Neurosurg Rev (2016) 39:429–436
DOI 10.1007/s10143-016-0701-3

ORIGINAL ARTICLE

Identification of specific age groups with a high risk for developing cerebral vasospasm after aneurysmal subarachnoid hemorrhage

Vesna Malinova[1] · Bawarjan Schatlo[1] · Martin Voit[1] · Patricia Suntheim[1] · Veit Rohde[1,2] · Dorothee Mielke[1]

Received: 6 April 2015 / Revised: 7 November 2015 / Accepted: 30 November 2015 / Published online: 4 March 2016

Abstract The impact of age on the incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) is a matter of ongoing discussion. The aim of this study was to identify age groups with a higher risk for developing vasospasm, delayed ischemic neurological deficit (DIND), or delayed infarction (DI) and to identify a cut-off age for a better risk stratification. We defined six age groups (<30, 30–39, 40–49, 50–59, 60–69, and >70 years). ROC analysis was performed to determine a cutoff age with the highest positive predictive value (PPV) for developing vasospasm, defined as a blood-flow-velocity-increase >120 cm/s in transcranial-Doppler-sonography (TCD). Multivariate binary-logistic-regression-analysis was then performed to evaluate differences in the incidence of cerebral vasospasm, DIND, and DI among the different age groups. A total of 753 patients were included in the study. The highest incidence (70 %) of TCD-vasospasm was found in patients between 30 and 39 years of age. The cutoff age with the highest PPV (65 %) for developing TCD-vasospasm was 38 years. Multivariate analysis revealed that age <38 years (OR 3.6; CI 95 % 2.1–6.1; $p < 0.001$) best predicted vasospasm, followed by the need for cerebrospinal fluid drainage (OR 1.5; CI 95 % 1.0–2.3; $p = 0.04$). However, lower age did not correlate with higher rates of DIND or infarcts. The overall vasospasm-incidence after aSAH is age-dependent and highest in the age group <38 years. Surprisingly, the higher incidence in the younger age group does not translate into a higher rate of DIND/DI. This finding may hint towards age-related biological factors influencing the association between arterial narrowing and cerebral ischemia.

Keywords Aneurysmal subarachnoid hemorrhage · Cerebral vasospasm · Transcranial Doppler sonography

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is still associated with high morbidity and mortality. Delayed cerebral vasospasm might lead to delayed ischemic neurological deficits (DINDs) and delayed cerebral infarction (DI) and is considered as one of the major contributors to poor clinical outcome [3, 23, 24].

Early recognition and initiation of antivasospastic therapy to prevent ischemia is of paramount importance [1, 4]. Tools, such as angiography, transcranial Doppler sonography (TCD), brain tissue oxygenation measurement, computerized tomography perfusion (CTP), allow diagnosing either arterial narrowing or hypoperfusion [9, 13, 17]. Identification of patient populations at risk of vasospasm allows gauging the intensity and invasiveness of monitoring.

Risk factors for cerebral vasospasm after aSAH are sex, clinical grade (Hunt and Hess grade, World Federation of Neurosurgical Societies (WFNS) grade), Fisher grade, smoking, alcohol abuse as well as history of hypertension [2, 12, 14]. The incidence of vasospasm is also age-related: by using cutoff ages of 60 [20, 28] or 68 [26], previous studies demonstrated that the elderly patient population is less frequently affected. The aim of this study was to study the age-specific incidence of vasospasm and to assess whether the risk of vasospasm translates into DIND and infarcts.

✉ Vesna Malinova
vesna.malinova@gmail.com

[1] Department of Neurosurgery, Georg August University, Robert-Koch-Straße 40, 37075 Göttingen, Germany

[2] Department of Neurosurgery, RWTH University, Aachen, Germany

Patients and methods

We included a total of 753 consecutive patients with aSAH in the study. The patient population consists of prospectively collected consecutive data from 1989 to 2004. The variables age, sex, WFNS grade, Fisher grade, aneurysm location (anterior vs. posterior according to ISAT criteria, i.e., posterior communicating artery is attributed to the posterior circulation) and aneurysm treatment were recorded. Age was stratified into the six following groups: <30 years, 30–39, 40–49, 50–59, 60–69, and >70 years. Vasospasm was defined as an increase in blood-flow-velocity (BFV) measured by transcranial Doppler sonography (TCD) >120 cm/s within 14 days after aSAH. DIND was defined as new neurological deterioration after exclusion of other causes such as hydrocephalus, seizures, metabolic disturbances, rebleeding infection, or brain edema. DI was defined as a newly diagnosed hypodensity on CT after day 3 that was not visible after treatment. These prospectively collected data were retrospectively analyzed for the objective of the current study.

CT scan with CT angiography was used to diagnose SAH. Digital subtraction angiography (DSA) was performed prior to treatment. All patients were treated at the intensive care unit for 14 days after onset of SAH. The aneurysm was secured within 48 h after the diagnosis by microsurgical clipping or endovascular coiling. The modality of aneurysm occlusion was chosen via interdisciplinary consensus on an individual basis. Eight neurosurgeons and two neuroradiologists were involved in aneurysm treatment. A postinterventional CT scan was performed routinely 4 h after aneurysm occlusion to exclude treatment-related complications. Diffusion-weighted magnetic resonance imaging was not performed for logistic reasons. Cerebral blood flow velocity of the middle cerebral artery was measured daily for 14 days after aSAH.

Statistical analysis

Incidence and age correlations were obtained by Pearson's correlation coefficients and receiver-operating characteristics where applicable. We performed binary logistic-regression-analysis to evaluate differences in the incidence of TCD-diagnosed cerebral vasospasm, DIND, and delayed infarcts above and below the cutoff age. The multivariable model included sex, WFNS grade, aneurysm localization, need for CSF drainage, treatment modality, and Fisher grade. For the determination of a cutoff age to define the highest positive predictive value (PPV) for cerebral vasospasm ROC (receiver operating characteristic) analysis was performed.

Results

Age distribution

The data of 753 patients were retrospectively analyzed, of whom 496 (65.9 %) were female and 257 (34.1 %) male. Mean age was 53.3 years (range 11–86). Forty-four patients were assigned to the age group <30 years (mean age 25.31), 90 patients to the age group 30–39 years (mean age 35.18), 161 patients to the age group 40–49 years (mean age 44.88), 178 patients to the age group 50–59 years (mean age 54.66), 185 patients to the age group 60–69 years (mean age 64.08), and 95 patients to the age group >70 years (mean age 73.87), respectively. Baseline characteristics are summarized in Table 1 and age distribution in Table 2 and Fig. 1.

Association of baseline variables with age: age group vs. gender, fisher, WFNS grade, aneurysm treatment, and CSF drainage

Poor grade WFNS (IV–V) were significantly more frequent in the age group <38 years (22/95; 23.2 %) compared to the age group ≥38 (242/591; 40.9 %; Chi^2 $p = 0.001$). Poor Fisher grades (3 and 4) were underrepresented in the younger than 38 age group (58/92 (63 %)) compared to the older than 38 group (482/604 (86.8 %); $p < 0.001$). Female sex was not differently distributed in the younger (67/107 (63 %)) and older than 38 (429/646 (66 %)) age groups ($p = 0.25$). The younger age group underwent surgical aneurysm treatment in all but one case (102/103; 99 %) while coiling was performed in 34/612 patients (94.5 %) aged 38 years or older ($p = 0.046$). Of the patients in the older age group, 218/646 (34 %) required no CSF diversion while 36/107 (33 %) in the younger age group had CSF drainage ($p = 0.984$).

Table 1 Baseline characteristics

		Number	Percent (%)
Sex	Female	496	65.9
	Male	257	34.1
Age (years)	Mean ± SD	53.3 ± 13.8	
Aneurysm localization	Anterior circulation	495	74.5
	Posterior circulation	169	25.5
WFNS grade	I-III	422	61.5
	IV-V	264	38.5
Fisher grade	I-II	156	22.4
	III-IV	540	77.6
Cerebrospinal fluid drainage	No	254	33.7
	Yes	499	66.3
Aneurysm occlusion	Surgical	680	95.1
	Endovascular	35	4.9

Table 2 Age distribution

Age group	Number	Percent (%)
<30 years	44	5.8
30–39 years	90	12.0
40–49 years	161	21.4
50–59 years	178	23.6
60–69 years	185	24.6
>=70 years	95	12.6
Total	753	100.0

Age-related incidence of TCD-vasospasm, DIND, and infarcts

The overall incidence of TCD-vasospasm was 44.6 % (336/753 patients). The highest incidence of TCD-vasospasm was 70.0 %, found in the patients aged between 30 and 39 years (Fig. 2). In the patient group <30 years of age, TCD-vasospasm was found in 50.0 % of patients, in the age group 40–49 years in 53.4 %, in the age group 50–59 years in 52.2 %, in the age group 60–69 years in 31.4 %, and in the age group >70 years in 14.7 %, respectively. With 21.6 %, the highest incidence of DIND was found in the patients <30 years. The incidence of DINDs in the other age groups was 12.4 % (30–39 years), 16.9 % (40–49 years), 13.6 % (50–59 years), 7.5 % (60–69 %), and 0.0 % (>70 years), respectively. The highest incidence of infarcts was also found in the patient group <30 years with 14.3 %, which was not statistically significant ($p=0.61$), again. The incidence of infarcts in the remaining age groups was 6.0 % (30–39 years), 13.0 % (40–49 years), 10.4 % (50–59 years), 8.3 % (60–69 years), and 0.0 % (>70 years), respectively. Figure 3 shows a summary of the incidence of TCD-vasospasm, DIND, and DI in the defined age groups.

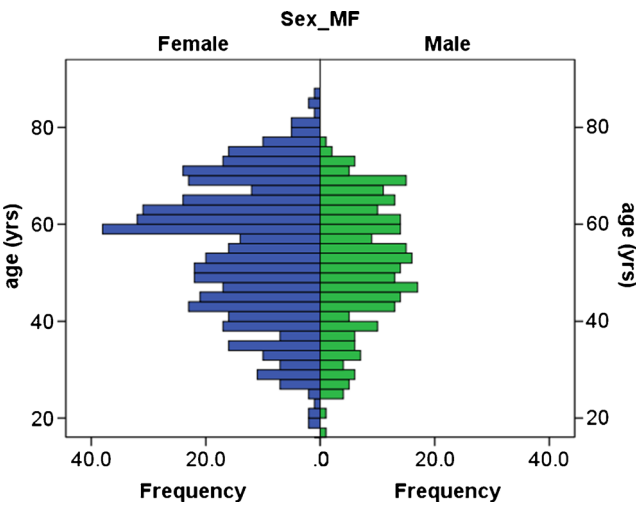


Fig. 1 Age distribution

Association of TCD-vasospasm, DIND, and infarcts with age

The presence of TCD-vasospasm and decreasing age were weakly albeit significantly correlated (Pearson correlation coefficient −0.291; $p<0.001$), while no association was found between DIND (Pearson correlation coefficient −0.080; $p=0.063$) and infarcts (Pearson correlation coefficient 0.0; $p=0.993$). The strength of the association of TCD-vasospasm with age was reflected in the receiver-operating characteristics analysis (ROC; AUC 0.675 (CI 95 % 0.637–0.713); $p<0.001$; where DIND (AUC 0.567 (CI 95 % 0.497–0.636); $p=0.070$) and infarct (AUC 0.505 (CI95 % 0.410–0.600); $p=0.924$) equally showed no association (Fig. 2).

Fitness of the multivariable model

The logistic regression model was statistically significant with a Chi^2 (7) = 33.8 and a p value of <0.0001. The model accounted for 8 % of the variance of vasospasm (Nagelkerke R^2) and provided a correct classification in 59 % of overall cases. Model sensitivity (true positive) was 61 % and specificity (true negative) was 57 % with a positive predictive value of 59 % and a negative predictive value of 58 %.

Multivariate analysis

Multivariate analysis revealed that age <38 years (OR 3.6; CI 95 % 2.1–6.1; $p<0.001$) best predicted vasospasm, followed by the need for cerebrospinal fluid drainage (OR 1.5; CI 95 % 1.0–2.3; $p=0.04$). However, lower age did not correlate with higher rates of DIND or infarcts (Table 3 and Fig. 4).

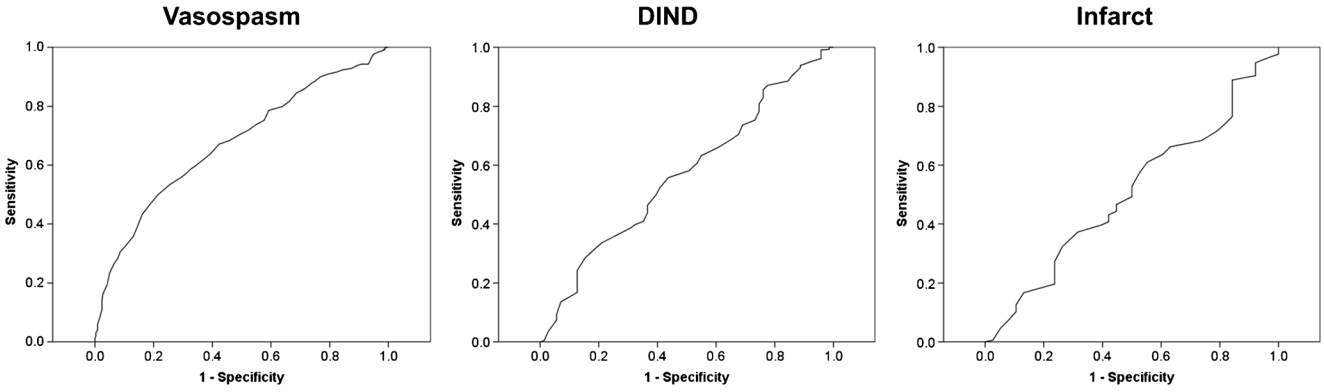
Discussion

Major finding

Age is one of several risk factors for the development of cerebral vasospasm after aSAH [13, 16, 20, 26–28]. We showed that patients aged between 30 and 39 years have a significantly increased risk and that patients aged between 60 and 69 years have a significantly reduced risk for the development of TCD-vasospasm. The cutoff age was 38 years. We could not find a statistically significant difference in the incidence of DINDs and/or DI between the defined age groups.

Correlation of age with TCD-vasospasm

Cerebral blood flow velocity in the MCA decreases with increasing age, probably due to increasing peripheral resistance and reduced vasomotor reactivity [18, 19, 24, 27]. Torbey



AUC (CI 95%)	p-value
0.675 (0.637-0.713)	<0.001

AUC (CI 95%)	p-value
0.567 (0.497-0.636)	0.070

AUC (CI 95%)	p-value
0.505 (0.410-0.600)	0.924

Fig. 2 Association of vasospasm, DIND, and DI with age

et al. analyzed the effect of age on changes in BFV measured by TCD and the effect of age on the incidence of vasospasm in a study group of 311 patients with aSAH. They found a lower baseline TCD-BFV in the middle cerebral artery (MCA) and internal carotid artery (ICA) as well as a significantly increase of the pulsatility index with advancing age [26]. Additionally, they identified a significantly higher incidence of TCD-vasospasm in younger (<68 years) compared to older (>68 years) patients [26].

Atherosclerotic arteries in the elderly seem to be the primary explanation for the low incidence of TCD-vasospasm in the older patients suffering from aSAH. This could explain the missing increase in BFV in the elderly even in case of vasospasm. Since we still do not have established reference values for BFV for every age group, the interpretation of TCD-vasospasm within the different age groups remains limited.

Magge et al. reported an association of younger age with symptomatic vasospasm, with a cutoff age of 51 years [20]. De Rooij et al. have developed a practical risk chart for the prediction of delayed cerebral ischemia after aSAH and found that a cutoff of 55 years was one of the strongest predictors for

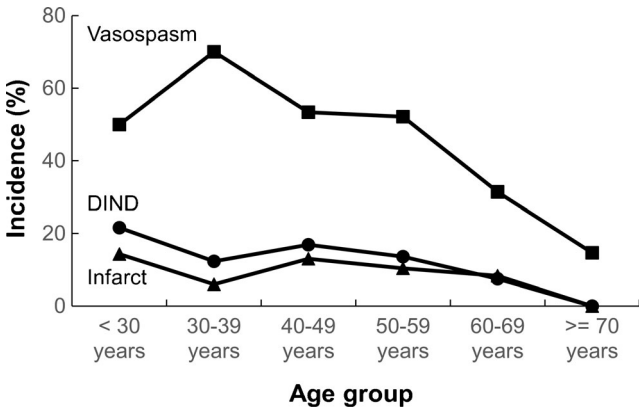


Fig. 3 Incidence of TCD-vasospasm, DIND, and DI in the defined age groups

delayed cerebral ischemia (DINDs and/or DCI) together with the clinical condition on admission as well as the amount of blood on cerebral computed tomography [6]. Although the cutoff age in the present study was lower compared to Magge et al. and de Rooij et al., our data seem to confirm the notion that vasospasm appears more frequently in younger patients. Obviously, different age groups carry different risks for developing TCD-vasospasm, which might be of importance concerning the question whether a more or less aggressive antivasospastic therapy should be applied and whether prophylactic triple-H-therapy could play a role in the high-risk patient group.

Correlation of age with DIND and DI

While BFV accelerations were clearly associated with younger age, this association disappeared for its supposed consequences, namely DIND and DI. Our results are consistent with the results of previously published studies approaching this issue. These results would still implicate the recommendation to perform more aggressive medical and interventional antivasospastic treatment in younger patients than in older patients in order to respond to the TCD-diagnosed vasospasm as an early marker for potential hypoperfusion [15]. On the other hand, aggressive antivasospastic therapy should be avoided in the elderly to reduce side effects in patients that already suffer from a lower cerebral as well as cardiac reserve capacity [11]. In the multivariate analysis in the present study, age <38 years was not associated with statistically significant higher risk for DIND.

DI after aSAH can develop either with or without the occurrence of DIND [24]. The development of asymptomatic DI is especially common in comatose patients. In a previous prospective study including 580 patients, DI was detected in 20 % of all patients [22]. In our study, we considered all patients

Table 3 Multivariate analysis

		Vasospasm				DIND				Infarct			
		OR	CI	95 %	*p* value	OR	CI	95 %	*p* value	OR	CI	95 %	*p* value
Sex	Female	0.984	0.685	1.413	0.93	1.247	0.663	2.344	0.364	1.300	0.530	3.190	0.566
Age	<38 years	3.538	2.050	6.104	<0.01	1.714	0.853	3.442	0.130	1.309	0.414	4.140	0.647
Circulation	Anterior	1.167	0.786	1.732	0.445	1.581	0.751	3.330	0.228	1.215	0.454	3.253	0.698
Fisher	3 and 4	1.296	0.837	2.007	0.246	1.431	0.660	3.104	0.364	7.224	0.926	56.38	0.059
WFNS	IV and V	1.088	0.751	1.576	0.657	0.871	0.459	1.654	0.672	0.567	0.271	1.593	0.352
CSF drainage	Present	1.532	1.025	2.290	0.038	0.821	0.430	1.569	0.551	0.970	0.355	2.649	0.953
Treatment	Clipping	2.581	0.892	7.463	0.08	0.723	0.083	6.294	0.769	1.071	0.001	100	0.999
Constant		0.176			0.006	0.102			0.060	0.000			0.999

with DI either with or without DINDs and found no statistically significant association between DI and age.

Known risk factors for delayed cerebral vasospasm after aSAH

Clinical grade of aSAH, amount of blood in the subarachnoid space on admission CT scan, sex, age, smoking, hypertension, diabetes, decreased platelet count and left ventricular hypertrophy appear to contribute to delayed cerebral vasospasm [7, 10, 14, 20, 28, 29, 31]. Most of these studies focused on the association of risk factors with symptomatic vasospasm and some of them focused additionally on angiographic vasospasm. De Oliveira et al. discussed the impact of treatment modality, e.g., surgical or interventional on delayed cerebral vasospasm based on the current literature found no significant difference between the aneurysm occlusion modality and the incidence of angiographic vasospasm, symptomatic vasospasm, or cerebral infarction after aSAH [5]. A multivariate analysis of 370 patients with aSAH has shown that the SAH grade III–IV (subarachnoid hemorrhage on the CT scan, grade III = severe clotting evident in one or two of three locations in the basal cistern; grade IV = severe clotting packed diffusely in all three basal cistern locations) was the most important risk factor for cerebral vasospasm. Other risk factors for cerebral vasospasm were left ventricular hypertrophy, cigarette smoking, and hypertension [12]. Temes et al. reported a significant association of left ventricular dysfunction with the occurrence of vasospasm-induced infarction after subarachnoid hemorrhage [25]. In a retrospective analysis of 321 consecutive patients with aSAH, a strong association of intraventricular hemorrhage and tobacco with symptomatic cerebral vasospasm in patients with aSAH was found after performing multivariate analyses [31]. Hamdan et al. [8] found that female patients suffering from aSAH are older than male patients and have a higher rate of multiple and bilateral aneurysms, but sex was not identified as an independent risk factor for cerebral vasospasm [8], which is in keeping with our multivariate analysis. Dumont et al. suggested a potential role for diabetes mellitus as a risk factor for symptomatic cerebral vasospasm [7], but their study had a relatively low patient number and was retrospective. In a prospective study including 172 patients, Naidech et al. found a significant association of moderate hypoglycemia

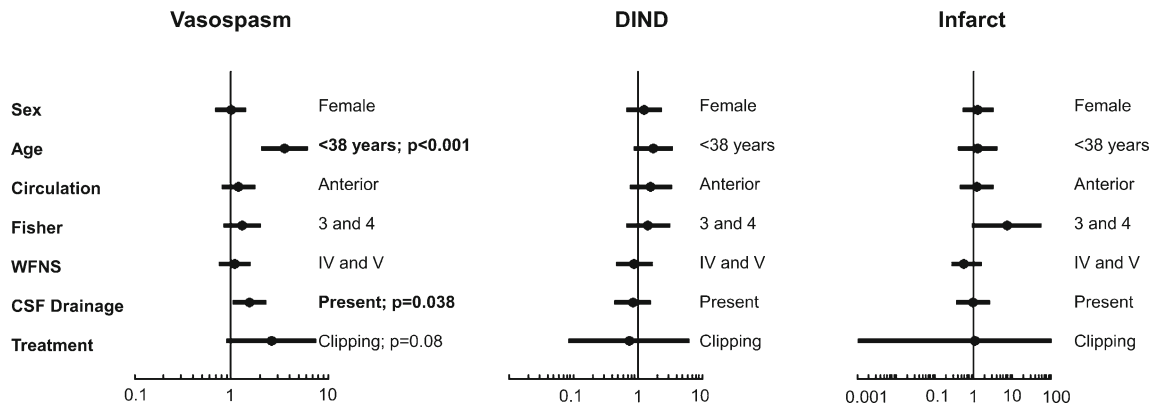


Fig. 4 Forestplots

Table 4 Recent studies about risk factors for cerebral vasospasm in the last 10 years

Authors	Journal and year of publication	Number of patients	Risk factors
Hirashima et al.	J Neurosurg 2005	100	Decrease in platelet count
Dumont et al.	Neurocrit Care 2009	145	Diabetes mellitus
Magge et al.	J Neurosurg 2010	291	Age <51 years
Temes et al.	Neurocrit Care 2010	119	Left ventricular dysfunction
Naidech et al.	Neurocrit Care 2010	172	Moderate hypoglycemia
Wachter et al.	Neurosurgery 2011	758	Age <60 years
Wachter et al.	J Neurosurg 2011	1016	Clipping of multiple aneurysms
Inagawa et al.	Neurol Med Chir 2014	370	Subarachnoid blood on admission CT
Hamdan et al.	J Neurosurg 2014	617	Sex
Wilson et al.	J Neurol Surg A Cent Eur Neurosurg 2015	321	Intraventricular hemorrhage, tobacco
Jabbarli et al.	J Cereb Blood Flow Metab 2015	632	Fisher score, Hunt and Hess scale, age cut-off at 55 years, multiple aneurysms, vasospasm on the initial angiogram and the necessity of cerebral spinal fluid drainage

(glucose <80 mg/dL) and the development of angiographic vasospasm, symptomatic vasospasm, and cerebral infarction after aSAH [21]. A decreased platelet count was equally suggested as an independent risk factor for symptomatic cerebral vasospasm [10]. A comprehensive scoring system was recently devised with the aim of identifying patients at high risk of DI [14]. This BEHAVIOR score includes Fisher score, Hunt and Hess scale, age cutoff at 55 years, multiple aneurysms, vasospasm on the initial angiogram, and the necessity of cerebral spinal fluid drainage due to acute hydrocephalus. The score showed a statistically significant correlation with the absolute risk for cerebral infarction as well as with poor outcome at discharge and after 6 months [14]. While its predictive value is excellent, the multitude of variables required, in particular intracranial pressure, render its application for individual patients cumbersome. In a series of 1016 consecutive patients, we found that treating multiple aneurysms in one surgery did not increase the risk for flow acceleration on TCD or symptomatic vasospasm [29]. In Table 4 the relevant studies cited in this paper are summarized.

Strengths and limitations of the study

Strength of this study is the high number of patients included in the analysis and the prospective data collection. Another strength is the more precise risk classification within the individual age decades, with respect to the incidence of TCD-vasospasm, DINDs, and DI separately. The limitation of the study is the retrospective analysis of the prospectively collected data.

Conclusion

The incidence of TCD-vasospasm is dependent on age of the patients with aSAH. The age group 30–39 years has the highest incidence of TCD-vasospasm with a cutoff age at 38 years. Age <38 years is the best predictor of TCD-vasospasm followed by the need of cerebrospinal fluid drainage.

Compliance with ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 [30].

References

1. Bauer AM, Rasmussen PA (2014) Treatment of intracranial vasospasm following subarachnoid hemorrhage. Front Neurol. doi:10.3389/fneur.2014.00072
2. Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, Connolly ES, Mayer SA (2001) Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the fisher scale revised. Stroke 32:2012–2020
3. Cossu G, Messerer M, Oddo M, Daniel RT (2014) To look beyond vasospasm in aneurysmal subarachnoid hemorrhage. Hindawi Publishing Corporation, BioMed Research International, Article ID 628597
4. Nogueira DG (2013) Current options for the management of aneurysmal subarachnoid hemorrhage-induced cerebral vasospasm: a comprehensive review of the literature. Interv Neurol 2:30–51
5. De Oliveira JG, Beck J, Ulrich C, Rathert J, Raabe A, Seifert V (2007) Comparison between clipping and coiling on the incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Neurosurg Rev 30:22–31

6. De Rooij NK, Greving JP, Rinkel GJE, Frijns CJM (2013) Early prediction of delayed cerebral ischemia after subarachnoid hemorrhage, Development and validation of a practical risk chart. Stroke 44:1288–1294
7. Dumont T, Rughani A, Silver J, Tranmer BI (2009) Diabetes mellitus increases risk of vasospasm following aneurysmal subarachnoid hemorrhage independent of glycemic control. Neurocrit Care 11(2):183–9
8. Hamdan A, Barnes J, Mitchell P (2014) Subarachnoid hemorrhage and the female sex: analysis of risk factors, aneurysm characteristics, and outcomes. J Neurosurg 121(6):1367–73
9. Han PY, Kim JH, Kang HI, Moon BG, Lee SJ, Kim JS (2008) Is transcranial Doppler ultrasonography old-fashioned? One institutional study. J Korean Neurosurg Soc 44:63–66
10. Hirashima Y, Hamada H, Kurimoto M, Origasa H, Endo S (2005) Decrease in platelet count as an independent risk factor for symptomatic vaospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 102(5):882–7
11. Hishikawa T, Takasugi Y, Shimizu T, Haruma J, Hiramatsu M, Tokunaga K, Sugiu K, Date I (2014) Cerebral vasospasm in patients over 80 years treated by coil embolization for ruptured cerebral aneurysms. Hindawi Publishing Corporation, BioMed Research International Article ID 253867
12. Inagawa T, Yahara K, Ohbayashi N (2014) Risk factors associated with cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Neurol Med Chir (Tokyo) 54:465–473
13. Ionita CC, Graffagnino C, Alexander MJ, Zaidat OO (2008) The value of CT angiography and transcranial Doppler sonography in triaging suspected cerebral vasospasm in SAH prior to endovascular therapy. Neurocrit Care 9:8–12
14. Jabbarli R, Reinhard M, Roelz R, Shah M, Niesen WD, Kaier K, Taschner C, Weyerbrock A, Van Veithoven V (2015) Early identification of individuals at high risk for cerebral infarction after aneurysmal subarachnoid hemorrhage: the BEHAVIOR score. J Cereb Blood Flow Metab 35(10):1587–92
15. Jarus-Dziedzic K, Juniewicz H, Wronski J (2002) The relation between cerebral blood flow velocities as measured by TCD and the incidence of delayed ischemic deficits. A prospective study after subarachnoid hemorrhage. Neurol Res 24:582–92
16. Kale SP, Edgell RC, Alshekhlee A, Haghighi AB, Sweeny J, Felton J, Kitschener J, Vora N, Bieneman BK, Cruz-Flores S, Abdulrauf S (2013) Age-associated vasospasm in aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 22:22–27
17. Killeen RP, Mushilin AI, Johnson CE, Comunale JP, Tsiouris AJ, Delaney H, Dunning A, Sanelli PC (2011) Comparison of CT perfusion and digital subtraction angiography in the evaluation of delayed cerebral ischemia. Acad Radiol 18(9):1094–1100
18. Krejza J, Szydlik P, Liebeskind DS, Kochanowicz J, Bronov O, Mariak Z, Melhem ER (2005) Age and sex variability and normal reference values for the V-MCA/V-ICA index. AJNR Am J Neuroradiol 26:730–735
19. Krejza J, Mariak Z, Lewko J (2003) Standardization of flow velocities with respect to age and sex improves the accuracy of transcranial color Doppler sonography of middle cerebral artery spasm. AJR 181:245–252
20. Magge SN, Chen HI, Ramakrishna R, Cen L, Chen Z, Elliott JP, Winn HR, Le Roux PD (2010) Association of a younger age with an increased risk of angiographic and symptomatic vasospasm following subarachnoid hemorrhage. J Neurosurg 112:1208–1215
21. Naidech AM, Levasseur K, Liebling S, Garg RK, Shapiro M, Ault ML, Afifi S (2010) Moderate hypoglycemia is associated with vasospasm, cerebral infarction and 3-month disability after subarachnoid hemorrhage. Neurocrit Care 12(2):181–7
22. Rowland MJ, Hadjipavlou G, Kelly M, Westbrook J, Pattinson KTS (2012) Delayed cerebral ischemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth 109(3):315–29
23. Schmidt JM, Wartenberg KE, Fernandez A, Claassen J, Rincon F, Ostapkovich ND (2008) Frequency and clinical impact of asymptomatic cerebral infarction due to vasospasm after subarachnoid hemorrhage. J Neurosurg 109(6):1052–9
24. Shimoda M, Takeuchi M, Tominaga J, Oda S, Kumasaka A, Tsugana R (2001) Asymptomatic versus symptomatic infarcts from vasospasm in patients with subarachnoid hemorrhage: serial magnetic resonance imaging. Neurosurgery 49(6):1341–8
25. Temes RE, Tessitore S, Schmidt JM, Naidech AM, Fernandez A, Ostapkovich ND (2010) Left ventricular dysfunction and cerebral infarction from vasospasm after subarachnoid hemorrage. Neurocrit Care 13(3):359–65
26. Torbey MT, Hauser TK, Bhardwaj A, Williams MA, Ulatowski JA, Mirski MA, Razumovsky AY (2001) Effect of age on cerebral blood flow velocity and incidence of vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 32:2005–2011
27. Vriens EM, Kraaier V, Musbach M, Wieneke GH, van Huffelen AC (1989) Transcranial pulsed Doppler measurements of blood flow velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy volunteers in relation to age and sex. Ultrasound Med Biol 15:1–8
28. Wachter D, Hans F, Kretschmann-Andermahr I, Rohde V (2011) Lower incidence of transcranial Doppler and symptomatic vasospasm after aneurysmal subarachnoid hemorrhage and aneurysm clipping in the elderly patient? Neurosurgery 69:261–267
29. Wachter D, Kreitschmann-Andermahr I, Gilsbach JM, Rohde V (2011) Early surgery of multiple versus single aneurysms after subarachnoid hemorrhage: an increased risk for cerebral vasospasm? J Neurosurg 114:935–941
30. Williams JR (2008) The declaration of Helsinki and public health. Bull World Health Organ 86(8):650–2
31. Wilson TJ, Stetler WR, Davis MC, Giles DA, Khan A, Chaudhary N, Gemmete JJ, Xi G, Thompson BG, Pandey AS (2015) Intraventricular hemorrhage is asscoaited with early hydrocephalus, symptomatic vasospasm, and poor outcome in aneurysmal subarachnoid hemorrhage. J Neurol Surg Cent Eur Neurosurg 76(2): 126–32

Comments

Mohsen Nouri, Ahvaz, Iran

The authors presented a large cohort of patients (more than 700 patients) with subarachnoid hemorrhage and monitored them for trans-cranial Doppler (TCD)-based vasospasm, delayed infarction (DI), and delayed neurological deficits (DND) to evaluate the effect of age on these variables. Large number of patients allowed them stratification and multivariate regression analysis where they found that younger patients at a cut-off age of 38 were more prone to TCD vasospasm and showed a trend toward higher chance of delayed infarction and DND (though not statistically significant). Although it had been showed by previous studies that younger patients are more prone to vasospasm and its consequences, the authors should be congratulated for providing solid evidence with very good analysis of the data. However, we should interpret results of this study cautiously as we know the false results (both positive and negative) of TCD in defining vasospasm. So, all the points reviewed below should be interpreted in the context of accepting TCD as a reliable measure of vasospasm.

Despite a high chance of TCD- vasospasm in younger patients, chance of DND/DI was nearly the same as older patients. One interpretation is that a more aggressive treatment in younger patients hampers the effect of vasospasm. This shows that current threshold of TCD-based diagnosis of pre-clinical vasospasm to start treatment is almost effective in preventing DND/DI. Yet, a more aggressive treatment at lower TCD thresholds in

younger patients may decrease the little higher chance of infarction in this age group. The other explanation is that a big proportion of TCD-diagnosed vasospasms will not develop into clinical spasm and remain silent. However, as the patients were receiving anti-vasospasm treatments, it is difficult to draw such a conclusion.

Another issue is the true rate of vasospasm in different age groups: as showed by previous studies, cerebral blood velocity (CBV) decreases by age, so, in the elderly despite a vasospasm, CBV may not exceed 120 leading to underestimation of the rate of vasospasm. In fact, before defining normal ranges of CBV in different age groups (especially elderly) we may not estimate the true incidence of vasospasm with TCD. Based on these results, we require future studies to define new TCD cut off points in different age groups for diagnosis of vasospasm and predicting DND/DI.

Karl Rössler, Erlangen, Germany

The authors analyzed a large cohort of aneurysmal subarachnoid hemorrhage patients concerning cerebral vasospasm (n = 753) after treatment by clip ligation. They found the highest incidence of post hemorrhagic vasospasm in young patients between 30 to 39 years of age. This is not totally new, as their review of the literature demonstrates and the common anecdotal arguments of arrested vessel diameter in arteriosclerotic vessels of the elderly refer to. But they were able to demonstrate, that this higher incidence of vasospasm in the young age group did not automatically lead to a higher incidence of DIND or strokes. This could lead to the conclusion, that in young age patients with post SAH vasospasm and basic treatment like dripple HHH and nimodipine, aggressive treatment like angioplasty on the basis of elevated TCD values alone is not justified (as long as they are clinically asymptomatic). Additionally, they found a significant positive correlation between vasospasm and CSF drainage, which seems to be a surrogate parameter for the amount of blood (but astonishingly did not significantly correlate with Fisher Scale grades). Altogether, this investigation represents a clinically useful summary of factors influencing cerebral vasospasm in patients following subarachnoid hemorrhage, valuable as a basis for therapeutical considerations.