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Original Investigation

Predictors of Symptomatic Vasospasm After Subarachnoid Hemorrhage: A Single Center Study of 457 Consecutive Cases

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ABSTRACT

AIM: We set forth to identify predictors of symptomatic vasospasm in patients with subarachnoid hemorrhage (SAH).

MATERIAL and METHODS: We used multivariate logistic regression analysis of the prospective, hospital based, single center register of the Department of Neurosurgery, University of Debrecen, Hungary.

Evaluated patients' characteristics were: sex, age, Hunt-Hess grade on admission, location of aneurysm, thickness of blood clot on initial CT scan (Fisher grade), hypertension.

RESULTS: Between 1987 and 2004, 567 SAH cases were registered, 457 were included in this study. Symptomatic vasospasm developed in 22.5% of the cases. In univariate analysis, Hunt-Hess grades 2 and 3 and female sex were predictive for symptomatic vasospasm. In multivariate analysis, female sex remained a significant predictor: OR: 1.8 (1.005-3.2).

CONCLUSION: Women are at more danger of developing symptomatic vasospasm after subarachnoid hemorrhage.

KEYWORDS: Subarachnoid hemorrhage, Vasospasm, Fisher grade, Age, Sex

INTRODUCTION

Subarachnoid hemorrhage (SAH) accounts for a minority of all stroke cases but its impact is severe as it strikes at a fairly young age and it is associated with high case fatality and disease burden. After the hemorrhage itself vasospasm is the leading cause of death and disability in SAH patients (14). Angiographic vasospasm develops in up to 70% of the patients, whereas symptomatic vasospasm in 20 to 30% of the cases (7). Several factors were proposed as predictors of vasospasm, such as age, sex, amount of blood on computed tomography (CT) (Fisher grade or other method), admission status etc. Results of these studies are controversial. Furthermore there are significant differences in definitions and methods used in these studies.

The aim of the present study was to identify predictors of symptomatic vasospasm in a prospective database of over 400 consecutive patients with SAH in a single neurosurgical center in Eastern Hungary.

MATERIAL and METHODS

Patient Population

Debrecen is the second largest city in Hungary. It is located in the Eastern part of the country. Data of primary SAH patients admitted or referred to the Department of Neurosurgery at the University of Debrecen between the 1st of January 1987 and the 31st of December 2004 were collected prospectively and entered in an anonymized database. Because University of Debrecen is a referring center of the region, patients are registered not only from Debrecen City, but also from several counties of the region with a catchment area of approximately 700 000 inhabitants. SAH was determined by clinical symptoms and neuroimaging findings (CT, angiography). Lumbar

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puncture was performed when CT scan could not confirm SAH in spite of strong clinical suspicion. Cases resulting from secondary SAH (trauma, coagulation disorder, neoplasm, etc.) were excluded. Evaluated patients' characteristics were: sex, age, presence of aneurysm, Fisher grade (5) on initial CT scan (Table I), hypertension, Hunt-Hess grade (9) on admission (Table II), symptomatic vasospasm, and case fatality. If the patients were not capable of cooperation, relatives were asked for information. We defined symptomatic vasospasm as a clinical entity that includes a new, delayed focal neurological deficit or mental status decline without evidence of any other cause in SAH patients (6, 19).

Statistical Analysis

Continuous variables were compared by one-way ANOVA, and categorical variables by χ^2 test. Univariate and multivariate logistic regression were applied to test predictive factors for symptomatic vasospasm. The following factors were tested as possible predictors: age (as a continuous variable and also as dichotomized at 50 years of age), sex, hypertension, Hunt-Hess and Fisher grade on admission, site of aneurysm (anterior versus posterior circulation). All of these factors were included in the multivariate logistic regression analysis. Stepwise backward model was applied to find the independent predictors of symptomatic vasospasm. Statistical analyses were performed on Statistical Package of Social Sciences (SPSS) 22 software, SPSS Inc.

RESULTS

Between 1987 and 2004, 567 SAH cases were registered. In 457 patients we had unequivocal data whether clinical signs of symptomatic vasospasm did or did not appear. These patients were included in the present study. Female patients were significantly older and had hypertension more frequently (Table III). Case fatality was 32.5%. There was no significant change in case fatality during the observational period. Aneurysms were verified in 94.9% of the patients.

Vasospasm

Symptomatic vasospasm developed in 22.5% of the patients, significantly more frequent in women. Only SAH cases with proved aneurysm were included in the logistic regression models. Applying univariate logistic regression Hunt-Hess grade 2 (OR: 2.9 (1.4-6.2) p=0.006) and 3 (OR: 2.4 (1.1-5.3) p=0.037), and female sex (OR: 1.8 (1.1-2.8) p=0.019) were predictive for symptomatic vasospasm (Table IV). In multivariate logistic regression (including age, sex, Hunt-Hess and Fisher grades, hypertension, aneurysm site) only female sex (OR: 1.8 (1.005-3.2) p=0.048) was predictive for symptomatic vasospasm. Age was tested as a continuous variable and also as dichotomized at 50 years of age.

DISCUSSION

Female preponderance is observed in most SAH study populations (3). Ruptured aneurysms are the cause of SAH in 85% of the cases (21). In the present study the rate was higher, probably due to referring bias. The case fatality did not change significantly during the observational period.

The rate of symptomatic vasospasm was similar to data in the literature (7).

Amount and Location of Blood

The predictive validity of the Fisher grade for vasospasm was questioned (19) and a modified Fisher scale was proposed (6). Kramer et al. (12) found that the clinical performance of the modified scale is better. Hijdra et al. (8) developed a more comprehensive grading scale that is superior to the modified

Table I: The Fisher Scale

Fisher group	Appearance of SAH on CT
1	No subarachnoid blood visualized
2	Diffuse thin layer (<1 mm)
3	Localized clot and/or thick vertical layer (>1 mm)
4	Diffuse or no SAH, but intraventricular or intraparenchymal clot

SAH: *Subarachnoid hemorrhage.*

Table II: The Hunt and Hess Scale

Hunt and Hess category	Clinical condtition
1	Asymptomatic, mild headache, slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness/confusion, mild focal neurologic deficit
4	Stupor, moderate-severe hemiparesis
5	Coma, decerebrate posturing

Fisher scale at predicting vasospasm (4), however, the Hijdra scale is cumbersome. The Barrow Neurological Institute Scale was also introduced and found to be more reliable than the Fisher scale (22). It was proposed that not only the amount of blood is important in prediction of vasospasm but the location as well. Abla et al. (1) found greater risk for ruptured pericallosal aneurysms. The distribution of the blood is important even in non-aneurysmal SAH (16). Although due to the earlier time period of the data collection we could not test the newer scales, our results support the necessity of re-evaluation of the original Fisher grading scale. In our study the location of the ruptured aneurysm was not predictive.

Sex and Age

Our results suggest that female gender is predictive for symptomatic vasospasm. There are data that female sex is a risk factor for angiographic vasospasm (17, 18), however the majority of the studies have shown no correlation between sex and the risk or incidence of vasospasm (7).

There are controversial reports regarding age (7, 14). Several studies suggest that young age is a predictor for symptomatic vasospasm (2, 10, 15, 20), however in our study young age did not predict symptomatic vasospasm. Smith et al. (19) concluded that sex, age, Hunt-Hess and Fisher grades are not predictive. Ryttlefors et al. (18) did not find age to be a significant predictor for either angiographic or symptomatic vasospasm. In Lanzino et al. large study (13) with 906 patients, using 5 age groups, there were more symptomatic vasospasms in the older age groups, but there were no significant difference in angiographic vasospasm among the age groups. Kale et al. (11) found that younger age (<50) predicted for symptomatic

Table III: Patient Characteristics

	Total (457)	**Men (188)**	**Women (269)**
Mean age (±SD) (years)	47.2±11.3	45.7±11.3	48.4±11.2[a]
Hypertension	232/456 (50.9%)	81/188 (43.1%)	151/268 (56.3%)[b]
Aneurysm	434/457 (94.9%)	176/188 (93.6%)	258/269 (95.9%)
ICA	108 (24.9%)	34 (19.3%)	74 (28.7%)[c]
MCA	141 (32.5%)	55 (31.3%)	86 (33.3%)
PCA	1 (0.2%)	0 (0%)	1 (0.4%)
ACA	18 (4.1%)	7 (4%)	11 (4.2%)
ACom	151 (34.8%)	76 (43.2%)	75 (29.1%)
Basilar	4 (0.9%)	2 (1.1%)	2 (0.8%)
VA-PICA	11 (2.5%)	2 (1.1%)	9 (3.5%)
Case fatality	32.5% (145/446)	29.1% (53/182)	34.8% (92/264)
Hunt-Hess 1	78/439 (17.8%)	31/179 (17.3%)	47/260 (18.1%)
2	193 (44%)	83 (46.4%)	110 (42.3%)
3	123 (28%)	48 (26.8%)	75 (28.8%)
4	34 (7.7%)	14 (7.8%)	20 (7.7%)
5	11 (2.5%)	3 (1.7%)	8 (3.1%)
Fisher 1	13/354 (3.7%)	6/137 (4.4%)	7/217 (3.2%)
2	118 (33.3%)	42 (30.7%)	76 (35%)
3	111 (31.4%)	46 (33.6%)	65 (30%)
4	112 (31.6%)	43 (31.4%)	69 (31.8%)
Symptomatic vsp	103/457 (22.5%)	32/188 (17.0%)	71/269 (26.4%)[d]
Symptomatic vsp*	99/434 (22.8%)	30/176 (17%)	69/258 (26.7%)[e]

*Denominators show how many patients provided data regarding certain characteristics. [a]p=0.007 [b]p=0.005 [c]p=0.058 [d]p=0.012 [e]p=0.018 comparing sexes *aneurysmal SAH **ACA:** Anterior cerebral artery, **ACom:** Anterior communicating artery, **AVM:** Arteriovenous malformation, **ICA:** Internal carotid artery, **MCA:** Middle cerebral artery, **PCA:** Posterior cerebral artery, **SAH:** Subarachnoidal hemorrhage, **SD:** standard deviation, **VA-PICA:** Vertebral artery (including posterior inferior cerebellar artery), **vsp:** Vasospasm.*

Table IV: Predictors of Symptomatic Vasospasm

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Young age (≤ 50)	1.05 (0.7-1.7)	0.843	1.2 (0.7-2.1)	0.503
Fisher grade 3	5.1 (0.6-40.6)	0.126	4.6 (0.6-38.0)	0.153
Fisher grade 4	4.4 (0.5-35.2)	0.164	3.7 (0.5-30.8)	0.219
Hunt-Hess 2	2.9 (1.4-6.2)	0.006	2.0 (0.7-5.2)	0.169
Hunt-Hess 3	2.4 (1.1-5.3)	0.037	1.4 (0.5-4.0)	0.528
Sex (female)	1.8 (1.1-2.8)	0.019	1.8 (1.005-3.2)	0.048
Hypertension	1.3 (0.8-2.0)	0.304	0.9 (0.5-1.6)	0.695
Aneurysm (anterior)	2.1 (0.5-9.5)	0.327	0.8 (0.2-4)	0.790

OR: *Odds ratio,* ***CI:*** *Confidence interval,* ***Aneurysm:*** *Anterior vs. posterior circulation.*

Table V: Studies Analyzing Multiple Predictors of Symptomatic Vasospasm

Study	N	Young age	Female sex	Fisher grade	Good Hunt-Hess*	Location
Charpentier 1999	244	+	neg	neg	+	neg
Smith 2005	134	neg	neg	neg	neg	ND
Ryttlefors 2010	413	neg	+§	ND	ND	ND
Kale 2013	108	+	neg	neg	neg	ND
Jabbarli 2014	70	+	neg	neg	neg	ND
Current study	457	neg	+	neg	neg	neg

Hunt-Hess grade 1-2; *§ for angiographic vasospasm;* ***ND:*** *no data.*

and angiographic vasospasms, whereas sex, Hunt-Hess and Fisher grade on CT were not predictive (Table V).

Others

In univariate analysis, we found that Hunt-Hess grade 2 and 3 is risk factor for vasospasm. However it is difficult to diagnose symptomatic vasospasm in patients with high Hunt-Hess grade, so we have to be cautious with the interpretation. Even in our study in multivariate analysis Hunt-Hess grade lost its significance.

The study designs, age limits and vasospasm definitions are different in the studies, making it difficult to compare their results and explaining at least partly the observed differences.

The limitation of our study is the long period of data collection. Although the diagnostic procedures did not change during this period, patient characteristics and routine treatment might have changed considerably between 1987 and 2004. However, the outcome of SAH did not change significantly during the observational period. Furthermore, not being available at the time of data collection, we had to stick to the Fisher grade and could not test the newer CT grading scales in our analysis.

■ CONCLUSION

From the analysis of this database, we concluded that the frequency of vasospasm was similar to previously published data. Age and Fisher grade on initial CT scan was not predictive for symptomatic vasospasm. Female sex was predictive.

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