# Stroke-induced Immune Depression–A Randomized Case Control Study in Kashmiri Population of North India

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*Background:* Stroke leads to transient immunedepression, which leads to increased incidence of poststroke infections. Because infection is one of the most common causes of increased mortality in patients with stroke, this study was undertaken to document immunedepression after stroke in our population. *Methods:* A case-controlled study wherein 39 patients with acute ischemic stroke in the age group of 18 and 60 years without any evidence of previous immunedepression were included. Interleukin 6 (IL-6) and interleukin 10 (IL-10) levels were checked in plasma in both the groups on day 3 and day 45. Also Cortisol and epinephrine levels were checked in the urine samples collected on day 3 and day 8. *Results:* No significant difference was seen between the IL-6 and the IL-10 levels in samples collected on day 3 between the controls and cases, whereas Cortisol and norepinephrine were significantly raised in samples collected on day 3 in cases who developed infection as compared with controls. *Conclusions:* The higher levels of urinary cortisol and norepinephrine were observed in patients with stroke who developed infections, which indirectly reflected increased amount of stroke related stress. Furthermore, the levels of plasma IL-6 and IL-10 were also elevated in the same group of patients, which means transformation of immunecompetence to immunedepression, which is responsible for higher mortality. Subsequently on recovery from infection the plasma levels of interleukins and urinary cortisol and norepinephrine did not show any difference, which indirectly means recovery of the immune system on recovery from acute stage of stroke. Mortality in the patients with infection was increased than controls. **Key Words:** Ischemic stroke—IL-6—IL-10—hypertension—urinary cortisol—urinary norepinephrine.


Stroke is the third leading cause of death after cardiac and cancer related deaths. Eighty-five percent of all patients with stroke have complications of which infections are the most common (23%-85%).[1,2] Among infections, pneumonia is the most important. Despite major developments in management of sick patients including development of specialized stroke units, infections remain one of the important causes of morbidity and mortality.[3] This increased incidence of infections has been attributed to transient immunodepression that occurs immediately after stroke.[1,4,5] Not only in stroke, immunodepression has been reported in other potentially life threatening conditions such as myocardial infarctions, polytrauma, or major surgery, which results in increased risk of infection and its complications thereafter.[6] Rapid T-lymphopenia and long lasting suppression of lymphocyte interferon γ production has been implicated for this process.[7] During acute stress, Corticotrophin releasing hormone is released from brain, which leads to release of

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Received February 5, 2014; revision received February 27, 2014; accepted March 5, 2014.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.03.002

adrenocorticotropic hormone and subsequently that of glucocorticoids that in turn facilitates the release of anti-inflammatory cytokines IL-4, IL-10, and TGF-β (transforming growth factor beta), which have strong antiproliferative properties.[8] In addition, there is apoptotic loss of lymphocytes and a shift of helper T type 1 to helper type 2 T-lymphocytes.[9] These changes lead to immunodepression with some contribution from adrenergic pathway as well.

## Aim of the Study

Incidence of death in patients with stroke with secondary infection and the use of interleukin 6 (IL-6) as a predictive marker for development of poststroke infections.

## Material and Methods

### *Subjects*

Thirty-nine patients of acute ischemic stroke between the age group of 18 and 60 years, admitted in Department of Accident and Emergency, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, who had no evidence of previous immunodepression such as diabetes, chronic kidney disease, organ transplant, human immunodeficiency virus (HIV)/AIDS, tuberculosis, immunosuppressive therapy in last 30 days, were included in the study. Of 19 patients 39 developed infection and were treated as cases and rest of the 20 patients who did not develop infection were treated as control group. Those with clinical signs of infection at the time of admission were also excluded from the present investigation. Patients suspected of having previous immunodepression were excluded per the exclusion criteria set forth. Patients older than 60 years of age, patients having a hemorrhagic stroke, and/or patients having signs of infection at the time of admission were excluded from the study. The patients that were included in the present investigation had an occurrence of ischemic stroke within 36 hours and the patients were more than 18 years of age. The patients with signs of cortical involvement such as aphasia, hemineglect were also used as inclusion criteria.

Immediate noncontrast computed tomographic scan of brain of these patients was done before shifting them to the neurology floor. Blood samples were taken on day 3 for all patients and subsequently patients were assigned to one of the 2 groups depending on whether they developed infection or not. Patient consent was taken before including them in the study, and the study was approved by the Sher-I-Kashmir Institute of Medical Sciences ethical committee.

### *Measurement of Cytokines, Catecholamines, and Cortisol Levels*

Blood samples were taken on day 3 and day 45 from both the groups. Plasma separation was immediately done by centrifugation and later stored at −70°C till further use. Twenty-four hours urine was collected on day 3 and day 8. Enzyme linked immunosorbent assay was performed to determine the IL-6 and IL-10 (ANOGEN, Mississauga, Ontario, Canada) urinary cortisol and norepinephrine levels (Labor Diagnostika Nord GmbH & Co.KG, Nordhorn, Germany) according to manufacturer's guidelines).

### *Statistical Analysis and Data Presentation*

The metric data was presented as mean ± standard deviation and intergroup comparison was done by Mann–Whitney *U* test. The nonmetric data were described as percentage and their intergroup comparison was done by chi-square and Mann–Whitney *U* test. Survival and death comparison, age, dwelling, hospital stay and gender, were done by Fischer exact test with 2/2 test. Significance of results was checked at 95% confidence interval. MS-Excel (Microsoft, Redmond, Washington) and SPSS (SPSS IBM, New York, New York) software and graph pad prism (GraphPad Software, San Diego, California) was used for data analysis.

## Results

Twenty-four hours urinary cortisol levels on day 3 of cases were found to be higher in patients, which subsequently developed infection and was significantly higher than those of the control cases ($P = .023$; Fig 1, A). Furthermore, at day 8 of illness, urinary cortisol levels decreased, with levels in patients consistently more than control group ($P = .063$). Twenty-four hours urinary norepinephrine levels decreased remarkably at day 8 in patients (Fig 1, B). However, urinary norepinephrine also showed a decrease in control group but not to the extent as shown in cases. Norepineprine level was more in cases at day 3 but was not statistically different from that of control group at day 3 ($P = .077$). Similar results were observed on day 8 ($P = .183$) as well.

Plasma IL-6 and IL-10 levels were determined at day 3 and day 45 in all the cases and controls. Plasma IL-6 showed a 15-fold decrease at day 45 in comparison with day 3 in patients, whereas controls showed an 8-fold decrease at day 45 in comparison with day 3 (Fig 1, C). However, plasma IL-6 levels though were higher in cases as compared with controls but the results did not reach statistical significance ($P = .060$). The levels of IL-6 in plasma on day 45 had a significant drop in both cases and controls and remained higher in cases than controls even on that day ($P = .841$; Fig 1, C). Although higher levels of IL-10 were observed on day 3 in comparison with day 45 in both groups under study these were statistically insignificant ($P$ value of .216 and .192, respectively; Fig 1, D).

A total of 12 patients of 39 died with mortality of 30.7%. When these patients were subdivided into cases and controls, the mortality showed statistically significant