Stroke Associated Infection: A Prospective Hospital-Based Study at A Tertiary Care Institution of North India

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ABSTRACT

BACKGROUND: Immune dysfunction is increasingly recognized to be contributing to stroke associated infections.

OBJECTIVE: The present study was aimed to study the magnitude of the stroke associated infection in a mixed population of hemorrhagic and ischemic strokes and its predisposing factors.

MATERIAL & METHODS: The study population consisted of 173 consecutive stroke admissions at SKIMS Srinagar, a tertiary care hospital. The patients developing fever at admission or in hospital were included and underwent neuroimaging and workup for the source of infection. The follow up was done upto death or discharge of the patient. A univariate and binary logistic regression analysis was done to find the patient characteristics associated with infection.

RESULTS: The stroke subtypes in the study were 60.1% hemorrhagic and 39.9% ischemic strokes. The majority of hemorrhagic strokes (65.4%) were located in putamina while as anterior circulation territory contributed about 80% of the ischemic strokes. Fifty eight (33.5%) patients developed stroke associated infection. Chest was the source of infection in 58.6% of the cases. The culture positivity rate was poor (18.9%) in the patient study. The presence of a comorbid illness (OR 3.4), volume of hematoma (OR 4.7), and ventricular extension of the hemorrhage (OR 4.9) significantly increased the odds ratio of stroke associated infection.

CONCLUSIONS: The frequency of post stroke infection is around 33%, chest being the commonest source. Presence of a comorbid illness, volume of hemorrhage and ventricular extension increase the risk of infection. JMS 2012;15(1):

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Medical and neurological complications are known to occur in 59% to 95% of the stroke patients as reported in various retrospective as well as prospective studies, depending on the period of observation.^{1,2,3} Survival analysis has shown an increased short and long term mortality in those with in hospital complications as compared to those without such complications. Hee-

Joon Bae *et al* have reported a mortality of 70.7% at 4 years in those with in hospital complications versus 22.4% in those without complications.⁴ Infections are one of the commonest medical complications in stroke patients.^{1,2} Infection and stroke have a reciprocal relationship. In a case control study by Gram *et al*, a preceding upper respiratory infection of bacterial origin carried an increased risk of ischemic strokes with an odds ratio of 4.5.⁵ Working on an experimental model of focal cerebral ischemia, Prass *K et al* produced evidence of increased susceptibility of the animals to septicemia and pneumonia, preventable partially by adrenoceptor blockade by propranolol and called the phenomenon as, "stroke induced immuno-deficiency syndrome".⁶ Defects in the immune system function after stroke

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include decrease in the peripheral blood lymphocyte count, impaired T lymphocyte and NK (natural killer) cell activity, reduced interferon gamma production and decreased mitogen induced cytokine production and proliferation of the immune cells.^{6,7,8} Similar to the experimental models, the post stroke infection (PSI) or stroke induced infection (SII) has been studied in populations of predominantly ischemic strokes patients. The aims of the present study were to determine the frequency of infection in a mixed population of stroke patients and to find out the characteristics associated with it that affect the final outcome.

Methods

Sheri-i-Kashmir Institute of Medical Sciences (SKIMS) is a 650 bed tertiary care university hospital with the only available department of Neurology catering to a population of six millions in the valley of Kashmir (North India). The study subjects comprised of one hundred and seventy three (173) consecutive stroke patients admitted with acute stroke via accidental emergency facility as well as outpatient department over a period of three months (from November 2007 to January 2008).

Inclusion Criteria

The study included patients of:

1. Both types (ischemic & hemorrhagic).
2. First ever or recurrent strokes with or without fever at admission.
3. The stroke patients with a comorbid condition were included only if there was no clinical history of fever prior to the index event of stroke.

Exclusion Criteria

1. Age 18 years or less.
2. Sub-arachnoid hemorrhage on admission CT scan.
3. Associated diseases known to cause fever like bacterial endocarditis and vasculitis.
4. Those needing intubation and mechanical ventilation at admission.

All the cases were diagnosed as stroke by the neurology resident followed by an urgent non-contrast computerized tomography (NCCT) scan of the head. In twenty seven (27) patients, a normal CT head at admission necessitated a repeat CT or MRI (Magnetic Resonance Imaging) of the head to confirm the stroke. After recording the vital signs, temperature and the level of consciousness by Glasgow Coma Scale, Ryle's tube and condom/Foleys catheter were used depending upon the presence of dysphagia, level of consciousness or retention of urine. The patient was seen by a consultant neurologist at the Level II of the hospital and shifted to neurology floor as per the bed availability. A 6 hourly temperature chart and an admission arterial blood gas analysis was done in all patients. A routine blood chemistry, electrocardiogram, X-ray chest and a hemogram was also done as usual in all cases. Since the cohort was studied prospectively, history was recorded regarding any cough, fever, dysuria before the onset of stroke as well as the records were checked about past

neurodeficit, stroke, risk factors like hypertension, smoking, diabetes and other co morbid diseases like renal disease, coronary artery disease, obstructive pulmonary disease, sleep apnea, diagnosis of malignancy, atrial fibrillation, cardiomyopathy, and cardiac conduction defects.

The patients who developed fever on admission or subsequently for more than 24 hours were evaluated for the cause. The evaluation included:

- Total and differential leukocyte count.
- Erythrocyte sedimentation rate (ESR).
- Routine urine examination.
- X-ray chest (PA View).
- Bacterial culture and sensitivity of blood, urine and respiratory secretions.
- Ultrasonography of the abdomen to look for a possible source of infection.

Such patients were empirically started on antibiotics and later on modified as per the pathogens drug sensitivity.

The blood counts, X-ray chest, cultures and ABG analysis were repeated to follow the response. The care was continued till the death/discharge of the patient.

Definitions

1. Fever was defined as the temperature elevation to 37.5°C recorded on two days by oral or axillary method. A single measurement of $\geq 37.8^\circ\text{C}$ also qualified for the definition. Fever was assumed to indicate infection if it was associated with tachycardia, tachypnea, raised ESR or TLC of 12,000 /cumm or signs of chest or urinary tract infection. A response to antibiotics was also taken as an indication of infection.
2. Chest infection – Based on presence of three or more of the following: fever, productive cough with purulent sputum, abnormal respiratory examination (tachypnea $> 22/\text{min}$, tachycardia, inspiratory crackles, bronchial breathing), abnormal chest radiograph, arterial hypoxemia ($\text{PaO}_2 < 70 \text{ mmHg}$) and isolation of relevant pathogen.
3. Urinary tract infection – Symptoms of UTI like dysuria, foul smelling urine, pyuria with positive urine culture.
4. Mixed infection – Fever with clinical and or laboratory features suggestive of a focus of infection at two places simultaneously.
5. Venous access infection – Fever with a positive blood culture with an evidence of infected puncture site.

The definitions are based on the modifications of those used by references^{9,10,11}.

Blood culture samples were drawn from two different venous sites under aseptic precaution as prescribed.

A urine sample collected from the sterile urosac or catheter were stored in a sterilized bottle.

The respiratory secretions drawn by a catheter suction

were stored in an sterilized bottle and all the specimens were transported to the microbiology lab and processed by standard methods for both aerobic and anaerobic organisms.

The Neuroimaging data was read by a radiologist and in correlation with clinical features, the ischemic stroke was subtyped according to the vascular territory and conforming to the classification used in Oxfordshire community Stroke Project (OCSP).¹² Watershed infarcts consisted of infarcts between vascular territory of anterior cerebral, middle cerebral, and posterior cerebral artery. The hemorrhagic stroke was classified as per the site involved and the volume of hemorrhage refers to the estimated volume of parenchymal hematoma as per the published method.¹³

Statistical analysis

The data is presented in descriptive statistical analysis for a mean standard deviation and percentage. For comparative analysis of variables, MannWhitney U test and students t test were used for non parametric and parametric data respectively for univariate analysis. The GCS score and volume of hemorrhage were dichotomized for analysis. All the significant factors were loaded for a binary logistic regression analysis with the dependent variable sepsis or no sepsis. A two tailed p value <0.05 was considered significant. The data was analyzed using SPSS 11.5 and Minitab 14.0 version of statistical software. The variables analysed in univariate analysis with a p value of <0.05 were entered into a binomial logistic regression analysis model. The variables included a dichotomized GCS score (≤ 8 and >8), presence of comorbid illness, volume of hematoma (25th percentile), ventricular extension of the hemorrhage and Ryles tube feeding.

Results

The study population consisted of one hundred and seventy-three (173) patients of age ranging from nineteen to eighty-five years (mean 61.4 ± 11.3) with a male female ratio of 1.8:1. Other characteristics of the study population are shown in Fig. 1. The majority of strokes were hemorrhagic (60.1%) with a volume of main parenchymal hematoma of 28.7 ± 26.1 ml and were located mainly at putamen (65.4%) and thalamus (25%) (Fig. 2). According to the infarct location on neuroimaging, anterior circulation (partial and complete) constituted about 80% of the ischemic stroke, including the lacunar and hemodynamic strokes. Hypertension defined as a blood pressure of $\geq 140/90$ mmHg before the index stroke and/or a history of antihypertensive intake was the commonest risk factor ($\approx 80\%$) followed by smoking (31.8%). Diabetes mellitus was diagnosed first time in the present hospital stay in three cases and twenty three cases had atrial fibrillation. Twenty four patients had a history of past stroke including a transient ischemic attack in four and two or more than two strokes in four patients. The four patients with two or more strokes in the past had atrial fibrillation (non-valvular) in three and congestive cardiac failure with left ventricular clot documented on echocardiography in one.

FIGURE 1. Risk Factors / Clinical characteristics associated with the study

FIGURE 2. Stroke type / Location and their incidence in the study group

Fifty eight (33.5%) patients developed infection in the present cohort, 42.3% vs. 20.3% in the hemorrhage and ischemic group respectively. Fever and infection occurred early (51.8%) as well as late (48.2%) during the hospitalization with respect to the time of onset of the index case available through history. However the mortality in the early infection group (90%) was markedly high as compared to those with late onset of infection (35%).

None of the patients of lacunar stroke developed infection while as both patients with an internal carotid artery territory infarction developed infection and died in the hospital. The incidence of infection was higher in middle cerebral artery stroke (23.8% and 30.0% respectively in complete and partial MCA territorial ischemic stroke respectively) (Fig. 3). Univariate analysis of the clinical characteristics revealed a GCS score of ≤ 8 ($p=0.008$), Ryle's tube feeding ($p=0.000$), presence of co morbid illness ($p=0.007$), Hemorrhagic stroke ($p=0.003$), mean volume of hematoma (37.1ml vs. 22.7 ml, $p=0.006$) and presence of ventricular extension ($p=0.001$) of hemorrhage as significant

FIGURE 3. Incidence of Infection in different stroke types and its relation with Stroke type/location

predictors of infection in this cohort of patients (Tables 1 & 2). The volume of hematoma was further divided into 25th, 50th and 75th percentiles and was found to increase the odds of infection (OR=4.7, 3.6 and 2.6 respectively). This reached statistical significance at 25th (0.00) and 50th percentile ($p=0.000$) only (Table 1).

TABLE 1. Volume of Hemorrhage

		Percentile description of Septicemia				
Volume (ml)		Present		Absent		Result
		n	%	n	%	
Volume 25th Percentile	≤10	5	17.9	23	82.1	OR=4.7, <i>p</i> =0.000 (Sig)
	>10	37	50.7	36	49.3	
Volume 50th Percentile	≤20	14	26.9	38	73.1	OR=3.6, <i>p</i> =0.000 (Sig)
	>20	28	57.1	21	42.9	
Volume 75th Percentile	≤40	30	37.0	51	63.0	OR=2.6, <i>p</i> =0.062 (NS)
	>40	12	60.0	8	40.0	

TABLE 2. Ventricular extension

		Septicemia across Stroke Characteristics				p value
		Present		Absent		
		n	%	n	%	
Ventricular Extension	Present	14	66.7	7	33.3	0.001
	Absent	44	28.9	108	71.1	

Chest was the commonest source of infection (56.8%) followed by urinary tract (29.3%). No source of infection could be ascertained in 12% of patients in the sepsis group. Risk factors correlating with infection are shown in Fig. 4. The yield of positive culture of the laboratory specimens was only 18.9% (Table 3). The hospital stay (9.3 ± 5.1 days vs. 8.7 ± 3.9) was not statistically significant between the groups of patients with and without infection ($p=0.436$). However the in hospital mortality between these two groups (80.4% vs. 19.6%, $p=0.000$) was markedly significant. Logistic regression analysis of the variables revealed a significant increase in the post stroke infection related

TABLE 3. Topography and microbiological data of infection

	Number of patients infected (n=58)	Percentage (%) of patients infected
Source of infection		
1. Chest	34	58.6%
- LRTI	25	43.1%
- URTI	9	15.5%
2. Urinary tract	17	29.3%
3. More than one site	10	17.2%
4. Unknown	7	12%
Culture positivity		
Total cases	11	18.9%
Blood	4	36.3%
Urine	8	72.7%
Tracheal secretions	1	9.0%
Blood as well as urine	2	18.1%
Mortality (n=58)		
Early infection*	27/30	90%
Late infection**	10/28	35%

Bacteria grown were - *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. Coli*, *Staphylococcus aureus*, *Acinetobacter*

*Early Infection- within 3 days of admission; **Late Infection- 3 days thereafter

FIGURE 4. Correlation of risk factors with infection

to the following variables: comorbidity (OR-3.4, 95% CI-1.4-8.4); volume of hematoma (OR-4.7, CI 1.7-13.3) and ventricular extension of the hemorrhage (OR-4.9, 95% CI 1.9-12.6).

Discussion

Fever has been reported to occur as a common complication of acute stroke patients. The incidence varies from 22%¹⁴, 25.2%¹⁵, 37.6%¹⁶, to 43%¹⁷ in the prospective, observational, hospital based studies. The variation of incidence appears to be

related to the length of observation in these studies. While as the etiology of fever in acute stroke patients is mostly infective, a fever without documented infection constitutes 10–16% of cases.^{15,16}

Vargas M, *et al*⁹ reported a post stroke infection in 26% of acute stroke patients within first seven days of stroke, while as the incidence of infection was 16% and 19% at 7 days and 30% and 33% at 3 months in the drug and placebo arms respectively in the antibiotic prophylaxis trial of Chamorro *et al*.¹⁸ Chest infections, mainly pneumonia predominate as the cause of infection early in the stroke patients while as urinary tract infection is common in the chronic phase.¹¹ The post stroke infection rates described in these studies may look to be different from our study (33.5%), the difference can be explained by the strict inclusion criteria regarding the time from onset of stroke in these studies as well as the bulk of study population consisting of ischemic strokes as compared to the proportion of hemorrhagic stroke patients (60%) in our study. In this regard our patient population is reflective of the in hospital stroke populations seen especially in Asia, Africa and South America where hemorrhagic stroke forms a sizeable chunk of the stroke patients.^{19,20,21}

Pneumonia (43%) and Urinary tract infection (29.1%) were the main sites of infection in the present study, a finding compatible with the past studies.^{1,2,3,15,16} Pneumonia is known to occur in 23% of acute stroke patients²² however, its incidence is higher (44%) in stroke patients fed via nasogastric tube in the acute phase.²³ Previous studies have linked pneumonia with aspiration²⁴ while as factors like multiple strokes, vertebrobasilar strokes, mechanical ventilation, initial severity of stroke and decreased level of consciousness increase the risk of this complication.^{23,25} A high percentage of tube fed patients and inclusion of stroke patients with co morbidity could explain the high rate of chest infections in the present study. The mortality of 90% in this cohort among the early infection group is not surprising in view of the association of infection with the severity of stroke and worsening of clinical outcome with fever and infection.^{15,17,22,26}

The microbial flora grown in the present study and low rates of culture yield (18.9%) are consistent with the data of studies done in the past.^{15,22} Gram AJ *et al*¹⁵ relate the low culture detection of bacteria to the early use of antibiotics on detecting fever in the patient. As the patients with fever at the time of admission were not excluded from our study, a prior use of antibiotics cannot be ruled out.

Though infections were divided into early onset and late onset in our study, we didn't try to equate this with community acquired or nosocomial origin of the infection as done in other studies.^{15,22} We agree with Sellars *et al* that this distinction is not practically possible in all patients.²⁷

The significance of factors like type of stroke, volume of hematoma and intraventricular extension of hemorrhage derived through logistic regression analysis in the present study replicates the findings of Georgilis K *et al* and Prezlowski M *et al*.^{14,16} The relationship between severity of stroke and fever and infection and early occurrence of majority of stroke associated infection has been shown in various studies in the past.^{9,15,16,23} This predominance of infections during the maximal neurological impairment

suggests that the infection might also be explained by stroke induced immunologic dysfunction.²⁸ Immunodeficiency after stroke can be detected within few hours in experimental models²⁹ and lasts for several weeks. A lower bacterial load is needed to induce pneumonia in experimental model of middle cerebral artery occlusion.³⁰ The experimental evidence of prevention of development of infection by moxifloxacin³¹ and neuroprotection via increased expression of glutamate transporter protein³² by ceftriaxone call for further preventive antibiotic trials in patients of acute stroke. In this connection, a beneficial effect of antibiotics as shown by a meta analysis recently is encouraging.³³ Our study, though a hospital based study with the possibility of referral bias, is more comprehensive in patient inclusion and representative of clinical scenario in a country like India.

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