Neuroradiology (2021) 63:253–257
https://doi.org/10.1007/s00234-020-02524-7

INTERVENTIONAL NEURORADIOLOGY

Are modified Fisher Scale and bleeding pattern helpful predictors of neurological complications in non-aneurysmal subarachnoid hemorrhage?

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Received: 16 April 2020 / Accepted: 13 August 2020 / Published online: 18 August 2020

Abstract

Purpose Non-aneurysmal subarachnoid hemorrhage (NA-SAH) is a clinical-radiological entity with a different prognosis than aneurysmal SAH (A-SAH). The purpose of this study is to assess the predictive value of the modified Fisher Scale (mFS) for neurological complications in patients with this diagnosis.

Methods We recruited patients admitted at our hospital services between 2009 and 2017 who were diagnosed with spontaneous SAH, with either perimesencephalic (PM-SAH) or diffuse pattern (D-SAH), an initial negative angio-CT, and at least one digital subtraction angiography of brain vessels discarding underlying brain aneurysms or other vascular malformations.

Results The retrospective observational study included 116 patients. The mean age was 54.4, and the sample included predominantly male subjects (62.9%). Hunt and Hess (HH) scores on admission ranged from 3 to 5 in 18.1% of patients. The prevalence of hydrocephalus requiring ventricular drainage was 18.1%. The prevalence of symptomatic vasospasm was 4.3%. A modified Rankin Scale (mRS) 0–2 at discharge was found in 95.6%. In a multivariate logistic regression for the presence of neurological complications including age, sex, admission HH 3-5 compared with < 3, mFS 4 compared with mFS < 4, D-SAH compared with PM-SAH, and mRS score at discharge of 0–2 compared with > 2, the only significant predictors were mFS 4 compared with mFS < 4 (OR 4.47 (95% CI 1.21, 16.66) p value = 0.03) and D-SAH compared with PM-SAH (OR 7.10 (95% CI 1.24, 40.8) p value = 0.03).

Conclusion In patients with NA-SAH, a mFS score of 4 and/or a D-SAH bleeding pattern in non-contrast cranial CT on admission predicted the development of relevant neurological complications.

Keywords Non-aneurysmal subarachnoid hemorrhage · Modified Fisher Scale · Vasospasm · Hydrocephalus

Introduction

Non-aneurysmal subarachnoid hemorrhage (NA-SAH) is a clinical-radiological entity which comprises almost 15% of cases of subarachnoid hemorrhage [1–3]. NA-SAH appears to follow a more benign clinical outcome compared with aneurysm-associated SAH (A-SAH) [4–6]. However, some cases may develop complications such as hydrocephalus and/or vasospasm, which require emergency treatment.

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The modified Fisher Scale (mFS) is a radiological scale applied on non-contrast CT widely used to predict the probability of vasospasm after SAH secondary to intracranial aneurysm rupture (A-SAH) [7]. It was developed from the original Fisher Scale, which was modified to account for patients with thick cisternal blood and concomitant intraventricular or intraparenchymal hemorrhage (see “Methods” for grading description and reference). Despite its wide use as a predictor of vasospasm in A-SAH, the application of mFS in NA-SAH has never been tested and remains unknown.

NA-SAH has also been classified according to the radiologic distribution patterns of the blood into perimesencephalic subarachnoid hemorrhage (PM-SAH) and diffuse subarachnoid hemorrhage (D-SAH). Recent studies suggest that these two subtypes of NA-SAH may also show different clinical courses [8–11], yet the value of this sub-classification in predicting specific neurological complications has not been determined.

In this study, we assess the population of patients with NA-SAH at our center during an 8-year time period and analyze the value of the mFS and bleeding pattern as tools for the prognosis of neurologic complications (hydrocephalus requiring ventricular drainage and/or symptomatic vasospasm).

Methods

We retrospectively reviewed the radiology and medical record database of all patients admitted at our hospital between January 1, 2009 and December 31, 2017. For the purpose of this study, we included those patients with (1) spontaneous SAH (either PM-SAH or D-SAH) and (2) an initial angio-CT with at least one digital subtraction angiography (DSA) of brain vessels discarding underlying brain aneurysms or other vascular malformations. Cases of isolated cortical or intraventricular subarachnoid hemorrhage were excluded. Patients with no available imaging studies in the radiology database were also excluded.

Imaging protocol At our institution, all patients with spontaneous SAH detected in the initial non-contrast head CT (NCCT) are taken into an emergency angio-CT. NCCT and angio-CT are then performed following standard protocols, using a 16 or 64 section helix CT scanner. Axial images are obtained using a 120–140 kV and a 0.625–2.5-mm section thickness reconstruction process. MPR, MIP, and volume rendering reconstructions are used to assess the images. The iodine contrast is administered with a power injector at a dose and rate of 50 ml and 4 ml/s, respectively. Patients without evidence of brain aneurysms in the initial emergency angio-CT must undergo a DSA within the following 24–48 h. The procedure is performed using a femoral or brachial arterial access. The internal and external carotids and the vertebral arteries are selectively catheterized and injected. The standard projections are anterior-posterior and lateral. Oblique and/or rotational 3D are obtained at the discretion of the neurologic intervention specialist in charge.

Image analysis For the purpose of the study, an experienced interventional neuroradiology specialist and a senior resident physician analyzed the images. The cases were classified according to the bleeding pattern (PM-SAH or D-SAH) and the mFS grade (1 to 4), following the criteria below:

- Bleeding pattern. PM-SAH: (1) The epicenter of the hemorrhage is immediately anterior to the midbrain, (2) possible extension of the hemorrhage to the posterior aspect of the interhemispheric fissure or to the base of the Sylvian ridge, (3) absence of a significant amount of intraventricular blood (sedimented blood within the occipital horns included), and (4) absence of brain hematoma [8, 9, 12]. D-SAH: Any SAH beyond the previous limits.
- mFS score: Criteria published by Frontera et al. [7] were followed. Grade 1, thin focal or diffuse SAH, no IVH; 2, thin focal or diffuse SAH, IVH present; 3, thick focal or diffuse SAH, no IVH; 4, thick focal or diffuse SAH, IVH present.

Data collection Medical records were reviewed with the assistance of an experienced stroke neurologist. The patients' age, sex, Hunt and Hess score on admission, relevant neurological complications (symptomatic vasospasm and/or hydrocephalus requiring ventricular drainage), and mRS score at discharge [13, 14] were recorded. Hunt and Hess score values ranging 3 to 5 were considered as severe for symptoms at the time of onset and mRS > 2 as a poor clinical outcome.

Statistical analysis Normally distributed data are presented as mean ± SD and non-normally distributed data as median and interquartile range (IQR). Categorical variables are expressed as percentages. A categorized analysis between groups was performed comparing the two types of NA-SAH (PM-SAH and D-SAH) and neurological complications. Student's *t* test was used for continuous variables, and $\chi 2$ test for categorical variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated at first with univariate analysis to identify association between each variable with type of NO-SAH and a second time with uni- and multivariate logistic regression analysis to identify the association between each variable with neurological complications. Statistical significance was set at $p < 0.05$, and all analyses were done with Statistical Package for the Social Sciences Software Version 22.0 (SPSS, Chicago, IL, USA).

Results

A total of 116 patients fulfilled the aforementioned criteria and were included in the study.

Baseline population demographics Table 1 (1st row) shows the baseline demographics of the global population. The mean age was 54.4 years, with a predominant male majority (62.9%). Hunt and Hess scores on admission ranging from 3 to 5 were found in 18.1% of patients. A mFS score of 4 was found in 33.6% of subjects. The proportion of patients who presented at least one neurological complication (symptomatic vasospasm or hydrocephalus requiring ventricular drainage) was 19.8%, being hydrocephalus more frequent than vasospasm (18.1 and 4.3%, respectively). A mRS 0–2 score at the time of discharge was considered as a good clinical outcome, found in 97.4% of the patients.

Table 1 Baseline and clinical/radiological characteristics of the total population and comparison between characteristics of sub-populations according to the SAH type

Variables	Total	Perimesencephalic	Diffuse	*p*
Number of patients (*n*, %)	116 (100)	60 (51.7)	56 (48.3)	< 0.05
Age (mean, SD)	54.43	53 (12.9)	56 (12.3)	0.20
Males (*n*, %)	73 (62.9)	37 (61.7)	36 (64.3)	0.77
Admission HH 3–5 (*n*, %)	21 (18.1)	1 (1.7)	20 (35.7)	*< 0.001**
Number of patients with a mFs of 4 at admission (*n*, %)	39 (33.6)	2 (3.3)	37 (66.1)	*< 0.001**
Vasospasm (*n*, %)	5 (4.3)	1 (1.7)	4 (7.1)	0.15
Hydrocephalus (*n*, %)	21 (18.1)	1 (1.7)	20 (35.7)	*< 0.001*
Number of patients with at least one neurological complication (*n*, %)	23 (19.8)	2 (3.3)	21 (37.5)	*< 0.001**
mRS 0–2 at discharge (*n*, %)	111 (95.6)	60 (100)	51 (91.1)	*0.02**

P probability value, *SAH* subarachnoid hemorrhage, *HH* Hunt and Hess scale, *mRS* modified Rankin Scale
Bolt: Statistically significant ($p < 0.05$)

Blood distribution pattern To test specifically the value of the blood pattern distribution to predict the development of neurological complications in NA-SAH, we considered the differences between patients with PM-SAH and those with D-SAH (Table 1, 2nd and 3rd rows). Sixty patients (51.7%) showed a PM-SAH, and 56 patients (48.3%) showed a D-SAH. No differences were found between both subgroups in regard to age and gender. The number of patients with an admission Hunt and Hess score between 3 and 5 and a mFS score of 4 was higher in those patients with D-SAH ($p < 0.001$). When considered as a group, relevant neurological complications (symptomatic vasospasm and hydrocephalus requiring ventricular drainage) were more frequent in patients with D-SAH ($p < 0.001$). However, this difference is due solely to the higher number of patients with hydrocephalus in the D-SAH group ($p < 0.001$), with an insignificant number of patients with vasospasm ($p = 0.15$). Good clinical outcome (assessed by a mRS 0–2 at discharge) was superior in patients with PM-SAH compared with those with D-SAH ($p = 0.02$).

Predictors of neurological complications We performed univariate and multivariate analysis to detect which of the variables involved may be related to the onset of relevant neurological complications. Results of the analyses are summarized in Table 2. In a multivariate logistic regression for the presence of neurological complication, which included as predictors age, sex, admission Hunt and Hess 3–5 compared with < 3, mFisher 4 compared with mFisher < 4, D-SAH compared with PM-SAH, and mRS at discharge of 0–1 compared with > 1, the only significant predictors were mFisher (OR 4.47 (95% CI 1.21, 16.66) *p* value = 0.03) and D-SAH compared with PM-SAH (OR 7.10 (95% CI 1.24, 40.8) *p* value = 0.03).

Modified Fisher Scale Table 3 shows the relation between the mFS grade and the number of patients that develop neurological complications (either vasospasm, hydrocephalus, or both). As it can be seen, the proportion of patients with neurological complications increased with the mFS grade (2.4%, 9.5%, 14.3%, and 46.2% for grades 1, 2, 3, and 4, respectively).

Discussion

In this study, we analyze the use of the mFS and radiological bleeding patterns (PM-SAH or D-SAH) for clinical assessment in a series of 116 patients with NA-SAH. Our results suggest that both of these tools are useful for prediction of neurological complications (mainly hydrocephalus requiring ventricular drainage and symptomatic vasospasm in second instance) in this setting, albeit with different meanings and implications than for aneurysmal SAH.

The main objective of our study was to focus on the applicability of mFS. This scale has been widely used in

Table 2 Univariate and multivariate analysis of clinicoradiological variables related to the patients' development or not of neurological complications

Variables	Patients' development of neurological complications*		Univariate		Multivariate	
	Yes (23)	No (93)	OR (CI 95)	*p*	Adjusted OR	*p*
Age per year increase (Mean, Standard Deviation)	59.6 (12.8)	53.15 (12.3)	1.04 (1.01–1.08)	*0.03**	1.04 (0.99–1.09)	0.11
Males vs females (*n*, %)	17 (73.9)	56 (60.2)	1.87 (0.67–5.26)	0.23	0.47 (0.14–1.53)	0.21
Admission HH 3–6 vs 1–2 (*n*, %)	16 (69.6)	5 (5.4)	40.23 (11.35–42.57)	*< 0.001**	NA	NA
mFS 4 vs 1–3 (*n*, %)	18 (78.3)	21 (22.6)	12.34 (4.09–37.22)	*< 0.001**	4.47 (1.21–16.55)	*0.03**
D-SAH vs PM-SAH (*n*, %)	21 (91.3)	35 (37.6)	17.40 (3.84–78.75)	*< 0.001**	7.10 (1.24–40.79)	*0.03**
mRS 0–2 vs 3–6 at discharge (*n*, %)	18 (78.3)	93 (100)	NA	NA	NA	NA

OR odds ratio, *CI* confidence interval, *NA* non-applicable, *P* probability value, *SAH* subarachnoid hemorrhage, *HH* Hunt and Hess scale, *mFS* modified Fisher Scale, *D-SAH* diffuse subarachnoid hemorrhage, *mRS* modified Rankin Scale

Bolt: Statistically significant ($p < 0.05$)

aneurysmal SAH settings, accurately predicting symptomatic vasospasm [7]. However, its meaning in patients with NA-SAH has not been tested, leading to confusion on the usefulness of mFS grading patients when there is no underlying aneurysm as cause of the bleeding.

Our patient series show that there is a correlation between the mFS score and the prevalence of relevant neurological complications in NA-SAH. However, this relation is statistically significant only for patients with a score of 4 ($p < 0.001$, OR 35.14), whereas scores of 2 and 3 do not show statistical significance (*p* 0.21 and 0.09, respectively). These results differ from those observed for aneurysmal SAH, which show a linear correlation between the mFS value and vasospasm that was also significant for scores of 2 and 3 [7].

Interestingly, the main symptomatic neurological complication in our series was hydrocephalus requiring ventricular drainage, rather than symptomatic vasospasm. Hydrocephalus was observed in 21 of the 23 patients who presented at least one neurological complication (91.3%), and it was significantly more common in patients with D-SAH than in PM-SAH ($p < 0.001$, Table 1), especially in the subset of patients with a mFS score of 4. The dilatation of the ventricular system is well established as the main complication in cases of NA-SAH [12]. Lin and Sprenker reported 12 out of 33 (36.3%) and 17 out of 26 (65.3%) patients with D-SAH that presented hydrocephalus requiring ventricular shunting in their respective series [15, 16]. Our study confirms not only that hydrocephalus is the most frequent complication of NA-SAH but also that this correlation may be predicted through the mFS and radiological blood patterns. Patients with a mFS score of 4 and/or a D-SAH are more likely to develop acute dilation of the ventricular system requiring ventricular drainage, while patients with a mFS score between 1 and 3 and/or a PM-SAH show a significantly lower prevalence of this complication. This finding is probably related to larger amounts of blood found in mFS score 4 patients [17, 18].

It is also noteworthy that the correlation between symptomatic vasospasm and mFS scores in our patient series with NA-SAH was poor. Only one patient with a mFS score of 1 and four with a mFS score of 4 developed this complication. This data supports conclusions from previous publications reporting a low prevalence of this complication in patients with NA-SAH [19]. As suggested in previous studies, the low prevalence of vasospasm found in patients with NA-SAH could be explained by the theoretical origin of NA-SAH in the venous system [20, 21] and the low concentration of oxyhemoglobin (key substance generating vasospasm), rather than blood quantity. This hypothesis is also supported by the similarly low prevalence of vasospasm found in both subtypes of patients with NA-SAH. Regardless, larger amounts of blood in patients with D-SAH showed no difference in vasospasm rates when compared with PM-SAH patients ($p = 0.15$, Table 1).

Finally, we analyzed differences within the remaining clinical and radiological variables between PM-SAH and D-SAH

Table 3 Relation between the modified Fisher Scale (mFS) grade and the number of patients with neurological complications (vasospasm, hydrocephalus, or both)

	Vasospasm	Hydrocephalus	Vasospasm and hydrocephalus	Total (*n*, %)
mFS 1 (*n*, %)	1 (2.4)	0 (0)	0 (0)	1 (2.4)
mFS 2 (*n*, %)	0 (0)	2 (9.5)	0 (0)	2 (9.5)
mFS 3 (*n*, %)	0 (0)	2 (14.3)	0 (0)	2 (14.3)
mFS 4 (*n*, %)	1 (2.6)	14 (35.9)	3 (7.7)	18 (46.2)

populations (Table 1, 2nd and 3rd rows). Our results support the idea that, despite being a non-aneurysmal disease, D-SAH has a more aggressive entity than PM-SAH. Patients with D-SAH show a worsened Hunt and Hess score on admission ($p < 0.001$) and worse mRS scores at discharge ($p = 0.02$), besides the abovementioned higher rate of hydrocephalus ($p < 0.001$) and a mFS score of 4.

Limitations of this research include selection bias due to the study taking place at a large, level 3 hospital and the retrospective nature of the study. Additional prospective studies are needed to confirm the conclusions of our findings.

Conclusion

In patients with NA-SAH, a mFS score of 4 and/or a D-SAH bleeding pattern in non-contrast cranial CT on admission predicted the development of relevant neurological complications. In this setting, hydrocephalus requiring ventricular drainage was much more frequent than symptomatic vasospasm. Patients with D-SAH had a more aggressive clinical course than those with PM-SAH.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval The Clinical Investigation Ethics Committee (CEIC) of Hospital Clínico Universitario Virgen de la Arrixaca approved the research protocol. All the procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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