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Original Article

# Evaluation of cerebral arterial and venous system in tuberculous meningitis

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ABSTRACT

*Background.* – Central nervous system infection especially pyogenic results in cerebral venous sinus thrombosis. Tuberculous meningitis (TBM) although associated with infarctions but there is no comprehensive study evaluating the role of CVST contributing in infarction.
*Purpose.* – To evaluate cerebral arterial and venous system using MR angiography (MRA) and MR venography (MRV) in TBM, and correlate with clinical and MRI findings.
*Materials and methods.* – Consecutive patients with TBM were evaluated clinically and their consciousness was assessed by using Glasgow Coma scale. Cerebrospinal fluid analysis was done. Patients were subjected to MRI, MRA and MRV studies. The severity of TBM was categorized as grades I to III. Presence of infarction on MRI and its cause as arterial or venous was noted based on MRA and MRV abnormalities.
*Results.* – Twenty-six patients were included whose median age was 23 years. Seven (26.9%) patients had stage I, 12 (46.2%) stage II and 7 (26.9%) stage III TBM. MRI revealed infarction in 13 (50%) patients and were in tubercular zone (caudate, lentiform nuclei, anterior limb and genu of internal capsule, and anterior thalamus) in all except one. MRA was abnormal in 11/25 (42.3%) patients; 7 had middle cerebral artery, 2 both posterior cerebral artery and middle cerebral artery, and 2 had narrowing of all intracranial vessels. MRV however did not reveal any evidence of CVST although revealed variation in normal anatomy in 14 (53.8%) patients, commonest being hypoplastic transverse sinus.
*Conclusion.* – In TBM, infarction occurs in 50% patients, and is of arterial in origin. Cerebral venous system is usually spared in TBM.



## Introduction

Tuberculosis is a major global health problem especially in the developing countries. In 2014, the estimated newly diagnosed tuberculosis was 9.6 million. About 23% of total tuberculosis patients reside in India, 10% in Indonesia and 10% in China [1]. Central nervous system tuberculosis is the worst form of tuberculosis and results in death in 20–50% patients, and permanent neurological sequelae in 20–30% of the survivors [2,3]. Tuberculous meningoencephalitis results in a wide range of pathological changes and includes basal exudates, hydrocephalous, tuberculoma and infarction. Studies on infarction in tuberculous meningitis (TBM) are mostly focused on arterial stroke, and have been reported in 13–35% patients on CT scan, up to 57% on MRI and 22–56% on autopsy reports [4,5]. The infarctions are mostly located in the tubercular zone, and stroke in TBM has been reported as a poor prognostic predictor [4,6]. There is no systematic study evaluating the occurrence of cerebral venous sinus thrombosis (CVST) in TBM although CVST has been reported in other central nervous system infections [7]. Tubercular infection has been reported to result in alternation in prothrombotic status (Protein C, Protein S, antiphospholipid antibody syndrome) and proinflammatory cytokines (TNFα, IL1), which may fulfill the Virchow's triad of thrombosis [8,9]. Despite being TBM the commonest cause of subacute to chronic meningitis in developing countries, but there are only 9 case reports of cerebral venous sinus thrombosis (CVST) in association with tuberculosis (PubMed search on 30.6.2016) using "cerebral venous sinus thrombosis"/"cerebral venous thrombosis" AND "tuberculosis/tuberculous meningitis" [10–17]. Some of these patients had associated prothrombotic conditions and other risk factors of CVST. There is no prospective study evaluating the occurrence of CVST in tuberculous meningitis (TBM). The treatment of infarction due to arterial origin is generally antiplatelet, and that

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of venous origin anticoagulant. It is therefore important to know about the cause of infarction in TBM. In this communication, we report the cerebral arterial and venous system abnormalities in the patients with TBM using MR angiography and venography, and correlate these with MRI and clinical findings.

## Subjects and methods

Consecutive patients with TBM during October 2015 to March 2016 were included. The study was approved by the Institute Ethics Committee (PGI/83/EMP/72). The investigations done in the patients were routine and needed for the management of the patients. Cranial MRI was done on a 3-T MRI machine (Sigma, GE Medical system, Milwaukee, USA) using 16 channel head coil. T1, T2, FLAIR, DW1 and T1 contrast images were obtained. For contrast study, 0.1 mmol/kg gadolinium was injected intravenously. The presence of exudates, hydrocephalous, tuberculoma and infarctions were noted. The location of infarctions and tuberculoma were also recorded. Presence of indirect evidences of venous thrombosis was also looked for. Intracranial MR angiography (MRA) was done, and arterial abnormality was recorded. MRA was performed using a quadrature head coil. The sequences used were multi slab (3 slab) 3D SPGR based on time of flight (TOF) sequence. The repetition time, echo time, and flip angle were 26 ms, 6.9 ms and 20°, respectively. The presence of occlusion or more than 50% narrowing of vertebral, basilar, and proximal portion of posterior cerebral artery (PCA), middle cerebral artery (MCA), and anterior cerebral artery (ACA) were considered abnormal [18,19]. Contrast MRV was done, and presence and extent of vein and sinus thrombosis was noted.

## Diagnosis

The diagnosis of tuberculous meningitis was done on the basis of following criteria:

- essential criteria: meningitis symptoms including fever with headache or vomiting for 2 weeks or more in whom malaria, septic and fungal meningitis were excluded;
- supportive criteria:
  - cerebrospinal fluid (CSF) cell $\geq 0.2 \times 109$/L with lymphocyte predominance, protein > 1 gm/L and sterile bacterial and fungal culture,
  - MRI evidence of exudates, hydrocephalous and tuberculoma in various combinations or in isolation,
  - evidence of extra CNS tuberculosis.

Presence of essential and 2 supportive criteria was considered TBM. Presence of acid fast bacilli (AFB) in CSF smear or BATEC culture, positive polymerase chain reaction (PCR) or IgM antibody in the CSF was considered definite and remaining probable TBM [20].

Clinical evaluation: a detailed history including their demographic information, duration of illness, alternation in sensorium, seizure and focal weakness were noted. Consciousness was assessed by Glasgow Coma Scale (GCS). Presence of papilloedema and cranial nerve palsy was noted. Weakness was categorized as hemiplegia, monoplegia and quadriplegia. In the co-operative patients, muscle power was assessed by Medical Research Council (MRC) scale. Muscle tone and tendon reflexes were categorized as normal, increased and reduced. Sensations and cerebellar signs were evaluated in the patients who could cooperate.

Presences of anemia, lymphadenopathy, osteomyelitis, organomegaly, ascites and chest finding were noted. Severity of meningitis was categorized as stages I (meningitis only), stage II (meningitis with focal deficit or GCS score 11–14) and stage III (meningitis with GCS score < 11) [4,21].

Laboratory investigation: lumbar cerebrospinal fluid (CSF) was analyzed for cell, protein and sugar. Cerebrospinal fluid was also subjected for smear and culture of AFB, other bacteria and fungus. ELISA for IgM antibody and PCR for M. tuberculosis DNA were also done. Blood counts, coagulation profile, hemoglobin, erythrocyte sedimentation rate, blood sugar, blood urea nitrogen and serum creatinine, albumin, bilirubin, transaminases, calcium, alkaline phosphatase, phosphorus and electrolytes were done. Radiograph of chest and electrocardiogram were also carried out in all.

Treatment: the patients were treated with standard 4 drugs antitubercular regimen (isoniazide 5 mg/kg, rifampicin 10 mg/kg, ethambutol 15 mg/kg and pyrazinamide 25 mg/kg). Some patients also received levofloxacin 500 mg daily. All the drugs were given for 6months and two drugs (rifampicin and isoniazide) for another 12 months. All the patients received aspirin 150 mg daily and prednisolone 0.75 mg/kg for 1 month followed by taper in the next month. Patients with hydrocephalous with clinical evidence of raised intracranial pressure were prescribed 100 ml of 20% mannitol intravenously. Patients with hydrocephalous having progressive deterioration in consciousness were subjected for ventriculoperitoneal shunt for CSF diversion.

Outcome: outcome was observed at 3 months and 6 months follow up based on modified Rankin Scale (mRS), and classified as good (mRS score 0–2) and poor (mRS score 3–6).

Statistical analysis: the frequency of CVST and intracranial MRA abnormalities were calculated and correlated with demographic, duration of illness, stage of TBM, seizure, papilloedema, GCS score, coagulation profile and outcome using $Chi^2$ test for categorical and independent t or Mann Whitney-U test for continuous variables. The predictors of outcome were evaluated using univariate followed by multivariate analysis. Statistical analysis was done using SPSS 16 version software.

## Results

Twenty-six patients with TBM were included whose age ranged between 11 and 75 (median 23) years, and 14 (53.8%) were females. The median duration of illness was 75 (15–240) days. All the patients had fever, 25 (96.2%) each had headache and vomiting, 14 (53.8%) had weight loss, 11 (42.3%) diplopia, 10 (38.5%) seizures and 16 (61.5%) had altered sensorium. Six patients had papilloedema. The majority of patients had stage II (12, 46.2%) to stage III (7, 26.9%) meningitis. Fourteen (53.8%) patients had definite and 12 (46.2%) probable TBM. Extra CNS tuberculosis was present in 9 patients; 4 pulmonary, 2 disseminated tuberculosis and one each had military, Pott's and abdominal tuberculosis. Three patients had comorbidities (hypertension in 1, diabetes in 2). Thirteen patents (50%) had focal motor weakness; hemiplegia in 9 (34.6%), monoplegia in 2 (7.7%), and paraplegia and quadriplegia in one (3.8%) each.

Cerebrospinal fluid analysis revealed predominantly lymphocytic pleocytosis (median 125/$mm^3$, range 20–800/$mm^3$) and increased protein (median 147 mg/dl, range 25–495 mg/dl). Sixteen patients (61.5%) had altered sensorium, and their GCS score ranged from 8 to 14 (median 11).

Cranial MRI, MRA and MRV findings: MRI revealed meningeal enhancement in 16 (61.5%), hydrocephalous in 15 (57.7%), tuberculoma in 18 (69.2%), exudates in 14 (53.8%) and infarctions in 13 (50%) patients. The infractions were located mostly in subcortical region except in one patient, who had cortical infraction. All but one patients had infarctions in the tubercular zone (caudate, anterior limb and genu of internal capsule, anterior thalamus and striatum), and only one patient had infraction in ischemic zone



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