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Relationship Between Leukocytosis and Vasospasms Following Aneurysmal Subarachnoid Hemorrhage

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Objective : Cerebral vasospasm is a devastating medical complication of aneurysmal subarachnoid hemorrhage (SAH). Therefore, prompt detection of vasospasms in aneurysmal SAH is important to the clinical outcome of the patient. For better prediction and effective management of vasospasms, identifying risk factors is essential. This study is aimed at evaluating the relationship between clinical hematologic values, especially white blood cell count, and cerebral vasospasms.

Methods : A retrospective review was conducted on 249 patients with aneurysmal SAH who underwent surgical clipping (230 cases) or endovascular intervention (19 cases) between 2003 and 2005. The underlying clinical conditions assessed were leukocytosis, fever, hypertension, diabetes, smoking, Hunt and Hess grade, Fisher grade, aneurysm location, and direct clipping versus endovascular intervention.

Results : Two hundred forty-nine patients were treated for aneurysmal SAH duringthis period. We selected 158 patients in Hunt and Hess grade I - III. Cases of infectious conditions, rebleeding and other surgical/clinical complications were excluded. Vasospasms occurred 7.0 ± 3.1 days after the onset of SAH. There were several independent predictors of vasospasm : Fisher grade III (p=0.002), fever within two weeks on admission (p<0.001), and a serum leukocyte count >$10.8 \times 10^3/mm^3$ on admission (p=0.018).

Conclusion : This study results indicate that leukocytosis and fever increase the risk of vasospasms. However, other known risk factors, such as hypertension and smoking, were not correlated with respect to predicting of cerebral vasospasm. Monitoring the serum leukocyte count may be a helpful and useful marker of vasospasms after aneurysmal SAH.

KEY WORDS : Aneurysmal subarachnoid hemorrhage · Cerebral vasospasm · Fever · Leukocytosis · Risk factors.

Introduction

Cerebral vasospasms is one of major causes of morbidity and mortality in subarachnoid hemorrhage (SAH). Symptomatic vasospasms are caused by the ischemia that results from cerebral arterial narrowing and are characterized by an insidious onset of decreased level of consciousness, followed by focal motor or speech impairment. Although significant advances in the treatment of SAH and vasospasms there have been over the past three decades, outcomes still remain poor[7].

Identifying risk factors may improve clinical outcome and allow more effective treatment of vasospasms. To date, a large blood burden is the only consistently demonstrated risk factor for vasospasms[4]. Data from several reports have revealed that patient age, smoking status, clinical status on admission, and location of an aneurysm may represent additional risk factors[7]. Such results await further validity study as reliable indicators of impending vasospasms.

The ongoing discovery of risk factors for vasospasms may supplement previous findings to strengthen clinical diagnosis, thereby improving prophylactic therapy and revealing new insights concerning causes of the disease and its treatment. In pursuit of these goals, we conducted a retrospective analysis of all patients who presented with SAH at our institution between 2003 and 2005 and performed a multivariate analysis to evaluate independent risk factors for cerebral vasospasms.

Materials and Methods

Medical records from all patients with SAH who had been admitted to our medical center between 2003 and 2005 were retrospectively reviewed. Information was analyzed : the

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patient demographics, clinical status on admission, and location of a ruptured aneurysm were initially screened and the, severity of the blood clot load, white blood cell (WBC) count on admission day and on post-operative days #1, #3, #5, and #7 and fever (up to 37.5℃) within two weeks of admission or prior to vasospasm were carefully evaluated based on recent reports[15,20]. Each patient's clinical status was graded at admission according to the Hunt and Hess classification system. The severity of SAH was demonstrated on the initial CT scan and classified according to the Fisher scale[4]. For this study, patients in Hunt and Hess grade I-III were included. Exclusion criteria included infections, such as pneumonia and urinary tract infections, and neurological worsening caused by rebleeding, hydrocephalus, and other identifiable causes of such worsening, such as electrolyte disturbances, surgical morbidity, hypoxia, and seizures. The onset of confusion or disorientation as a decline in the level of consciousness, or a focal neurological deficit occurring 3 to 14 days after SAH, as previously described[6], was classified as a symptomatic clinical vasospasm only when supported by one of the following : 1) arterial narrowing demonstrated on conventional angiography or CT angiography, 2) transcranial doppler (TCD) ultrasonography flow velocities indicative of vasospasm (mean velocity 120-180cm/second), or 3) acute reversal of deficits with the administration of hypervolemia-hypertension therapy. Modified Rankin's disability scores at hospital discharge were estimated from discharge summary notes.

To assess the statistical significance, continuous variables were analyzed using the Student t-test. Nonparametric data were compared using the Mann-Whitney U-test, and frequencies were evaluated with the chi-square test. Variables that were statistically significant by univariate analysis were included in a multivariate logistic regression model (SPSS for Windows version 13.0 : SPSS INC. Chicago, IL). P-values less than 0.05 were considered significant.

Table 1. Summary of characteristics in 158 consecutive patients with or without cerebral vasospasm following SAH

Variable	No. of patients (%)		p Value
	No vasospasm	Vasospasm	
No. of patients	112	46	-
Age(yrs)†	52.6±11.0	47.3±7.7	0.073
Female sex	68 (60.7)	30 (65.2)	0.596
History of hypertension	49 (43.8)	11 (23.9)	0.084
Smoking	42 (37.5)	16 (34.8)	0.748
Alcohol abuse	16 (14.3)	6 (13.0)	0.564
Location of aneurysm			
ACA	7 (6.3)	0 (0)	0.518
Acho	5 (4.5)	0 (0)	-
ICA	2 (1.8)	1 (2.2)	-
ACoA	37 (33.0)	19 (41.3)	-
PCoA	15 (13.4)	8 (17.4)	-
MCA	36 (32.1)	18 (39.1)	-
V-B	5 (4.5)	0 (0)	-
Other posterior circulation	5 (4.5)	0 (0)	-
Multiple aneurysm	9 (8.0)	2 (4.3)	0.408
Aneurysm stabilization procedure			
Craniotomy & clip application	100 (89.3)	46 (100)	0.013
Endovascular intervention	12 (10.7)	0 (0)	-
Hunt-Hess grade			
I	19 (17.0)	5 (10.9)	0.606
II	52 (46.4)	22 (47.8)	-
III	41 (36.6)	19 (41.3)	-
Fisher grade			
1,2 or 4	69 (61.6)	16 (34.8)	0.002
3	43 (38.4)	30 (65.2)	-
Status at discharge (Modified RDS)			
0 (No symptoms)	27 (24.1)	1 (2.2)	0.033
1, 2 (With symptoms & slight disability)	75 (67)	39 (84.8)	-
3, 4, 5 (Moderete to severe disability)	10 (8.9)	6 (13.0)	-

*ACA : anterior cerebral artery, Acho : anterior choroidal artery, ICA : interal carotid artery, ACoA : anterior communicating artery, PCoA : posterior communicating artery, MCA : middle cerebral artery, V-B : verterbro-basilar artery, RDS : Rankin's disability scale. †Values are presented as the means±standard deviation

Results

Two-hundred-forty-nine patients with SAH were admitted to our institution between 2003 and 2005 and were treated with either surgical clipping or endovascular coiling. Of course, a total of 158 cases were included in this study. Sixty patients (38%) were male and 98 (62%) were female. On admission, 60 patients (38%) showed Hunt and Hess grade III, and 73 patients (46%) showed Fisher Grade 3. One-hundred-forty-six patients (92.4%) underwent craniotomy for the surgical treatment of an aneurysm, and 12 patients (7.6%) underwent endovascular coil insertion. The SAH was localized to an anterior circulation in 148 patients (94%) and to a posterior circulation aneurysm in 10 patients (6%). Sixty patients (38%) had associated chronic essential hypertension, and 8 (5%) with diabetes mellitus.

Table 2. Result of analysis on fever and leukocytosis between patients with vasospasm and without vasospasm group

Variable	No. of patients (%)		p Value
	No vasospasm	Vasospasm	
No. of patients	112	46	-
Fever	44 (39.3)	32 (69.6)	0.001
Severe leukocytosis (WBC>15000) in post-operative day #7	39 (34.8)	18 (39.1)	0.608
Leukocytosis (WBC>11000)			
On admission	45 (40.2)	28 (60.9)	0.018
Immediate post-operative	48 (42.9)	21 (45.7)	0.748
Post-operative day #1	67 (59.8)	32 (69.6)	0.250
Post-operative day #3	24 (21.4)	16 (34.8)	0.079
Post-operative day #5	16 (14.3)	9 (19.6)	0.114
Post-operative day #7	26 (23.2)	12 (26.1)	0.462

In overall, 46 (29.1%) patients developed symptomatic cerebral vasospasms. The mean onset of symptomatic vasospasms was 7.0±3.1 days following SAH. The mean patient age among those who developed vasospasms was 47.3±7.7 years.

As demonstrated in previous studies, patients who developed symptomatic vasospasms more often exhibited Fisher Grade 3 SAH (p=0.002) on admission (Table 1). In addition, those who developed symptomatic vasospasms had higher peak leukocyte counts on admission (p=0.018) and fever within two weeks on admission (p<0.001) (Table 2). In multivariate analysis using multiple linear regression, leukocytosis on admission was the only independent risk factor for symptomatic vasospasms (p=0.024). Endovascular intervention correlated with reduced incidence of symptomatic vasospasms (p=0.013). Also, vasospasms were associated with poor clinical outcome (p=0.033).

Age, sex, Hunt-Hess classification at admission, location of the aneurysm, past clinical conditions such as history of hypertension and diabetes mellitus, smoking, alcohol abuse, blood loss during surgery, and blood transfusion, were not correlated with the development of symptomatic vasospasms.

Discussion

The incidence of symptomatic vasospasms in this series (29.1%) is consistent with previously reported studies (20-40%)[15,19]. Angiography studies alone may not be sensitive enough to classify neurological deficits related to vasospasms, a fact supported by growing evidence that distal artery vasospasms and microcirculation pathologies may play a role in this complex disease[14,16]. In this study, TCD ultrasonography velocities and patient response to hypervolemia-hypertension therapy were additionally evaluated to better classify the delayed neurological deficits related to vasospasms.

Fisher Grade 3 SAH has been consistently associated with a higher incidence of symptomatic vasospasms[4,11]. Similarly, a Fisher Grade 3 SAH was the strongest risk factor for the development of vasospasm in our series. Fever subsequent to SAH has also been shown to increase the risk of developing vasospasm[15,20], but fever was not an independent risk factor in our study. Parkinson and Stephensen[17] studied a series of 171 patients with SAH with WBC counts taken within 48 hours of onset. Patients with a WBC count greater than 20,000/mm^3 at admission had no normal outcomes, and the mortality in this group was 90%. The pathogenesis of Vasospasm is thought to be mediated through various blood degradation products and substances released near blood clots. Prostaglandins E_2 and $F_{2\alpha}$ are known to increase in the cerebrospinal fliud (CSF) of SAH patients with vasospasms and may fluctuate with neurologic symptoms[3]. The possible association between Fisher group and fever may be explained by the direct effects of more blood in the CSF or substances released around the clot causing both vasospasm and fever[17].

The relationship between the location of a ruptured aneurysm and vasospasm is less clear. Ruptured aneurysms on anterior circulations have been found to increase the risk of subsequent vasospasm[18]. However, Bonilha et al. demonstrated no difference in the incidence of vasospasm as a function of aneurysm location[1].

Our results indicate that endovascular intervention can reduce the incidence of symptomatic vasospasms (p=0.013). In a large consecutive series of patients with acute aneurysmal SAH, patients with better clinical grades at hospital admission were less likely to suffer symptomatic vasospasms, if they were treated with endovascular coil occlusion, instead of craniotomy and clip application[21]. Additionally, results of recent studies are consistent with our finding that endovascular stabilization does not influence the risk of vasospasm[2,5,8]. In our study, patients were not randomized and outcomes may have been influenced by other factors, such as clinical grade, presence of intracranial hemorrhage, intraventricular hemorrhage, and aneurysmal location. Thus, our results need to be verified with future studies.

Both increasing and decreasing patient age have been implicated as risk factors for the development of vasospasms[2,7]. However, in our study, there was no association between patient age and vasospasms. Neil-Dwyer and Cruickshank[12] first demonstrated the prognostic significance of leukocytosis in the outcome of patients with SAH. Maiuri et al observed a similar

association and hypothesized that arterial spasm may account for this association[9]. More recently, increased serum leukocyte counts were reported in patients who developed vasospasms after aneurysmal SAH[13,20,22]; however, there authors did not adjust for confounding variables, and therefore, cannot assess an independent association between leukocyte count and cerebral vasospasms. In our series, we have found that WBC in 24 hours at onset of SAH was a risk factor for the subsequent onset of vasospasm, independent of other factors. In addition, the trend of increasing of WBC count after operation revealed that the group with vasospasm showed higher WBC count than the group without vasospasm.

There results indicate that daily monitoring of serum leukocyte counts is typically included in postoperative management in patients with SAH and therefore represents a potentially useful marker for assessing the risk of vasospasms. Measuring the leukocyte count throughout the entire risk period of vasospasm may provide more useful information regards to the possible development of vasospasm. Significant leukocytosis may identify patients who require additional imaging studies, using TCD ultrasonography, spiral CT scanning, or angiography, and may indicate which patients could benefit either from more aggressive hypertension, hypervolemia, and hemodilution therapy, or from early angioplasty[10].

Conclusion

This study reveals that leukocytosis independently increases the risk of developing vasospasms. Also, fever in SAH patient is a predictor for symptomatic vasospasm that is associated with poor clinical outcome. Therefore, daily monitoring of serum leukocyte counts and body temperature are potentially useful markers for assessing the risk of vasospasm and poor clinical outcome.

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