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Clinical Article

Seizures and Epilepsy following Aneurysmal Subarachnoid Hemorrhage : Incidence and Risk Factors

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Objective : Although prophylactic antiepileptic drug (AED) use in patients with aneurysmal subarachnoid hemorrhage (SAH) is a common practice, lack of uniform definitions and guidelines for seizures and AEDs rendered this prescription more habitual instead of evidence-based manner. We herein evaluated the incidence and predictive factors of seizure and complications about AED use.

Methods : From July 1999 to June 2007, data of a total of 547 patients with aneurysmal SAH who underwent operative treatments were reviewed. For these, the incidence and risk factors of seizures and epilepsy were assessed, in addition to complications of AEDs.

Results : Eighty-three patients (15.2%) had at least one seizure following SAH. Forty-three patients (7.9%) had onset seizures, 34 (6.2%) had perioperative seizures, and 17 (3.1%) had late epilepsy. Younger age (< 40 years), poor clinical grade, thick hemorrhage, acute hydrocephalus, and rebleeding were related to the occurrence of onset seizures. Cortical infarction and thick hemorrhage were independent risk factors for the occurrence of late epilepsy. Onset seizures were not predictive of late epilepsy. Moreover, adverse drug effects were identified in 128 patients (23.4%) with AEDs.

Conclusion : Perioperative seizures are not significant predictors for late epilepsy. Instead, initial amount of SAH and surgery-induced cortical damage should be seriously considered as risk factors for late epilepsy. Because AEDs can not prevent early postoperative seizures (< 1 week) and potentially cause unexpected side effects, long-term use should be readjusted in high-risk patients.

KEY WORDS : Aneurysm · Antiepileptic drug · Complication · Epilepsy · Risk factors · Seizure.

INTRODUCTION

Seizures and epilepsy are well-known complications following aneurysmal subarachnoid hemorrhage (SAH)[1,9,11,26]. The reported incidence of epilepsy after surgery for ruptured intracranial aneurysms has varied between 1% and 27.5%, and it appears to be related to the SAH itself, the effects of craniotomy, or both[17]. Because they can be developed after initial ictus or rebleeding, prophylactic use of antiepileptic drugs (AEDs) in patients with aneurysmal SAH is a common neurosurgical practice. But, both indications and duration of seizure prophylaxis still remained poorly defined over the last three decades[23]. This prescription has been more habitual or narrative-based fashion, instead of evidence-based approach. The AEDs also have been associated with several adverse effects.

In this study, we evaluated the incidence and risk factors of seizures and epilepsy following aneurysmal SAH, with special reference to the surgical insult, and complications regarding use of the AEDs.

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MATERIALS AND METHODS

Patient population

During 8 consecutive years, from July 1999 to June 2007, 547 patients with aneurysmal SAH who underwent operative treatments (microsurgical clipping) and received AEDs medication were included in this study. In this study, the exclusion criteria were patients who refused to operate for aneurysmal SAH (n = 73), surgery for unruptured aneu-

rysm (n = 31), endovascular coil embolizations (n = 28).

For these 547 patients, the incidence of seizures or epilepsy, and relevant risk factors were retrospectively studied. Collected data were related to demographic variables (sex, age, medical co-morbidity and medication history), initial clinical and radiologic information (Glasgow Coma Scale score, Hunt and Hess grade, Fisher grade, location of aneurysm, acute hydrocephalus, vasospasm, infarction), operative intervention besides clipping (ventricular drainage, shunting), and seizures or epilepsy based on their occurring time. And, available AEDs and their complications were also investigated.

Glossary

For the purpose of this study, seizure was defined as repetitive, rhythmic jerking, with or without preceding tonic spasm that was focal or generalized in nature, with or without loss of consciousness. When seizures occurred outside the hospital, only seizures observed by medical staffs, relatives, care-givers, or paramedics were included. The incidence of seizures was classified as follows according to the time of seizure attack : 1) onset seizure that occurred within 12 hours of the initial hemorrhage; 2) preoperative seizure; 3) postoperative seizure < 1 week; and 4) postoperative seizure > 1 week. Epilepsy or late epilepsy is defined as a disorder in which at least 2 spontaneous seizures occurring after the first week, and were separated temporally by a minimum interval of 24 hours.

Statistical method

All retrieved data were converted into categorical variables, either dichotomization or stratification. To assess the relationship between variables and onset seizure or late epilepsy, statistical method was used by using SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA). The chi-square test (Fisher's exact test) or student T-test was first used, where appropriate, significance was set at a probability value of 0.05, and 95% of CI was calculated. The univariate analysis was used to identify risk factors, and to calculate odds ratio (OR) and 95% CI. And, then multivariate analysis was performed with backward elimination manner to control possible confounding variables.

RESULTS

Among 547 patients, 83 patients (15.2%) had at least one seizure following aneurysmal SAH. In overall, 43 patients (7.9%) had onset seizures, 8 (1.5%) had preoperative seizures, 6 (1.1%) had postoperative seizures (< 1 week), and 28 (5.1%) had at least one seizure episode after the first week postoperatively. Among the patients with perioperative seizure (n = 42), only two had onset seizure. Fifty-six patients with seizures developed within 1 week postoperatively, only 2 patients (3.6%) had late epilepsy. Of 28 patients with postoperative seizures (> 1 week), 15 patients (53.6%) had late epilepsy. So, a total of 17 patients (3.1%) developed late epilepsy (Fig. 1).

In onset seizure group, 38 patients experienced generalized tonic-clonic (GTC) type seizures, and 5 patients had focal motor seizures. Forty-one cases of these episodes occurred within 1 hour after the ictus. There were 2 patients suffering from seizure recurrence who later developed epilepsy 12 and 22 months post-SAH. Of 8 patients with preoperative seizure, none experienced postoperative seizures or late epilepsy. Of 6 patients with postoperative seizures within 1 week postoperatively, one patient had an onset seizure, and developed late epilepsy. The mean latency from operation to seizure onset was 3.7 ± 2.5 days. In late epilepsy group, 12 patients experienced GTC type seizures, and 3 patients had complex partial seizures progressed to GTC type, and 2 patients had simple focal motor seizures. The mean latency from operation was 3.5 months (0.3 - 2.2 months). The seizures occurred within 3 months in 4 patients, between 3 and 12 months in 11

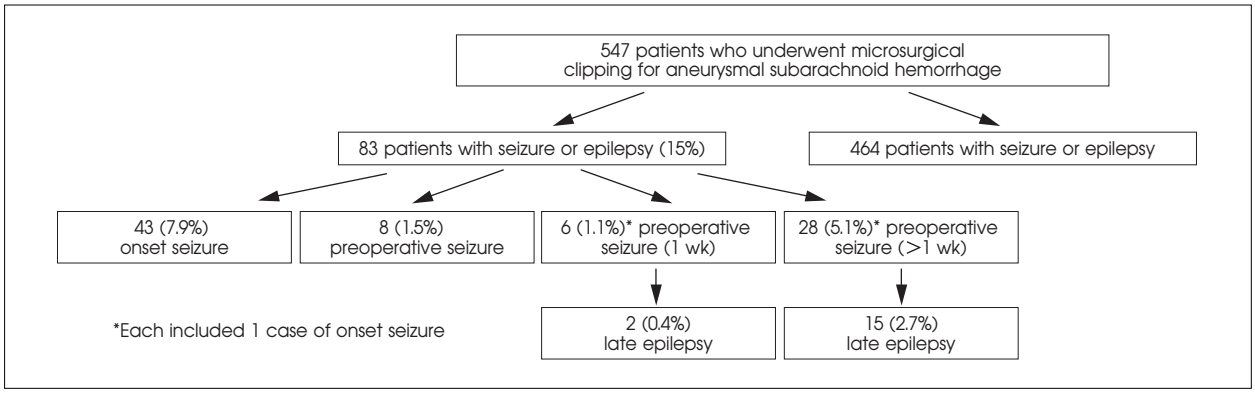

Fig. 1. Schematic flow of patients enrolled in this study

Table 1. Summary based on detailed seizure characteristics*

Seizure characteristics	Seizure subtype		Time	Recurrence / Late epilepsy
	Generalized	Focal motor		
Onset seizure (43)	38	5	Within 1hr (41)	2
Preoperative seizure (8)	7	1	Within 24 hr	0
Early postoperative seizure (6)	5	1	3.7 ± 2.5 days	2†
Late postoperative seizure (28)	20‡	8	3.5 mo (0.3-22 mo) < 3 mo : 7 3-12 mo : 17 12-22 mo : 4	15†

*Numbers in parentheses represent corresponding patient numbers, †Each group included 1 case of onset seizure, ‡Included 4 patients with secondarily generalized seizure

Table 2. Characteristics of 547 SAH patients according to presence of onset seizure

Characteristic	Pt. No.	Onset Sz (+)	Onset Sz (-)	*p*-value	OR (95% CI)
Male (Female)	228 (319)	18 (25)	210 (294)	0.915	0.4 (0.1-1.1)
Age (yr)					
-40	36	5	31	0.001	3.5 (1.9-9.2)
41-65	113	9	104	0.071	1.2 (0.4-1.8)
65-	79	4	75	0.162	0.6 (0.1-1.5)
Hypertension (+)	92	8	84	0.083	1.1 (0.5-1.7)
Hunt-Hess					
I & II	128	6	122	0.304	0.5 (0.2-1.3)
III & IV	96	12	84	0.015	2.7 (1.3-6.1)
V	4	0	4	1.000	NA
Fisher grade III & IV	102	14	88	0.003	5.1 (2.6-10.4)
Acute hydrocephalus	51	11	40	0.001	6.6 (2.4-18.6)
Rebleeding (before op.)	14	8	6	0.001	9.1 (4.6-16.3)
Aneurysm location					
ICA	73	7	67	0.458	1.4 (0.5-4.0)
ACA	82	5	76	0.606	0.8 (0.2-1.7)
MCA	61	5	55	0.207	0.7 (0.1-1.2)
VBA	12	1	11	0.098	1.3 (0.7-1.8)
Preop seizure	3	0	3	1.000	NA
Postop seizure	14	2	12	0.819	0.6 (0.2-1.1)
Late epilepsy	11	2	9	0.635	0.8 (0.1-6.7)

ACA : anterior cerebral artery, CI : confidence interval, ICA : internal carotid artery, MCA : middle cerebral artery, NA : not applicable, OR : odds ratio, op : operation, SAH : subarachnoid hemorrhage, Sz : seizure, VBA : vertebro-basilar artery

patients, and between 13 and 22 months in 2 patients (Table 1).

The relationships between clinical parameters and the development of onset seizures are summarized in Table 2. Younger age below 40 years (OR 3.5, 95% CI 1.9-9.2; p = 0.001), Hunt-Hess grade III & IV (OR 2.7, 95% CI 1.3-6.1; p = 0.015), Fisher grade III & IV (OR 5.1, 95% CI 2.6-10.4; p = 0.003), acute hydrocephalus (OR 6.6, 95% CI 2.4-18.6; p = 0.001), and rebleeding prior to the operation (OR 9.1, 95% CI 4.6-16.3; p = 0.001) were related to the development of onset seizures.

The characteristics of 547 patients with aneurysmal SAH according to presence of late epilepsy are illustrated in Table 3. Several predictive risk factors for late epilepsy were identified. Hydrocephalus (OR 4.5, 95% CI 1.9-9.7; p = 0.003), cortical infarction (OR 8.5, 95% CI 2.4-13.9; p = 0.001), Fisher grade III & IV (OR 1.4, 95% CI 1.1-1.8; p = 0.025), and younger age (OR 1.8, 95% CI 1.2-2.8; p = 0.002) were related to the occurrence of late epilepsy. However, onset seizures were not predictive of late epilepsy. Independent risk factors for seizure recurrence or late epilepsy were assesses by multivariate analysis. Only two variables had statistically significant relationship with development of late epilepsy: initial amount of SAH (OR 1.81, 95% CI 1.07-2.15; p = 0.038) and newly developed cortical infarction (OR 2.04, 95% CI 1.24-2.86; p = 0.001) (Table 4).

Antiepileptic drugs (AEDs), including valproate, phenytoin, phenobarbital, carbamazepine, zonisamide, and/or topiramate were used in 528 patients (96.5%). Valproate was the most frequently prescribed drug (72.4%), followed by phenytoin (17.6%). We used AEDs until 3 months postoperatively with monitored tapering. However, prophylactic efficacy of AEDs medication against seizure and late epilepsy could not be elicited from our study. Furthermore, adverse effects occurred in 128 patients (23.4%) who received AEDs, irrespective of severity. The adverse effects consisted of drug eruption (skin rash), fever, dizziness, thrombocytopenia, toxic hepatitis (fulminating), hypotension, amenorrhea, and vasospasm.

DISCUSSION

General overview

The reported incidence of seizures after SAH ranges from 3% to 26% and postoperative seizures in aneurysm patients without AED prophylaxis occur in 3% to 22%[1,11,12,21,22,27,29]. In the current study, the incidence of seizures following aneurysmal SAH was 15.2%. Onset (ictal or immediate) seizures have been traditionally defined as episodes occurring within the first 12 hours of SAH, as classified in our study[11,12,17,22]. Onset seizures occurred at

Table 3. Characteristics of 547 SAH patients according to presence of late epilepsy

Characteristic	No.	Onset Sz (+)	Onset Sz (-)	*p*-value	OR (95% CI)
Male (Female)	228 (319)	10 (7)	218 (312)	0.071	2.5 (0.8 - 6.2)
Age (yr)					
-40	36	5	30	0.002	1.8 (1.2 - 2.8)
41-65	113	3	94	0.749	0.7 (0.3 - 1.2)
65-	79	2	76	0.311	0.5 (0.1 - 1.1)
Hypertension (+)	92	4	88	0.102	1.9 (0.9 - 3.5)
Hunt-Hess III & IV	96	5	91	0.059	1.6 (0.5 - 2.3)
Fisher Grade III & IV	102	6	96	0.025	1.4 (1.1 - 1.8)
Aneurysm location					
ICA	73	4	68	0.249	1.2 (0.7 - 1.9)
ACA	82	3	78	0.736	0.9 (0.4 - 2.1)
MCA	61	3	57	0.445	1.4 (0.2 - 3.6)
VBA	12	0	12	1.000	NA
Symptomatic vasospasm	68	6	62	0.007	2.7 (0.8 - 6.3)
EVD	73	5	68	0.038	1.8 (0.9 - 2.7)
Hydrocephalus	64	7	57	0.003	4.5 (1.9 - 9.7)
VP shunt	51	4	47	0.074	1.5 (0.7 - 2.3)
Cortical infarction	45	11	34	0.001	8.5 (2.4 - 13.9)
Onset seizure	18	2	16	0.627	1.3 (0.8 - 2.1)
Preop seizure	3	0	3	1.000	NA
Postop seizure	14	1	13	1.000	NA

ACA : anterior cerebral artery, CI : confidence interval, EVD : external ventricular drainage, ICA : internal carotid artery, MCA : middle cerebral artery, NA : not applicable, OR : odds ratio, SAH : subarachnoid hemorrhage, Sz : seizure, VBA : vertebro-basilar artery, VP Shunt : ventriculo-peritoneal shunt

Table 4. Independent risk factors for late epilepsy following aneurysmal SAH

Variables	*p*-value	OR (95% CI)
Young age (< 40 yrs)	0.08	1.12 (0.84 - 1.41)
Hunt-Hess III & IV	0.103	1.74 (0.94 - 2.56)
Fisher grade III & IV	0.038	1.81 (1.07 - 2.15)
MCA aneurysm	0.16	1.08 (0.87 - 1.15)
Hydrocephalus	0.052	1.04 (0.91 - 1.23)
Rebleeding	0.064	0.95 (0.77 - 1.34)
Cortical infarction	0.001	2.04 (1.24 - 2.86)
Onset seizure	0.08	1.03 (0.91 - 1.17)

CI : confidence interval, OR : odds ratio, MCA : middle cerebral artery, SAH : subarachnoid hemorrhage

near time of initial aneurysm rupture before grabbing medical attention. In almost all instances, AEDs were prescribed with loading dose via intravenous route after SAH patients arrived at emergency room. In this series, despite routine AED prescription (96.5%), 34 patients (6.2%) had at least one seizure episode after operation; craniotomy with aneurysmal neck clipping. The efficacy and benefit of AED in prophylaxis of postoperative seizures and epilepsy could not be delineated from our data due to varied use of AEDs and insufficiency of planned therapeutic drug monitoring. In other series, effect of AEDs medication on prevention of late epilepsy was unclear[17,23,24]. These data were similar to those noted for patients with traumatic closed head injury in whom early AED use did not change the incidence of delayed epilepsy[6,10,28,31].

Risk factors of onset seizures

Seizures and epilepsy are well-recognized complications of traumatic brain injury and major brain surgery. The risk of epilepsy depends on surgical insult and/or degree of the underlying lesion[8,14,17]. Risk factors of onset seizures after SAH reported on previous papers include presence of intracerebral hemorrhage, anterior circulation aneurysms, hypertension, ischemic infarcts revealed on late computed tomographic (CT) scans, initial loss of consciousness lasting longer than 1 hour, hemiparesis, Hunt and Hess grade greater than III, the amount of subarachnoid blood, younger age (< 40 years), and confirmed presence of an aneurysm[11,17,21,22,25]. In this study, onset seizures developed in 43 patients (7.9%) of 547 patients with aneurysmal SAH, and was associated with younger age (< 40), Hunt-Hess grade (III-IV), Fisher grade (III-IV), acute hydrocephalus, and rebleeding prior to the operation. However, hypertension and location of aneurysm were not related to the occurrence of onset seizures. Onset seizures in aneurysmal SAH were believed to be an important risk factor for delayed epilepsy[4,11,23]. In contrast, other reports demonstrated that onset seizures are not predictive factor of late epilepsy[1,2,12,22,23,27]. In our series, only 2 patients (4.6%) of 43 patients with onset seizures suffered late epilepsy. In multivariate analysis, there was no significant statistical correlation of onset seizure and late epilepsy (OR 1.03, 95% CI 0.91-1.17; $p = 0.08$)

Risk factors of late epilepsy

Recent retrospective clinical studies found late or recurrent epilepsy in 7% to 12% of their SAH populations[2,7,15,30]. The observed frequency of epilepsy after SAH in our study of 3.1% at 22 months is comparable to that of prior reports of 7 to 12%. From these data, a number of predictors have been implicated, including ischemia and postoperative vasospasm, poor preoperative neurologic grade, anterior circulation aneurysm location, general severity of hemorrhage as reflected by blood on CT, rebleeding, large intra-

cerebral hemorrhage and shunt-dependent hydrocephalus[2,7,12,15,20,29]. In our study (Table 3), late epilepsy was associated with hydrocephalus, cortical infarction, Fisher grade III and IV, and younger age (< 40 years). As stated above, onset seizures however, were not predictive of late epilepsy. The discrepancy of risk factors between previous reports and ours may accrue because of varying inclusion criteria and follow-up length, along with different treatment modality.

Other risk factors

As suggested for posttraumatic and poststroke seizures, mechanisms underlying acute seizures and late seizures may be substantially different. In this paradigm, early seizures are attributed to cellular biochemical dysfunction and late seizures to gliosis and the development of meningocerebral cicatrix, respectively[3,13]. The surgical insult resulted from craniotomy and clip application as a risk factor for late epilepsy is controversial. Kvam et al.[16] suggested that seizures after elective craniotomy may be due to postoperative hematoma, metabolic abnormalities, inadequate seizure prophylaxis, pre-existing epilepsy, and severity of surgical insult. Surgical insult to the brain seems to generate free radicals, which in turn leads to formation of epileptogenic focus. However, some recent studies have not supported the prophylactic efficacy of AEDs in most craniotomized patients, but further studies are required[18]. We excluded patients with endovascular coil embolization, hence the contribution of surgical insult as a risk factor for late epilepsy could not be compared with that of minimally invasive endovascular technique. There was no reported seizure in 28 patients treated solely with endovascular coil embolization at our institution. But, this result is insignificant because of too small case volume. According to Byrne et al.[5], 233 patients treated solely by coil embolization had no seizure in the periprocedural period despite a 11% incidence of onset seizures. Late epilepsy occurred de novo in only 0.85% during a follow up of as many as 7.7 years (mean 21.9 months). In International Subarachnoid Aneurysm Trial (ISAT) collaborate group, the risk of epilepsy was substantially lower in patients allocated to endovascular treatment[19].

Limitations and future perspectives

Several limitations of this study include chance of over-reporting, with other neurological events being labeled as seizure or epilepsy because medical and nursing personnel rarely witness the seizures on the spot and there was no electroencephalographic (EEG) evidence. Hence, we might have slightly overestimated the real incidence of epilepsy after SAH. Second, we excluded endovascular treatment from our study conducted in a single center, which may cause selection bias. Third, routine prescription of AEDs in most patients, beginning at the time of hospitalization without specific indication hampered evaluating efficacy of the AEDs prophylaxis for late epilepsy. Fourth, our study could not identify the relationship between the seizure occurrence and characteristics of AED such as classification and duration of use. Fifth, there might be bias and error because of retrospective study design. Therefore, randomized, prospective, multicenter studies should be recommended in future.

CONCLUSION

In this study we found that perioperative seizures, from ictus to 1 week postoperatively, do not have significant predictive value for development of late epilepsy after microsurgery for aneurysmal SAH. Because AEDs can not sufficiently prevent early postoperative seizures (< 1 week) and available AEDs potentially cause unexpected side effects, long-term use for AEDs after aneurysmal SAH should be readjusted and selected in such high-risk patients with Fisher grade III and IV on CT scan and cortical infarction, and possibly with younger age (< 40 years) and hydrocephalus. To estimate the efficacy and safety of AEDs for preventing or reducing late epilepsy after aneurysmal SAH, prospectively designed multicenter study with unified regimen should be followed.

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