Role of clinical, radiological, and neurophysiological changes in predicting the outcome of tuberculous meningitis: a multivariable analysis

U K Misra, J Kalita, A K Roy, S K Mandal, M Srivastava

Abstract

Objectives—The role of EEG and evoked potentials has not been evaluated in predicting the prognosis of tuberculous (TB) meningitis. The present study was aimed at evaluating the prognostic significance of clinical, radiological, and neurophysiological variables using multivariable analysis.

Methods—Patients with TB meningitis diagnosed on the basis of clinical, radiological, and CSF criteria have been prospectively evaluated. All the patients were subjected to a detailed neurological evaluation. The outcome was defined 6 months after starting treatment on the basis of the Barthel index (BI) score into poor (BI<12) and good recovery (BI≥12). Death was included in the poor recovery group for statistical analysis. Thirteen clinical (age, sex, seizure, focal weakness, stage of meningitis, Glasgow coma scale score, methyl prednisolone therapy), CT (infarction, hydrocephalus, tuberculoma) and neurophysiological (EEG, motor and somatosensory evoked potentials) variables were evaluated employing single variable logistic regression followed by multivariable logistic regression analysis. The best set of predictors were obtained by step-down logistic regression analysis.

Results—Fifty-four patients were included in the present study. Their age ranged between 5 and 62 years. Eleven were children younger than 12 years and 14 were female. Nine patients were in stage I meningitis, 12 in stage II, and 33 in stage III. On single variable logistic regression analysis the significant predictors of 6 months outcome of TB meningitis included focal weakness, Glasgow coma scale (GCS), motor evoked potential (MEP) and somatosensory evoked potential (SEP). On multivariable analysis the best set of predictors comprised focal weakness, GCS, and SEP.

Conclusions—In patients with TB meningitis focal weakness, GCS, and SEP are the best predictors of 6 month outcome.

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Keywords: meningitis; tubercular evoked potential; motor evoked potential; somatosensory evoked potential; prognosis

Prediction of prognosis of tuberculous (TB) meningitis is difficult because of its protracted course, diversity of underlying pathological mechanisms, variation of host immunity, and virulence of mycobacterium tuberculosis. Initially only the clinical indices were used for predicting the outcome, such as level of consciousness, stage of meningitis, BCG vaccination, CSF findings, and evidence of raised intracranial pressure. After the availability of CT, radiological findings such as hydrocephalus, infarction, severity of exudate, and tuberculoma were also considered for predicting prognosis of TB meningitis. In TB meningitis, there are few studies on neurophysiological changes. Electroencephalography has been reported to be better in assessing the gravity of lesions and was recently reported to help in prediction of outcome. Motor (MEPs) and somatosensory evoked potentials (SEPs) have also been reported recently to predict 3 month outcome of TB meningitis. Most of the mentioned studies have employed single variable analysis, which does not study the significance of each variable independently; this is achieved by multivariable analysis. Single variable analyses test the significance of each variable separately. Multivariable analyses test the independent effect of each variable after allowing for the effect of other variables in the model. In the present study, for the first time we report the role of clinical, radiological, and neurophysiological indices in predicting 6 month outcome of TB meningitis.

Patients and methods

Sixty-three patients with TB meningitis were managed between 1994 and 1998. The present study is based on 54 patients; Nine patients were excluded because of lack of follow up or incomplete data. The patients’ ages ranged between 5 and 64 (mean 26.3) years. Eleven were children below 12 years, and 14 were females. The patients were subjected to a detailed neurological examination. Consciousness was assessed by Glasgow coma scale (GCS). History of seizure, focal weakness, sensory impairment, cranial nerve palsy, fundus changes, and behavioural and micturition abnormalities were also noted. The diagnosis of TB meningitis was based on clinical, radiological, and CSF criteria. The clinical criteria included fever, headache, and neck stiffness for more than 2 weeks. Supporting evidence was obtained from CSF cell count (0.02 × 10⁶/µL or more with lymphocytic
predominance, sterile bacterial and fungal culture, evidence of hydrocephalus and exudate on CT, and evidence of tuberculosis outside the CNS. Response to antituberculous therapy was also noted. The patients were categorised into highly probable, comprising those with clinical and three supportive criteria.11 All our patients were highly probable except three, who were definite cases of TB meningitis because of the presence of AFB in CSF. Severity of meningitis was graded into stage I: presence of meningitis only, stage II: meningitis with neurological signs, and stage III: meningitis, neurological signs, and altered sensorium.11 Cranial CT was carried out in all the patients using a third generation CT scanner. Axial sections were obtained at 10 mm parallel to the orbitomeatal line. In CT, the presence of hydrocephalus, tuberculoma, infarctions, and exudates were recorded.

An EEG was carried out on a 10 or 18 channel machine employing a 10–20 system of electrode placement on admission. Horizontal and vertical montages were used for the EEG recording. Hyperventilation and photic stimulation were assessed in those patients who could cooperate, right to left asymmetry, and spike wave discharges or any focal abnormalities were noted. Central motor conduction time (CMCT) to abductor digiti minimi and tibialis anterior were recorded bilaterally in all the patients on admission using standard techniques.14 Median and tibial SEPs were also measured on both sides employing standard techniques. Median SEPs were obtained by stimulating the median nerve at the wrist by a 0.1 ms square wave pulse at 3 Hz at an intensity sufficient to produce a painless twitch of the thumb. The active surface recording electrodes were placed at Erb’s point and at the contralateral parietal cortex 3 cm behind and 7 cm lateral to the vertex using a midfrontal reference. For tibial SEPs, the posterior tibial nerve was stimulated below the medial malleolus at 3 Hz, sufficient to produce a painless twitch of the big toe. The recording electrode was placed on the spinous process the first lumbar vertebra (L1) and 2 cm caudal to Cz (Cz1), the reference electrodes were placed at L3 and Fz respectively. The impedance of the electrode was kept below 5 kΩ, frequency band pass was 2–3000 Hz, and analysis time 100 ms. Five hundred and twelve responses were passed was 2–3000 Hz, and analysis time 100 ms.

Median and tibial SEPs were also measured on both sides employing standard techniques. Median SEPs were obtained by stimulating the median nerve at the wrist by a 0.1 ms square wave pulse at 3 Hz at an intensity sufficient to produce a painless twitch of the thumb. The active surface recording electrodes were placed at Erb’s point and at the contralateral parietal cortex 3 cm behind and 7 cm lateral to the vertex using a midfrontal reference. For tibial SEPs, the posterior tibial nerve was stimulated below the medial malleolus at 3 Hz, sufficient to produce a painless twitch of the big toe. The recording electrode was placed on the spinous process the first lumbar vertebra (L1) and 2 cm caudal to Cz (Cz1), the reference electrodes were placed at L3 and Fz respectively. The impedance of the electrode was kept below 5 kΩ, frequency band pass was 2–3000 Hz, and analysis time 100 ms. Five hundred and twelve responses were passed was 2–3000 Hz, and analysis time 100 ms.

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**STATISTICAL ANALYSIS**

Thirteen clinical, radiological, and neurophysiological variables were evaluated. The independent variables were categorised as sex (male=1, female=2), seizure (present=1, absent=2), focal weakness (tetraparesis=1, hemiparesis, paraparesis, monoparesis=2, normal=3), stage of meningitis (stage III=1, stage II=2, stage I=3), brain CT evidence of infarction, hydrocephalus, and tuberculoma (present=1, absent=2), SEP and MEP abnormalities (abnormal in all 4 limbs =1, abnormal in 3 to 1 limb=2, normal=3), EEG (abnormal=1, normal=2), and methyl prednisolone therapy (given=2, not given=1). The raw scores of GCS and age were used for statistical analysis. The dichotomous dependent variable recovery was assigned the value 1 when the outcome was good and 0 when outcome was poor. To study the significance of independent variables in the prognosis, single variable logistic regression analysis was employed. To study the simultaneous effect of different variables on recovery, multivariable logistic regression analysis was used employing the logreg statistical package. Initially all the variables were included but the best model was derived using stepwise logistic regression analysis. The indices of the model were obtained by the maximum likelihood method.15

**Results**

In our study group 17 out of 54 had history of seizure. The seizures were generally of partial motor type with secondary generalisation and were well controlled by antiepileptic drugs. Focal weakness was present in 27 patients, which included tetraplegia in 10, hemiplegia and paraplegia in 16, and monoplegia in one. Thirty three patients were in stage III, 12 in stage II, and nine in stage I meningitis. The mean GCS score was 11.5 (range 4–15). On CT, hydrocephalus was present in 29 patients and tuberculoma in 12. Tuberculoma was mostly located in the supratentorial region except in one patient, in whom it was situated in the midbrain. Infarctions were present in 25 patients and were located in the basal ganglia.
Comparison of single and multivariable analysis of predictors of tuberculous meningitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single variable analysis</th>
<th>Multivariable analysis</th>
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<tr>
<td></td>
<td>Odd ratio</td>
<td>Upper</td>
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<tr>
<td>Focal weakness 2</td>
<td>3.00</td>
<td>16.00</td>
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<tr>
<td>Focal weakness 3</td>
<td>14.00**</td>
<td>77.60</td>
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<tr>
<td>GCS</td>
<td>1.30**</td>
<td>1.54</td>
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<tr>
<td>SEP 2</td>
<td>2.33</td>
<td>17.54</td>
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<tr>
<td>SEP 3</td>
<td>6.75*</td>
<td>43.84</td>
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</table>

GCS = Glasgow coma score; SEP = somatosensory potential.

Category 1 of focal weakness and SEP is taken as reference category. *p<0.05, **p<0.01.

Discussion

This is the first study evaluating the prognostic significance of clinical, radiological, and neurophysiological changes in predicting the 6 month outcome of TB meningitis employing multivariable analysis. The best set of predictors of 6 month outcome of TB meningitis comprised focal weakness, GCS score, and SEP. The GCS is one of the most established predictors of outcome of TB meningitis. The importance of altered sensorium in the outcome of TB meningitis has been highlighted in earlier studies.1 2 6 TB meningitis is associated with a variable degree of encephalitis, which is primarily responsible for altered sensorium. The other factors contributing to altered sensorium in TB meningitis may include hydrocephalus, infarction, or tuberculosis in a strategic location.

Focal weakness in TB meningitis may range from mild weakness of one limb to severe tetraplegia. It is attributed to the involvement of the motor pathway at various levels of the nervous system. Diseases such as encephalopathy, vasculitis resulting in infarction, granuloma formation, and arachnoiditis in isolation or in combination can result in focal weakness depending on the involvement of the motor pathway. The importance of the primary motor area and its connections resulting in severe and persistent weakness in patients with stroke has been reported.10 11 In an earlier study, the presence of infarction was found to be an important predictor of TB meningitis.8 Infarction, however, has not figured as an important predictor in the present study; focal weakness was present in 27 and infarction in 25 patients. In an earlier study, presence of focal weakness was an important predictor of 3 month outcome and infarction was an important predictor of 6 and 12 month outcome of TB meningitis.6 8 In these studies, however, the neurophysiological indices were not evaluated. It is possible that in the presence of evoked potential studies the mere presence of infarction becomes a less important prognostic predictor. The focal weakness, however, may include the infarctions along the motor pathways. The neurophysiological indices—that is, MEPs, SEP, and EEG—are invaluable in documenting the respective clinical deficit in a comatose or uncooperative patient.

In the present study, SEPs and MEPs both were significant prognostic predictors in single variable analysis but SEPs figured in the final model employing multivariable logistic regression analysis. In a comatose patient SEPs are helpful for the diagnosis and documentation of sensory deficit. We have included both upper and lower limb SEPs bilaterally, which helped in bringing out even localised abnormalities. The MEPs, although they evaluate the motor pathway similarly, are limited by difficulty of preactivation in a comatose or uncooperative patient or in patients with severe weakness. Lack of preactivation may render the MEP unrecordable or CMCT prolonged.1 3 The SEPs on the other hand have the advantage of not requiring any patient cooperation. Most of our patients were in stage II or III and in these patients SEPs may be helpful in documenting the sensory deficit. Based on the regression coefficient (0.56) and odds ratio (1.75) SEPs significantly contribute to the prediction of outcome of TB meningitis.

In the earlier studies employing multivariable analysis, only clinical and radiological
The predictors of outcome in these studies included stage, age, focal weakness, and cranial nerve palsy. The difference in the earlier studies and the present study may be due to differences in the patient population, variables analyzed, and end points. The model proposed by the present work is simple, requiring clinical examination and SEP studies only. Most of the neurology and medical departments have facilities for SEP studies. Supplemeting the clinical examination with SEPs may provide valuable information.

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