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Cerebral inflammatory response and predictors of admission clinical grade after aneurysmal subarachnoid hemorrhage

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Abstract

Poor admission clinical grade is the most important determinant of outcome after aneurysmal subarachnoid hemorrhage (aSAH); however, little attention has been focused on independent predictors of poor admission clinical grade. We hypothesized that the cerebral inflammatory response initiated at the time of aneurysm rupture contributes to ultra-early brain injury and poor admission clinical grade. We sought to identify factors known to contribute to cerebral inflammation as well as markers of cerebral dysfunction that were associated with poor admission clinical grade. Between 1997 and 2008, 850 consecutive SAH patients were enrolled in our prospective database. Demographic data, physiological parameters, and location and volume of blood were recorded. After univariate analysis, significant variables were entered into a logistic regression model to identify significant associations with poor admission clinical grade (Hunt–Hess grade 4–5). Independent predictors of poor admission grade included a SAH sum score >15/30 (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.5–3.6), an intraventricular hemorrhage sum score >1/12 (OR 3.1, 95% CI 2.1–4.8), aneurysm size >10 mm (OR 1.7, 95% CI 1.1–2.6), body temperature $\geq 38.3^{\circ}\text{C}$ (OR 2.5, 95% CI 1.1–5.4), and hyperglycemia >200 mg/dL (OR 2.7, 95% CI 1.6–4.5). In a large, consecutive series of prospectively enrolled patients with SAH, the inflammatory response at the time of aneurysm rupture, as reflected by the volume and location of the hemoglobin burden, hyperthermia, and perturbed glucose metabolism, independently predicts poor admission Hunt–Hess grade. Strategies for mitigating the inflammatory response to aneurysmal rupture in the hyper-acute setting may improve the admission clinical grade, which may in turn improve outcomes.

Keywords

Clinical grade; Early brain injury; Fever; Hyperglycemia; Inflammation; Neuro-intensive care unit; Subarachnoid hemorrhage; Subarachnoid hemorrhage sum score

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1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) affects nearly 30 000 individuals each year in the United States. [1,2] Although early surgical and neuroendovascular interventions as well as aggressive postoperative management strategies have improved outcomes, mortality in the acute phase following aneurysm rupture is significant: 12% of aSAH patients die within the first 24 hours and 25% within the first 48 hours. [3] Early brain injury (EBI) is a recently coined term that describes the immediate injury to the brain after aneurysm rupture and the response to hemorrhage within the subarachnoid space.[4–9] A number of critical, interrelated pathways have been implicated in EBI, including apoptotic mechanisms and ischemic pathways, which lead to neuronal cell death, cerebral edema, and a global cerebral inflammatory process.[6,7, 10] This early inflammatory response may underlie the host of metabolic, hormonal, neuronal, and vascular derangements that occur following SAH, including cerebral vasospasm, myocardial stunning, acute lung injury, cerebral salt wasting, perturbed glucose metabolism and alterations in thermal regulation.[6,7,10] Treatment strategies that target these complications in isolation, such as those used in recent trials for the treatment and prevention of vasospasm, have failed to yield improvements in morbidity and mortality,[11–13] perhaps because they fail to address inflammation as the putative underlying etiology.

Poor admission clinical grade (Hunt–Hess) is one of the most important determinants of outcome after aSAH.[14] We hypothesized that poor admission clinical grade may reflect the extent of ultra-early brain injury and the cerebral inflammatory response initiated at the time of aneurysm rupture. Therefore, we sought to identify factors known to contribute to cerebral inflammation, and markers of early cerebral dysfunction, in one of the largest clinical series of patients with aSAH presented to date, in an effort to test the hypothesis that early brain injury and inflammation are associated with poor admission clinical grade in this patient population.

2. Materials and Methods

2.1. Patient population

As part of the Columbia University Subarachnoid Hemorrhage Outcomes Project, 850 consecutive patients with SAH admitted to the Neurological Intensive Care Unit of Columbia University Medical Center between 15 September 1997 and 14 July 2008 were prospectively enrolled [15,16]. The study was approved by the Columbia University Institutional Review Board. The diagnosis of SAH was established on the basis of computed tomography (CT) scans obtained at admission or xanthochromia of the cerebrospinal fluid. Patients with SAH caused by trauma, arteriovenous malformation rupture, vasculitis, and other structural lesions were excluded.

2.2. Clinical management

A standardized protocol was used in the treatment of all aSAH patients, which has been described elsewhere [17]. Briefly, while the patient was in the Neurological Intensive Care Unit, transcranial Doppler sonography was performed daily or every other day, and all patients received oral nimodipine. A ventricular catheter was placed in all patients with ventriculomegaly or intraventricular hemorrhage and a decreased level of consciousness that could not be attributed to causes other than hydrocephalus. CT scanning was performed to evaluate all instances of clinical deterioration. CT angiography and perfusion were used as adjuncts when there was clinical suspicion of vasospasm. All patients were administered 0.9% saline and supplemental 5% albumin to maintain central venous pressure at >8 mmHg, and those who displayed clinical deterioration arising from delayed cerebral ischemia were treated with hypertensive hypervolemic (triple-H) therapy to maintain systolic blood pressure at >200

mmHg. When significant clinical symptoms persisted despite triple-H therapy, balloon angioplasty or intra-arterial vasodilator treatment was attempted [15,16,18,19].

2.3. Clinical variables

Baseline demographic (age and sex) and physiological parameters (blood pressure, heart rate, glucose, etc.) were recorded on admission to the Neurological Intensive Care Unit. Each patient's worst Hunt–Hess score in the first 24 hours was used for analysis. Admission and follow-up CT scans were independently evaluated by a study neurointensivist (who was blinded to the admission grade) to assess the amount and location of subarachnoid blood (SAH sum score, scaled such that 0 = no blood, 30 = all cisterns and fissures completely filled), [20] the amount and location of intraventricular blood (intraventricular hemorrhage [IVH] sum score, scaled such that 0 = no blood, 12 = all ventricles completely filled), [21] the presence and degree of hydrocephalus, [22] the presence of cerebral edema, [23] cerebral infarction, and aneurysm size.

2.4. Statistical analysis

Data were analyzed using commercially available statistical software (SPSS 12.0; SPSS Inc., Chicago, IL, USA). Univariate analysis using the χ^2 test was conducted to identify significant associations between poor clinical grade (Hunt–Hess 4–5) and demographic, physiological, and radiological variables. Significant variables ($p < 0.05$) were then included in a multivariable forward stepwise logistic regression to identify independent predictors of poor clinical grade. For significant variables from the logistic regression, p value, 95% confidence interval (CI), and odds ratio (OR) are reported.

3. Results

Between 15 September 1997 and 14 July 2008, 850 patients were admitted to the Neurological Intensive Care Unit of Columbia University Medical Center with a diagnosis of aSAH. The median age of these patients was 54 years, with a 25th percentile of 44 years and a 75th percentile of 64 years. Fifty-one percent were Caucasian, and 67% were female. Twenty-five percent of these patients ($n = 213$) were admitted with Hunt–Hess grade 4–5 (Table 1).

Patients with a poor admission clinical grade (poor-grade patients) were significantly older than those with a good admission clinical grade (good-grade patients; $p < 0.001$), but there was no significant difference between the 2 groups in terms of sex, ethnicity, or proportion of patients with a body-mass index >30 . Patients with a history of hypertension ($p < 0.001$) or diabetes mellitus type I or II ($p < 0.025$) were significantly more likely to be poor-grade patients. There was no association with a history of stroke, myocardial infarction, or peripheral artery disease (Table 1).

Hyperglycemia (serum glucose >200 mg/dL) and fever (body temperature $\geq 38.3^\circ\text{C}$) at admission were both significant predictors of poor-grade status ($p < 0.001$), while anemia, systolic blood pressure and white blood cell count at admission were not significantly associated with clinical grade at admission. Radiographic predictors of poor clinical grade at admission were the presence of IVH ($p < 0.001$), a SAH sum score >15 ($p < 0.001$), and aneurysm size >10 mm ($p < 0.001$). Global cerebral edema was not a significant univariate predictor of admission clinical grade (Table 1).

A multivariable logistic regression model revealed that, after adjusting for significant effects of age, a history of hypertension, and a history of diabetes mellitus, poor-grade patients were almost twice as likely to have an aneurysm >10 mm and 3 times more likely to have IVH on admission (OR 3.1, 95% CI 2.1–4.8). Additionally, poor-grade patients were approximately

2.5 times more likely to have a fever (OR 2.5, 95% CI 1.1–5.4), hyperglycemia (OR 2.7, 95% CI 1.6–4.5), and an initial SAH sum score >15 (OR 2.3, 95% CI 1.5–3.6) on admission (Table 2).

4. Discussion

Despite recent advances in the treatment of patients after SAH, morbidity and mortality rates have failed to improve significantly.[7] Vasospasm is one of the most significant causes of morbidity and mortality after SAH, yet recent trials aimed at improving cerebral blood flow or mitigating vasospasm following aSAH have had limited success in improving overall outcome.[11–13] These failures may be explained in part by a perspective that incorporates cerebral vasospasm as but one sequela of a larger inflammatory process that occurs throughout the brain, initiated at the time of aneurysm rupture. In EBI processes after SAH, interactions between neurons, vasculature, and microglia following aneurysm rupture initiate an immediate cerebral response similar to the inflammatory cascade that characterizes the early stages of sepsis or the systemic inflammatory response syndrome (Fig. 1)[6,7,10]. This response may be responsible for the host of metabolic, hormonal, neuronal, and vascular derangements that occur following SAH[7]. However, this process has not been fully characterized, and clinical studies describing the pathophysiology of aSAH within this context are lacking.

In a series of 850 consecutive patients with aneurysmal SAH, we identified acute variables at the time of admission that were associated with poor admission grade (Hunt–Hess 4–5). We hypothesized that these early measures would reflect the cerebral inflammatory response initiated at the time of aneurysm rupture. After controlling for the effects of age and medical history, the blood burden within the brain at the time of admission (reflected by the SAH and IVH sum scores), large aneurysm size, fever on admission, and hyperglycemia on admission all independently predicted poor admission clinical grade.

A role for inflammation in each of the significant associations we identified is supported by the literature. The presence and subsequent lysis of red blood cells in the subarachnoid space and cerebral cisterns produces a known inflammatory response mediated by pro-inflammatory cytokines [24,25]. Free hemoglobin decreases expression of the nitric oxide receptor, causing localized vasoconstriction and hypoxia.[24,25] In addition, the presence of free hemoglobin leads to increased expression of endothelin-1; as well as activation of microglia, tumor necrosis factor- α , and interleukins; and initiation of apoptotic factors.[4–6,10,25] Pyretic cytokines increase arachidonic acid production, impair neuronal metabolism, and induce fever.[24] Inflammation is also a well-known mediator of insulin resistance, in both the acute and chronic settings. [21] By controlling for a previous history of diabetes mellitus in our regression, we feel confident that the derangement of glucose metabolism seen following aSAH reflects the extent of early brain injury and the cerebral inflammatory response initiated at the time of aneurysm rupture.

The fact that aneurysm size is independently associated with both poor admission clinical grade and poor outcome suggests that size may be proportional to the severity of the initial inflammatory response. A correlate to support this idea is seen in studies of the inflammatory and oxidative cascades produced by coronary plaques causing myocardial infarction, with extent of oxidative stress shown to correlate with severity of atherosclerosis in the coronary arteries. [26,27] Additionally, evidence exists that tumor necrosis factor- α , a known key inflammatory mediator, significantly modulates the risk for aneurysm formation and aSAH [28]

We recognize that our study has several limitations. Retrospective analysis of prospectively collected data has many of the methodological shortcomings of purely retrospective studies

and, as such, it remains difficult to accurately assess causality. We attempted to control for significant medical history and all possible contributors to poor admission clinical grade, but given the retrospective nature of the analyses, we were unable to account for all possible confounders. Also due to the limitations of the dataset, we did not assess more direct serum or cerebrospinal fluid markers of inflammation to correlate with clinical and radiographic findings. However, all the factors we identified are supported by previous work, which suggests that they reflect, and support the concept of, a cerebral inflammatory response initiated at the time of aneurysm rupture.

Our results lend support to the mechanisms of early brain injury put forth by Cahill et al., particularly that inflammatory and apoptotic cascades occur very early after aneurysm rupture and may be related directly to physiologic sequelae commonly associated with SAH[6,7]. While much attention and investigation has been devoted to the treatment and prevention of cerebral vasospasm and other late complications of SAH, a shift in focus to elucidating the early molecular and cellular events that occur immediately after SAH may yield a more far-reaching strategy for the development of future therapies.

In conclusion, in a large series of prospectively enrolled, consecutive patients with aSAH, we demonstrated that the volume and location of the hemoglobin burden, large aneurysms, hyperthermia, and perturbed glucose metabolism all independently predict poor admission Hunt–Hess grade (4–5). The extent to which these variables reflect an underlying cerebral inflammatory response cannot be determined from retrospective analysis. Nevertheless, this study highlights the importance of investigation into the early mechanisms of brain injury following aSAH.

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Fig. 1.

Signal transduction pathways implicated in the cerebral inflammatory response after aneurysmal subarachnoid hemorrhage (aSAH), showing clinical parameters. Significant predictors of poor admission grade (Hunt–Hess) aSAH are underlined. HIF-1 α = hypoxia inducible factor-1 α ; IL-1 = interleukin-1; IL-6 = interleukin-6; IVH = intraventricular hemorrhage; iNOS = inducible nitric oxide synthase; TNF- α = tumor necrosis factor- α .

Table 1Patient characteristics (*n* = 850)

	Hunt–Hess grade		
	0–3	4–5	<i>p</i>
<i>Demographic variables</i>			
<i>Total no.</i>	637 (75)	213 (25)	
Age >54 years (median)	285 (47)	145 (59)	0.001
Female	400 (66)	170 (70)	NS
Caucasian	293 (48)	122 (51)	NS
Body mass index >30	140 (22)	48 (23)	NS
<i>Medical history</i>			
Hypertension	273(44)	133 (59)	0.001
Myocardial infarction	17 (3)	9 (4)	NS
Peripheral artery disease	14 (2.5)	8 (3.5)	NS
Diabetes mellitus	43 (6)	26 (11)	0.025
Cerebrovascular accident	20 (3)	13 (6)	NS
<i>Physiological variables on admission</i>			
Fever (>38.3°C)	20 (3)	22 (10)	0.001
Hyperglycemia (>200 mg/dL)	57 (10)	88 (36)	0.001
Anemia (hematocrit <30%)	19 (3)	13 (5)	NS
Systolic blood pressure >140 mmHg	411 (68)	179 (74)	NS
White blood cell count ^A	249 (41)	97 (40)	NS
<i>Radiographic variables on admission</i>			
IVH sum score >1	251 (41)	192 (80)	0.001
SAH sum score >15	255 (42)	179 (74)	0.001
Global cerebral edema	170 (28)	69 (29)	NS
Aneurysm size >10 mm	166 (26)	82 (39)	0.001

^AWhite blood cell count <4000 or >12 000/mm³.Data are given as *n* (%). IVH = intraventricular hemorrhage; NS = not significant; SAH = subarachnoid hemorrhage.

Table 2

Predictors of poor-grade aneurysmal subarachnoid hemorrhage on admission

Factor	OR	95% CI	<i>p</i>
Fever (>38.3°C)	2.5	1.1–5.4	0.028
Hyperglycemia (>200 mg/dL)	2.7	1.6–4.5	0.001
SAH sum score >15	2.3	1.5–3.6	0.001
IVH sum score >1	3.1	2.1–4.8	0.001
Aneurysm size >10 mm	1.7	1.1–2.6	0.011

CI = confidence interval, IVH = intraventricular hemorrhage, OR = odds ratio, SAH = subarachnoid hemorrhage. Adjusted for age and medical history of hypertension and diabetes mellitus.