Risk Factors for Cerebral Vasospasm in Patients with Spontaneous Subarachnoid Hemorrhage

Factores de riesgo para vasoespasmo cerebral en pacientes con hemorragia subaracnoidea espontánea

Mónica Royero Arias[1]
Carlos Díaz Pacheco[2]
Yuli Agudelo[3]

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[1]Radiologist, Universidad de Antioquia. Medellín, Colombia.

[2]Neurointerventional radiologist, Radiology service Hospital Universitario San Vicente Fundación. Professor, Universidad de Antioquia. Medellín, Colombia.

[3]Clinical toxicologist doctor and clinical epidemiologist, Universidad de Antioquia and Hospital Universitario San Vicente Fundación. Medellín, Colombia.

Summary

Objectives: Establish the association between cerebral vasospasm, detected by transcranial doppler, with the clinical condition according to the scale of the World Federation of Neurosurgical Societies (WFNS) and other risk factors in patients with spontaneous subarachnoid hemorrhage. *Materials and methods:* This is an observational retrospective case-control study, including 141 patients with a diagnosis of spontaneous subarachnoid hemorrhage who underwent transcranial doppler monitoring in the radiology department of the University Hospital San Vicente Foundation (HUSVF) from 8 March 2011 to 15 March 2015. Of the total number of patients with subarachnoid hemorrhage, 47 cases with vasospasm, detected by transcranial Doppler, and two controls without vasospasm (94 patients) were consecutively chosen. Subsequently, we review the medical records and images stored in the hospital´s radiology department and established the association between vasospasm detection by trasncranial Doppler with clinical neurological status at the time of the study and other risk factors. For the analysis of the qualitative variables, absolute and relative frequencies were used. Quantitative variables were tested for normal distribution with a Shapiro Wilk test. Data with normal distribution were presented with means and standard deviations and those without normal distribution with medians and interquartile ranges. Homogeneity between the two groups were evaluated by Chi-square test and test for homogeneity of variances, Levene's test, according to the type of variable (qualitative and quantitative respectively). Results were considered statistically significant if $p \leq 0.05$. *Results:* Data from 141 patients (47 cases and 94 controls) were analyzed. The bivariate analysis didn´t show statistically significant results in the relationship between vasospasm and clinical neurological condition but found that patients younger than 50 years had more vasospasm. In the adjusted model for patients with this age, the OR was 3.55 (95 % CI, 1.52-7.39) and p: 0.003 when compared with older patients. *Conclusions:* This study found that patients under 50 have a higher risk of developing vasospasm compared with older patients and that there is no association between clinical condition and the results of transcranial Doppler.

Resumen

Objetivos: Establecer la asociación de vasoespasmo cerebral detectado por Doppler transcraneal y la condición clínica, de acuerdo con la escala de la Federación Mundial de Sociedades de Neurocirugía, y con otros factores de riesgo en pacientes con hemorragia subaracnoidea espontánea. *Materiales y métodos:* Estudio observacional retrospectivo de casos y controles, con 141 pacientes diagnosticados con hemorragia subaracnoidea espontánea a quienes se les realizó Doppler transcraneal de seguimiento entre el 8 de marzo de 2011 y el 15 de marzo de 2015. Del total de pacientes se escogieron 47 con vasoespasmo

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detectado por Doppler transcraneal y 2 controles, sin vasoespasmo, por cada caso (94 pacientes). En las historias clínicas y las imágenes de los pacientes se estableció la asociación entre la detección de vasoespasmo por Doppler transcraneal con la condición clínica neurológica en el momento del examen, y otros factores de riesgo. Para el análisis de las variables cualitativas se utilizaron frecuencias absolutas y relativas. Para variables cuantitativas se utilizó la prueba de Shapiro Wilk. Los datos con distribución normal se presentan con medias y desviaciones estándar y aquellos sin distribución normal con medianas y rangos intercuartiles. Se evaluó la homogeneidad entre los dos grupos a través de la prueba de Chi cuadrado y el test de homogeneidad de varianzas (Levene) de acuerdo con el tipo de variable. Se consideró estadísticamente significativa una p ≤ 0,05. *Resultados:* El análisis bivariado no demostró resultados estadísticamente significativos en la relación entre la condición clínica neurológica y el vasoespasmo, pero sí encontró que pacientes menores de 50 años de edad presentaron más vasoespasmo (OR de 3,55 [95 % IC; 1,52-7,39]), y p: 0,003 que los de mayor edad. *Conclusiones:* Los pacientes menores de 50 años de edad tienen más riesgo de desarrollar vasoespasmo y no existe asociación entre la condición clínica y los resultados del Doppler transcraneal.

Introduction

Subarachnoid hemorrhage (SAH) is the appearance of blood between the arachnoid and pia mater due to rupture of intracranial vessels. It may be of sporadic or traumatic origin and represents 5 % of the causes of cerebrovascular events (1). 85 % of sporadic SAH are due to ruptured brain aneurysms (2-4), which can be multiple and reappear after treatment (5).

It is estimated that of the high proportion of potential life years lost due to aneurysmal SAH (6), vasospasm is the main cause of morbidity and mortality.

The diagnosis of SAH is established using imaging techniques such as computed tomography (CT), angiotomography (angio CT), magnetic resonance (MR), angio-resonance (angio MR) arteriography. Non-contrast CT scanning is considered the initial diagnostic study that is most useful because of its availability, sensitivity and speed. As for accuracy, angiography is the gold standard for establishing the cause of spontaneous SAH (7).

For the prognosis of patients in the emergency department, the degree of neurological deterioration can be assessed by the application of scales (8), such as Glasgow (9), Hunt and Hess (10) or the classification scale of the World Federation of Neurosurgical Societies (WFNS); The latter stages patients in five categories to assist the interventional radiologist or neurosurgeon in deciding between invasive or conservative management in cases of aneurysmal SAH (11-12). In this study, the WFNS scale was used to classify the neurological status of the patients at the time of transcranial Doppler and to determine the association with the result of vasospasm.

There may be secondary complications, such as hydrocephaly, seizures, rebleeding, and vasospasm. The prevention of these plays an important role in the treatment of SAH and for this different strategies are used (13-16).

Vasospasm is the most common complication of aneurysmal SAH. The typical manifestation is neurological deterioration between days 3 and 12 (7). When compromise is on the middle cerebral artery there may be hemiparesis or hemiplegia and sensory deficit. In the vasospasm of the vertebrobasilar circulation the clinical signs are more nonspecific. It has been reported that up to 50 % of patients with angiographic vasospasm are asymptomatic, which increases mortality and the risk of permanent neurological deficit, which is why strict follow-up is necessary to detect it in a timely manner (17).

The imaging diagnosis of vasospasm can be made by two studies: arteriography of cerebral vessels or transcranial Doppler. The latter is noninvasive and more available for patients in intensive care units (18).

It is important to investigate the risk factors associated with vasospasm in patients with SAH, in order to establish preventive and therapeutic treatments in a timely manner.

The aim of this study was to determine the association between the clinical condition of the patient with subarachnoid hemorrhage, graded according to the WFNS scale, and transcranial Doppler results, based on the hypothesis that patients with stage IV and V on the WFNS scale develop more vasospasm than those in stages I to III. In addition, other variables were analyzed as possible risk factors associated with the development of vasospasm.

Materials and methods

A retrospective observational study of cases and controls was performed. We reviewed 141 cases of patients with spontaneous SAH who underwent transcranial Doppler follow-up between March 8, 2011 and March 15, 2015. Seventy-seven cases were consecutively included with vasospasm and two consecutive controls without vasospasm were searched for each case (94 patients) to complete the sample. The sample size was calculated with the program Epidat version 3.0.

Afterwards, clinical histories and images of patients were reviewed and the association between vasospasm and neurological clinical condition was established through an analysis with the SPSS® software (PASW statistics 21). Other baseline variables that were taken into account were personal history, Fisher ratings, modified Fisher, Glasgow and Hunt and Hess scores.

Vasospasm was diagnosed with transcranial Doppler when the mean flow velocities (MFV) in the middle cerebral artery were greater than 120 cm / sec, and hyperemia was ruled out with a Lindegaard index of less than 3 (19-21).

Results

A total of 141 patients (47 cases and 94 controls) and 533 transcranial Doppler were included. Of the 141 patients, 135 had aneurysm rupture (figure 1); in the remaining 6, the cause of the SAH

was not demonstrated, and they received conservative treatment without developing vasospasm (figure 2).

Table 1 shows the epidemiological and clinical characteristics of the patients included. In the variable age there was no normal distribution, which is why the median and their respective interquartile ran-ges are also shown. The groups were heterogeneous only in relation to the age variable (p <0.05), therefore it was included in the multivariate analysis of the model. In addition, the baseline radiological characteristics of the patients included are shown, cases (patients with vasospasm) or controls.
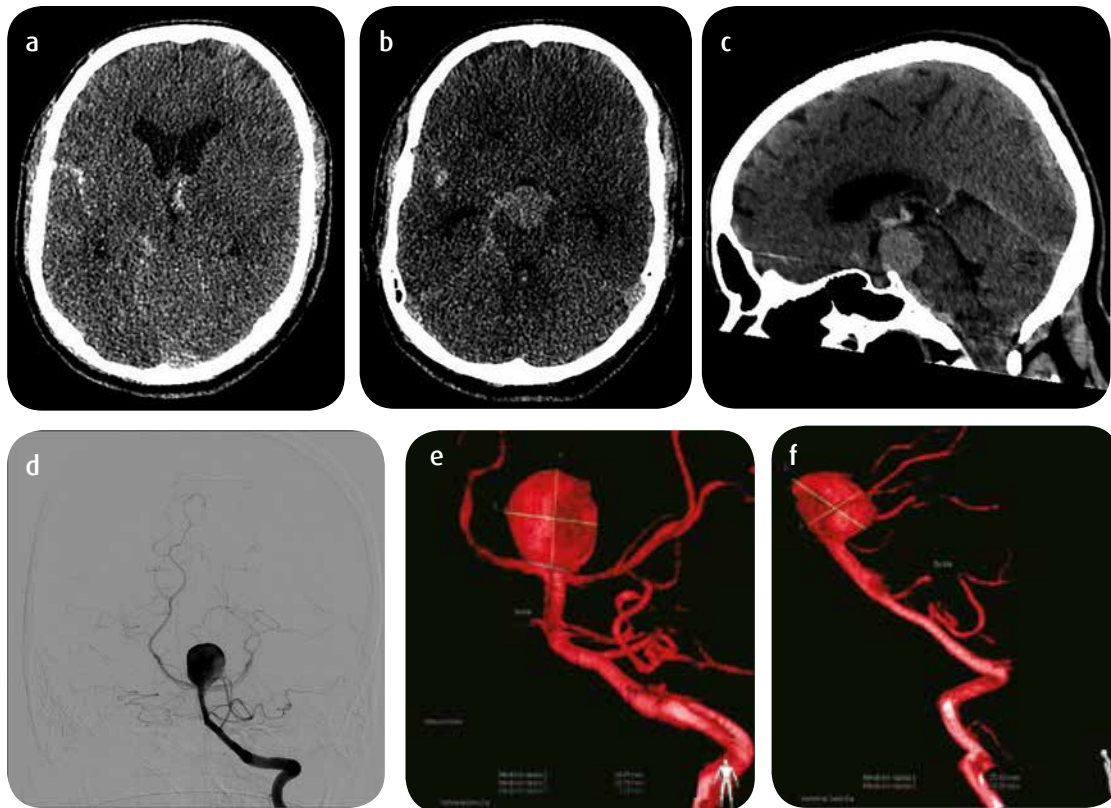

Figure 1. Male patient, 47 years old. History of heavy smoking. Consultation for severe headache. WFNS grade I. a and b) axial single skull CT: modified SAH Fisher grade 2. c) Sagittal: compatible image with basilar aneurysm. d, e and f) Arteriography: confirms broken giant aneurysm of the basilar top, 25 mm in diameter, with a broad neck of 7 mm. The patient did not develop vasospasm in serial transcranial Doppler controls.
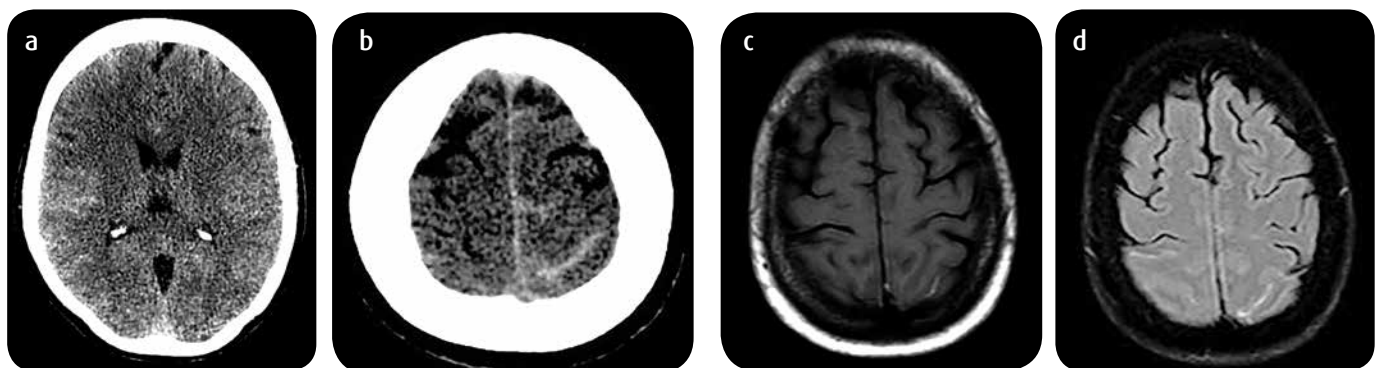

Figure 2. Female patient, 50 years old. Headache consultation. WFNS grade I. a and b) axial simple CT of skull: SAH, Fisher modified grade 1 of cortical pattern. Arteriography did not show aneurysms. Contrast MR was performed to rule out other causes. C) Sequences T1 and d) FLAIR: Confirm SAH without other findings. The patient did not develop vasospasm in serial transcranial Doppler controls and was discharged after 15 days of hospitalization.

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Table 1. Epidemiological and clinical characteristics of the patients

Variable	With vasospasm (*n* = 47)	Without vasospasm (*n* = 94)	Value of *p*
Epidemiologic			
Age (mean, SD)	50,1 ± 11,8	58,2 ± 10,8	<0,01*
Median, IQR $_{25-75\%}$	51, 42-56	59, 50,7-66,2	
Female (n, %)	31 (66 %)	64 (68 %)	0,79**
Clinical history (n, %)			
PA of hypertension	19 (40 %)	50 (53 %)	0,15**
PA smoking	15 (32 %)	30 (32 %)	1,00**
PA SAH	2 (4 %)	4 (4 %)	1,00**
FA of aneurysm	2 (4 %)	2 (2 %)	0,47**
Clinical characteristics			
Patient under sedation	6 (13 %)	10 (11 %)	0,71**
Score in Glasgow Scale			
Mild	38 (81 %)	69 (73 %)	
Moderate	6 (13 %)	10 (11 %)	0,27**
Serious	3 (6 %)	15 (16 %)	
Score according to the WFNS scale			
Good prognosis (grades I, II, III)	37 (79 %)	71 (76 %)	0,67**
Poor prognosis (grades IV, V)	10 (21 %)	23 (24 %)	
Classification according to the Hunt and Hess scale			
Good prognosis (grades I, II)	31 (66 %)	63 (69 %)	0,89**
Poor prognosis (grades III, IV, V)	16 (34 %)	31 (31 %)	
Tomographic Classification of SAH			
Fisher Classification			
Grade 1	2 (4 %)	11 (12 %)	
Grade 2	11 (23 %)	22 (23 %)	
Grade 3	18 (38 %)	22 (23 %)	0,19**
Grade 4	16 (34 %)	39 (42 %)	
Fisher Classification Modified			
Grade 0	2 (4 %)	11 (12 %)	
Grade 1	11 (23 %)	23 (25 %)	
Grade 2	3 (6 %)	12 (13 %)	0,24**
Grade 3	16 (34 %)	19 (20 %)	
Grade 4	15 (32 %)	29 (30 %)	

Notes: *: t test; **: χ^2; N: number; SD: Standard deviation; IQR $_{25\%-75\%}$: interquartile range of 25 % and 75 %; PA: personal antecedent; FA: family history; WFSN: World Federation of Neurosurgical Societies.

Mortality was 19 % in patients with vasospasm and 9 % in controls. Table 2 shows the results of the bivariate analysis in which the outcome was the development of vasospasm and the relationship with age, gender, personal and family history, clinical condition classified by the scales of the WFNS, Glasgow and Hunt and Hess, and tomographic classification of the SAH according to the modified Fisher and Fisher scales.

Table 2. Results of the bivariate analysis of outcome

Variable	RR (CI$_{95\%}$)	p
Age less than 50 years	3,55 (1,67-7,55)	0,0008
Female	1,1 (0,52-2,31)	0,80
Personal history of hypertension	0,6 (0,29-1,21)	0,15
Smoking	1,0 (0,47-2,12)	1,00
SAH personal history	1,0 (0,18-5,67)	1,00
Family history of aneurysm	2,04 (0,28-14,99)	0,47
Sedation	1,22 (0,42-3,62)	0,71
WFNS categorized	0,83 (0,36-1,94)	0,67
Glasgow moderate or severe	0,65 (0,28-1,54)	0,33
Hunt and Hess with poor prognosis (III, IV and V)	1,05 (0,5-2,2)	0,89
Fisher with poor prognosis (3 y 4)	1,41 (0,66-3,05)	0,37
Modified Fisher with poor prognosis (2-4)	1,48 (0,69-3,19)	0,31
Variable	OR (IC 95 %)	p
History of hypertension	0,84 (0,39-1,80)	0,65
Age less than 50 years	3,35 (1,52-7,39)	0,003

By Hosmer and Lemeshow's law, the following were included in the multivariate model: p <0.25: age less than 50 years and personal history of arterial hypertension. But only the age greater than 50 years entered the equation. Table 2 also shows the results of the multivariate analysis. In the adjusted model, being less than 50 years increases the risk of vasospasm 3.35 times.

Discussion

In this study, there was no proven relationship between the clinical neurological condition and vasospasm detected by transcranial Doppler in the follow-up of patients with SAH. However, a higher incidence of vasospasm was found in patients younger than 50 years of age, with spontaneous SAH with a relative risk (RR) of 3.55 (95 % CI, 1.67-7.55) and p: 0.0008, and an OR of 3.35 compared to those of older age. There are several theories that explain the pathophysiological mechanisms in the development of vasospasm in patients with SAH, such as denervation of the arterial wall by blood in the subarachnoid space with loss of sympathetic system influence, vasoconstriction effect secondary to compounds of degradation of blood clots and

other substances, and the late proliferative vasoconstrictor effect due to the inflammatory phenomenon (22).

Some research agrees with the results of this work. The lower incidence of vasospasm in patients older than 50 years could be explained by a failure in the elasticity and contractility of the muscular wall of the cerebral vessels, which could be secondary to intracranial atherosclerosis characteristic of elderly patients (23).

The most studied association between SAH and vasospasm was designed by Fisher, who classified it tomographically in four grades, taking into account cases where there were blood clots of subarachnoid or blood layers> 1 mm thick in vertical fissures and cisterns, vasospasm developed in 95.8 % (24). A modified Fisher scale was then performed, where crude OR for grade 2 vasospasm (intraventricular hemorrhage isolated or with fine bleeding <1 mm) was 1.6 (95 % CI, 1.0-2.5), for grade 3 (diffuse or localized bleeding> 1 mm thickness) of 1.6 (95 % CI, 1.1-2.2) and grade 4 (diffuse or localized bleeding> 1 mm thick with intraventricular hemorrhage) of 2.2 (95 % CI, 1.6-3.1) (25). In this paper no association was found between the tomographic classifications of SAH with the development of vasospasm. Other risk factors studied for vasospasm in patients with SAH are neurological impairment, measured with the Glasgow coma scale, female sex, and surgical clipping as a therapeutic modality (26, 27), variables that were considered in this study, but which did not present statistically significant results.

Conclusion

In this retrospective case-control study, it has been shown that patients younger than 50 years with SAH are at greater risk of developing vasospasm compared to older patients and that there is no association between clinical condition and transcranial Doppler results. Therefore, it is recommended that the treating physicians (interventional radiologists or neurosurgeons) request a close transcranial Doppler follow-up to patients with SAH, regardless of their neurological condition, and especially those under 50 years of age.

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Correspondence

Mónica Royero Arias

Radiology service, Universidad de Antioquia

Hospital Universitario San Vicente Fundación

Calle 64 # 51D-154, bloque 12

Medellín, Colombia

mroyero@hotmail.com