Factors Associated with Fever in Intracerebral Hemorrhage

Sabreena J. Gillow, MD,* Bichun Ouyang, PhD,† Vivien H. Lee, MD,‡ and Sayona John, MD†

Background: Fever is common in patients with intracerebral hemorrhage (ICH). We sought to identify predictors of fever in patients hospitalized with ICH, and compare infectious fever with noninfectious fever. *Methods:* A retrospective review on consecutive spontaneous ICH patients from April 2009 to March 2010 was performed. Fever was defined as temperature 100.9°F or higher and attributed to infectious versus noninfectious etiology, based upon the National Healthcare Safety Network criteria. Univariate analysis and multivariable logistic regression model were used to determine factors associated with fever and with infection. *Results:* Among the 351 ICH patients, 136 (39%) developed fever. Factors associated with fever included mean ICH volume, intraventricular hemorrhage (IVH), external ventricular drain (EVD) placement or surgical evacuation, positive microbial cultures, longer length of stay (LOS), and higher in-hospital mortality. Among patients with fever, 96 (71%) were noninfectious and 40 (29%) were infectious. Infectious fever was associated with higher LOS. Noninfectious fever was associated with higher in-hospital mortality. In multivariable analysis, ICH volume (OR = 1.01, $P = .04$), IVH (OR = 2.0, $P = .03$), EVD (OR = 3.7, $P < .0001$), and surgical evacuation (OR = 6.78, $P < .0001$) were significant predictors of fever. Infectious fever (OR = 5.26, $P = .004$), EVD (OR = 4.86, $P = .01$), and surgical evacuation (OR = 4.77, $P = .04$) correlated with prolonged LOS when dichotomized using a median of 15 days. *Conclusions:* Fever is common in ICH patients and is not associated with a clear infectious etiology in the majority of patients. Patients with noninfectious fever have higher in-hospital mortality, but survivors have shorter LOS. Further studies are warranted to better understand fevers in ICH. **Key Words:** Fever—central fever—noninfectious fever—intracerebral hemorrhage.

Introduction

Intracerebral hemorrhage (ICH) comprises about 10%-15% of all cases of stroke, with an incidence of 15 per 100,000 cases.[1,2] Fever occurs in 30% of patients after initial ICH and is more common in patients with intraventricular hemorrhage (IVH) and deep location of ICH.[3,4] Fever can be attributed to infections, surgery, and central mechanisms.[5,6] Infection associated with pneumonia or bronchitis is the most common cause of fever in patients admitted to the intensive care unit.[3] Craniotomy, endotracheal (ET) intubation, and catheter placement (including central venous, arterial, or ventricular) are also associated with an increased risk of fever.[3] It is difficult to establish the diagnosis of central fever with certainty, and it is routinely diagnosed by exclusion in practice.

There has been a paucity of studies in previous literature analyzing fever as well as etiologies of fever in a

From the *Division of Vascular Neurology, Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, Ohio; †Section of Neurocritical Care, Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois; and ‡Section of Cerebrovascular Disease and Neurocritical Care, The Ohio State University Wexner Medical Center, Columbus, Ohio.

Received November 16, 2016; accepted January 12, 2017.

Study Site: Section of Neurocritical Care, Department of Neurological Sciences, Rush University Medical Center, 1725 W. Harrison St #1121, Chicago, IL 60612.

Address correspondence to Sabreena J. Gillow, MD, Division of Vascular Neurology, Department of Neurology and Rehabilitation Medicine, University of Cincinnati, 260 Stetson St, Suite 2300, Cincinnati, OH 45267. E-mail: sabreena.gillow@gmail.com.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.01.007

large number of intraparenchymal hemorrhagic cases. Further investigation into fever in ICH would help determine potential areas of intervention to prevent or manage fever in this population, as it has been shown to be associated with hematoma growth and poor long-term functional outcome.[7] We sought to identify predictors of fever in patients hospitalized with ICH. We additionally tried to identify characteristics of patients with infectious versus noninfectious etiology of fever.

Methods

With Institutional Review Board approval, we performed a retrospective review on consecutive spontaneous nontraumatic ICH patients admitted to our institution from April 2009 to March 2010. Patients were included if they had the presence of primary spontaneous intraparenchymal hemorrhage on brain computed tomography (CT) and were aged 18 years or older. We excluded patients with pure IVH and ICH due to other secondary causes including trauma and hemorrhagic conversion of ischemic infarct.

Data collected included age, sex, medical history of hypertension and diabetes mellitus, ICH location, presence of IVH, ICH volume, external ventricular drain (EVD) placement, surgical evacuation, ET tube placement, central line or hemodialysis catheter placement, maximum temperature (Tmax) recorded during hospitalization, maximum white blood cell (WBC) count during hospitalization, positive microbial cultures, length of stay (LOS), and in-hospital mortality. ICH location was categorized as lobar, deep, and infratentorial, and ICH volume was measured on CT brain scans by standard ABC/2 formula.[8] Fever was defined as temperature higher than or equal to 100.9°F during hospitalization based upon standard critical care diagnostic criteria.[9] Data on microbial cultures were collected, including sputum, urine, cerebrospinal fluid, blood, pleural, stool, and joint sources, which were obtained based on routine clinical care. The diagnosis of infection was based on the results of the microbial cultures and the National Healthcare Safety Network and Centers for Disease Control criteria.[10]

Univariate analysis was performed to compare ICH patients who had fever to patients without fever. Univariate analysis was also performed to compare patients with fever from infectious etiology to patients with fever not due to clinical infection. Chi-square test or Fisher's exact test was used for categorical variables and t test for continuous variables. Multivariate logistic regression was used to determine the predictors of fever. Multivariate logistic regression was also performed to examine the association between LOS among survivors and other variables, including infectious status. LOS was dichotomized using the median of 15 days. A P value < .05 was considered statistically significant. All statistical analyses were performed using statistical software SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

Our search of patients with primary, nontraumatic ICH admitted to our institution over our time period yielded 363 patients. We excluded 9 patients with pure IVH without parenchymal component, 2 patients who were readmitted with previously diagnosed ICH, and 1 patient who had missing temperature data.

Among the 351 ICH patients in our analysis, mean age was 61.9 years (SD = 14) and 186 (53%) were male. Hypertension was present in 287 (82%) patients and diabetes mellitus was present in 92 (26%). ICH location was 122 (35%) lobar, 171 (49%) deep, and 58 (17%) infratentorial. Mean ICH volume was 28.8 mL (SD = 37.7). One hundred sixty (46%) patients had associated IVH. Ninety-three (26%) patients had an EVD and 49 (14%) had a craniotomy for evacuation of hemorrhage. Median LOS was 15 days and in-hospital mortality occurred in 71 (20%) patients. Fever was present in 136 (39%) of patients.

Patients with fever did not differ from patients without fever based on age, sex, history of hypertension or diabetes, or location of ICH. In the univariate analysis, factors associated with fever were as follows: presence of IVH (68% versus 32%, P < .0001); mean ICH volume (41 mL versus 21 mL, P < .0001); EVD placement (50% versus 12%, P < .0001); surgical evacuation (29% versus 4%, P < .0001); maximum WBC count (17.7 versus 11.7, P < .0001); positive microbial cultures from blood, urine, sputum, or other fluids (63% versus 21%, P < .0001); ET tube placement (74% versus 27%, P < .0001); and central line or hemodialysis catheter placement (59% versus 18%, P < .0001). There was a longer LOS in patients with fever (mean days 13.1 versus 5.1, P < .0001) and among survivors with fever (mean days 15.9 versus 5.8, P < .0001). There was also a higher in-hospital mortality in patients with fever (27% versus 16%, P = .01) (Table 1). In multivariable logistic regression model, the variables that remained significant predictors of fever were as follows: ICH volume (OR = 1.01, 95% CI = [1.0, 1.02], P = .04); IVH (OR = 2.0, 95% CI = [1.07, 3.74], P = .03); EVD (OR = 3.7, 95% CI = [1.92,7.13], P < .0001); and surgical evacuation (OR = 6.78, 95% CI = [2.74, 16.64], P < .0001) (Table 2).

Among the 136 ICH patients with fever, 96 (71%) had no clear infectious source of fever and 40 (29%) had fever attributed to infection. Patients with infectious fever did not differ from patients without infection in terms of age, sex, medical history, Tmax, ICH location, ICH volume, IVH, EVD placement, or surgical evacuation. Infectious fever was associated with significantly higher LOS (18.2 versus 11.1 days, P < .001), and this remained significant when analyzed in survivors only (18.6 versus 14.2 days, P = .01). Noninfectious fever was associated with significantly higher in-hospital mortality (35% versus 8%, P = .0006) (Table 3). Multivariate analysis revealed that infectious fever (OR = 5.26, 95% CI = [1.68, 16.45], P = .004), surgical evacuation (OR = 4.77, 95% CI = [1.06, 21.46],