Early Predictors of Fever in Patients with Aneurysmal Subarachnoid Hemorrhage

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Background: Fever is commonly observed in patients who have had aneurysmal subarachnoid hemorrhage (SAH), and it has been associated with the occurrence of delayed cerebral ischemia and worse outcomes in previous studies. Frequently, fever is not the result of bacterial infections, and distinction between infection-related fever and fever secondary to brain injury (also referred as central fever) can be challenging. *Objectives:* The current study aimed to identify risk factors on admission for the development of central fever in patients with SAH. *Methods:* Databank analysis was performed using information from demographic data (age, gender), imaging (transcranial Doppler ultrasound, computed tomography, and cerebral angiogram), laboratory (white blood cell count, hemoglobin, renal function, and electrolytes), and clinical assessment (Hunt–Hess and modified Fisher scales on admission, occurrence of fever). A multivariate logistic regression model was created. *Results:* Of 55 patients, 32 developed fever during the first 7 days of hospital stay (58%). None of the patients had identifiable bacterial infections during their first week in the neurocritical care unit. Hunt–Hess scale >2 and leukocytosis on admission were associated to the development of central fever, even after correction in a logistic regression model. *Conclusion:* Leukocytosis and a poor neurologic examination on admission might help predict which subset of patients with SAH are at higher risk of developing central fever early in their hospital stay. **Key Words:** Subarachnoid hemorrhage—fever—predictors—aneurysm.

Introduction

Fever is commonly observed in patients who have had aneurysmal subarachnoid hemorrhage (SAH),[1-3] and it has been associated with the occurrence of delayed cerebral ischemia and worse outcomes in previous studies.[2,3] Some authors suggest that fever is part of a state of systemic inflammation triggered by SAH, where vasospasm is its most striking manifestation.[4-7] Frequently, this hyperthermic state is not associated to the presence of bacterial infections,[3,8] and distinction between infection-related fever and fever secondary to brain injury (also referred to as central fever) can be challenging. The current study aimed to analyze clinical, radiographic, and laboratory information on admission that could help identify patients with aneurysmal SAH at a higher risk of developing central fever during their early hospital stay.

Methods

Study Population

A databank on aneurysmal SAH was created using patients admitted from 2010 to 2012, in a large quaternary academic center in Cleveland, Ohio (USA). Fifty-five patients admitted through this period with SAH were included in the current study. The entry criteria consisted of any patients with confirmed aneurysmal SAH

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Table 1. *Demographic characteristics of participating patients*

Demographics	Patients with fever during the first 7 days	Patients without fever during the first 7 days	Statistical difference between groups
Age (median)	55 years	56.2 years	$P < .769$
Gender:			
Male	12	10	$P < .549$
Female	19	13	
Modified Fisher scale (most prevalent)	4 (40%)	4 (48%)	$P < .524$
Hunt–Hess scale (most prevalent)	3 (42%)	2 (46%)	$P < .629$
Total	32 (58.18%)	23 (41.81%)	

on cerebral angiogram, who stayed at least 7 days in the hospital (counted from the day of bleeding), and with information available for all the study variables. We decided to analyze the first 7 days after bleeding, as this would be a period long enough to observe fever related to SAH (central fever) but early enough to minimize the occurrence of infections secondary to prolonged stay in a critical care unit (e.g., ventilator-associated pneumonia, catheter-related infections). Characteristics of participant patients are disclosed on Table 1.

Variables of Interest

Information from demographic data (age, gender), imaging (transcranial Doppler ultrasound, computed tomography, and cerebral angiogram), laboratory (white blood cell [WBC] count, hemoglobin, renal function, and electrolytes), and clinical assessment (Hunt–Hess and modified Fisher scales on admission, occurrence of fever) was collected. We decided to define WBC count of ≥10.000 leukocytes per mm^3 as leukocytosis as there is no clear consensus about the cutoff of WBC counts in the literature, and reference values for the majority of laboratory testing kits are close to this number. For statistical purposes, Hunt–Hess scale was dichotomized in 1-2 and >2 (good grade versus disfavorable grade), and modified Fisher scale was dichotomized in 1-2 and 3-4.

Outcome Measures

Fever was defined as any episodes of sublingual temperature equal to or higher than 38.5°C (101.3 Fahrenheit) in the first 7 days after admission. Central fever was defined as any fever episodes without identifiable bacterial infection or other causes of noninfectious fever (e.g., medications, deep venous thrombosis, atelectasis) other than SAH.

Statistical Analysis

First, the selected laboratory, clinical, and radiologic variables were independently tested to check association to the outcome variable (occurrence of central fever) using Pearson's chi-square and Fisher's exact test for categorical variables, *t* test for normally distributed continuous variables, and Mann–Whitney *U* test for nonparametric continuous variables. Afterward, variables with significant association (cutoff of $P < .05$) were entered in a step-forward logistic regression model to identify the ones that would most influence the prediction of the outcome. Finally, the variables with statistical significance were added to a multivariate logistic regression model to assess whether statistical significance would persist after correction for predefined important demographic and clinical variables (Hunt–Hess, modified Fisher scale, age, and sex). All variables were independent, and no collinearity was detected. Finally, Hosmer–Lemeshow test was performed to assess goodness of fit of the final model. Statistical software BioStat (version 5.4, Instituto Mamirauá, Brazil) was used for all analyses.

Results

Of 55 patients, 32 developed fever during the first 7 days of hospital stay (58%). None of the patients had identifiable bacterial infections during their first week in the neurocritical care unit. Five patients (9%) were started on antibiotics during the first 7 days but were later discontinued after negative bacterial culture results. Hunt–Hess scale of >2 (HH > 2) on admission and leukocytosis on the first day after bleeding were the only variables statistically correlated with occurrence of fever during the first 7 days of hospital stay ($P < .0151$, confidence interval [CI] 1.31-12.65, odds ratio [OR] 4.07 for HH > 2 and $P < .0349$, CI 1.09-10.59, OR 3.39 for leukocytosis). Table 2 shows the results for all tested variables. The calculated probability of developing fever during the first 7 days of hospital stay with the presence of leukocytosis on day 1 was 67.65% and with HH > 2 on admission was 100% (probabilities calculated using logistic regression data), but only 29,6% when none of the variables were present. These were the only variables significantly related to the outcome in univariate logistic regression. A multiple logistic regression model was created to assess the influence of the other nonsignificant variables when analyzed in conjunct. HH > 2 and leukocytosis remained statistically significant after adjustment for age, gender, and modified