



Risk Factors for Cerebral Vasospasm in Patients with Aneurysmal Subarachnoid Hemorrhage: A Tertiary Care Center Experience

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Abstract

Objectives Cerebral vasospasm in subarachnoid hemorrhage (SAH) is associated with high morbidity and mortality. There is a lack of consensus on the risk factors leading to cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage (aSAH). In this retrospective study, our objective was to determine the association of risk factors for cerebral vasospasm aSAH.

Methods A total of 259 charts of aSAH patients consecutively admitted to the surgical intensive care unit of Hamad General Hospital from January 2007 to December 2016 were reviewed and included. The patient's demographic data, including comorbidities like hypertension (HTN), was recorded. Variables of interest included measurements of the neurological deficit on admission, the severity of SAH, treatment modality, and the initial computerized tomography scan of the head for intraventricular hemorrhage, intracerebral hemorrhage, or hydrocephalus. Multivariate analysis and multiple logistic regression analyzed the relationship to identify the association of independent variables.

Results Out of the 259 patients, 34% ($n = 87$) suffered from cerebral vasospasm. The severity of SAH was associated with the development of cerebral vasospasm ($p < 0.05$). The presence of HTN and neurological deficits on admission were associated with an increased risk of cerebral vasospasm ($p < 0.05$, $p < 0.01$, respectively). Hydrocephalus requiring treatment using external ventricular drains decreased the risk of cerebral

Keywords

- ▶ cerebral aneurysm
- ▶ clinical vasospasm
- ▶ delayed cerebral ischemia
- ▶ subarachnoid hemorrhage
- ▶ vasospasm

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vasospasm ($p < 0.05$). Intraventricular and intracerebral hemorrhage were not associated with cerebral vasospasm ($p = 0.25$, $p = 0.16$). The endovascular treatment of cerebral aneurysms was associated with an increased risk of cerebral vasospasm ($p < 0.05$).

Conclusion Cerebral vasospasm is common among patients admitted with aSAH. It is significantly associated with the history of HTN, the neurological deficit on admission that correlates more strongly to the motor deficit on admission, the severity of hemorrhage (modified Fischer score), and endovascular treatment. External ventricular drainage was associated with a decrease in cerebral vasospasm. The present study's findings shed light on cerebral vasospasm's risk factors in the country and the region.

Introduction

Spontaneous subarachnoid hemorrhage (SAH) is a neurosurgical emergency. Approximately 80% of SAH are due to ruptured cerebral aneurysms (aneurysmal subarachnoid hemorrhage, aSAH). Significant complications related to aSAH are postprocedure hemorrhage, hydrocephalus, or cerebral vasospasm (CV), which might increase morbidity and mortality. CV is known as the narrowing of cerebral blood vessels, resulting in reduced distal blood flow. The vasospasm can be either symptomatic, known as clinical vasospasm or delayed ischemic neurologic deficit or delayed cerebral ischemia (DCI), or radiographic vasospasm, known as angiographic vasospasm. Radiographic vasospasm is detected by digital subtraction angiography, transcranial Doppler, and computed tomography (CT) angiography. Clinical vasospasm or DCI is the development of increasing intensity of headaches, focal neurological signs, or deterioration in the patient's consciousness level with aSAH.^{1,2} Seventy percent of aSAH patients develop angiographic vasospasm, while only 30% develop evident clinical vasospasm. Clinical vasospasm leads to poor functional outcomes and increased mortality.^{1,2} About half of the patients who experience clinical vasospasm suffer severe permanent neurological dysfunction or death.³ In this study, we aim to determine the clinical relevance of risk factors for vasospasm in aSAH in a cohort representative of the Arabian Gulf region. We identified demographic, clinical, and radiographic risk factors and determined the strength of association of these risk factors with vasospasm.

However, there is not much literature about aSAH and symptomatic CV in the Arabian Gulf region. The population of countries in the Arabian Gulf region is unique in being more heterogeneous than any other country due to the significant number of expatriates, compared to other parts of the world. Qatar's general population during the period of study was about 2.3 million. About 15% of the population is Qatari National, and the remaining is expatriates, with about 60% from South Asia. Women account for just 25% of the population, due to Qatar's male-dominant construction sector. The analysis is of interest as it is performed in Qatar's only center to handle cases of SAH. Hence, the data represents the entirety of SAH cases requiring admission to an intensive care unit in Qatar with aSAH for 10 years.

Methods

Patient Population: In this single-center study conducted in Hamad General Hospital, the main tertiary care center in Qatar, a total of 259 subjects admitted to the surgical intensive care unit were enrolled retrospectively from January 2007 to December 2016. The institutional medical research committee approved the study. As the data was collected retrospectively, a waiver of informed consent was approved by the ethical committee at the medical research center, Hamad Medical Corporation, Qatar, with IRB #16387/1. All patients with aSAH were identified from the surgical intensive care unit registry, patient's demography, including arterial blood pressures (BPs) on admission, history of pre-existing hypertension, World Federation of Neurological Surgeons (WFNS) score, Hunt and Hess (H&H) score, and modified Fisher grades. The neurological deficit, pupillary size and reaction, location of cerebral aneurysms, presence of intraventricular, intracerebral, and intracerebellar hemorrhage, treatment modality (coiling vs. clipping), and the presence of CV were recorded.

aSAH was diagnosed by the noncontrast CT of the brain. In contrast, cerebral aneurysms were identified either by CT angiography or by cerebral catheter angiography. Pediatric, traumatic subarachnoid, cerebral arterial venous malformation, and patients with other brain vascular pathologies were excluded from this study. Enrolled patients were managed postintervention with the standard of care, irrespective of aneurysms that were clipped or coiled endovascularly. Patients requiring external ventricular drain (EVD) and decompressive craniotomy followed the standards of care protocols. SAH patients with increasing headaches, altered sensorium, and/or new focal neurological deficits were investigated for CV by using transcranial Doppler, CT angiogram, CT perfusion, or conventional catheter cerebral angiography.

Definition of Vasospasm

Symptomatic or clinical vasospasm was defined as the development of increasing intensity of headaches, new focal neurological signs, or deterioration in consciousness level after other possible causes of worsening had been excluded.

Angiographic vasospasm was defined as moderate-to-severe arterial narrowing on digital subtraction angiography or CT angiography attributable to SAH as determined by a neuro-radiologist. Vasospasm on transcranial Doppler was defined as a mean flow velocity in any vessel more than 120 cm/s.^{4,5,6}

Clinical Management: After identification, aneurysms were either clipped or coiled endovascularly. Enrolled patients were managed postintervention with the standard of care, irrespective of the intervention type for the aneurysm. Patients requiring EVD and decompressive craniotomy also followed the standards of care protocols. SAH patients with an increasing headache, altered sensorium, or new focal neurological deficits were investigated for CV using transcranial doppler, CT angiogram, or digital subtraction angiography.

Clinical and Radiographic Assessment

We recorded baseline demographic data and patient's comorbidities, including a history of pre-existing hypertension. Neurological status was evaluated with the H&H, the WFNS score, and modified Fisher grades. Clinical variables included arterial BP on admission, neurological deficit, pupillary size and reaction, and clinical vasospasm presence as defined earlier. Radiologic measurements included the location of cerebral aneurysms, intraventricular, intracerebral, or intracerebellar hemorrhage, and the presence of angiographic vasospasm. Treatment modalities, including surgical intervention, coiling, or clipping, were recorded.

Statistical Analysis

We evaluated predictors of symptomatic vasospasm. Descriptive and inferential statistics were used. Descriptive results (including graphical displays) for all continuous variables are presented as mean \pm standard deviation for normally distributed data, or median with interquartile range for data not normally distributed. Numbers and percentages were reported for all qualitative variables. The bivariate analysis was performed using an independent sample *t*-test or Mann-Whitney U test to compare all quantitative variables between patients with and without CV. All qualitative variables between patients with and without CV were compared using the Pearson chi-squared test or Fisher's exact test as appropriate. Logistic regression analysis was used to measure the odds ratio (OR) and 95% confidence interval (CI) for OR to assess each predictor's effect on patients with and without clinical vasospasm.

Multiple logistic regression was used to identify significant independent factors associated with patients with and without CV after adjusting for potentially confounding factors. The Wald test was computed on each predictor to determine which were significant. The adjusted OR and 95% CI for the adjusted OR were reported. A *p*-value less than 0.05 (two-tailed) was considered statistically significant.

All statistical analyses were performed using Statistical Package for Social Sciences Version 22 (SPSS).

Results

Out of the 259 patients admitted with spontaneous aSAH, eighty-seven patients (34%) had CV. Male patients had a trend toward a higher incidence of CV than females; however, it was not statistically significant (34.5 vs. 31.4%, *p* = 0.29). There was no significant difference between the mean age of patients with and without CV (47.98 \pm 102.98 vs. 46.30 \pm 11.77 years, *p* < 0.296). There was a statistically significant difference in the WFNS score and the occurrence of CV (*p* < 0.01). Patients with a lower WFNS score and lower H&H score (*p* < 0.01) had a statistically significant lower incidence of CV. There was no correlation between the Fisher grading and the occurrence of CV (*p* < 0.122).

Table 1a Risk factors for clinical cerebral vasospasm

Factors	Vasoplasm		p-Value
	Yes 87 (34%)	No 172 (66%)	
Age in years	47.98 \pm 12.98	46.30 \pm 11.77	0.296
Gender	0.662		
Male	61 (34.5%)	116 (65.5%)	
Female	26 (31.7%)	56 (68.3%)	
Clinical			
World Federation of Neurosurgeons (WFNS) Score	0.005		
1	18 (19.1%)	76 (80.9%)	
2	28 (38.4%)	45 (61.6%)	
3	4 (30.8%)	9 (69.2%)	
4	20 (50.0%)	20 (50.0%)	
5	11 (39.3%)	17 (60.7%)	
Fischer grade	0.122		
1	14 (23.0%)	47 (77.0%)	
2	22 (31.0%)	49 (69.0%)	
3	10 (38.5%)	16 (61.5%)	
4	38 (40.9%)	55 (59.1%)	
Hunt and Hess score	0.002		
1	14 (16.9%)	69 (83.1%)	
2	33 (36.7%)	57 (63.3%)	
3	13 (48.1%)	14 (51.9%)	
4	12 (50.0%)	12 (50.0%)	
5	10 (38.5%)	16 (61.5%)	
History of HTN	0.113		
Yes	48 (38.4%)	77 (61.6%)	
No	39 (29.1%)	95 (70.9%)	
Neurological deficit	0.004		
Yes	23 (52.3%)	21 (47.7%)	
No	64 (29.8%)	(151) 70.2%	
Pupillary size	0.908		
Equal and reactive	(72) 32.9%	(147) 67.1%	
Anisocoric	9 (34.6%)	17 (65.4%)	
Fixed	5 (38.5%)	8 (61.5%)	
Admission SBP	167.1 \pm 33.8	154.4 \pm 34.9	0.007
Admission DBP	92.6 \pm 15.4	88.4 \pm 17.3	0.063

Table 1b Risk factors for clinical vasospasm

Factors	Vasospasm		p-Value
	Yes (%) 87 (34%)	No (%) 172 (66%)	
Intraventricular haemorrhage			0.251
Yes	45 (37.2%)	76 (62.8%)	
No	42 (30.4%)	96 (69.6%)	
Intracerebellar haemorrhage	0.732		
Yes	6 (37.5%)	10 (62.5%)	
No	81 (33.3%)	162 (66.7%)	
Intracerebral haemorrhage	0.161		
Yes	21 (42.0%)	29 (58.0%)	
No	66 (31.6%)	143 (68.4%)	
Insertion of EVD (external ventricular drain)	0.031		
Yes	44 (41.1%)	63 (58.9%)	
No	43 (28.3%)	109 (71.7%)	
Decompressive craniectomy	0.055		
Yes	8 (57.1%)	6 (42.9%)	
No	79 (32.2%)	166 (67.8%)	
Clipping	0.161		
Yes	21 (42.0%)	29 (58.0%)	
No	66 (31.6%)	143 (68.4%)	
Coiling	0.174		
Yes	40 (38.5%)	64 (61.5%)	
No	47 (30.3%)	108 (69.7%)	

There was no significant difference in the occurrence of CV with pre-existing hypertension or diastolic pressure. A neurological deficit on admission was associated with the development of CV ($p < 0.01$). Intraventricular, intracerebellar, or intracerebral hemorrhage was not associated with an increased risk of CV (► **Table 1**). EVDs were significantly associated with the absence of the CV ($p < 0.05$). Decompressive craniotomy was not associated with a significantly decreased incidence of CV ($p < 0.055$).

There was no association between the development of CV and the aneurysms location (p -value > 0.075) and treatment modalities. Our patient population was multiethnic. Clinical vasospasm was frequent in the Asian subcontinent, Arab, and southeast Asian populations compared to the European and African populations (► **Table 1**).

► **Table 2** shows the multiple regression analysis of independent parameters associated with the occurrence of clinical vasospasm. Admission systolic BP was significantly associated with the development of clinical vasospasm ($p < 0.05$). The patient's age and neurological deficit were not associated with clinical vasospasm development ($p > 0.296$). The endovascular coiling was associated with the development of clinical vasospasm ($p < 0.05$) (► **Table 2**).

Discussion

aSAH has an annual impact of 10/100, and 25% of the patients die instantly. Improvement in surgical and endovascular

Table 1c Ethnicity and location cerebral aneurysm and vasospasm

Ethnicity	Vasospasm		p-Value
	Yes	No	
European	2 (20%)	8 (80%)	0.75
Subcontinent	29 (31.9%)	62 (68.1)	
Arabs	28 (35%)	52 (65%)	
Southeast Asian	24 (35.8%)	43 (64.2)	
Africans	4 (44.4%)	5 (55.6%)	
Turkey	0 (0%)	2 (100%)	
Location of aneurysms			
No aneurysm	2 (20.0%)	8 (80.0%)	
ACOM	29 (38.2%)	62 (61.8%)	
Vertebral	2 (50.0%)	2 (50.0%)	
MCA	41 (31.8%)	30 (68.2%)	
Basilar	3 (50.0%)	3 (50.0%)	
ACA	2 (25.0%)	6 (75.0%)	
ICA	12 (52.0%)	13 (48.0%)	
PCA	1 (33.0%)	2 (66.7%)	
SCA	0 (0%)	1 (100%)	
PCOM	12 (46.2%)	14 (53.8%)	
CALLOSM	1 (100%)	0 (0%)	

Abbreviations: ACA, anterior cerebral artery; ACOM, anterior communicating artery aneurysm; CALLOSUM, callosal arteries; DSP, diastolic blood pressure; EVD, external ventricular drain; HTN, hypertension; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PCOM, posterior communicating artery; SBP, systolic blood pressure; SCA, superior cerebral artery; WFNS, World Federation of Neurosurgeons.

treatment of the cerebral aneurysms has decreased the major rebleeding. In 1951, Ecker and Riemenschneider described the syndrome of CV in patients with aSAH.⁷ A significant number of cases develop clinical vasospasm manifested by increasingly severe headaches, new focal neurological deficits, or cognitive deficits between the 4th to 14th day after aSAH.⁸ A literature review revealed the use of the term "vasospasm" without identifying the clinical or radiologic nature of the diagnosis. Also, there has been no consensus on a unifying definition of vasospasm. A variety of terms are used in the literature for clinical vasospasm, including clinical vasospasm or delayed ischemic neurologic deficit, or DCI. There is a dearth of literature on risk factors for clinical vasospasm associated with aSAH from the Arabian Gulf region.

Most studies suggest no association between patient age and the development of CV. Magge et al suggested a higher risk of CV in younger patients.⁹ Mijiti et al reported that the age more than 53 years is a risk for CV development.¹⁰ Age was not associated with an increased risk of CV in our patients.

Table 2 Multiple regression models to identify independent risk factors associated with vasospasm

Factors	Adjusted odds ratio	95% CI for adjusted odds ratio	p-Value
Admission SBP	1.008	1.000–1.017	0.046
Hunt & Hess score	0.055		
1	2.470	1.176–5.188	0.017
2	3.631	1.308–10.079	0.013
3	3.216	1.096–9.441	0.033
4	3.141	1.008–9.791	0.048
Motor deficit	1.948	0.922–4.117	0.081
Coiling	1.860	1.021–3.389	0.042
Age	1.003	0.978–1.028	0.835

Abbreviations: CI, confidence interval; CT, computed tomography; OR, odds ratio; SBP, systolic blood pressure.

Note: p-Value has been calculated using binary multiple logistic regression Wald test. Growth rate = (Infarct volume at 2nd CT – Infarct volume at 1st CT) / (Time at 2nd CT – Time at 1st CT).

Nasser et al reported a higher incidence of CV in males.¹¹ In contrast, a lower incidence was reported by Dumont et al.¹² Our cohort had a statistically nonsignificant trend toward increased incidence in males.

Concerning racial differences, the Japanese and the Han Chinese are at a higher risk of developing CV, with no difference between Caucasians and African-Americans.^{10,13,14} No significant ethnicity-based risk differences exist in our cohort.

Most of our patients had CV with a rupture of middle cerebral artery aneurysms. The location of SAH is inconsistently associated with varied risk of CV.^{15,16,17} In our cohort, no such association was noted.

Higher H&H grades and higher WFNS score correlated with the development of CV, which is in line with available literature.^{10,14,18,19}

Previous studies reported a negative relationship between hypertension and CV and a positive correlation with the admission systolic BP.^{10,17,20} It is interesting to note that hypertension was not associated with the risk for the development of CV; however, multiple regression analysis established a positive relationship between CV and systolic BP on admission.

A significant finding in this study is the correlation of neurological deficit on admission with CV. To the best of our knowledge, this association is not reported.

Arguably, our cohort's most exciting finding was the insertion of an EVD associated with a significantly lesser CV. The authors propose that earlier clearance of blood degradation products may play a role. This finding is in line with earlier cohorts that underwent spinal CSF drainage or EVD insertion.^{21,22}

The multiple regression analysis demonstrated that coiling procedures had a significantly higher incidence of CV than surgical clipping of a ruptured aneurysm. A review of the literature on this association produced inconsistent findings.^{23,24,25,26}

Conclusion

Our study population demonstrates region-dependent risk factors associated with CV. SAH severity, the presence of neurological deficit or systolic hypertension on admission, and coiling procedures were associated with an increase in CV. EVD insertion decreased the occurrence of clinical vasospasm. A prospective cohort study is needed to delineate the risk factors in this multiethnic population further.

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Conflict of Interest

None declared.

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