Original Research
Clinical Case Series

Middle Cerebral Artery Infarction in Central Nervous System Tuberculosis

Naila Shahbaz[1], Yasmeen Hassan[2], Saima Kashif[3], Mohammed Abdullah[4]

ABSTRACT

Objective: To show the occurrence of medium vessel vasculitis in patients with central nervous system tuberculosis, meningitis and/or tuberculomas, which we do not see infrequently, but which is rarely reported in the literature.

Methodology: It was a prospective, observational study conducted at Department of Neurology, Dow University of Health Sciences, Karachi from January 2008 to June 2010. (Only five cases presented to Civil Hospital, Karachi directly; out of other five three patients were seen by the primary author at a charitable hospital which does not provide admitting facilities and therefore were brought to Civil Hospital and other two were seen at a private clinic which does offer admission facilities but patients could not financially afford to stay in those hospitals were also brought to Civil Hospital).

Results: A total of 10 patients with central nervous system tuberculosis who also had stroke as a result of medium vessel vasculitis, middle cerebral artery infarction in all of our cases, were analyzed. There was equal number of male and female patients with an age range of 7-54 years. Two patients had stroke at presentation and two developed after 8 weeks of treatment while remaining patients had stroke between 1-4 weeks. None of the patients had evidence of extrneural tuberculosis and only two patients had other risk factors for stroke which were convincingly ruled out as cause for stroke at that time. Three patients also had small vessel vasculitis in addition to larger stroke. Only one patient expired, one made complete recovery and 8 patients made partial recovery.

Conclusion: Although small vessel vasculitis is a known complication of CNS tuberculosis, medium vessel vasculitis is not uncommon and contribute significantly to the mortality and morbidity of the infection.

KEY WORDS: Central nervous system tuberculosis, Stroke.

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1. Dr. Naila Naeem Shahbaz FCPS (Neurology)
Assistant Professor,
2. Dr. Yasmeen Hassan FCPS (Neurology)
3. Dr. Saima Kashif FCPS (Neurology)
4. Prof. Mohammed Abdullah FCPS
1-4: Department of Neurology,
Dow University of Health Sciences & Civil Hospital,
Baba-e-Urdu, Karachi, Pakistan.

Correspondence:

Dr. Naila Naeem Shahbaz,
E-mail: naila.shahbaz@gmail.com

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INTRODUCTION

According to WHO report 2009, Pakistan ranks eight among 22 high burden countries of tuberculosis (incidence 181 per 100,000) with a death toll of 50,000 annually.[1] Tuberculous meningitis is the fifth commonest form of extrapulmonary TB, accounts for 5.2% of all cases of exclusively extrapulmonary disease and 0.7% of all reported cases of TB.[2] It complicates approximately 1 of every 300 untreated primary TB infections. In an American epidemiological study of extrapulmonary tuberculosis, up to 10% of cases showed CNS involvement[3] while CDC data indicated that 6.3% of extrapulmonary cases (1.3% of total

tuberculosis cases) had CNS TB.[4] In a Taiwan study, 1.5% of TB deaths between 1997 and 2001 were attributable to CNS disease, a percentage that had increased from previous years.[5] Tuberculous meningitis (TBM) is quite prevalent and frequently diagnosed in tertiary care hospitals in Pakistan.[6-9] To date, little literature is available regarding incidence and prevalence of TBM in Pakistan. A recently published local study showed an incidence of 9.3% cases of CNS tuberculosis, third commonest in their series of their total 194 cases of extrpulmonary tuberculosis.[10] There are few reports from the region regarding the demographic data and complications of TBM.[6-9]

TBM is associated with many acute, sub-acute and delayed complications, of which stroke is a leading cause of residual disability among survivors.[11] Cerebro-vascular events present in diverse way and continue to evolve during initial days of treatment. Patients with tuberculous meningitis develop stroke in up to 6-41% of cases[12], usually involving the small, terminal lenticulostriate branches[13], explaining the usual and more severe distribution of infarctions in the region of basal ganglia. However, involvement of medium and large sized vessels is rare and only rarely infarcts are seen in pattern of territorial distribution of major cerebral arteries.

METHODOLOGY

We present the data of ten patients of tuberculous meningitis reporting to us with various clinical features who developed clinical stroke at the time of presentation or during the course of treatment.

Diagnosis of tuberculous meningitis was made on the basis of history and clinical examination correlating with CSF abnormalities and MRI and MRA appearances. MRA was done in all patients and CT angiography was done for one patient. CSF abnormalities considered included abnormal proteins, cell count, low sugar and positive culture or PCR for Mycobacterium tuberculosis. Stroke onset from the presentation was divided into 6 groups ranging from stroke at presentation to more than 8 weeks from the presentation. Imaging abnormalities showing infarction in territorial distribution with or without tuberculomas and or basal meningeal enhancement were taken into account. Patients with small vasculitic infarcts alone and hemiparesis caused by tuberculomas were excluded from the study. However, patients with vasculitic infarcts and co-existing territorial infarcts were included. Evidence of extraneural tuberculosis was also sought. Presence of other complications of tuberculous meningitis was also noted. Patients with history of other risk factors for stroke were assessed for the control of risks.

All our patients were given conventional anti-tuberculous therapy along with steroids for eight weeks. ATT was continued for a period of at least 18 months, which is our routine in case of CNS tuberculosis. Six patients had completed this period, one expired and three were still on treatment at the time of Re-writing of this report. Residual disability in patients who survived was assessed on Barthel index. All patients remained in follow up excluding the one who expired, for approximately three months after stopping treatment and five these patients are still attending our OPD for treatment follow up or for other reasons like physiotherapy guidance and other minor issues.

Data of all these patients was analyzed on SPSS 15 in terms of onset of infarction, territory involved,

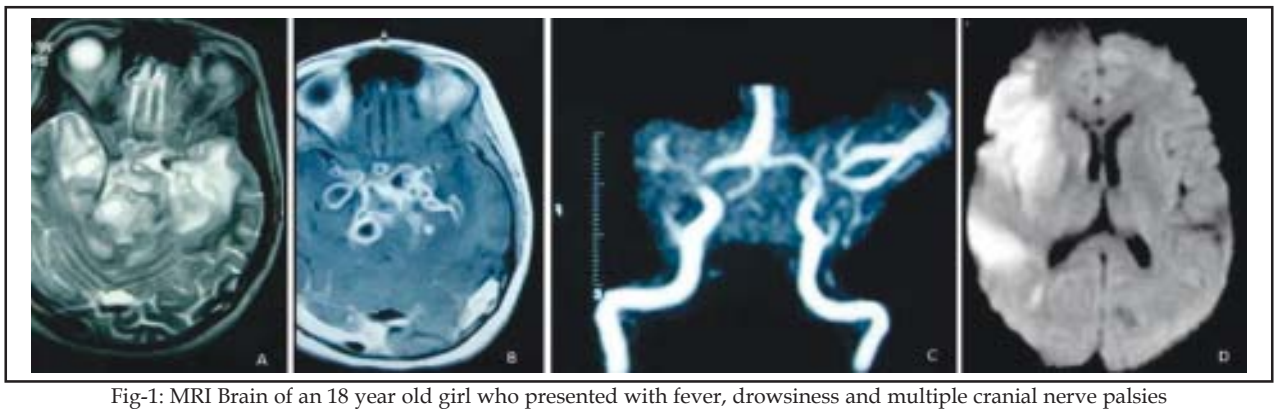

Fig-1: MRI Brain of an 18 year old girl who presented with fever, drowsiness and multiple cranial nerve palsies and developed weakness of left side of body approximately 2 weeks after the initial symptoms.
A. T2Wimage showing multiple tuberculomas with surrounding edema in suprasellar region bilateral temporal lobes and midbrain.
B. T1W gadolinium enhanced image showing typical nodular and rim enhancement of tuberculomas along with enhancement of supresellar cistern and adjacent meninges. C. MRA showing at bifurcation of internal carotid artery in circle of Willis bilaterally and poor visualization of right middle cerebral artery.
D. Diffusion weighted image showing wedge shaped areas of infarctions in right middle cerebral artery territory.

clinical presentation of tuberculomas, meningitis or both, associated risk factors for stroke, and outcome.

RESULTS

Total number of patients with tuberculous meningitis and coexisting middle cerebral artery stroke was 10. Of these five were males and five females with an age range of 7-54 years. All patients had clinical stroke correlating with MRI appearances of infarcts. All patients had elevated CSF proteins, and low glucose; only three patients had predominant neutrophilic pleocytosis and rest had predominant lymphocytosis. Two patients presented with stroke onset, two developed stroke within one week of symptom onset, four had stroke within first month of treatment and two developed stroke later than 8 weeks. Interestingly and co-incidentally all territorial, larger infarcts were located in the right middle cerebral artery territory! Also 3 patients had vasculitic infarcts in addition to territorial infarcts. Six patients had associated mild to moderate hydrocephalus. Seven of our patients developed clinical seizures, one had EEG evidence of seizure activity and two had neither clinical seizures nor EEG activity suggestive of seizures.

In addition to infarction, imaging also revealed tuberculomas in 3 patients with meningitis. Some very interesting observations were made. None of the patient had evidence of active extraneural tuberculosis on investigation, but one patient had history of pulmonary tuberculosis in childhood about 20 years before presenting symptoms.

Two of the patients had other risk factors for stroke, that is, diabetes and hypertension and these were the patients whose presentation was most atypical and initially misleading. Patient no. four, 35 years, known diabetic and hypertensive, both uncontrolled at the time of admission to ER, presented with history resembling stroke-in-evolution for last two days, treated initially as atherosclerotic disease, developed progressive drowsiness and right third cranial nerve palsy and left third and sixth cranial nerve palsy on third day of admission. Initial MRI and MRA showing right MCA infarction with non visible MCA remain unchanged for the area of infarction on repeat imaging on day five but there was development of an enhancing lesion in genu of corpus callosum which was labeled as tuberculomas and mild enlargement of ventricles compared previous one. CSF examination was suggestive of chronic meningitis and anti-tuberculous was added. Diagnosis was later confirmed by positive CSF PCR for tuberculous bacilli. Patient had history of fever two week prior to the onset of symptoms but remained afebrile at presentation and throughout hospital stay. Another patient aged 54 years, also diabetic and hypertensive with poor treatment compliance presented with acute onset left sided weakness, was found to have occluded right cerebral artery with corresponding infarction in the same territory. Patient was stabilized and discharged from the hospital and was taken by the family for "rest" to his village in Kashmir. He was brought again with history of increasing drowsiness and was found to have significant hydrocephalus on imaging. CSF examination and later positive PCR for tuberculosis and negative fungal culture confirmed the diagnosis of tuberculous meningitis. However, during further course patient developed multiple problems, including aspiration pneumonia and could not be saved. Another patient was smoker, but history and laboratory all supported tuberculous etiology of his territorial infarct.

Lastly, all of our patients except one survived. Two patients were left with mild disability (Barthel index score 60-79) and six patients had moderate residual disability (Barthel index score 40-59). One patient made complete recovery to health. All patients were still in our follow up and this neurological status was static for approximately last six months, except for one patient who died approximately within three months of initial diagnosis.

DISCUSSION

Lehrer[14] described an angiographic triad in tuberculous meningitis which included a hydrocephalic pattern, narrowing of the vessels at the base of the brain and narrowed or occluded small and medium sized vessels with scanty collaterals.

Clinical characteristics of patients with Tuberculous Meningitis and MCA Infarction.

Gender:	***Evidence of extra-neural tuberculosis***
M=5	None
F=5	***Previous hx of tuberculosis:***
Stroke onset:	Yes-1 (pulmonary, 20y back)
At Presentation=2	No=9
Within 1 week=2	***Other risks for stroke:***
Within 4 weeks= 4	Yes=2
After 8 weeks= 2	No=8
Type of infarct:	***Outcome:***
MCA infarction: 10	Expired=1
MCA infarction with small vasculitic infarcts: 3	Survived=9
Seizures:	Moderate disability=6
Clinical seizures=7	Mild disability=2
Subclinical seizures=1	Complete recovery=1

Infarction through vasculitis is the mechanism by which many of the clinical neurological abnormalities in TBM occur, and accounts for an appreciable part of the mostly irreversible neurological sequelae like hemiparesis, seizures and movement disorders.[15] The majority of infarctions in chronic tuberculous meningitis are located in the basal ganglia, internal capsule, and thalamus, and rare in the major vascular territory and brain stem.[15-17] This occurs because meningeal inflammatory exudate is known to involve the small and medium-sized arteries in necrotizing, proliferative and infiltrative vasculopathic processes. Larger arteries commonly show periarteritis alone. Capillaries and veins are rarely involved. If ventricular dilatation occurs situation is further compromised due to stretching of vessels.

The stem and/or cortical branches of the MCA are vulnerable in the sylvian fissure and the supraclinoid portion of the ICA may also be damaged. These findings were well described by Ninan T et al when they described angiographic features in tuberculous meningitis.[16] All our patients belonged to this group as none had stroke in vertebro-basilar territory. Finding of involvement of right middle cerebral artery in all cases is most probably coincidental because we could not find any etiological or pathogenetic significance of implication of on particular vessel or other. Involvement of the vertebrobasilar system is uncommon,[18] although occasionally extensive infarctions in the distribution of both posterior cerebral arteries or small brainstem lesions may be observed.

Timing of stroke from the onset is variable. We found no study mentioning timing of stroke from the onset of symptoms for comparison, although few have mentioned presentation to hospital from onset of symptoms. In contrast to study presented by Koh SB et al,[19] who reported neutrophilic pleocytosis more in association with stroke in patients with tuberculous meningitis, only three of our patients had this finding, rest had lymphocytosis.

Finally, mortality was one out of ten patients. Nine patients were left with mild to moderate disability. One patient recovered completely. This 10% mortality rate was close to observance made by Van Well GT, et al, who noted a mortality rate of 13% in South African children in a recent study.[20] However, a study from Spain reported a very high mortality rate of 41% in adults with tuberculous meningitis.[21] This difference is probably because of very high index of suspicion for tuberculous meningitis in endemic areas when it presents and very early and sometimes empirical initiation of anti-tuberculous therapy.

CONCLUSION

Tuberculous meningitis is potentially a fatal condition associated with serious morbidity, caused by many of its attending complications of which stroke is the most feared sequel. It should therefore be recognized early and promptly treated. Vasculitis should always be suspected when patients develop focal neurological deficits although tuberculomas or tuberculous encephalitis can also cause this.

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Authors' Contribution:

NNS conceived, designed, statistically analyzed and did the final manuscript writing.
YH helped in clinical assessment, data collection and manuscript writing.
SK did the data collection, and helped in literature search.
MA finally reviewed and approved the paper.