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Original Article

Influential factors of epilepsy following aneurismal subarachnoid hemorrhage

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Abstract: Objective: To explore the risk factors for epilepsy following aneurismal subarachnoid hemorrhage (ASH). Methods: Clinical data of patients with ASH who underwent microsurgical clipping in our hospital between January 2006 and July 2014 were retrospectively analyzed. Clinical data included age, a history of hypertension, duration of consciousness disorder (≥ one hour, < one hour), score of Glasgow Coma Scale (GCS) and Fisher grade on admission, ruptured aneurysms, complications (rebleeding, cerebral vasospasm and hydrocephalus), surgical timing and score of Glasgow Outcome Scale (GOS). The secondary epilepsy was divided into early epilepsy (< 24 h) and late epilepsy (> 24 h), and then the influential factors of epilepsy occurring in different periods were respectively analyzed. Results: Of 177 patients with ASH, 14 had early epilepsy, 16 had late epilepsy and 3 had both early and late epilepsy. The patients with a history of hypertension readily had early epilepsy ($P < 0.05$), and the patients with GCS of 8-14 or hydrocephalus readily had late epilepsy ($P < 0.05$). Conclusion: Hypertension is a risk factor of early epilepsy, and GCS of 8-14 or hydrocephalus are risk factors of late epilepsy. This study provides a basis for early diagnosis, prevention and treatment of epilepsy.

Keywords: Aneurysm, subarachnoid hemorrhage, epilepsy, influential factors

Introduction

Epilepsy, as a manifestation of rain damage, is usually caused by tow factors [1]. One refers to brain diseases including inflammation, tumor and vascular disease, and another is iatrogenic injury such as surgical operation. Epilepsy following aneurismal subarachnoid hemorrhage (ASH) is not exception, and it is also caused by bleeding itself, surgery or both [2]. The incidence of epilepsy following ASH is about 3-35% [2-5]. It may exhibit grand mal or petit mal and it may occur at the onset, before or after operation. However, we do not understand the risk factors for epilepsy following ASH. This may be that there are too many potential influential factors, clinical data are relatively complex and long follow-up duration readily leads to loss of follow-up. Epilepsy, an important complication of ASH, should never be neglected because it severely affects daily life of patients with epilepsy following ASH. Therefore, we retrospectively analyzed influential factors of early and late epilepsy following ASH in this study.

Materials and methods

All study methods were approved by the Ethics Committee of the Third Affiliated Hospital, Sun Yat-sen University. All the subjects enrolled into the study gave written formal consent to participate.

Subjects

The patients with ASH who underwent microsurgical clipping in our hospital between January 2006 and July 2014 were enrolled in this study. The patients who had an incomplete clinical data or a history of epilepsy were excluded from this study. A total of 177 patients were consistent with inclusion criteria. Of 177 patients, 72 were male and 104 female, with a mean age of 53.66±11.86 years (range 1-81).

All patients were diagnosed with brain aneurysm and subarachnoid hemorrhage by 320 slice CT (Aquillion One, Japan). The patients who could not be diagnosed by CT angiography

Table 1. Single factor analysis of influential factors for early seizures following aneurismal subarachnoid hemorrhage

Influential factors	Cases (n)	Seizures	No seizures	*P* Value	OR (95% CI)
Sex					
Male	72	4	68	0.342	0.559 (0.168-1.856)
Female	105	10	95	0.337	1.789 (0.539-5.945)
Age group					
< 60	117	13	114	0.102	5.588 (0.711-43.899)
≥ 60	60	1	59	0.057	0.136 (0.017-1.063)
Hypertension	74	12	62	0.003	9.774 (2.117-45.138)
Duration of consciousness disorder ≥ 1 hr	22	3	19	0.297	2.067 (0.529-8.080)
GCS on admission					
15	130	9	121	0.659	0.774 (0.247-2.420)
8~14	37	4	33	0.465	1.576 (0.465-5.342)
< 8	10	1	9	0.801	1.316 (0.155-11.211)
Fisher Grade					
3 or 4	129	13	116	0.114	5.267 (0.670-41.409)
Location of ruptured aneurysm					
ACoA	56	5	51	0.733	1.220 (0.389-3.823)
MCA	45	3	42	0.721	0.786 (0.209-2.953)
PCoA	31	2	29	0.741	0.770 (0.163-3.628)
ICA	31	2	29	0.741	0.770 (0.163-3.628)
ACA	11	2	9	0.211	2.852 (0.553-14.715)
PICA	2	0	2	1	NA
BA	1	0	1	1	NA
Anterior circulation aneurysm	174	14	160	1	NA
Posterior circulation aneurysm	3	0	3	1	NA
GOS score					
1	14	1	13	0.912	0.888 (0.107-7.331)
2~4	43	4	39	0.698	1.272 (0.378-4.282)
5	120	9	111	0.770	0.843 (0.269-2.641)

Notes: GCS: Glasgow Coma Scale; ACoA: Anterior communicating artery; MCA: Middle cerebral artery; PCoA: Posterior communicating artery; ICA: Internal carotid artery; ACA: Anterior cerebral artery; PICA: Posterior inferior cerebellar artery; BA: Basilar artery; GOS: Glasgow Outcome Scale; NA: Not applicable.

must receive digital subtraction angiography (DSA). The intracranial conditions during peroperative period were observed by 320 slice CT or 1.5 T magnetic resonance (GE, USA).

Clinical data included a history of hypertension, duration of consciousness disorder (≥ one hour, < one hour), score of Glasgow Coma Scale (GCS) and Fisher grade on admission, ruptured aneurysms, complications (rebleeding, cerebral vasospasm and hydrocephalus), surgical timing and score of Glasgow Outcome Scale (GOS), duration of epileptic seizure and manner of epileptic seizure.

The secondary epilepsy was divided into early epilepsy (< 24 h) and late epilepsy (> 24 h). All patients underwent microsurgical aneurysm clipping.

Statistical analysis

Statistical treatment was performed with SPSS19.0 software. Measurement data consistent with normal distribution were expressed as mean ± standard deviation. Categorical data were expressed as frequencies and per cent of total. Chi-square test was first used in the single-factor analysis of epilepsy-related risk factors, and then multiple-factor logistic regression analysis was performed on the epilepsy-related risk factors showing statistical significance in chi-square test. Statistical significance was established at $P < 0.05$.

Table 2. Single factor analysis of influential factors for later seizures following aneurismal subarachnoid hemorrhage

Influential factors	Cases (n)	Seizures	No seizures	*P* Value	OR (95% CI)
Sex					
Male	72	8	64	0.429	1.516 (0.541-4.243)
Female	105	8	97	0.426	0.660 (0.236-1.847)
Age group					
< 60	117	12	105	0.434	1.000 (0.493-5.192)
≥ 60	60	4	56	0.434	0.625 (0.193-2.028)
Hypertension	74	6	68	0.714	0.821 (0.284-2.367)
Duration of consciousness disorder ≥ 1 hr	22	2	20	0.993	1.007 (0.213-4.763)
GCS on admission					
15	130	10	120	0.303	0.569 (0.195-1.664)
8~14	37	6	31	0.026	2.516 (0.580-7.449)
< 8	10	0	10	1	NA
Fisher Grade					
3 or 4	129	12	117	0.842	1.128 (0.345-3.684)
Location of ruptured aneurysm					
ACoA	56	2	54	0.103	0.283 (0.062-1.291)
MCA	45	5	40	0.576	1.375 (0.450-4.197)
PCoA	31	3	28	0.892	1.096 (0.293-4.103)
ICA	31	5	26	0.139	2.360 (0.757-7.361)
ACA	11	1	10	0.995	1.007 (0.120-8.412)
PICA	2	0	2	1	NA
BA	1	0	1	1	NA
Anterior circulation aneurysm	174	16	158	1	NA
Posterior circulation aneurysm	3	0	3	1	NA
GOS score					
1	14	2	12	0.481	1.774 (0.360-8.734)
2~4	43	7	36	0.065	2.701 (0.940-7.756)
5	120	7	113	0.038	0.330 (0.116-0.938)
Hydrocephalus	24	8	16	0.000	9.062 (2.994-27.435)
Rebleeding	6	1	5	0.516	2.080 (0.228-18.988)
Vasospasm	29	3	26	0.789	1.198 (0.319-4.502)
Surgical timing					
0-3 d	70	6	64	0.861	0.909 (0.315-2.625)
4-14 d	58	8	50	0.131	2.220 (0.788-6.251)
> 14 d	49	2	47	0.172	0.347 (0.076-1.584)
Early seizures	14	3	11	0.108	3.147 (0.779-12.719)

Notes: GCS: Glasgow Coma Scale; ACoA: Anterior communicating artery; MCA: Middle cerebral artery; PCoA: Posterior communicating artery; ICA: Internal carotid artery; ACA: Anterior cerebral artery; PICA: Posterior inferior cerebellar artery; BA: Basilar artery; GOS: Glasgow Outcome Scale; NA: Not applicable.

Results

Of the 177 patients, 161 had single aneurysm and 16 had multiple aneurysms, with a total of 194 aneurysms. In this study, there were 177 ruptured aneurysms including 56 in anterior communicating artery, 45 in middle cerebral artery, 31 in posterior communicating artery, 31 in internal carotid artery, 11 in anterior cerebral artery, 2 in posterior inferior cerebellar artery and one in basilar artery. A history of hypertension, duration of consciousness disorder, score of GCS and Fisher grade on admission are shown in **Tables 1** and **2**.

Table 3. Multiple-factor logistic regression analysis of influential factors for later seizures following aneurismal subarachnoid hemorrhage

Influential factors	β values	SE	*P* Values	OR (95% CI)
GCS of 8-14 on admission	0.470	0.682	0.491	1.60 (0.420-6.092)
GOS of 5	-0.352	0.614	0.567	0.703 (0.211-2.343)
Hydrocephalus	2.235	0.605	0.000	9.350 (2.856-30.605)

Notes: GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale.

Microsurgical aneurysm clipping was successful in all patients. Six patients had preoperative rebleeding, 29 patients had postoperative cerebral vasospasm and 24 had postoperative hydrocephalus which was treated by ventriculoperitoneal shunt. The score of GOS was 5 in 120 patients, 4 in 16 patients, 3 in 20 patients, 2 in 7 patients and one in 14 patients (**Tables 1** and **2**).

In this study, 14 patients had early epilepsy. Of the 14 patients, 13 manifested grand mal and one exhibited petit mal. The duration of epileptic seizure was 8.50±2.54 h (range 0-24). Sixteen patients had late epilepsy. The 16 patients all manifested grand mal. The duration of epileptic seizure was 133.87±17.75 d (range 28 h-540 d). Three patients had both early and late epilepsy.

The results of single-factor analysis for the correlations of potential influential factors with early epilepsy and late epilepsy are respectively shown in **Tables 1** and **2**.

For early epilepsy, single-factor analysis indicated that there was statistical significance only in hypertension. For late epilepsy, single-factor analysis displayed that there was statistical significance in GCS of 8-14, GOS of 5 and hydrocephalus, so the three factors were further subjected to multiple-factor logistic regression analysis. Multiple-factor logistic regression analysis indicated that only hydrocephalus was risk factor for late epilepsy (**Table 3**).

Discussion

Epilepsy following ASH

Epilepsy is a serious complication of ASH with an incidence of 3-35% [2-5]. In this study, epilepsy occurred in 27 patients among 177 patients with an incidence of 15.3%. Epilepsy following ASH may exhibit systemic tonic clonic seizure or petit mal. Lin et al [6] reported that only 4 patients had petit mal among 46 patients with epilepsy. In this study, only one patient had petit mal among 27 patients with epilepsy. This suggests that the main manner of epilepsy following ASH is grand mal (systemic tonic clonic seizure).

Epilepsy following aneurysm rupture is mainly caused by subarachnoid hemorrhage, surgery or both [6, 7]. In general, the epilepsy caused by subarachnoid hemorrhage occurs in early stage, and the epilepsy caused by surgery, rebleeding, vasospasm or/and hydrocephalus occurs in late stage. In this study, the secondary epilepsy was divided into early epilepsy (< 24 h) and late epilepsy (> 24 h) because their influential factors are different.

Risk factors for early epilepsy following ASH

The influential factors of early epilepsy following ASH include age, a history of hypertension, duration of consciousness disorder, intracranial hematoma, Fisher grade, Hunt-Hess scale, GCS on admission and location of ruptured aneurysm [2, 7-9]. The factors above may be divided into two categories. One category is patients' own factors including age and hypertension, and another category refers to bleeding-related factors such as duration of consciousness disorder, intracranial hematoma, Fisher grade, Hunt-Hess scale, GCS on admission and location of ruptured aneurysm.

After subarachnoid hemorrhage, hemoglobin degradation products and iron ions can cause brain tissue to produce active substances, such as glutamate, oxygen radicals and arachidonic acid, which induce epilepsy [6, 10]. The factors including duration of consciousness disorder, intracranial hematoma, Fisher grade, Hunt-Hess scale and GCS on admission reflect the amount of bleeding, so these factors induce epilepsy mostly though the mechanism above. The location of ruptured aneurysm is also associated with epilepsy. It has been reported that the incidence of epilepsy is higher in middle

cerebral artery aneurysms than in other artery aneurysms because the blood supply of cortical motor area is from the middle cerebral artery and hematoma is readily formed after middle cerebral artery aneurysm rupture, which lead to paradoxical discharge of neurons in motor area [2, 4, 6, 7].

Our results indicated that a history of hypertension is a unique risk factor for early epilepsy. We believe that hypertension as a risk factor for epilepsy is not associated with the amount of bleeding and the location of ruptured aneurysm, instead hypertension more easily leads to vasospasm which induces epilepsy [11]. Our results displayed that many bleeding-related factors were not directly related to early epilepsy. This may be caused by small sample.

Risk factors for late epilepsy following ASH

It is reported that the incidence of late epilepsy following ASH is about 3-27.5% [6, 7, 9, 10]. In this study, 16 patients (9.04%) had late epilepsy among 177 patients. The time point between early and late epilepsy is 24 h after onset or 7 d after surgery [6, 12]. In order to observe effects of bleeding and surgery on epilepsy, we chose postoperative 24 h as a time point between early and late epilepsy. In this study, the latest epilepsy occurred 540 d after onset in one patient. The patient has had no epileptic seizure after taking antiepileptics for one year followed by gradual drug reduction to discontinuation.

Subarachnoid hemorrhage, complications (rebleeding, hydrocephalus and vasospasm) and surgery (surgical timing and recovery situation) are the influential factors of late epilepsy following ASH. It has been reported that the influential factors of late epilepsy following ASH include preoperative state, location of ruptured aneurysm, rebleeding, vasospasm, hydrocephalus, infarction, early epilepsy, surgical timing and postoperative GOS [6, 7, 9, 12, 13].

Late epilepsy may be caused by nerve cell degeneration or astrocyte proliferation [6, 14]. In this study, single-factor analysis indicated that the patients with GCS (8-14 scores), GOS (5 scores) or hydrocephalus readily had late epilepsy, but multiple-factor logistic regression analysis displayed that only hydrocephalus was risk factor for late epilepsy. This may be that consciousness disorder (GCS 8-14 scores) becomes a confounding factor due to interaction among variables, while hydrocephalus leads to epilepsy through increasing intracranial pressure which brings damage on neurons [7, 8, 15].

This study indicated that late epilepsy was not significantly associated with location of ruptured aneurysm, rebleeding, vasospasm, occurrence of early epilepsy and surgical timing.

Prevention and treatment of epilepsy following ASH

Although it is still controversial whether epileptic seizure affects the prognosis of patients with ASH [4, 6, 14], it certainly affects daily life of patients with ASH. Hart et al [2] have discussed how long the patients with ASH may receive a driver's license after operation.

Early discovery and treatment of epilepsy following ASH is important for improving life quality of patients. In our clinical practice, the patients with epilepsy following ASH are first given intravenous sodium valproate (15 mg/kg, > 5 min), and then are given a maintenance dose (1 mg/kg/h). After pathogenetic condition is stable, intravenous sodium valproate is changed into oral sodium valproate. At the same time, blood drug level is monitored. Sodium valproate is generally given for 3 months for patients with early epilepsy and one year for patients with late epilepsy. The patients without epilepsy do not receive preventive medication.

Knowledge of risk factors for epilepsy is conducive to early discovery and treatment of epilepsy, improving life quality of patients.

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Disclosure of conflict of interest

None.

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