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Determinants of Fever in Acute Stroke Patients

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The aim of this study was to determine the frequency and origin of fever in patients admitted with acute stroke and the characteristics associated with the development of fever.This was a cross sectional observational study involving 151 patients admitted with acute stroke. The various attributes associated with the development of fever were documented and their characteristics were analyzed.

Fever was noted in 21.2% of 151 patients; 11.9% had a documented infection and 9.3% had no documented infection. Older age was associated with the presence of fever (P = 0.009). The development of fever was associated with haemorrhage rather than ischemic infarct (P = 0.0001), presence of mass effect (P =0.03), and larger size of ischaemic infarct and haemorrhage (P = 0.002 and 0.0001, respectively). Patients with fever had lower scores on admission on the Glasgow Coma Scale (GCS) (P = 0.009) and higher score on the National Institute of Health Stroke Scale (NIHSS) (P = 0.0001). The development of fever was associated with prior use of an invasive technique (P =0.0001), particularly urinary catheterization and endotracheal intubation (P = 0.0001 and 0.0001). In multivariate analysis, age, NIHSS and endotracheal intubation were found to be significantly associated with fever (P = 0.018, P = 0.001 and P = 0.0001, respectively). Patients with fever without documented infection had an earlier onset than those with infection (P = 0.012).

Fever in acute stroke patients is associated with older age, severity of stroke and the use of invasive techniques. Urinary tract and respiratory infections are the most common infections. Fever starts earlier where a focus of infection is not identified.

Key Words: fever, infection, intracerebral haemorrhage, ischaemic infarct, stroke

Fever is common in patients with acute stroke and usually is due to infections. In some patients a focus of infection cannot be identified and these patients often receive empirical broad-spectrum antibiotic treatment, which increases their risk for adverse reactions and the cost of their medical care. Central nervous system lesion is thought to be cause of fever in these cases. The presence of fever, in general, has been associated with a poor outcome.[12, 2]

In this cross sectional observational study, we attempted to define a) the types of infection that develop in patients hospitalized for acute stroke; b) the relation between type and severity of stroke and development of fever with or without apparent infection; c) the relation between infection and factors predisposing to its development; and d) differences between patients who develop a documented infection and those who develop fever with no apparent focus of infection.

Materials and Methods

Tribhuvan University Teaching Hospital is a tertiary care hospital with a dedicated Neurology department with 40-bedded Neurology ward and a common Medical ICU. This study included all patients hospitalized for acute stroke between April 2014 and March 2015. All patients admitted within 48 hours of onset of stroke were included, both ischaemic infarct and intracerebral haemorrhage.

Exclusion criteria were hospitalization for less than 1 day because of transfer out to another hospital; transfer in from another hospital; development of stroke during hospitalization for another illness; presence of fever and/or infection before the onset of stroke; presence of primary or metastatic brain tumour.

Patients were evaluated using a standard protocol. On admission, they were examined by an internist experienced in the care of patients with stroke and on the following day by a neurologist. Glassgow Coma Scale (GCS) [13] and NIHSS were used for clinical evaluation on admission. A head computed tomography (CT) scan was obtained on the first day and a second head CT scan and/or a brain magnetic resonance imaging (MRI) scan was obtained between the 7th and the 10th day of hospitalization. The size (volume) of the brain lesion was calculated from the second head CT scan using a published method.[3] Patients underwent extracranial colour-coded duplex ultrasonography, transthoracic echocardiography routinely. But digital subtraction angiography, Holter monitoring and transthoracic or transoesophageal echocardiography were done when needed. Stroke classification followed National Institute of Neurological and Communicative Disorders and Stroke (USA) criteria.[8]

In the present analysis, determination of the aetiology of fever was based on data derived from the patients' daily observation during admission in hospital. A patient was considered febrile, if his/her temperature exceeded 37.58°C on more than two occasions on two consecutive days. On a routine basis, an axillary temperature measurement was taken every 3 h in all patients with acute stroke. When analysing the data, in cases where rectal temperatures were noted, 0.58°C was subtracted from the recorded measurements.

We used clinical data from history and examinations, as well as laboratory and radiographic data derived from the patients' medical records, to determine the cause of fever. In cases where a focus of infection could not be identified, the fever was characterized as fever without documented infection. A documented infection was characterized as nosocomial if fever or other signs of infection started more than 48 h after admission.

Categorical variables were compared using Fisher's exact test, whereas continuous variables were compared using t-test. Stepwise logistic regression was used to assess the ability of independent variables to predict the presence of fever without documented infection versus fever with documented infection. All P values reported are two-sided.

Results

Data from 151 acute stroke patients were obtained when they were admitted. Fever developed in 21.2% of the patients. One or more infections developed in 11.9% and in 9.3% of the patients fever was noted but an infection could not be documented. The frequency of types of infection in patients hospitalized for acute stroke is shown in **Table 1**. The most common type was respiratory tract infection followed by urinary tract infection.

Table 2 shows the comparison between patients who developed fever (with or without documented infection) and those who did not (univariate analysis). There was no sex difference (P = 0.575). Older age was strongly associated with the presence of fever (P = 0.009). The development of fever was very significantly associated with intracerebral haemorrhage rather than with ischaemic infarct (P = 0.0001). It was associated with mass effect (P = 0.03) a larger size of ischaemic infarct (P = 0.0001) or with large haemorrhage size (P = 0.002). Patients with fever had lower scores on admission on the Glasgow Coma Scale (P = 0.009) and higher NIHSS (P = 0.0001). The development of fever was unrelated to the presence of risk factors for infection (risk factors considered are shown in **Table 2**). However, it was strongly associated

Origin of Fever	Number of patients (% of patients)
Documented Infections	18 (56.2)
Respiratory tract	15 (46.9)
Urinary tract	3 (9.4)
Fever without focus of infection	14 (43.8)

Table1: Frequency and Origin of Fever

	Number of patients (%)		
Variable	**No Fever (119)**	**Fever (32)**	**p Value**
Sex			
Male	67	18	
Female	52	14	0.575
Age(years; mean±SE)	62.83± 1.39	70.00 ± 2.24	0.009
Type of Stroke (Imaging)			
Ischemic	81	10	
Hemorrhagic	38	22	<0.0001
Imaging Findings			
Mass Effect-Yes	29	14	
No	90	18	0.03
Infarct Size- Large	23	08	
Small	58	02	0.002
Hemorrhage Size- Large	08	19	
Small	30	03	<0.0001
Severity of Stroke			
Glasgow Coma Scale (mean ± SE)	13.54 ± 0.23	12.19 ± 0.56	0.009
Severe Stroke (GCS<9)-Yes	10	14	
No	109	18	<0.0001
NIHSS (mean ± SE)	11.89 ± 0.77	18.09 ± 1.61	<0.0001
Risk Factors For Infections			
COPD- Yes	20	5	
No	27	99	0.557
CRF- Yes	2	0	
No	117	32	0.62
Diabetes Mellitus -Yes	17	1	
No	102	31	0.068
Invasive procedure preceding fever			
Urinary Catheter-Yes	82	32	
No	37	0	<0.0001
Endotracheal tube- Yes	7	11	
No	112	21	<0.0001
Central line- Yes	4	7	
No	115	25	0.002

Table 2: Comparison of variables between patients without fever and those with fever

SE, standard error; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure

	Number of patients (%)		
Variable	**Documented Infection(n=18)**	**Fever without documented Infection(n=14)**	**p**
Sex			
Male	11	7	
Female	7	7	0.721
Age (years; mean±SE)	73.39 ± 2.84	65.00 ± 3.33	0.888
Type of Stroke (Imaging)			
Ischemic	8	2	
Hemorrhagic	10	12	0.073
Imaging Findings			
Mass Effect-Yes	9	5	
No	9	9	0.328
Infarct Size- Large	7	1	
Small	1	11	0.378
Hemorrhage Size- Large	8	11	
Small	2	1	0.429
Severity of Stroke			
Glassgow Coma Scale (mean ± SE)	11.56 ± 0.81	13.00 ± 0.73	0.194
Severe Stroke (GCS<9)-Yes	7	7	
No	11	7	0.393
NIHSS (mean ± SE)	19.24 ± 2.05	16.57 ± 2.58	0.419
Risk Factors For Infections			
COPD-Yes	3	2	
No	15	12	0.624
Diabetes Mellitus -Yes	1	0	
No	17	14	0.562
Invasive procedure preceding fever			
Endotracheal tube- Yes	8	3	
No	10	11	0.163
Central line- Yes	5	2	
No	13	12	0.318
Peak of fever (F; mean ± SE)	101.45 ± 0.39	100.95 ± 0.29	0.251
Time of fever from onset of stroke	7.11 ± 1.74	2.14 ± 0.42	0.012
(D; mean ± SE)			

Table 3: Comparison of variables between patients documented infection and those with fever without documented infection

SE, standard error; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure

with prior use of an invasive technique (P = 0.0001), and more specifically with prior urinary catheter (P = 0.0001) or endotracheal tube (P = 0.0001) insertion.

Multivariate logistic regression analysis was used to explore the association of fever with intracerebral haemorrhage versus ischaemic infarct and their pathophysiological consequences, as well as age, gender, severity of illness. Using the stepwise elimination procedure, age, NIHSS and endotracheal intubation were found to be significantly associated with fever (P = 0.018, P = 0.001 and P = 0.0001, respectively).

Table 3 shows the comparison between patients with documented infection and those with fever without a documented infection (univariate analysis). All other variables were not significantly different. Age, sex, type of stroke, mass effect and time of fever from onset of stroke were the independent variables examined in a stepwise regression analysis comparing these two categories of febrile patients. The only factor predictive of fever without documented infection versus fever with documented infection was earlier onset of fever (P = 0.012).

Discussion

In this cross sectional observational study of 151 acute stroke patients, 21.2% (n=32) patients developed fever, 11.9% (n=18) was due to infective cause and 9.3% (n=14) was due to non-infective cause. Majority of infections were caused by respiratory tract infection 9.9% (n=15). A similar result was found in an earlier study where fever was documented in 23 patients out of 104 subjects (22.1%), infective cause contributed to 18.3% and respiratory tract infection was the major cause of infection 12.5%.[11] In another study of 330 patients, 37.6% developed fever; 22.7% had a documented infection and 14.8% had fever without a documented infection, other findings were similar as findings of our analysis.[6] Most of the respiratory tract infections were community-acquired. This finding probably results from inclusion of aspiration pneumonia, which often occurs early in the course of a stroke,[7] in the category of respiratory tract infections. Our data show that insertion of a urinary catheter significantly increased the risk for urinary tract infection and suggest caution in the use of this common (and sometimes unnecessary) invasive technique. We did not find an association between known risk factors for infection and development of infection. This could be explained by the fact that the occurrence of infections was strongly related to the severity of stroke, which probably affected negatively the significance of risk factors. Severe stroke with immobilization is associated with atelectasis in the dependent lung, and pooling of mucus in dependent bronchi is also associated with atelectasis, frequently resulting in pneumonia.[11] In addition, patients with more severe stroke are at great risk for aspiration.[7]

In our study, approximately 9.3% of all patients had fever without a documented infection (43.7% of febrile patients). The pathogenesis of fever implies the production and release of endogenous pyrogens, such as interleukin-1 (IL-1), tumour necrosis factor-a (TNF-a) and interleukin-6 (IL-6), into the circulation after the onset of certain diseases. In patients with central nervous system disease, these pyrogens are thought to reach the thermoregulatory centre by a direct route and induce fever, a hypothesis that provides a possible pathogenic explanation for the fever of central origin. [5-10]

In prospective studies, the value of markers of infection could be assessed in the differential diagnosis of fever from infection versus fever of central origin. C-reactive protein (CRP) has not been evaluated in patients with acute stroke. Serum CRP levels may prove useful in determining the aetiology of fever in acute stroke, as they have been previously shown to be only slightly elevated in inflammation, but significantly more elevated in infection.[9] Also, serum levels of procalcitonin have been shown to increase in patients with infection.[1] Secretion of procalcitonin is stimulated, for as yet unknown reasons, by the presence of bacterial endotoxin.[4]

In our attempt to separate patients with fever due to infection from those with fever and no infection (fever of central origin), using a logistic regression model, we found that the only factor predictive of fever of central origin was earlier onset of fever. If all non-infectious cases of fever were due to `fever of central origin', then earlier onset of fever would make sense, since an incubation period for an infection to develop would not be needed. As a result, some overlap between the two groups is expected, since, as we have shown, patients with severe stroke are prone to develop both infections and fever of central origin. Another confounding factor is the possible existence of undiagnosed subclinical infections, especially in patients with severe stroke. Finally, although we excluded patients with infections that occurred prior to the stroke, in some cases this information may not have been definitively known.

Conclusion

This cross sectional observational analysis has shown that, patients with acute stroke who develop fever are older, suffer severe stroke and the fever is associated with the use of invasive techniques; most common infections are of respiratory or urinary tract and fever starts earlier in cases where a focus of infection is not identified.

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