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ORIGINAL COMMUNICATION

Elevated C-reactive protein and white blood cell count at admission predict functional outcome after non-aneurysmal subarachnoid hemorrhage

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Abstract

Introduction Patients with non-aneurysmal subarachnoid hemorrhage (SAH) are considered to have an overall benign course of disease compared to patients suffering from aneurysmal SAH. Nevertheless, a small but significant number of such patients might only achieve unfavorable outcome. Therefore, the purpose of the present study was to determine if routine laboratory markers of acute phase response are associated with unfavorable outcome in patients with non-aneurysmal SAH.

Methods From 2006 to 2017, 154 patients suffering from non-aneurysmal SAH were admitted to our institution. Patients were stratified according to the distribution of cisternal blood into patients with perimesencephalic SAH (pSAH) versus non-perimesencephalic SAH (npSAH). C-reactive protein (CRP) and white blood cells (WBC) assessments were performed within 24 h of admission as part of routine laboratory workup. Outcome was assessed according to the modified Rankin Scale (mRS) after 6 months and stratified into favorable (mRS 0–2) vs. unfavorable (mRS 3–6).

Results The multivariate regression analysis revealed "CRP > 5 mg/l" ($p = 0.004$, OR 143.7), "WBC count > 12.1 G/l" ($p = 0.006$, OR 47.8), "presence of IVH" ($p = 0.02$, OR 13.5), "poor-grade SAH" ($p = 0.01$, OR 45.2) and "presence of CVS" ($p = 0.003$, OR 149.9) as independently associated with unfavorable outcome in patients with non-aneurysmal SAH.

Conclusion Elevated C-reactive protein and WBC count at admission were associated with unfavorable outcome after non-aneurysmal SAH.

Keywords Non-aneurysmal subarachnoid hemorrhage · Outcome · Perimesencephalic · C-reactive protein

Introduction

A ruptured intracranial aneurysm is usually the source of bleeding in patients suffering from spontaneous subarachnoid hemorrhage (SAH). Nevertheless, in approximately 15% of patients suffering from SAH, identification of the bleeding source is not possible [1–3]. This subgroup has been described as patients suffering from non-aneurysmal, non-traumatic, spontaneous subarachnoid hemorrhage previously [4]. Patients with non-aneurysmal SAH are considered to have an overall benign course of disease compared to patients suffering from aneurysmal SAH [2, 5, 6]. Nevertheless, some of these patients can develop delayed cerebral ischemia (DCI) during treatment course [3, 7]. Although the functional outcomes of most patients with non-aneurysmal SAH are favorable, a small but significant number of such patients might only achieve unfavorable outcome [1, 8, 9]. Thus, it is important to identify patients at risk of unfavorable functional outcomes during the early stage in the treatment course. Following, there is growing evidence of the prognostic value of c-reactive protein (CRP) and white blood cell (WBC) in patients with aneurysmal SAH [10, 11]. However, the independent value of CRP and WBC for risk prediction of unfavorable outcome after non-aneurysmal SAH has not been established. Therefore, the purpose of the present study was to determine if markers of acute phase response (CRP, WBC) are associated with unfavorable outcome in patients with non-aneurysmal SAH. Furthermore, we analyzed our institutional data in order to elucidate possible risk factors associated with unfavorable

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outcome in patients suffering from non-aneurysmal subarachnoid hemorrhage.

Materials and methods

Patients

Between January 2006 and July 2017, 978 patients suffering from spontaneous SAH were admitted to our institution. SAH was diagnosed by computed tomography (CT) or lumbar puncture. All patients with spontaneous SAH underwent four-vessel digital subtraction angiography (DSA). All patients with confirmed bleeding source (intracranial aneurysm, vascular malformation) or traumatic origin of SAH were excluded from further analysis. In patients with angiogram-negative SAH, a spinal magnetic resonance imaging (MRI) scan was performed in order to rule out any spinal bleeding source of SAH. Furthermore, patients underwent a second four-vessel DSA 6 weeks after ictus if a potential bleeding source was not identified during the first diagnostic work-up. Patients with spontaneous, non-traumatic SAH without identification of a bleeding source after diagnostic screening were then included for further analysis in the present study.

Information, including patient characteristics on admission and during treatment course, radiological features, and functional neurological outcome were collected and entered into a computerized database. The World Federation of Neurological Surgeons (WFNS) scale was used in order to grade patients on admission [12, 13]. Patients suffering from spontaneous SAH were divided into good grade (WFNS grades I-III) versus (vs.) poor grade (WFNS grades IV-V) on admission. Patients with SAH were stratified into two groups according to the subarachnoid blood distribution into (1) patients suffering from perimesencephalic SAH (pSAH) and (2) patients suffering from non-perimesencephalic SAH (npSAH) [3, 4]. In addition, further radiological features were identified and collected, including presence of intraventricular hemorrhage (IVH), and new delayed cerebral ischemia (DCI) during treatment course. Furthermore, C-reactive protein (CRP) and white blood cells (WBC) assessments were performed within 24 h of admission as part of routine laboratory workup. WBC counts (normal range: 3.9–10.2 G/l) were dichotomized > 12.1 G/l to indicate moderate inflammation. CRP (normal range: 0–3 mg/l) was dichotomized > 5 mg/l to suggest moderate inflammation.

Patients with acute hydrocephalus (AH) were treated by ventriculostomy for external CSF diversion [14]. All patients with spontaneous SAH received nimodipine from the day of clinical admission. Screening for cerebral vasospasm (CVS) was performed daily using neurological examination and transcranial Doppler ultrasound (TCD) measurements. If CVS was suspected on the basis of TCD or delayed ischemic neurological deficit (DIND), CT-angiography/-perfusion (CT-A, CT-P) were performed in order to confirm CVS. Presence of clinical-relevant CVS was defined as CVS-associated DIND and/or CVS-related perfusion deficit in CT-P. In cases of onset of clinical-relevant CVS, hypertension was induced with catecholamines during treatment course [15]. DCI was defined as occurrence of new ischemic lesions on any radiological imaging during treatment course compared to the initial CT scan on admission.

Outcome was assessed according to the modified Rankin Scale (mRS) after 6 months and stratified into favorable (mRS 0–2) vs. unfavorable (mRS 3–6).

Statistics

Data analyses were performed using the computer software package SPSS (version 25, IBM Corp., Armonk, NY). Unpaired *t* test was used for parametric statistics. Categorical variables were analyzed in contingency tables using Fisher's exact test. Results with $p < 0.05$ were considered statistically significant.

Furthermore, in order to find potential confounding factors between potentially independent predictors a multivariate analysis was performed to find independent predictors of unfavorable outcome in patients suffering from non-aneurysmal SAH using binary logistic regression. Variables with significant *p* values in the univariate analysis were considered as potentially independent variables in a multivariate analysis. A backward stepwise method was used to construct a multivariate logistic regression model in relation to unfavorable outcome as a dependent variable with an inclusion criterion of a *p* value < 0.05.

Results

Patient characteristics

Between January 2006 and July 2017, 978 patients suffering from spontaneous SAH were admitted to our institution, and in 154 patients of which, no bleeding source was found initially and throughout the follow-up (16%). Patient characteristics, including age, clinical admission status, radiological features, development of CVS and/or DCI, WBC count, CRP, presence of acute hydrocephalus, information concerning the use of anticoagulation agents prior SAH, and clinical outcome of the present series are shown in detail in Table 1.

Table 1 Functional outcome in patients with non-aneurysmal SAH

	Favorable outcome (mRS 0–2)	Unfavorable outcome (mRS 3–6)	*P* value
No. of patients	138 (90%)	16 (10%)	
Mean age (yrs)	56 ± 12	71 ± 13	$p < 0.0001$, 95% CI 8.5–20.9
WFNS grade I-III	134 (97%)	10 (63%)	$p < 0.0001$, OR 20.1, 95% CI 4.9–83.1
Acute hydrocephalus	25 (18%)	11 (69%)	$p < 0.0001$, OR 9.9, 95% CI 3.2–31.2
Anticoagulation medication prior SAH	29 (21%)	8 (50%)	$p = 0.03$, OR 3.8, 95% CI 1.3–10.9
Fisher 3 grade	73 (53%)	15 (94%)	$p = 0.01$, OR 10.1, 95% CI 1.3–78.7
Perimesencephalic blood distribution	69 (50%)	0 (0%)	$p < 0.0001$, OR 33, 95% CI 1.9–561.3
Presence of IVH	31 (22%)	10 (63%)	$p = 0.002$, OR 5.8, 95% CI 1.9–17.1
CRP ≤ 5 mg/l	105 (76%)	2 (13%)	$p < 0.0001$, OR 22.3, 95% CI 4.8–103.4
WBC count ≤ 12.1 G/l	109 (79%)	4 (25%)	$p < 0.0001$, OR 11.3, 95% CI 3.4–37.6
CVS	6 (4%)	6 (38%)	$p = 0.0003$, OR 13.2, 95% CI 3.6–48.5
DCI	1 (1%)	6 (38%)	$p < 0.0001$, OR 82.2, 95% CI 9.0–751.4

Values represent number of patients unless otherwise indicated

SAH subarachnoid hemorrhage, *mRS* modified Rankin scale, *No* number, *yrs* years, *OR* odds ratio, *CI* confidence interval, *WFNS* World Federation of Neurological Surgeons, *IVH* intraventricular hemorrhage, *CRP* c-reactive protein, *WBC* white blood cell, *CVS* cerebral vasospasm, *DCI* delayed cerebral ischemia

Factors influencing functional outcome after non-aneurysmal SAH

Influence of clinical and radiological features

Overall, 138 patients (90%) suffering from non-aneurysmal SAH achieved favorable outcome. Patients with unfavorable outcome were significantly more often older than 65 years compared to patients who achieved favorable outcome (63% vs. 18%; $p = 0.0003$, OR 7.5, 95% CI 2.5–22.7). Additionally, patients with unfavorable outcome after non-aneurysmal SAH presented significantly more often with anticoagulation medication intake prior ictus compared to patients who achieved favorable outcome (50% vs. 21%; $p = 0.03$, OR 3.8, 95% CI 1.3–10.9).

Patients with non-aneurysmal SAH and IVH achieved significantly less often favorable outcome compared to patients with non-aneurysmal SAH without additional IVH (22% vs. 63%; $p = 0.002$, OR 5.8, 95% CI 1.9–17.1). Patients with unfavorable outcome presented significantly more often with Fisher 3 grade blood distribution compared to patients with favorable outcome (94% vs. 53%; $p = 0.01$, OR 10.1, 95% CI 1.3–78.7). Patients with favorable outcome presented significantly more often with perimesencephalic blood distribution compared to patients with unfavorable neurological outcome (50% vs. 0%; $p < 0.0001$, OR 33.0, 95% CI 1.9–561.3).

Influence of laboratory values

Furthermore, patients who achieved favorable outcome presented significantly more often with CRP ≤ 5 mg/l compared to patients with unfavorable outcome after non-aneurysmal SAH (76% vs. 13%; $p < 0.0001$, OR 22.3, 95% CI 4.8–103.4; Fig. 1A). Patients who achieved favorable outcome presented significantly more often with WBC counts ≤ 12.1 G/l compared to patients with unfavorable outcome

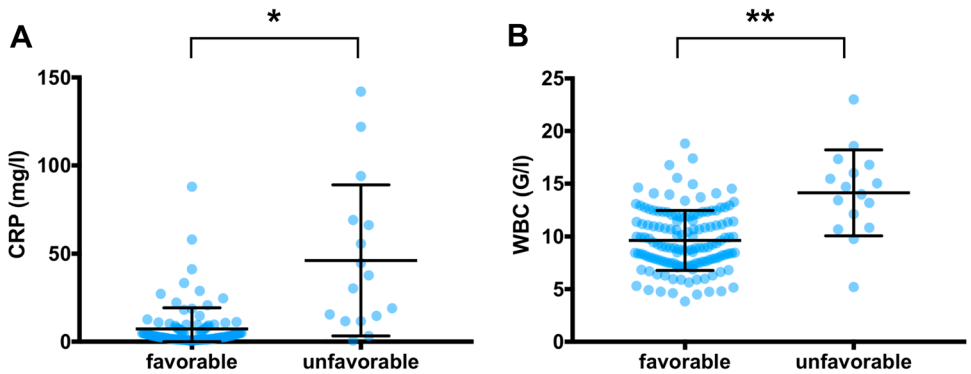

Fig. 1 Scatter blots for C-reaction protein levels (**a**) and WBC counts (**b**) at admission related to functional outcome after non-aneurysmal SAH. *$p < 0.0001$, OR 22.3, **$p < 0.0001$, OR 11.3

after non-aneurysmal SAH (79% vs. 25%; $p < 0.0001$, OR 11.3, 95% CI 3.4–37.6; Fig. 1B).

Detailed results of univariate analysis concerning factors influencing functional outcome in patients suffering from non-aneurysmal SAH are given in Table 1.

Multivariate analysis

We performed a multivariate logistic regression analysis of those variables significantly associated with unfavorable outcome in patients suffering from non-aneurysmal SAH.

Multivariate analysis revealed the variables "CRP > 5 mg/l" ($p = 0.004$, OR 143.7, 95% CI 4.9–4144.2), "WBC count > 12.1 G/l" ($p = 0.006$, OR 47.8, 95% CI 3.1–747.8), "presence of IVH" ($p = 0.02$, OR 13.5, 95% CI 1.5–125.8), "poor-grade SAH" ($p = 0.01$, OR 45.2, 95% CI 2.5–818.9), and "presence of CVS" ($p = 0.003$, OR 149.9, 95% CI 5.5–4035.5) as significant and independent predictors for unfavorable outcome in patients with non-aneurysmal SAH (Nagelkerke's R^2 78%).

Discussion

In the present analysis of patients with non-aneurysmal SAH, it was found that initial elevated CRP values, increased WBC count, presence of intraventricular hemorrhage, poor clinical admission status, as well as presence of CVS are independent and significant predictors for unfavorable outcome in patients with non-aneurysmal SAH. Furthermore, the occurrence of CVS was the only independent and significant predictor for development of DCI during treatment course in patients with non-aneurysmal SAH. The present results are generally in line with the previous studies [3, 16–18]. However, potential influence of individual and routine laboratory tests (CRP, WBC) on functional outcome were not investigated in these reports.

Influence of CRP and WBC on outcome in patients with non-aneurysmal SAH

Despite well-known risk factors for unfavorable outcome after non-aneurysmal SAH, the present study revealed a strong and independent association between CRP, WBC count and functional outcome in these patients.

Several studies have reported that increased levels of acute inflammatory markers, such as CRP and WBC count are associated with increased risk of unfavorable outcome in patients with aneurysmal SAH [10, 11, 19–22]. However, data on inflammatory response in patients suffering from non-aneurysmal SAH is scarce. Muroi et al. reported lower interleukin-6-levels in patients with non-aneurysmal SAH compared to patients with aneurysmal SAH [23]. The present study demonstrate that elevated CRP values and WBC counts are independent of confounding factors predict an unfavorable outcome following non-aneurysmal SAH. The pathophysiological reason for an association between, CRP, WBC and outcome in patients with non-aneurysmal SAH is uncertain. Frontera et al. stated that inflammation markers are associated with early brain injury in patients with aneurysmal SAH [24]. However, CRP and WBC are relatively non-specific inflammatory markers [24]. Previously, Turner et al. reported an elevated baseline CRP as predictor for unfavorable outcome in patients with aneurysmal SAH and therefore as a potential selection tool for good grade patients with SAH who are at higher risk for unfavorable outcome [25]. Therefore, future studies should evaluate further inflammation markers in order to better comprehend potential correlation between inflammation and its impact on functional outcome in patients with non-aneurysmal SAH.

Nevertheless, CRP and WBC are routinely collected in patients presenting with SAH and are therefore, a potential simple way to determine the risk of unfavorable outcome for patients who are assumed to have a more benign illness compared to patients with aneurysmal SAH.

Limitations

The present study has several limitations. Statistical analysis and data collection were retrospective and the present data represent only a single-center experience. Furthermore, there is only a small number of patients with unfavorable outcome in the present patient collective, which might also influence statistical results. Although our data show a strong association between CRP, WBC count and outcome, a causal relationship remains to be established. Nevertheless, the results of the present study should be considered for further validation in future studies.

Conclusions

Elevated C-reactive protein and WBC count at admission were associated with unfavorable outcome after non-aneurysmal SAH. The results of the present study provide valuable information on functional outcome in patients suffering from non-aneurysmal SAH and should be taken in consideration during management of these patients.

Compliance with ethical standards

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

Ethical approval The present study was approved by the local ethics committee.

Informed consent Informed consent was not sought as a retrospective study design was used.

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