Human Immunodeficiency Virus - Associated Stroke: An Aetiopathogenesis Study


Abstract
Objective: To describe the nature of human immunodeficiency virus (HIV) associated stroke and further establish its etiopathogenesis

Methods: A retrospective study of 19 patients of HIV associated stroke, admitted in Regional Institute of Medical Sciences, Imphal between November 2010 and November 2011. History was taken stressing importance on mode of transmission of HIV, risk factors for stroke, antiretroviral treatment (ART) and regimen. All necessary haematological, serological and neuroradiological investigations, cerebrospinal fluid (CSF) examination were undertaken in relevant cases. A final diagnosis of stroke aetiology was made with the corroborative evidence of clinical examination and investigational data.

Results and Observations: Out of the 19 patients of Stroke in HIV, male-female ratio was 1.1:1. The mean age at presentation was 39.47 ± 8.1 yrs (Range 28 - 60). Only 3 (15.78%) patients were on ART and other 16(84.42%) patients were ART naive. In 15 out of 19 patients(78.94%) stroke was the first presentation of HIV infection. 3 patients (16.67%) had recurrent cerebrovascular accident (CVA). Computerised tomography (CT) Brain revealed Infarction in 17 patients (89.47%), 1 patient (5.26%) had Haemorrhage and 1 patient (5.26%) had both haemorrhage and infarction. 9(47.36%) patients had an associated opportunistic infection (OI) in the central nervous system (CNS). In 52.64% patients who had no OIs in the CNS, further work up revealed no aetiology in 3 cases(15.78%) and Indeterminate aetiology (HIV associated coagulopathy and HIV vasculopathy) in 7 (36.84%) patients. Mean CD4 cell count in HIV and Stroke patients was found to be 178.3 ± 115.38 cells/mm³.

Conclusion: Stroke is being reported more often as the first presentation of HIV infection. Thus it is worthwhile to screen for HIV infection in the work up for stroke in the young, and after confirmation of HIV infection, should further proceed to establishing an aetiopathogenesis for Stroke in HIV.

Introduction
Stroke in HIV is on the rise and data from developed countries confirm HIV infection as a risk factor for stroke, the mechanism still being unclear.¹ In 2004 Cole JW et al published the first population-based study which showed that HIV is strongly associated with both ischaemic and haemorrhagic stroke.² Several possible mechanisms have been hypothesised to account for stroke in association with HIV: a pro-thrombotic state³ or a covert HIV-induced vasculopathy⁴,⁵ or in the context of infections or meningitis.⁶

HIV is an emerging aetiology for stroke in the young, particularly in a population with high seroprevalence for retroviruses. Studies reveal that HIV as a cause for stroke is increasing even in the general population stroke data. Presentations where stroke as the first manifestation of HIV infection are not unheard of in the present day clinical practice, furthermore stressing the importance of this topic.

There are about 2.5 million HIV infected patients in India, with Manipur...
contributing to 8% of India’s total HIV positive cases. Our objective was to describe the nature of stroke in HIV infected patients in a high seroprevalence region like ours and further establish its aetiopathogenesis.

Table 1: Showing characteristics of the patients included in the Study

<table>
<thead>
<tr>
<th>Sl no</th>
<th>Age</th>
<th>Sex</th>
<th>Risk factors for Stroke (Age, Sex, Smoking, Type 2 DM, HTN, Dyslipidaemia, Cardiac anomalies)</th>
<th>IVDU</th>
<th>Neuroradiology CT/MRI Brain</th>
<th>CSF for OI’s</th>
<th>CD4 cell count</th>
<th>ART</th>
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<tr>
<td>1</td>
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<td>F</td>
<td>Age</td>
<td>No</td>
<td>Infarction Left frontotemporoparietal region</td>
<td>CMV and Toxoplasmosis IgG positive</td>
<td>107</td>
<td>No</td>
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<tr>
<td>2</td>
<td>32</td>
<td>F</td>
<td>---</td>
<td>Yes</td>
<td>Infarction of left posterior limb of internal capsule</td>
<td>---</td>
<td>92</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>---</td>
<td>Yes</td>
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<td>Toxoplasmosis IgG positive Tubercular Meningitis</td>
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<td>---</td>
<td>No</td>
<td>Multifocal Infarction</td>
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<tr>
<td>5</td>
<td>40</td>
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<td>Smoking Alcohol</td>
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<td>Right posterior periventricular and parietal subcortical infarct</td>
<td>---</td>
<td>60</td>
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<tr>
<td>6</td>
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<td>Smoking Alcohol</td>
<td>Yes</td>
<td>Infarction involving left cerebellar hemisphere, cerebellar peduncle and left pons</td>
<td>CMV and Toxoplasmosis IgG positive Cryptococcal Meningitis</td>
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<td>No</td>
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<td>CMV IgG positive Toxoplasmosis IgG intermediate</td>
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<tr>
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<td>CMV-IgG reactive</td>
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<td>46</td>
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<td>11</td>
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<td>---</td>
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<td>No</td>
<td>Infarction in Left internal Capsule</td>
<td>---</td>
<td>233</td>
<td>No</td>
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<tr>
<td>13</td>
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<td>M</td>
<td>Smoking Alcohol</td>
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<td>Infarction in Left temporoparietal region</td>
<td>Toxoplasmosis IgG positive</td>
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<td>Dyslipidaemia</td>
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<td>M</td>
<td>Smoking</td>
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<td>---</td>
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<td>Yes</td>
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<td>M</td>
<td>Smoking Age</td>
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<td>Right Basal Ganglia Infarction</td>
<td>Cryptococcal antigen positive IgG CMV positive IgG Toxo-intermediate</td>
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<tr>
<td>19</td>
<td>44</td>
<td>M</td>
<td>---</td>
<td>No</td>
<td>Lacunar Infarction in the left internal capsule</td>
<td>CMV-IgG reactive</td>
<td>224</td>
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</table>

Material and Methods

This is a retrospective study undertaken in the Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur between time period of November 2010 and November 2011. 19 patients including known HIV patients presenting with stroke and a stroke patient who was found to be having HIV infection subsequently on work up, in the Medicine Ward were studied for establishment of a causal relationship between the two.

Stroke was defined according to the criteria of the World Health Organisation as a focal neurological deficit of sudden onset with symptoms lasting > 24 hours or leading to death before this period with no other cause than cerebrovascular disease. This definition excludes patients with subarachnoid haemorrhage and transient ischaemic attack. The definitions of cerebral infarction and Intra-cerebral Haemorrhage (ICH) were based on the criteria of
Fig. 1 : MRI brain in an HIV infected patient showing multifocal infarction (CD4 count- 46 cells/mm³, Age-35 yrs)

the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke. Their age and sex were recorded. A detailed history for mode of transmission of HIV, risk factors for CVA like smoking, alcohol, type 2 diabetes mellitus, hypertension, cardiac disorders (valvular heart disease and cardiomyopathies) and bleeding diathesis were enquired and recorded (Table 1). An enquiry into the patient’s ART regimen and duration was recorded. Their routine laboratory investigations were also noted with particular interest to random blood sugar and ECG. HIV status was confirmed as per national AIDS control organisation (NACO) guidelines and CD4 cell count by fluorescence activated cell sorter (FACS) method also obtained in every patient. All patients were screened for syphilis with venereal disease research laboratory (VDRL) test. CT brain was obtained from every patient and patients who needed further neuroradiological investigations were subjected to magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) brain (Figure 1 & 2). CSF examination was done in all patients unless contraindicated. Serum for toxoplasma-cryptococcus antigen-varicella zoster virus, fasting lipid profile, coagulation profile, anti nuclear antibody (ANA), anti phospholipid antibody (APLA) profile, echocardiogram, carotid doppler were also obtained in relevant patients when necessary. Patients were also screened for hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infections. A final diagnosis of stroke aetiology was made with the corroborative evidence of clinical examination and investigational data.

Results

Out of the 19 patients of stroke in HIV, 10 were male and 9 were female with male-female ratio of 1.1:1. The mean age at presentation was 39.47 ± 8.17 yrs (Range 28 - 60). 12 (63.15%) patients had risk factors for stroke like age, smoking, alcohol and dyslipidaemia with presence of other confounding factors. None of the patients were diabetic, hypertensive or had known bleeding diathesis. 8 (42.1%) patients had intravenous drug use (IVDU) history with 5 (26.31%) of them having HCV co-infection. None of the patients had syphilis (Table 1).

Only 3(15.78%) patients were on ART and other 16(84.42%) patients were ART naive. 2 patients were on ART for a duration of 1 year and the other patient had just been initiated. In 15 out of 19 patients (78.94%) stroke was the first presentation of HIV infection. 3 patients (16.67%) had recurrent CVA.

CT brain revealed infarction in 17 patients (Figure 1) (89.47%), 1 patient (Figure 2) (5.26%) had Haemorrhage and 1 patient (5.26%) had both haemorrhage and infarction. 9(47.36%) patients had an associated OI in the CNS. The contributing OIs found were cytomegalovirus (CMV) (77.78%), toxoplasma (44.45%), tuberculosis (22.23%) and cryptococcus (22.23%). 4 out of 8 cases had 2 co-existent CNS OIs and 1 patient had Triple OI in the CNS.

10 (52.63%) out of 19 patients who had no OIs in the CNS, further work up revealed no aetiology in 3 cases(15.78%) and indeterminate aetiology (HIV associated coagulopathy and HIV vasculopathy) in 7 (36.84%) patients. Patients were put under indeterminate aetiology as HIV associated coagulopathy and HIV vasculopathy were most probable in those patients but it could not be proved due to un-affordability of the patients for further work up.

Mean CD4 cell count in HIV and stroke patients was found to be 178.3 ± 115.38 cells/mm³.
Discussion

In our study, HIV associated stroke affected young population with a risk factor profile that differed from the HIV negative young population in that hypertension, diabetes, hyperlipidaemia and smoking were not significant risk factors. Mean age at presentation was 39.47 ± 8.17 yrs which are consistent with findings of Tipping et al which showed mean age of 33.4 years.7 This finding is further consistent with other studies viz JW Cole et al, JJ Kumwenda et al.2,10

Mean CD4 cell count in HIV and stroke patients was found to be 178.3 ± 115.38 cells/mm³ in the present study. In Deshpande AK et al study there were 20 cases of stroke that were apparently due to HIV infection per se, ten patients had a CD4+ cell count between 200 and 500 cells/mm³, whereas 8 cases (40%) had a CD4+ cell count between 100 and 200 cells/mm³ and mean CD4+ cell count was 212 cells/mm³.11

Indian study by Deshpande AK et al showed stroke syndromes affected 29.8% (n=20) patients in 67 HIV patients with non-opportunistic neurological manifestations.11 Tipping et al showed that 6.2% were HIV associated in all-cause morbidity for stroke in general population which proves that HIV is an important association for stroke in general population, not just young population (< 45 yrs).

Three (15.78%) of our HIV patients were receiving ART. 2 of them were on ART for a duration of 1 year. A large study in a very different population group has demonstrated an association with ART and an increased risk of cardiovascular and cerebrovascular events. This risk increases over time but is evident within the first year of therapy.12

Cerebral infarction occurred in 94.73% and ICH in 10.5% patients in our study, consistent with findings of many studies.13,14

Tipping et al observed primary aetiologies comprising of infectious meningitides/vasculitides in 28% patients, coagulopathy in 19% patients and cardio-embolism in 14% patients, multiple aetiologies in 11% patients and HIV associated vasculopathy in 20% patients. Kumwenda et al stated brain infection seems to play an important role in the differential diagnosis of stroke because evidence for this was found in 23% of HIV-positive patients in their study. They also mention in those who are HIV positive, brain infection should be considered for which the presence of fever and examination of cerebrospinal fluid seems most useful in diagnosis. Since our study was conducted in a population with high seroprevalence of HIV with relatively high incidence of CNS manifestations as a result of OIs, 47.36% patients had an associated OI in the CNS. OIs noted were CMV (77.78%), Toxoplasma (44.45%), Tuberculosis (22.23%) and Cryptococcus (22.23%). 4 out of 8 cases had 2 co-existent CNS OIs and 1 patient had Triple OI in the CNS. This high percentage could be attributed to the newer serology tests for Toxoplasma and CMV in the CSF.

In our study, 52.63% patients had no evidence of OIs in the CNS, further work up revealed no aetiology in 3 cases(15.78%) and Indeterminate aetiology(HIV associated coagulopathy and HIV vasculopathy) in 7(36.84%) patients.

Protein S deficiency has been recently recognised as an epiphenomenon of HIV infection with no recognised relation to stroke.15 This casts doubt on the reported aetiological association with stroke in previously reported studies which attributed this as a cause for infarcts.16 Coagulopathy attributed to the presence of elevated anticardiolipin antibodies have been reported to occur in up to half of patients infected with HIV and correlate highly with the presence of perfusion defects on single positron emission computed tomography scanning.16

HIV associated vasculopathy is a poorly defined vasculopathy reported in adults as involving either large or medium extracranial or intracranial arteries.14,17-19 The extracranial large arteries may manifest with both aneurysmal and non-aneurysmal disease.18 Similarly, the intracranial vasculopathy may manifest with both aneurysmal and non-aneurysmal lesions. In addition to large and medium vessel involvement, an intracranial small vessel vasculopathy has been described in an autopsy series of patients that died with acquired immunodeficiency syndrome (AIDS).20

In our study, 15 out of 19 patients(78.94%) stroke was the first presentation of HIV infection. 3 patients (16.67%) had recurrent CVA. Data for comparison for both these variables is not available till date from the published studies.

There are still many grey areas in HIV associated stroke, especially the role of antiplatelets as there is no literature available till date. Furthermore relationship between ART and HIV associated stroke should be studied in the coming years as ART is now available globally.

Apart from a small sample size, our study is not population based or age and sex matched comparative study, which are drawbacks. Prospective, age and sex matched population based studies with large sample size and also study of outcome will improve the results of such a study.

Conclusion

That HIV infection puts the patient at risk for cerebrovascular events is now an established association. Stroke is being reported more often as
the first presentation of HIV infection. Thus it is worthwhile to screen for HIV in the routine work up for stroke in the young, and after confirmation of HIV infection work up should further proceed to establishing an aetio-pathogenesis for stroke in HIV. Larger population based age and sex matched and outcome studies are needed to strengthen the aetiological association as well as throw light on grey areas like use of antiplatelets, impact of ART on HIV associated stroke.

References