</td>
</tr>
<tr>
<td>ACA</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>1.000 NA</td>
</tr>
<tr>
<td>OphA</td>
<td>5 (2)</td>
<td>2 (12)</td>
<td>3 (2)</td>
<td>1.000 (5.4–65.5)</td>
</tr>
<tr>
<td>multiple</td>
<td>17 (8)</td>
<td>0 (0)</td>
<td>17 (9)</td>
<td>0.089 NA</td>
</tr>
</tbody>
</table>

* BA = basilar artery; ICA = internal carotid artery; LOC = loss of consciousness; NA = not applicable; neurodef = neurological deficit; sz = seizure.
† Seventeen patients experienced onset seizures and 200 did not.
‡ Vasoactive monitoring, and with alterations in anticonvulsant regimens epilepsy in these patients has been controlled.

Discussion

Epilepsy has long been recognized as a sequela of head injury and major brain surgery, with the risk varying depending on the localization and severity of the underlying lesion and/or the nature of the operation. The reported incidence of postoperative epilepsy in patients with ruptured intracranial aneurysms has varied between 1 and 27.5%. Unfortunately, the lack of a uniform definition of postoperative epilepsy, coupled with problems of varying durations of follow up and inconsistent case selection hamper the formulation of adequate comparisons between studies. The risk of epilepsy developing may arise from the SAH itself, the operation, or both. The evolution of management paradigms and microsurgical techniques witnessed over the last 30 years may be associated with reduced morbidity and mortality rates (including reduced occurrence of epilepsy).

Onset or ictal seizures have been traditionally defined as episodes occurring within the first 12 hours of SAH, as classified in our study. Nevertheless, others, including Sundaram and Chow, and Butzkueven, et al., chose a 24-hour cutoff to differentiate between onset and late seizures. In the former study, 32 patients were identified as having onset seizures, all of which occurred within 6 hours post-SAH. In our study we encountered a frequency of 7.8% for onset seizure, a figure concurring with results reported in the preponderance of cited literature (range 4–26%). Notably, in a minority of series (such as those of Bonita and Thomson, and Bassi, et al.), no occurrence of seizures at onset was reported.

Some movements of the decorticate state (posturing), caused by acutely elevated intracranial pressure during transient loss of consciousness at the onset of SAH may simulate seizures. Some authors have given this seizure-like activity terms such as cerebellar seizures, tonic fits, decorticate fits, mesencephalic seizures, and so forth, in patients...
who have a multitude of causes of acutely increased intracranial pressure. To avoid including this aforementioned seizure-like activity in our study, only unequivocal seizures observed by the medical staff, patients' relatives, or ambulance personnel were included. Our definition of seizure activity was selected to achieve the most reproducible criteria that could be observed by medical and ancillary staff and relatives and we did not routinely use EEG monitoring. There are limitations inherent to the present definition, however, and it is possible that some episodes (especially those that are difficult for nonmedically trained personnel to identify) were missed, leading to an underestimation of seizure incidence in this study.

Risk factors previously reported to be associated with onset seizures after SAH include the presence of ICH and anterior circulation aneurysms, a history of hypertension, ischemic infarcts revealed on late CT scans, initial loss of consciousness lasting longer than 1 hour, verteobasilar aneurysms, hemiparesis, Hunt and Hess grade greater than 3, the amount of subarachnoid blood, and the confirmed presence of an aneurysm. In our series, younger age (< 40 years), loss of consciousness for more than 1 hour at ictus, and a Fisher grade of 3 or greater on CT scans proved to be significantly related to onset seizure. In contrast, a history of hypertension, location of aneurysm, vasospasm, and admission GCS score were not predictive of onset seizures. All of these analyses were univariate in nature. Butzkueven, et al., used logistical regression analysis and found onset seizure after SAH correlated with the sum score of blood on the initial CT scan, but that there was no significant correlation with duration of loss of consciousness at onset, GCS score, presence of aneurysm, or history of hypertension or epilepsy. Our series included only patients who underwent surgery for ruptured aneurysms, so comparison with the study of Butzkueven, et al., cannot be made directly.

As mentioned, a large amount of subarachnoid cisternal blood seemed to be significantly more common in patients with SAH who suffered seizures. The mechanical effect of the blood near the motor cortex or the insula, the release of large amounts of glutamate, and the generation of lipid peroxides from oxygen-free radical reactions catalyzed by iron and by hemoglobin degradation products, as well as by the oxidative catabolism of arachidonic acid, may account for the occurrence of onset seizures post-SAH. The exact mechanisms, however, await further elucidation.

In one clinical study from 1981 in which patients with proven aneurysmal SAH were examined, no significant relationship was demonstrated between onset seizure and prognosis. Nevertheless, as a consequence of a number of improvements in treatment and shifts in management paradigms, a contemporary cohort of patients with SAH is likely to have characteristics different from earlier ones. In 1997, in a series of 253 patients, onset seizure was reported to be a risk factor for poor outcome, and the analysis was univariate. In a more recent logistic regression analysis of 412 patients with all types of SAH it was documented that onset seizure independently predicted poor outcome post-SAH. In our series, patients who survived more than 1 year after surgery were included. The occurrence of onset seizures was related to persistent neurological deficits. Only four patients died during follow up, and the small number makes it difficult to discern any association between onset seizure and death. Some authors have demonstrated that ultra-early arterial vasospasm was associated with poor outcome at 3 months. In this study we did not find a correlation of symptomatic vasospasm with onset seizure, in agreement with the report of Butzkueven, et al., however, it is still plausible that onset seizure is a surrogate marker for the severity of the acute cerebral insult, and that this insult is related to poor functional recovery.

Onset seizures are an important risk factor for the occurrence of delayed seizures in patients who suffer strokes. Late epilepsy was reported in up to 21 to 36% of patients with onset seizures post-SAH. In the series of Rhoney, et al., eight (14%) of 56 patients suffered seizures after hospital discharge; all of them had experienced preadmission seizures. Nevertheless, other reports have accrued different and contradictory results.

Administration of anticonvulsant drugs in the management of acute SAH varied across most studies. Routine use of anticonvulsant medications was reported in all cases of SAH in the series of Ukkola and Heikkinen, and Butzkueven, et al., and postoperative epilepsy was found in 8 and 5.1%, respectively, of patients in these two series. In the latter study, 35% of patients with onset seizure (≤ 24 hours of the start of headache) experienced late seizures (24 hours–6 weeks post-SAH). Administration of postoperative anticonvulsant medication in the study of Baker, et al., was restricted to a mean of 3 days in low-risk patients with intracranial aneurysms, and early postoperative and long-term seizure rates were 1.9 and 3.5%, respectively. Nonetheless, epilepsy did not develop in any patient who experienced early seizures. In a study in which routine anticonvulsant prophylactic treatment was not given after aneurysm operation, eight (7%) of 121 patients experienced seizures during the follow-up period of 12 months. Anticonvulsant medications were routinely used during hospitalization in our study. Late epilepsy developed in only one (6%) of 17 patients with onset seizures. Patients with onset seizures did not experience preoperative or postoperative seizures. Our study was not designed to evaluate the efficacy of prophylactic anticonvulsant therapy and, therefore, no conclusions may be gleaned from this data in that regard. In fact, the efficacy/benefit of this therapy remains unclear after analyzing the existing body of literature. Further randomized studies may clarify the putative role of prophylactic anticonvulsant therapy in patients with SAH.

The possible contribution of craniotomy as a risk factor for epilepsy is controversial. A summary of previous studies in which postoperative seizures and/or epilepsy in patients with aneurysms who underwent craniotomy were reported demonstrated an incidence ranging from 3 to 27.5% (Table 3). Comparisons among these studies are rather difficult because of varying criteria for patient inclusion and different follow-up periods, along with discrepant timing and methods of surgery across reports.

Some previous studies have incorporated different definitions for postoperative epilepsy, whereas others do not adequately define this entity. Keränen, et al., and Ohkuma, et al., suggested that late or postoperative epilepsy referred to the condition occurring when at least two spontaneous seizures, separated by a minimum interval of 24 hours, manifest after the 1st week following the operation. Sundt, et al. also defined seizure(s), even single ones, occurring 1 week after operation as late seizures. Bidziński, et
### Table 3

Literature review of the frequency and latency of late epilepsy after aneurysm surgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Definition of Postop Sz/Epilepsy</th>
<th>No. of Patients</th>
<th>Frequency</th>
<th>Latency</th>
<th>Follow Up</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose &amp; Sarner, 1965</td>
<td>szs, even single, any time postop</td>
<td>508, op &amp; nonop cases</td>
<td>10.4%</td>
<td>72% w/in 1 yr, 94% at 2 yrs</td>
<td>NI</td>
<td>young age, ICH, MCA aneurysm, neurodef</td>
</tr>
<tr>
<td>Storey, 1967</td>
<td>NI</td>
<td>224</td>
<td>10%</td>
<td>NI</td>
<td>NI</td>
<td>neurodef, mental symptom</td>
</tr>
<tr>
<td>Krayenbühl et al., 1972</td>
<td>any time postop epilepsy (no definition)</td>
<td>250</td>
<td>4.8%</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Cabral et al., 1976</td>
<td>sz, any time postop</td>
<td>199 selected cases</td>
<td>4.5%</td>
<td>w/in 1 day–54 mos</td>
<td>18 mos–5.5 yrs</td>
<td>MCA aneurysm, intraop damage</td>
</tr>
<tr>
<td>North et al., 1980</td>
<td>epilepsy, any time postop</td>
<td>55</td>
<td>16%</td>
<td>&lt;1 yr</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Fabinyi &amp; sz, 1980</td>
<td>any time postop</td>
<td>4.5%</td>
<td>&lt;2 yrs</td>
<td>&gt;5 yrs</td>
<td>MCA aneurysm, ICH, intraop damage</td>
<td></td>
</tr>
<tr>
<td>Artiola-Fortuny, 1980</td>
<td>szs, even single, any time postop</td>
<td>252</td>
<td>15%</td>
<td>all &lt;2 yrs</td>
<td>&gt;5 yrs</td>
<td>MCA aneurysm, ICH, intraop damage</td>
</tr>
<tr>
<td>Wittonpanich et al., 1980</td>
<td>NI</td>
<td>93</td>
<td>12%</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Foy et al., 1981</td>
<td>szs, even single, any time postop</td>
<td>late sz: 12 hrs post-SAH, before op or discharge</td>
<td>13%</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Hart et al., 1981</td>
<td>1st wk postop, even single sz</td>
<td>75</td>
<td>13%</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Jeffrey et al., 1981</td>
<td>1st wk postop</td>
<td>722</td>
<td>3%</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Ise et al., 1985</td>
<td>sz(s) after the 1st wk postop</td>
<td>192</td>
<td>9.4%</td>
<td>NI</td>
<td>&lt;2 yrs</td>
<td>EEG abnormality, LDA on CT scan</td>
</tr>
<tr>
<td>Keränen et al., 1985</td>
<td>single sz included, any time postop</td>
<td>177 selected cases</td>
<td>12%</td>
<td>all ≥1 yr, mean 3.4 yrs</td>
<td>1–24 mos, mean 8.4 mos</td>
<td>MCA aneurysm, ICH, resection of gyrus, MTLE, retraction, persistent postop def</td>
</tr>
<tr>
<td>Sbeih et al., 1986</td>
<td>early sz (≥2 wks post-SAH), late sz (&gt;2 wks post-SAH); frequency 2–4 szs</td>
<td>100</td>
<td>3%</td>
<td>2 cases &lt;1 day, 1 case at 2 mos</td>
<td>15 mos–5 yrs</td>
<td>MTL traction</td>
</tr>
<tr>
<td>Sundaram &amp; Chow, 1986</td>
<td>early sz (≥2 wks post-SAH), late sz (&gt;2 wks post-SAH); frequency 2–4 szs</td>
<td>131 w/ SAH (104 aneurysms)</td>
<td>20%</td>
<td>late szs at 2–70 mos, mean 23 mos</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Ohkuma et al., 1990</td>
<td>any time postop, even single sz</td>
<td>55</td>
<td>23.6%</td>
<td>9–120 mos</td>
<td>8 days–5 yrs, mean 11 mos</td>
<td>multiple lesions, preop severity, severe SAH, ICH, hydrocephalus, neurodef, EEG abnormality, LDA on CT scan, preop grade, MCA, hydrocephalus, vasospasm, ICH, neuro def</td>
</tr>
<tr>
<td>Öhman, 1990</td>
<td>epileptic szs, any time postop</td>
<td>307 (276 ops)</td>
<td>9.4%</td>
<td>0 days–2 yrs</td>
<td>1–3 yrs, mean 1.4 yrs</td>
<td>NI</td>
</tr>
<tr>
<td>O’Laoire, 1990</td>
<td>classified as early sz &amp; late repeated szs (epilepsy)</td>
<td>100</td>
<td>3%</td>
<td>late epilepsy (2 yrs)</td>
<td>2–6 yrs</td>
<td>NI</td>
</tr>
<tr>
<td>Shaw, 1990</td>
<td>any time postop, even single sz</td>
<td>252</td>
<td>21.5%</td>
<td>all &lt;2 yrs</td>
<td>&gt;5 yrs unless patient died</td>
<td>1.5–5.5 yrs, mean 3.6 yrs</td>
</tr>
<tr>
<td>Ukkoala &amp; Hiikkinen, 1990</td>
<td>any time postop</td>
<td>183</td>
<td>8%</td>
<td>0–23 mos, mean 10 mos</td>
<td>MCA, temporary intraop clip occl, wrapping technique, vasospasm</td>
<td></td>
</tr>
<tr>
<td>Robinowicz et al. 1991</td>
<td>sz, any time postop</td>
<td>19 unruptured aneurysms</td>
<td>15.7%</td>
<td>2 days–13 mos</td>
<td>2–68 mos, mean 24 mos</td>
<td>NI</td>
</tr>
<tr>
<td>Bidziński et al. 1992</td>
<td>≥2 epileptic szs, 2 wks postop &gt;12 hrs post-SAH, even single sz</td>
<td>381 (167 ops)</td>
<td>9%, op in 7%</td>
<td>0.5–1761 days, median 18 days, 86% &lt;2 yrs</td>
<td>0.5–4315 days, median 129 days</td>
<td>WFNS Grade III</td>
</tr>
<tr>
<td>Hasan et al. 1993</td>
<td>early postop sz (&lt;14 days), late postop sz (&gt;14 days)</td>
<td>316 selected cases (low risk, 200 ruptured &amp; 116 unruptured)</td>
<td>19%</td>
<td>early sz, 1.9%, late sz, 3.5%</td>
<td>11 mos–5 yrs, mean 2.4 yrs</td>
<td>cisternal blood, rebleeding</td>
</tr>
<tr>
<td>Baker et al. 1995</td>
<td>early postop sz (&lt;14 days), late postop sz (&gt;14 days)</td>
<td>123 SAHs (aneurysm in 86.2%)</td>
<td>18%</td>
<td>88% &lt;1 yr</td>
<td>4–7 yrs</td>
<td>relative youth, ischemic neurodef, poor GOS score</td>
</tr>
<tr>
<td>Ogden et al. 1997</td>
<td>single or &gt;1 sz postop</td>
<td>412 aneurysms in 331, ops in 272</td>
<td>5.1%</td>
<td>NI</td>
<td>6 wks</td>
<td>rebleeding, onset sz (&lt;24 hrs of SAH)</td>
</tr>
<tr>
<td>Butzkueven et al., 2000</td>
<td>1 day–6 wks post-SAH</td>
<td>412 aneurysms in 331, ops in 272</td>
<td>5.1%</td>
<td>NI</td>
<td>6 wks</td>
<td>rebleeding, onset sz (&lt;24 hrs of SAH)</td>
</tr>
<tr>
<td>Olafsson et al. 2000</td>
<td>in-hospital &amp; posthospital szs</td>
<td>44</td>
<td>25%</td>
<td>91% &lt;2 yrs, 100% ≤4 yrs</td>
<td>2–37 person-yr</td>
<td>severe neural sequelae, acute sz (&lt;24 hrs of SAH)</td>
</tr>
<tr>
<td>Rhoney et al. 2000</td>
<td>in-hospital &amp; posthospital szs</td>
<td>95 (intracranial op in 88.5%)</td>
<td>14%</td>
<td>in-hospital sz, mean 14.5 days, posthospital sz, mean 326.5 days</td>
<td>1 yr</td>
<td>thickness of cisternal clot</td>
</tr>
</tbody>
</table>

* CA = carotid artery; LDA = low-density area; MTL = medial temporal lobe; NI = no information; occl = occlusion; WFNS = World Federation of Neurosurgical Societies.*
al.,3 adopted the term late epilepsy for seizures occurring within 2 weeks after surgery. In our study, late epilepsy was defined as two or more seizures, at least 24 hours apart, beginning 1 week after surgery. This is admittedly arbitrary; however, 1 week after surgery the acute posthemorrhagic and postoperative excitation of the brain has perhaps abated.

In our study we did not categorize patients with a single seizure as having late epilepsy. Seizures, whether single or repeated, which occur at the onset of SAH, after SAH, or within a few days after surgery are usually a reaction to hemorrhagic or surgical trauma and are seldom a predictive factor for late epilepsy.3 The incidence of late epilepsy was 6.9% in our study, which is comparable with previous reports.1,3,6,7,12–16,19,21,27–32,35,36,38,40,41,43–45,46,48,50 The latency of late epilepsy has been reported to be as long as 120 months, although the vast majority of patients manifest this condition within 2 years post surgery (Table 3). For this reason patients were followed for at least 2 years after surgery in our study. Indeed, all cases of late epilepsy occurred within 2 years postsurgery, with a mean occurrence of 8.3 months in this series. These data may be useful in the rehabilitation of this group of patients, and particularly in deciding whether to recommend resumption of driving privileges.19

In this series late epilepsy was associated with GOS scores of 2 to 4 and loss of consciousness at ictus, in agreement with previous studies.19,28–31,33,39,40 Other factors, such as younger age, onset seizures, preoperative condition, the amount of SAH, presence of ICH, multiple aneurysms, history of hypertension, location of lesions (MCA or ACA), cerebral injury during operation, vasospasm, hydrocephalus, infarction (low density documented on CT scans), abnormalities on EEG studies, and rebleeding have been found to be associated with late epilepsy (Table 3). Nevertheless, our results did not demonstrate a significant relationship between late epilepsy and the following factors: sex; age; history of hypertension; admission GCS score; Fisher SAH grade; locations of aneurysms; vasospasm; rebleeding; timing of surgery; hydrocephalus; the need for VP shunt placement; or onset, preoperative, or postoperative seizures. The discrepancy between studies may be due to different case selection criteria, statistical methods used for analyses, variable definitions of late epilepsy, and the length of follow up. Persistent neurological deficits during follow up seemed to be a constant variable associated with late epilepsy.19,28–31,33,39,40,43 In this series, three (2.3%) of 128 patients with good recovery (GOS Score 1) experienced late epilepsy, compared with 12 (14%) of 85 patients with neurological deficits (GOS Scores 2–4).

Late epilepsy developed in only one of 26 patients with onset, preoperative, or postoperative seizures. The recurrence rate of seizures was 3.8%. The frequency of late epilepsy in patients with perioperative seizures (7.8%) was not significantly higher than in those without perioperative seizures (6.8%). This type of seizure did not recur frequently and was not a significant predictor for late epilepsy; perioperative seizures appear truly to be distinct phenomena (part of an acute cerebral disorder). Routine use of anticonvulsant drugs during hospitalization in all patients in this study may have prevented the recurrence of seizures in the acute phase. Nevertheless, the effect of anticonvulsant medications on prevention of late epilepsy could not be delineated from our findings. Future, prospective, multicenter examinations are warranted to resolve definitively the controversy of prophylactic administration of anticonvulsant therapy in patients who undergo treatment for ruptured intracranial aneurysms.

Conclusions

The characterization of seizures and late epilepsy after surgery for ruptured aneurysms has been heretofore inadequate. In this study we have attempted to contribute to the evaluation of the incidence, timing, and predictive factors of perioperative seizures and late epilepsy after SAH and surgery for ruptured intracranial aneurysms. We find that the incidence of late epilepsy after such surgery is relatively low (15 [6.9%] of 217 patients in this series). Late epilepsy does not appear to be associated with perioperative seizure(s), which include onset, preoperative, and postoperative seizures within 1 week of surgery. Putative risk factors for the development of onset seizures are younger patient age (<40 years), Fisher SAH Grades 3 and 4, and loss of consciousness longer than 1 hour at ictus. The risk factors predictive of late epilepsy are persistent neurological deficits (GOS Scores 2–4) and loss of consciousness longer than 1 hour at ictus. The indications, efficacy, regimens, and length of anticonvulsant therapy for perioperative seizures and epilepsy after SAH, as well as the treatment for ruptured intracranial aneurysms should be reevaluated, and further study is warranted to clarify these issues.

References

Perioperative seizures and epilepsy after aneurysmal SAH


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