Stroke in patients with tuberculous meningitis in a low TB endemic country: an increasing medical emergency?

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SUMMARY

Stroke due to brain vascular disease is a serious complication of tuberculous meningitis (TBM). This study evaluated the frequency, clinical characteristics, risk factors and outcomes of patients with TBM complicated by stroke admitted to the Infectious Disease Clinic, University of Perugia Hospital, Italy from 1971 to 2010.
Over four decades, 419 patients were admitted with tuberculosis, of these 30 (7.1%) were diagnosed with TBM: 20 definite, one probable and nine possible. Twenty-six were evaluable for stroke and six (23%) had stroke. The latter six had advanced stages of meningitis, two tested HIV positive, three HIV negative and in one HIV was not performed. Of seven patients without stroke tested for HIV, only one resulted positive. No differences were found regarding CSF cell count, sugar, protein, microscopy or growth of *Mycobacterium tuberculosis* among patients with or without stroke. The overall survival rate at discharge was 83% in patients with stroke and 95% in those without stroke. It was found that stroke can be frequent among patients with TBM and the presence of HIV infection might be associated with a higher rate of stroke. Further research is needed on these findings, especially in low TB endemic countries.

KEY WORDS: Stroke, Tuberculous meningitis, HIV co-infection.

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Meningitis is the most frequent manifestation of central nervous system (CNS) disease due to *Mycobacterium tuberculosis*, making up 1-10% of all TB cases (Rock *et al.*, 2008; Kalita *et al.*, 2009; Garg, 2010). However, the global incidence and prevalence of tuberculous meningitis (TBM) is not precisely known (Garg, 2010). Being a child, HIV co-infected or having other immunocompromised diseases are recognised risk factors for TBM. Additionally, non-native persons residing in developed countries also tend to be at higher risk of TBM (Rock *et al.*, 2008; Kruijshaar *et al.*, 2009; Peto *et al.* 2009; Garg, 2010; Garg *et al.* 2011; Christensen *et al.*, 2011; Marais *et al.*, 2011). In a five year retrospective study carried out in Spain between 1985 and 1990, HIV antibodies were detected in 10% of culture proven TBM but only 2% of HIV-negative individuals were diagnosed with culture proven TBM (Berenguer *et al.*, 1992). A large Indian study reported TBM in 25 (7%) out of 163 HIV co-infected patients admitted with TB between 2001 and 2003 (Attili *et al.*, 2005). The reported rate of HIV-associated TBM was also 7% among 43 patients with TBM in a Thailand study (Helbok *et al.* 2006). From a prospective Indonesian adult meningitis cohort study, including 183 patients with meningitis, *M. tuberculosis* resulted the most frequent aetiology, a total of 153 cases, with 31 being HIV-infected (Ganiem *et al.*, 2009).

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TBM is challenging to diagnose, and when diagnosed its complications are problematic at best. One of the most serious complications of TBM is stroke due to TB-associated vascular disease which can lead to higher rates of mortality and long-term morbidity (Koh *et al.*, 2007; Shukla *et al.*, 2008; Kalita *et al.*, 2009; Lammie *et al.*, 2009; Anuradha *et al.*, 2010; Garg, 2010; Misra *et al.*, 2011). Stroke can occur throughout the course of TBM (Koh *et al.*, 2007; Lammie *et al.*, 2009; Springer *et al.*, 2009; Anuradha *et al.*, 2010; Kalita *et al.,* 2009; Misra *et al.*, 2011), however, the more advanced stages of disease have been statistically associated with the greatest risk of stroke (Koh *et al.*, 2007; Lammie *et al.*, 2009; Anuradha *et al.*, 2010). Koh *et al.* compared the clinical and laboratory findings in patients with TBM with and without stroke and found that polymorphonuclear leukocytosis in the CSF, menigeal enhancement on CT, and the advanced stage of disease had the closest relationship with stroke (Koh *et al.*, 2007). The reported rates of TBM-associated stroke differ according to the types of investigations performed (Rock *et al.*, 2008; Shukla *et al.*, 2008; Lammie *et al.*, 2009; Misra *et al.*, 2011; Singh *et al.*, 2012). Additionally, TBM-related stroke can be difficult to diagnose clinically because it may occur in a silent area of the brain, the patient may be comatose making impossible to detect neurologic changes, or confusion may arise from a pre-existing deficit (Misra *et al.*, 2011). Most TBM-associated brain infarcts are multiple, bilateral, sometimes symmetric, located in the basal ganglia, anterior thalamus, anterior limb, and/or the genu of internal capsule (Lammie *et al.*, 2009; Misra *et al.*, 2011). Cortical, subcortical white matter, brainstem and hindbrain involvement are less common, except in cases prolonged by treatment and HIV co-infection (Lammie *et al.*, 2009; Katrak *et al.*, 2000; Misra *et al.*, 2011; Garg *et al.*, 2011). Stroke in TBM is due to vasculitis or intimal proliferation or both, with or without superimposed thrombosis or spasm (Lammie *et al.*, 2009; Misra *et al.*, 2011). Other types of blood vessel damage include: aneurysmal dilatation, ruptured mycotic aneurysms, septic embolisms and arteries strangulated by inflammatory exudates (Lammie *et al.*, 2009; Misra *et al.*, 2011).

Over the last two decades, mostly due to increasing rates of immigration from high TB endemic countries as well as HIV co-infection (Scotto *et al.*, 2009; Peto *et al.*, 2009; Kruijshaar *et al.*, 2009; Pasticci *et al.*, 2012), low TB endemic nations have been observing rising rates of extrapulmonary TB, including meningitis (Peto *et al.*, 2009; Kruijshaar *et al.*, 2009; Garg *et al.*, 2011).

The aim of this study was to evaluate the frequency, clinical characteristics, risk factors and clinical outcome of patients with TBM complicated by stroke.

A retrospective analysis of patients with TBM admitted to the Infectious Disease Clinic, University of Perugia Hospital, Italy from 1971-2010 was performed. TBM was diagnosed from: clinical evidence of meningitis plus cerebrospinal fluid (CSF) abnormalities (leucocytes ≥6 mm^3, with a lymphocyte predominance, protein ≥60 mg dl, CSF glucose to plasma glucose less than 0.5, sterile stain and culture for bacteria and fungi) and ≥1 of: presence of acid fast bacilli (AFB) in CSF smear or identification of *M. tuberculosis* from culture or with nucleic acid amplification (SDA) from CSF, AFB found in any other specimen other than CSF, clinical evidence of pulmonary or extrapulmonary TB, improvement with prescription of anti-TB treatment. Severity of TBM at admission was re-assessed based upon the modified Medical Research Council criteria (Rock *et al.*, 2008) and the interval between symptom onset and TBM diagnosis was determined. The evolution of TB was recorded until discharge or death for all patients.

Stroke was defined according to the World Health Organization's criteria as sudden onset of signs of focal or global disturbance of cerebral function lasting more than 24 h (unless interrupted by specific treatment, surgery or death), without any cause other than vascular. Prior to the availability of computed tomography (CT) or brain magnetic resonance (MRI), patients with clinical signs of stroke underwent conventional cerebral angiography. TBM patients manifesting sudden neurological deterioration or death, who had not undergone radiological or autopsy investigations, were considered non-evaluable for stroke and not included in the analysis.

The chi-square test, with a correction for continuity and the Fisher exact test (when appropriate), were used to compare risk factors and clinical characteristics in patients with TBM and stroke and patients with TBM without stroke. The

Wilcoxon rank-sum test was used to compare the continuous variables.

Over the study period, 419 patients with TB were admitted: 50 (11.9%) HIV-positive, 245 (58.4%) HIV-negative and 124 (29.6%) HIV status unknown. Overall, 30/419 (7.1%) were diagnosed with TBM: ten from 1971 to 1980, five from 1981 to 1990, 11 from 1991 to 2000 and four from 2001 to 2010. Of these 30 cases, 20 were definite, one probable and nine possible (Marais *et al.*, 2010). TBM was diagnosed in 4/50 (8%) HIV-infected and 9/245 (3.6%) HIV-negative subjects (p=0.2). HIV status was not known for 17 patients: ten were admitted before 1986 when HIV serology was not available, while seven were admitted after 1986. Four out of 30 TBM cases were judged non-evaluable for stroke as neuroimaging and/or autopsy investigations to determine the vascular

TABLE 1 - *Variables in patients with TBM with and without stroke.*

Variable	*Stroke (N=6)*	*No stroke (N=20)*	*P*
Age (years) >12 y	5 (83%)	20 (100%)	0.23
Sex (M)	3 (50%)	7 (35%)	0.6
Diabetes mellitus	1 (17%)	2 (10%)	0.5
Italian nationality	5 (83%)	18 (90%)	0.5
HIV positive	2/5 (40%)	1/7 (14%)	0.5
Hypertension	1 (17%)	0	0.2
TBM stage			
I	0 (0%)	11 (55%)	0.02
II	0 (0%)	8 (40%)	0.08
III	6 (100%)	1 (5%)	<0.01
Focal neurologic deficit	6 (100%)	1 (5%)	<0.01
Altered mental status	6 (100%)	9 (45%)	0.02
Cranial nerve deficit	3 (50%)	6 (30%)	0.33
Seizures	2 (33%)	0 (0%)	0.04
Symptoms/diagnosis weeks (range)	8.50 (2-25)	4.20 (1-11)	0.42°°
CSF			
Cells mm^3 (range)	215.5 (16-320)	218.3 (6-744)	0.52°°
Protein mg dl (range)	95.5 (42-150)	154.8 (26-1700)	0.42°°
Sugar mg dl (range)	27.3 (9-44)	27.0 (9-53)	0.66°°
Microscopy positive	1 (17%)°	11 (55%)°,#	0.1
Culture positive	1 (17%)	6 (30%)	0.47
Steroids	4 (66%)	12 (60%)	1.0
Survival*	5 (83%)*	19 (95%)*	0.41
Overall survival	24/30 (80%)*		

°Not the same patient with positive culture; #4/11 also culture positive; *at discharge, including all 30 patients. Four patients were non-evaluable for stroke: 3 died of sudden neurologic deterioration, 1 had neurological deterioration and was transferred to intensive care but lost at follow-up. °°Wilcoxon rank-sum test.

origin of the presenting or newly developed neurological disturbances were not performed. Of the 26 patients evaluable for stroke (Table 1), six (23%) had suffered stroke at a mean of eight weeks (2-25) after onset of TBM symptoms. All six patients with stroke had stage III meningitis on admission. Two of these patients, tested HIV-positive, three HIV-negative and in one HIV testing was not performed; this latter patient had been diagnosed in 1976. One out of seven patients with TBM without stroke tested positive for HIV infection. For the 26 patients evaluable for stroke, no differences were found regarding CSF cell count, sugar, protein, microscopy or growth of *M. tuberculosis*.

Five of the cerebral lesions were located in the anterior circulation: two cortical associated with a striato-capsular lesion (one with secondary hemorrhagic transformation), two striato-capsular lesions (one with secondary hemorrhagic transformation) and one cortical. One patient had cerebral lesions in the posterior circulation with secondary hemorrhagic transformation. In four patients, large vessel involvement was documented: two middle cerebral artery, one right internal carotid siphon and one posterior cerebral artery.

All 30 patients with TBM were administered a combination of anti-TB drugs including: 29 isoniazid, 26 ethambutol, 24 rifampin, 15 pyrazinamide, ten streptomycin, two rifabutin, three levofloxacin, one ciprofloxacin, one moxifloxacin, one amikacin, one morfazinamide, one ethinamide and one clarithromycin.

Corticosteroids were administered to 4/6 and 12/20 patients with and without stroke, respectively and in 3/4 non-evaluable for stroke (Thwaittes *et al.*, 2004; Thwaittes *et al.*, 2009). One patient received aspirin 100 mg per day starting 48 h following stroke.

There was no significant difference between the two groups regarding outcome. The survival rate at discharge for the 30 TBM patients was 80%; specifically: 83% with stroke and 95% without stroke.

This study reports that the rate of TBM among HIV-infected patients was twice that of HIV-negative patients. However, over the first three decades of this forty year review, the prevalence of admissions was for extrapulmonary TB disease.

Based on clinical manifestations, thereafter confirmed by radiographic investigations, 23% of patients with TBM had a stroke. This rate is in agreement with other studies (Lammie *et al.*, 2009; Misra *et al.*, 2011). Overall, all the patients with stroke had stage 3 meningitis, and the presence of HIV infection seemed to be associated with an increased rate of stroke, even though this difference was without statistical significance.

A higher incidence of brain infarcts, more often involving the cortical and subcortical areas and located in the cortex, has also been reported in HIV co-infected patients (Katrak *et al.*, 2000; Schutte, 2001, Lammie *et al.*, 2009; Garg *et al.*, 2011). However, there are no readily available data regarding the frequency and clinical characteristics of HIV co-infected patients with TBM who have stroke or its management (Thwaittes *et al.*, 2004; Thwaittes *et al.* 2009; Lammie *et al.*, 2009; Misra *et al.*, 2010).

Regarding HIV-positive patients with TBM, fever, impaired cognition, focal signs, seizures and lymphadenopathy are more often reported (Berenguer *et al.*,1992; Katrak *et al.*, 2000; Lammie *et al.*, 2009; Marais *et al.*, 2011; Croda *et al.*, 2011; Garg *et al.*, 2011). The classic triad of fever, headache and meningeal signs was present in only 15% of the 108 patients with HIV-associated TBM admitted from 1999 to 2007 at the Emilio Ribas Institute in Sao Paolo, Brazil (Croda *et al.*, 2011). In this Brazilian study, the drug susceptibility of *M. tuberculosis* was also examined, reporting a rate of primary isoniazid resistance and multidrug resistance (MDR) of 8% (7/90) and 9% (8/90), respectively. Six out of eight patients with MDR TBM had a history of tuberculosis. None of the isolates tested were reported to have an extensive drug resistance pattern (Croda *et al.*, 2011). Twaittes *et al.* carried out a large study published in 2005, which examined clinical manifestations at onset and response to treatment of TBM among 96 HIV co-infected and 432 HIV uninfected patients. It was reported that HIV did not alter the neurologic features of TBM, however, mortality was higher in this group. At presentation, significant ($p<0.5$) clinical differences of HIV-associated meningitis were: male sex, younger age, lower body weight, lower Glasgow coma score and a lower hematocrit, peripheral blood leukocyte count as well as lower plasma sodium levels. HIV co-infected patients were al-

so reported to have higher concentrations of aspartate and alanine aminotransferase, as well as higher rates of hepatitis B surface antigen, positive CSF cultures for *M. tuberculosis* and drug-resistant isolates. However, some of these differences were related to the epidemiologic pattern of the HIV-infected cohort and to the effect of systemic immunocompromise and extrapulmonary TB (Thwaittes *et al.*, 2005). Schutte reviewed clinical, CSF fluid and pathological findings in 20 HIV co-infected and three HIV non-infected patients with TBM admitted over a five year period to the neurology word of the Pretoria Academic Hospital, South Africa and reported similar clinical features and outcome in HIV-positive and HIV-negative patients. Ventricular dilatation and brain infarcts occurred more commonly among HIV co-infected subjects. Moreover, in the same study, Glasgow coma score on admission resulted a better indicator of outcome than CD4+T cell counts for HIV-positive patients (Schutte, 2001). Regarding CT findings, HIV-positive patients had less basal enhancement, which occurred later after anti-TB therapy, and less frequently developed obstructive hydrocephalus (Katrak *et al*., 2000). Histopathological data indicated thinner exudates and no obstruction to CSF outflow and higher bacterial loads (Katrak *et al*., 2000).

Overall, clinical differences in HIV co-infected patients can be directly linked to the degree of immune compromise. In fact, patients with lower levels of CD4+T lymphocytes are more likely to have subtle and less specific manifestations of meningitis along with lower levels of inflammatory reaction (Garg, 2010).

This review has the following limits:

1) retrospective analysis;
2) radiological techniques, microbiological investigations and treatment guidelines were not uniform;
3) follow up was limited to time of discharge in most cases;
4) a low number of patients were examined.

In conclusion, in low TB incidence countries, the increasing numbers of patients at risk for all forms of TB, including TBM (Peto *et al.*, 2009; Kruijshaar *et al.*, 2009), could be the cause of an increase in TBM secondary stroke. In order to determine this, a national/international registry of TBM cases needs to be set up with all-inclusive standardized guidelines.

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