Fever, headache, vomiting, and altered Conscious level are the most common symptoms at presentation. Neck rigidity, cranial nerve palsies, and papilledema are the most common signs observed.

Clues to diagnosis of TBM (Tubercular meningitis) come from history of contact with a known case of TB. Such history is available in 20% to 30% of the cases only.

Diagnosis of TBM is difficult and often a dilemma because the dreaded infection can mimic a variety of CNS diseases.

The presence of pulmonary TB in a patient with aseptic meningitis may be suggestive tuberculous etiology, but its absence does not rule it out. However, 50% of the adults and 90% of the children have an abnormal chest X-ray.

Cerebrospinal fluid analysis is an important diagnostic aid in TBM. CSF smear positivity for AFB has been seen in 10% to 90% of cases in various studies and less than 10% of the cases by others. Computed axial tomographic scanning with contrast and magnetic resonance imaging have brought most of the intracranial pathology visible to the naked eye.

Treatment should be started as swiftly as possible on clinical grounds. Delay in starting treatment is dangerous.

Impact of clinico-radiological parameters on the outcome of treatment in brain tuberculosis

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ABSTRACT

Objectives: The Aim of this study was to evaluate the impact of clinico-radiological parameters on the outcome of the treatment in brain tuberculosis.

Materials and Methods: This study was conducted in the Department of Neurosurgery and Neurology Skims Srinagar India for a period of two years from November 2009 to November 2011. A total of 61 patients presenting with brain tuberculosis admitted at skims during these two years were included in the study. Patients having clinical, laboratory and radiological findings suggestive of brain tuberculosis were included in the study. On correlating the CT characteristics-tuberculomas, basal exudates and hydrocephalus with sequelae at 6, 12 and 18 months - focal deficit, cognitive impairment, and diplopia.

Results: It was seen that basal exudates correlated with all the three neurological sequelae i.e.; with focal deficit \( P = 0.001 \), cognitive impairment \( P = 0.011 \), and diplopia \( P = 0.021 \). Hydrocephalus correlated well with cognitive impairment \( P = 0.031 \) and tuberculoma correlated with none of these clinical characteristics.

Conclusion: We concluded that the mortality and neurologic sequelae were directly related to the clinical stage of disease at presentation. Correlating the CT characteristics we concluded that basal exudates correlated with all the three sequelae i.e.; with focal deficit, cognitive impairment, and diplopia. Hydrocephalous correlated well with cognitive impairment and tuberculoma correlated with none of these clinical characteristics.

Key words: Adenosine deaminase, computed tomography, polymerase chain reaction, tuberculosis

Introduction

Tuberculosis (TB) continues to be a major health problem throughout the world. About 2 billion (one third of the world’s population) people are infected with TB of which about 10% develop clinical disease. The most common form of TB is pulmonary, and the most dangerous is CNS tuberculosis accounting for 5.2% of clinical TB and almost 50% morbidity.
and often leads to worse prognosis. Reliable independent prognosticators in TBM are extremes of age and advanced disease at presentation. Mortality of treated cases is 10% to 30%. The risk of neurological impairment despite treatment is also a direct correlate of stage of illness at presentation. Neurologic disabilities ranging from mild to severe are reported in 10% to 50% of both adults and children who survived the infection. Complications of CNS tuberculosis, such as shunting procedures for the treatment of hydrocephalus. When the diagnosis is not ensured and there is no response to therapy within 8 weeks, a stereotactic biopsy on a suspected tuberculoma could be performed. If the largest lesion is not located in high risk deep regions of the brain, it could be totally removed surgically. With this combined management, a satisfactory outcome can be obtained in the majority of cases.

**Materials and Methods**

**Methods**

This study was conducted in the Department of Neurosurgery and Neurology Skims Srinagar India for a period of two years from November 2009 to November 2011. A total of 61 patients presenting with brain tuberculosis admitted at skims during these two years were included in the study.

The patients were subjected to thorough clinical examination: To establish a diagnosis of tuberculosis of brain.

**Clinical-laboratory tests**

Complete hemogram, ESR, chest x-ray, Montaux test were done. CSF of these patients was subjected to detailed cytology, biochemistry ADA and PCR analysis. CSF was also taken for ZN staining and culture.

History: Of contact with a known patient of pulmonary tuberculosis, history of recent or past intake of ATT was also taken. The diagnosis of brain tuberculosis was based on the following parameters:-

- Clinical symptoms-headache, vomiting, fever, and signs of meningism of more than 4 weeks duration
- positive ziel-Neelsen of the CSF
- Patients with CSF cytology and biochemistry suggestive of TBM
  - CSF Positive for PCR
  - CSF with raised ADA
- Therapeutic response to ATT
- Imaging findings suggestive of tuberculosis like meningeal enhancement, hydrocephalus, basal exudates, tuerculomas.

The patients selected were classified into three stages according to clinical features and three types according to CT findings.

**Clinical staging**

Stage I: Patients fully conscious, oriented with signs of meningisms but no focal sign of hydrocephalus

Stage II: Patient is confused and/or with focal signs such as squint and hemiparesis

Stage III: Patient having stupor, delirium, or coma with complete hemiplegia or paraplegia.

**Radiological staging**

On the basis of CT scan findings patients were divided in to three grades:

- Grade I: Isolated meningeal involvement
- Grade II: Isolated parenchymal involvement
- Grade III: Compound parenchymal and meningeal involvement.

**Medical or Combined Surgical and Medical**

The patients were put on medical or combined surgical and medical treatment and followed for a period of 18 months and were assessed serially for demonstration of clinical and radiographic resolution with or without radiographic sequelae or with radiographic sequelae like atrophy/calcification with persistent enhancement.

**Medical treatment**

Was started with 4 drugs daily, that is, isoniazid 5 mg/kg (maximum 300 mg, rifampicin 10 mg/kg, pyrazinamide 25 mg/kg, and ethambutol 20 mg/kg or streptomycin 20 mg/kg (maximum 1 g) for 2 months and isoniazid and rifampicin daily for 4 to 24 months depending upon the response. The response to treatment was determined by clinical improvement or in some by repeat CSF analysis; six monthly CT-scan in those with tuberculomas or other findings at the start of treatment. The patients with tuberculomas needed prolonged treatment. Steroids were added for first 4 weeks and tapered over a similar period in clinical stage II and III disease.

**Surgical treatment**

Was done in the form of ventriculoperitoneal shunt for hydrocephalus and excision of tuberculomas with considerable mass effect.

**Results**

**Age of the studied patients**

The total number of study subjects were 61 with age range of 1-65 years with a mean age of 30.85 ± 16.91 years; 27 of 61 (44.3%) were males and 34 (55.7%) were females. Six of the patients were below 10 years of age and most were 11-40 years. There was a higher incidence of tubercular meningitis in younger (<40 years) age group (P < 0.05). The most presenting symptom of the study subjects was headache found in 95.10% followed by vomiting found in 86.90% of subjects, fever in 78.70% CONSCIOUS LEVEL in 49.20%, seizures in 19.70% and diplopia in 18%.

**Clinical characteristics in studied subjects**

In our study of 61 patients of brain tuberculosis on clinical examination cranial nerve involvement was found in 34 (55.73%)
with 11 having more than two cranial nerves involved. The most common cranial nerve involved was III and VI. Focal deficit (monoparesis or hemiparesis) was found in 14 (22.95%) and neck stiffness was found in 35 (74.40%) of patients.

In our study of 61 patients of brain tuberculosis on clinical examination 20 patients (32.80%) were in clinical stage I, 36 patients (59.00%) were in clinical stage II and 5 patients (8.2%) were in clinical III at the time of presentation. Five patients were deeply comatose on admission with a GCS of <6/15.

CT stage at presentation in studied subjects
CT scan of head was abnormal in 56 of 61 patients (91.8%), on admission. The study subjects were divided into three stages on the basis of CT scan finding at the time presentation and out of total 56 subjects 12 (19.70%) were in stage I (meningeal involvement only), 29 (47.50%) were in stage II (parenchymal involvement only) and 15 (24.60%) were in stage III (both parenchymal and meningeal involvement). The most common finding in CT head was meningeal enhancement in 43 patients, hydrocephalus in 37 patients and tuberculomas in 14 patients. The most common sites of tuberculomas were frontal lobe (n = 6; 42.8%), parietal lobe (n = 4; 28.5%), followed by cerebellum in 2 patients and occipital in two. Nine patients had single and five multiple tuberculomas. Of the 14 patients with tuberculomas, hydrocephalus on CT was seen in 6 patients.

There was no correlation of higher clinical stage at presentation with higher CT stage (P = 0.627). Ninety five percent (95%) of patients (19 of 20) in clinical stage I had abnormal CT scan in comparison to 88% of stage II. All the patients in stage III had abnormal CT. CT scan is a better diagnostic modality even in stage I of the disease.

Clinical stage of meningitis across mortality
Five of our subjects died during the hospital stay within 4 weeks of presentation and no mortality was seen on follow up. Out of the five patients who died three were in clinical stage III at presentation. Maximum mortality was seen in stage III meningitis (60%). A statistically significant association mortality was observed with higher clinical stage (III) at presentation (P = 0.013). All the patients who died underwent VP shunting. Two of the three patients in stage III who died had severe obstructive hydrocephalus with a GCS of <6/15 and died in post-operative period due to sepsis because of aspiration pneumonia. One patient in stage III, a 6 year old boy, died of brainstem compression by tuberculoma. The mortality seen in stage I was an elderly male with underlying type 2 diabetes with hypertensive cardiovascular disease and chronic obstructive airway disease (COAD), developed hospital acquired pneumonia and died of a massive pulmonary thromboembolism. The patient who died in stage II disease presented with status epilepticus with anoxic brain injury and died of a sudden cardiac arrest in the ward.

Modalities of treatment in our patients
Thirty one patients in our study received medical and 30 patients combined medical and surgical treatment. Of the five patients who died one was on medical and four combined medical and surgical management. All the patients received four antitubercular drugs (H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol) for a period of three months followed by isoniazid and rifampicin for 15 months. Steroids were given to all patients in stage III and most of the patients in stage II. Only one patient deteriorated during initial six weeks of medical management with increase in size and number of tuberculomas. Thirty patients needed surgical intervention; VP shunts in 26 (11 patients had mild hydrocephalus who didn't need shunt) and excision of tuberculomas in 4 patients. Of the 26 shunted patients, 18 were shunted during the first 4 weeks of admission whereas in 6 patients shunting was done in initial 6 months of follow up in view of development of hydrocephalus and worsening of clinical stage on medical management only. Excision of tuberculomas in all the four patients was done in initial 4 weeks. The indication of excision in three patients was the mass effect produced by tuberculomas leading to drop in GCS and worsening of clinical stage. In all these patients the size of tuberculoma exceeded four cms. The average size of tuberculomas which were managed conservatively was 2.8 mms. The most common sites of excision of tuberculomas were from frontal and parietal lobe. In one patient excision was done as a part of diagnostic procedure with an initial impression of meningioma and histopathology proved it to be a tuberculoma. This was one of the eight patients who presented with tuberculomas only with no evidence of meningitis.

Serial clinical and CT findings on follow up
Of the 61 patients included in the study, 56 were followed for a period ranging from 6 months to 18 months with a mean follow up period of 12 months. At 6 month follow the mean GCS of the patients improved from 10.7 at admission to 13.4. One patient improved from clinical stage III to II, one from stage III to stage I and 15 from stage II to I. Six patients worsened from stage I to II on initial medical management and needed surgical intervention in the form of VP shunting. Fourteen patients (25%) achieved full recovery while 42 patients (75%) had some form of functional impairment. CT was abnormal in 51 patients at 6 months, with hydrocephalus in 38 patients (including 6 patients who developed new hydrocephalus). Basal exudates resolved in 7 patients and tuberculomas in none.

At 12 months we had a total of 49 patients on follow up. Seven patients were lost to follow up. The mean GCS improved to 15/15. At 12 months 22 patients achieved full recovery and 27 partial. Two patients worsened from stage I to stage II and needed revision of shunt surgery. Hydrocephalus had resolved in all the patients except the two who needed revision of shunt surgery. Exudates...
disappeared in 6 more patients and tuberculomas in 5 patients. Two patients developed calcification on CT scan; one of them was the patient who had undergone excision of tuberculoma.

At 18 months we had 18 patients on our follow up who made full clinical recovery but these were among the same patients who made full recovery at 12 months. No further patient made any improvement in functional recovery from their 12 month status. Two patients improved from stage I to stage II but with partial recovery of their functional status. Tuberculoma resolved in one more patient. At 18 months tuberculomas resolved completely in 50% of the patients (7 of 14) who initially had tuberculomas and in another 50% there was a significant decrease in the size of tuberculomas.

Maximum recovery was seen in stage I with 47% at 6 months, 68% at 12 months and 78% at 18 months compared to overall 37% at 18 months in stage II. Three of the five patients in stage III died (60% mortality) and only one made full recovery.

On correlating the worst CT characteristics-tuberculomas, basal exudates and hydrocephalus with sequelae at 6 months – focal deficit, cognitive impairment, and diplopia it was seen that basal exudates correlated with all the three neurological sequelae i.e.; with focal deficit \(P = 0.001\), cognitive impairment \(P = 0.011\), and diplopia \(P = 0.021\). Hydrocephalus correlated well with cognitive impairment \(P = 0.031\) and tuberculoma correlated with none of these clinical characteristics.

Discussion

Tubercular meningitis is common in developing countries, with a high morbidity and mortality. The diagnosis of TBM is based mainly on clinical and laboratory findings, particularly in adults.\(^{14}\) Tubercular meningitis in developing countries is more common in infants and children with an increasing incidence in adolescents and young adults. In populations with low prevalence of TB, most cases of TBM occur in adults, and HIV has definitely increased the risk in adults.

In our study of 61 patients of brain tuberculosis on 32.80% patients were in clinical stage I, 59.00% were in clinical stage II and 8.2% were in clinical III of meningitis. Sixty seven percent of the patients presented with severe disease (stages II and III). Five patients were deeply comatose on admission with a GCS of <6/15. Similar findings have been reported by Abdul Majid et al.\(^{15}\) wherein about 89.47% of the patients presented with severe disease, that is, stage II (50%) and stage III (39.47%). Our results were also matching with Mishra et al.\(^{16}\) where 83% of patients presented with severe disease.

Computed axial tomographic scanning with contrast and magnetic resonance imaging have brought most of the intracranial pathology visible to the naked eye\(^{16}\). Abnormalities reported on CT scan done in stages II and III disease are hydrocephalus, infarcts, basal enhancement, and cerebral edema.\(^{10}\) Normal study is reported in up to 20% of the cases. Abdul Majid et al.\(^{15}\) reported abnormal CT findings in 73.52% patients as basal enhancement in 36%, hydrocephalus in 28%, tuberculomas in 52%, infarcts in 12.0%, cerebral edema in 8.0%, and more than 1 finding in 32.0% of the patients. Normal study was in 26.4%. All patients in stage I disease had abnormal CT findings in comparison to 50% of stage II and 83.3% of stage III disease. Thus, CT scan is a useful diagnostic tool even in very early stages of TBM. Hydrocephalus frequently accompanies tuberculous meningitis. The hydrocephalus is probably a result of basal adhesive meningeal reaction wherein the flow of the CSF is obliterated in its course from the point of exit from the fourth ventricle to the site of its absorption in the arachnoid villi. The intraventricular pressure in cases of hydrocephalus with tuberculous meningitis is generally low or only marginally raised.\(^{17}\)

CT scan of head was normal in 5 of 61 patients (9%) of our subjects on admission. The study subjects were divided into three stages on the basis of CT scan finding at the time presentation and out of total 56 subjects 19.70% were in CT stage I, 47.50% were in stage II and 24.60% were in stage III (depending upon the involvement of meninges, parenchyma or both). The most common finding in CT head was meningeal enhancement in 76% of patients, hydrocephalus in 66% patients and tuberculomas in 25% patients. There was no correlation of higher clinical stage at presentation with higher CT stage \(P = 0.627\). Ninety five percent (95%) of patients (19 of 20) in clinical stage I had abnormal CT scan in comparison to 88% of stage II. All the patients in stage III had abnormal CT. CT scan is a better diagnostic modality even in stage I of the disease.

Despite the introduction of new and potent anti-tuberculous drugs, the mortality and morbidity in patients with CNS tuberculosis remains exceptionally high. The mortality and sequelae are directly related to the stage of the disease at the time of initiation of appropriate therapy. The treatment strategy for tuberculous meningitis and hydrocephalus should be aggressive anti-tuberculous drugs and wherever necessary institution of steroids. Ventricular CSF diversionary surgery may not be necessary in most cases and can be avoided. Shunt surgery on the basis of radiological imaging diagnosis and for the sake of helping the situation of hydrocephalus in presence of other florid evidence of tuberculous meningitis, more often than not, is of no benefit. Monitoring of intraventricular pressure can be helpful in situations where there is doubt about the need of a shunt operation. Due to an immunocompromised state of patients with tuberculous meningitis, chances of shunt tube related infection are more predominant. In adolescents and adults with tuberculous meningitis and hydrocephalus, the signs of increased intracranial pressure and drowsiness are more predominant. Such patients are usually benefited by a shunt. In some cases, when the disease process is dying...
down, hydrocephalus can develop and result in symptoms of headache, drowsiness and impairment of level of conscious level. Such situations also can occasionally be helped by a shunt surgery.\textsuperscript{[18]} Before a shunt is done it may be a good idea to assess the intraventricular pressure.

Jacobs and others\textsuperscript{[19]} and Kent and others\textsuperscript{[19]} found that the mortality in patients admitted in stage III was approximately 50\% while for those in stages II and I it was 30\% and 15\%, respectively. Five of our subjects died during the hospital stay and no mortality was seen on follow up. Out of the five patients who died three had stage III disease at presentation (60\%). Maximum mortality was seen in stage III. The mortality and neurologic sequelae were directly related to the stage of disease on admission (\textit{P} = 0.013). Girgis NI, et al.\textsuperscript{[20]} also reported similar results in their study with 72\% mortality in stage III disease. Similarly, the number of patients who recovered completely without any sequelae was significantly higher (\textit{P} = 0.03) in patients admitted in stage I (15 of 19; 78\%) compared with those in stages II (13 of 35; 37\%). At 18 months follow up 60\% of the patients attained full recovery and 40\% were left with some functional impairment (29\% of the patients were left with permanent sequelae). This is much lower than the 53\% observed by Idriss\textsuperscript{[21]} and others.

In our study nine patients deteriorated during the initial six weeks of treatment. A number of clinical and radiological phenomena in TBM may be due to ongoing infection or inflammation which could result in continued deterioration. The initial deterioration in TBM could be due to an immunological reaction resulting in liberation of cytokines and lymphokines and subsequent appearance or organization of basal exudates, termed a “paradoxical response”. This is an uncommon hypersensitivity reaction to massive release of tuberculo protein into the subarachnoid space, manifest clinically within days of commencement of treatment; the patient may rapidly deteriorate to coma or even death.\textsuperscript{[19]} This therapeutic paradox has been regarded as pathognomonic of TBM.\textsuperscript{[22]} The initial deterioration in at least three of our patients could be due to a paradoxical response.

Within 6 months, however, most of our patients, including those who deteriorated initially either became or started improving. Radiological follow up revealed new hydrocephalus in 6 patients which could be due to organization of basal exudates, in these patients. At 6 months no patient worsened clinically or radiologically but 51 of 56 CT studies remained abnormal. In one serial study of CT and MRI in TBM all abnormal CT findings except infarcts disappeared.\textsuperscript{[23]} This difference from our study could be attributed to milder illness and use of MRI in the previous study. More severe illness in our patients is evidenced by stage II and III meningitis in 67.2\% and hydrocephalus in 60\%. In a clinical and CT follow-up of 25 patients with TBM, 18 had hydrocephalus on admission and hydrocephalus developed in three during follow-up. In seven patients exudates persisted for 11-96 months. New tuberculomas appeared even after 7 months of treatment in our study however exudates resolved in all the patients at 18 months. It can be concluded that close monitoring of patients with TBM during the first 6 weeks of treatment is essential as 14\% of patients may deteriorate, especially those with low GCS and weakness. Repeating CT can be valuable in their management. Most CT abnormalities persist even after 6 months despite clinical improvement.

On correlating the worst CT characteristics-tuberculomas, basal exudates and hydrocephalous with sequelae at 6 months – focal deficit, cognitive impairment, and diplopia it was seen that basal exudates correlated with all the three sequelae i.e.; with focal deficit (\textit{P} = 0.001), cognitive impairment (\textit{P} = 0.011), and diplopia (\textit{P} = 0.021). Hydrocephalous correlated well with cognitive impairment (\textit{P} = 0.031) and tuberculoma correlated with none of these clinical characteristics. P Ranjan\textsuperscript{[24]} correlated the worst CT appearances with 6-month clinical sequelae and found that motor deficit correlated with exudates (\textit{P} < 0.05) and infarcts (\textit{P} < 0.05). Hydrocephalous and tuberculoma did not correlate with sequelae. Correlating the 6-month CT findings with neurological sequelae at 6 months, cognitive impairment correlated with exudates (\textit{P} < 0.05) and tuberculomas (\textit{P} < 0.05). Functional outcome at 6 months was related to the presence of exudates at 6 months (\textit{P} < 0.05).

**Conclusion**

We concluded that the mortality and neurologic sequelae were directly related to the clinical stage of disease at presentation. Maximum mortality was seen in stage III. Correlating the CT characteristics-tuberculomas, basal exudates and hydrocephalous with sequelae at 6 months – focal deficit, cognitive impairment, and diplopia we concluded that basal exudates correlated with all the three sequelae i.e.; with focal deficit, cognitive impairment, and diplopia. Hydrocephalous correlated well with cognitive impairment and tuberculoma correlated with none of these clinical characteristics.

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