Incidence of Fever in Patients Diagnosed with Cerebrovascular Diseases in a Tertiary Care Hospital in Northern Thailand

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Abstract

Background: Fever, arising from cerebrovascular diseases (CVD) or infection, may affect outcomes in patients with CVD. This study assessed the incidence of fever and factors associated with fever in patients diagnosed with CVD.

Materials and Methods: The incidence of fever was prospectively evaluated in patients aged ≥18 years diagnosed with CVD and admitted to Maharaj Nakorn Chiang Mai Hospital, between July 1, 2013 and June 30, 2014. Factors associated with fever were evaluated.

Results: During the study period, 361 consecutive patients, 182 (50.4%) males, of median age 65 years (interquartile range 54, 76 years), were diagnosed with CVD, 279 (77.3%) with cerebral infarction and 82 (22.7%) with cerebral hemorrhage. One-hundred and thirty-nine (38.5%) patients had fever, 81/279 (29.0%) with cerebral infarction and 58/82 (70.7%) with cerebral hemorrhage (p < 0.001). Multivariate analysis showed that known foci of infection (OR 32.27, 95% CI 13.09, 79.61, p < 0.001), cerebral hemorrhage (OR 5.03, 95% CI 2.68, 9.44, p < 0.001), and white blood cell count ≥10,000 cells/µm³ (OR 2.04, 95% CI 1.16, 3.57, p = 0.013) were significantly associated with fever in CVD patients. Among the 139 patients who had fever, 68 (48.9%) had foci of infection; age ≥ 65 years was associated with fever with foci of infection (OR 2.49, 95% CI 1.26, 4.93, p = 0.013), whereas body temperature over seven days was not different between patients with and without foci of infections. The mortality rate was 6.1% and fever was the only factor associated with death.

Conclusion: Fever was common among patients with CVD, particularly in those with cerebral hemorrhage. Sources of infections should be investigated since half of the patients with fever had foci of infection. Fever patterns may not be helpful in determining the cause of fever in these patients.

Keywords: Cerebrovascular Diseases; Fever

Abbreviations

CVD: cerebrovascular diseases

Introduction

Fever is not uncommon in patients with acute stroke, with incidence ranging from 24.4% to 37.6% [1,2]. Fever in these patients may be caused by the stroke itself or by infections. Stroke can cause fever as high as 41°C, [3,4] depending on the type and location of stroke, and on the size or volume of the stroke area [5].

Fever in acute stroke patients has been associated with poor patient outcomes [6–13]. In animal models, increased body temperature after induced cerebral infarction can increase the cerebral infarction volume [14–16]. In humans, post-stroke hyperthermia was associated with increases in morbidity and mortality rates [17]. Therefore, current guidelines recommend maintaining body temperature below 38°C to reduce stroke-associated morbidity [3].

Stroke patients are frequently prescribed both antipyretic and antimicrobial agents empirically [3]. However, infectious processes have been reported to cause fever in only 22.7% of stroke patients, mostly from pneumonia and urinary tract infections [1]. Therefore, a large proportion of these patients may have received unnecessary antimicrobial therapy. These agents may have adverse effects, increase the cost of treatment, and enhance the likelihood of future antimicrobial resistance.

Although it is difficult to differentiate fever caused by the stroke itself against by infection, antimicrobials should be prescribed only to patients who need them. As a first step in differentiating between fever caused by stroke and infection, it is important to determine the incidence and characteristics of fever in stroke patients. The primary aim of this study was to determine the incidence of fever in patients diagnosed with acute stroke. The secondary objectives were 1) to compare the incidence of fever between patients diagnosed with cerebral infarction and cerebral hemorrhage, 2) to determine the causes of fever in these patients, and 3) to compare the pattern of fever between patients with and without foci of infection.

Materials and Methods

Study Setting and Study Population

This prospective study consecutively enrolled patients admitted with acute stroke between July 1, 2013 and June 30, 2014 to the Stroke Unit of Maharaj Nakorn Chiang Mai Hospital, a 1,500-bed, tertiary-care hospital in northern Thailand. Patients were included if they were aged ≥ 18 years; had been diagnosed with acute stroke, as determined by American Stroke Association criteria; and underwent brain computerized tomography. Fever was defined as a single body temperature of ≥ 38.5°C or a body temperature of ≥ 39.0 °C for at least 2 time points within seven days after hospitalization. Patients who had fever after seven days were excluded. Mortality was assessed at the time of discharge from the hospital.

The study protocol was approved by the Faculty of Medicine, Chiang Mai University Ethical Committee.

Data Collection

Data were prospectively collected using pre-printed data collection forms. Demographic data, underlying diseases, physical examination, body temperature every 4 hours during the first 7 days of hospitalization, criteria for diagnosis of stroke, blood chemistry, brain computed tomography, and drugs used (antipyretic, antibiotics, and thrombolytic agents) were collected.

Statistical Analysis

Data are reported as number (%), mean ± standard deviation (SD), and median (interquartile range [IQR]), as appropriate. Parameters were compared using Student’s t-test or Mann-Whitney
U test for continuous data and the chi-square test or Fisher’s exact test for categorical data. Factors associated with fever, fever with focus of infection, and death were tested in univariate models. Factors with the p-value < 0.10 from univariate analysis were then tested in a multivariate logistic regression model using backward stepwise procedure. The Change in body temperature over time was analyzed using regression models with a generalized estimating equation (GEE) and robust variance estimation, which allows for repeated measurements in the same individuals. All statistical analyses were performed using Stata statistical software version 11.0 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.). A two-sided p-value < 0.05 was considered statistically significant.

Table 1: Characteristics of patients diagnosed with cerebrovascular diseases. Data were presented in number (%) or median (IQR) as appropriate (IQR: Interquartile Range, *One patient may have > 1 underlying diseases).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>182 (50.4)</td>
</tr>
<tr>
<td>Age (years) (median, IQR)</td>
<td>65 (54.76)</td>
</tr>
<tr>
<td>Underlying diseases*</td>
<td>283 (78.4)</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>183 (50.7)</td>
</tr>
<tr>
<td>- Dyslipidemia</td>
<td>125 (34.6)</td>
</tr>
<tr>
<td>- Atrial fibrillation</td>
<td>78 (21.6)</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>50 (13.8)</td>
</tr>
<tr>
<td>- Chronic kidney disease</td>
<td>18 (5.0)</td>
</tr>
<tr>
<td>Fever</td>
<td>89 (24.6)</td>
</tr>
<tr>
<td>Duration of stroke onset (hours)</td>
<td>2.1 (1.35)</td>
</tr>
<tr>
<td>Computed tomography of the brain</td>
<td></td>
</tr>
<tr>
<td>Infarction</td>
<td>279 (77.3)</td>
</tr>
<tr>
<td>- Middle cerebral artery (MCA)</td>
<td>163/279 (58.4)</td>
</tr>
<tr>
<td>- Anterior cerebral artery (ACA)</td>
<td>18/279 (6.4)</td>
</tr>
<tr>
<td>- Lacunar</td>
<td>78/279 (28.0)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>82 (22.7)</td>
</tr>
<tr>
<td>- Volume (N=70) (ml) (median, IQR)</td>
<td>39.5 (20.64)</td>
</tr>
</tbody>
</table>

Table 2: Comparisons of characteristics in patients with and without fever. Patients with fever were more likely to have dyslipidemia, cerebral hemorrhage, have a higher white blood cell count, and known focus of infection. Among those who had cerebral hemorrhage, the volume of ≥ 120 ml was associated with fever. Multivariate analyses showed that factors associated with fever in patients with stroke were known foci of infection (OR 32.27, 95% CI 13.09, 79.61, p < 0.001), cerebral hemorrhage (OR 5.03, 95% CI 2.68, 9.44, p < 0.001), and white blood cell count ≥ 10,000 cells/mm³ (OR 2.04, 95% CI 1.16, 3.57, p = 0.013).

Of the 139 patients with fever, 68 (48.9%) had foci of infection: pneumonia (23 patients, 33.8%), urinary tract infection (19,27.9%), tracheobronchitis (17,25.0%), thrombophlebitis, and meningitis or ventriculitis (2, 3%each), upper respiratory tract infection, infective endocarditis, and diarrhea(1, 1.5%each). Two patients (3%) had pneumonia and urinary tract infections. Univariate analysis showed that patients aged ≥ 65 years was...
associated with fever with foci of infection (OR 2.49 95% CI 1.26, 4.93, \( p = 0.009 \)), whereas there were no significant differences between those with and without foci of infection in terms of gender, underlying diseases, type of cerebrovascular diseases, onset of fever, and body temperature over seven days. Adjusted for known foci of infection, body temperature over 7 days was 0.5°C (95% CI 0.4°C, 0.6°C, \( p < 0.001 \)) higher in patients with cerebral hemorrhage compared to those with cerebral infarction.

Of the 361 patients, 49 (13.6%) underwent surgery; 118 (32.7%) were treated with thrombolytic agents (rtPA), 50 (13.8%) were treated with anticoagulants, 95 (26.3%) received aspirin, and 49 (13.6%) received none of the above. Antibiotics were prescribed in 88 of the 139 patients (63.3%) with fever and 17 of the 222 patients (7.7%) without fever (\( p < 0.001 \)). Antibiotics were prescribed in 67 (98.5%) of the 68 patients with foci of infection, and 21 (29.6%) of 71 without foci of infection (\( p < 0.001 \)). One patient with viral upper respiratory tract infection did not receive antibiotic.

Twenty-three patients died (6.4%), 11 of the 82 patients (13.4%) with cerebral hemorrhage and 12 of the 279 patients (4.3%) with cerebral infarction (\( p = 0.008 \)). The cause of death was related to stroke in 18 patients (78.3%) and related to infection in 5 patients (21.7%). Patients who died were more likely to have fever (OR 1.227, 95% CI 1.37, 4.91, \( p = 0.001 \)), cerebral hemorrhage (OR 3.45, 95% CI 1.46, 8.14, \( p = 0.005 \)), and white blood cell count \( \geq 10,000 \) cells/mm\(^3\) (OR 3.06, 95% CI 1.28, 7.28, \( p = 0.012 \)). Among patients with cerebral hemorrhage, those with volume of \( \geq 120 \) ml were more likely to die (OR 7.3, 95% CI 1.54, 34.96, \( p = 0.012 \)). However, in multivariate analysis, fever was the only factor associated with death. Among 50 patients who had fever without foci of infection and did not receive antibiotic, 13 (26%) died and the cause of death was related to stroke itself.

**Discussion**

In contrast with previous studies, which showed that the incidence of cerebral hemorrhage was similar to that of cerebral infarction [5], this study found that, among patients with acute stroke, 77% had cerebral infarction and 23% had cerebral hemorrhage. This discrepancy may have been due to our hospital being a tertiary care hospital, with patients with cerebral infarction referred to our hospital for thrombolytic therapy. The incidence of fever among patients with stroke was 38.5%, similar to previously reported rates of 24.4%–37.6% [1.2]. We also found that the incidence of fever was higher in patients with cerebral hemorrhage than cerebral infarction, similar to previous finding [5]. Central hyperthermia has been observed in patients with cerebral hemorrhage, with the most frequent site of hemorrhage being the brainstem (64%), followed by the putaminothalamus (24%), cerebellum (4%), and intraventricular locations (1%). Central hyperthermia was also observed in a minority of patients with cerebral infarction, including in patients with large cortical infarction (4%) and basilar artery infarction (3%) [18].

This study showed that body temperature patterns differed in patients with cerebral hemorrhage and cerebral infarction. Patients with cerebral hemorrhage had higher body temperature, although these differences might not indicate clinical relevance.

Fever caused by stroke itself may be due to massive tissue necrosis, which can elevate body temperature, or the presence of blood in the brain [9,19-21]. Infusion of heme into rat brains has been shown to produce fever [20,22,23]. Fever may develop in patients with stroke involving a territory or area of thermoregulation, such as large artery atherosclerosis and hemorrhagic stroke [2]. This study found that, of the 139 patients who had fever,71 (51.1%) had no documented source of infection, suggesting that fever in these patients may have been caused by stroke itself, and that patients with cerebral hemorrhage were more likely to have fever than patients with cerebral infarction. Furthermore, patients with higher volume compared with lower volume of cerebral hemorrhage were more likely to have fever similar to previous report [5].

However, patients with stroke are at risk to become infected and develop fever. For example, these patients are at risk for pneumonia due to loss of consciousness; for urinary tract infection in case of the need for urinary catheters; or for phlebitis due to their requirement for intravenous therapy. Of the 139 patients in this study who developed fever, 60 (48.9%) had foci of infection, and pneumonia was the most common.

Factors associated with fever included known foci of infection, cerebral hemorrhage, and white blood cell count \( \geq 10,000 \) cells/mm\(^3\). Other studies found that factors associated with fever included older age, male sex, hemorrhagic stroke, transtentorial herniation, and intraventricular hemorrhage [1]. White blood cell counts were higher in patients with than without fever. High white blood cell count may be associated with stress, the presence of necrotic tissue, and/or infection [9]. This study also showed that patients with lacunar infarction were less likely to have fever; however, this factor was co-linear with cerebral hemorrhage in the multivariate model. Unlike large artery infarction, patients with lacunar infarction were less likely to have fever as there was no mass effect on the brain parenchyma and the location of lacunar stroke was less likely to involve the thermoregulatory area of the brain [5].

In our study, age \( \geq 65 \) years old was the only factor significantly different between those with and without foci of infection, whereas an earlier onset of fever was associated with fever without foci of infection in another study [1].

Fever, irrespective of the cause, was associated with poor outcome similar to previous studies [6-13], which might reflect massive tissue necrosis or involving area of thermoregulation as mention above [2].

In this study, 17 of 222 (16.4%) patients without fever and 21 of 71 (29.6%) \% patients who had fever without foci of infection received antibiotics. Thus, of the 361 patients, 38 (10.5%) were prescribed unnecessary antibiotics. However, based on our observation, it is difficult to provide an algorithm for handling patients with stroke and fever. Thorough physical examinations and related investigations must be performed. The decision to prescribe the empirical antibiotics pending microbiologic studies depends upon clinical features. Empirical antibiotics should be avoided if the source of infection cannot be identified and the patients are not critically ill. In addition, the decision to continue and discontinue antibiotics after negative investigations should be considered on a case by case basis. Infectious diseases specialist consultation, if available, is helpful to reduce the inappropriate use of antibiotics in these patients.

This study has several limitations. First, as this study involved patients from a single tertiary care center, with an inherent selection bias due to referral, its results may not be applicable to the general population. Second, patients who had documented sources of infection might also have fever from stroke itself, resulting in difficulty in differentiating characteristics of fever from stroke alone. Third, we could not identify the foci of infection in half of the patients who had fever; occult infection might be possible in these patients. However, with our best practices, the foci of infection were not documented during that time point.

**Conclusions**

About 40% of acute stroke patients experience fever and half...
of them had foci of infection. Determining a source of infection is mandatory before determining that fever was due to stroke itself. Fever is more likely in patients with hemorrhagic stroke than those with lacunar infarction. Fever patterns may not be helpful in determining the cause of fever in these patients.

References


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