Outcome predictors in patients (older than 14 years) with acute febrile encephalopathy: Role of cerebrospinal fluid analysis

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ABSTRACT

Background: Managing patients with acute febrile encephalopathy (AFE), characterized by fever and altered mental status, are one of the primary reasons for hospitalization and mortality. Understating the predictors of AFE outcome will assist the physician in providing early clues and subsequent inventions to tackle the problem. Aims and Objectives: This study aims to evaluate the predictors of outcome in patients with AFE, focusing on the cerebrospinal fluid (CSF) analysis. Materials and Methods: A prospective observational study was performed on 507 patients with fever and altered mentation (above 14 years of age) in the Department of General Medicine between December 2017 and May 2019. CSF analysis was done to obtain protein, glucose, cell count, and adenosine deaminase (ADA). Computed tomography/magnetic resonance imaging and PS for malaria parasites were also performed. Results: AFE was more common in males (54.63%). Tuberculous meningitis (TM) (44.8% vs. 41.6%) followed by bacterial meningitis (BM) (25.7% vs. 25%) was the most common diagnosis in females and males, respectively. Mortality was more common in TM (57.4%) followed by BM (21.3%) patients. Of the 211 patients with TM, those who died had CSF protein ≥90 (49.7%; P = 0.012), CSF glucose ≥35 (53.2%; P = 0.002), CSF cells ≥60 (47%; P = 0.012), and ADA ≥15 (47%; P = 0.012), and ADA ≥15 (31.5%; P = 0.001). Of the 127 patients with BM, those who died had CSF protein ≥90 (100%; P < 0.001), CSF glucose ≥35 (78.3%; P < 0.001), and CFS cells ≥60 (100%; P < 0.001). Conclusion: CSF analysis could be important for predicting the outcome and should be done as soon as possible after the clinical judgment of the AFE.

Key words: Acute febrile encephalopathy; Bacterial meningitis; Cerebrospinal fluid analysis; Mortality; Tuberculous meningitis

INTRODUCTION

Acute febrile encephalopathy (AFE) is characterized by short febrile illnesses with altered mental states. AFE is one of the commonly encountered problems by the physician in emergency departments.1

There are distinct regional and seasonal variations in the symptoms and prognosis of AFE. Bacterial meningitis (BM), Japanese encephalitis (JE), cerebral malaria (CM), and typhoid encephalopathy are the common types of AFE and result in fever with an altered mental state.2 AFE is most commonly caused by CM, JE, and BM in tropical countries like India, while tuberculous meningitis (TM) can have a subacute or chronic history.3

Many epidemiological investigations have failed to shed light on the presentation of acute onset fever and altered sensorium, particularly in the Indian states of Uttar Pradesh, Bihar, and West Bengal.4 Most AFE patients were found to make complete neurological recovery once the underlying cause was identified and treated promptly, appropriately, and adequately.4

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Despite AFE being a significant cause of hospital admissions of adults in India, only a few pieces of evidence have focused on the predictors of outcome in patients over 14 years. Hence in the present study, we tried to analyze the cause of encephalopathy following a short febrile illness in patients older than 14 years.

Aims and objectives
To analyze the cause of encephalopathy following a short febrile illness in patients older than 14 years and compare it with the outcome

MATERIALS AND METHODS
This prospective observational study was performed on 507 patients with fever and altered mentation (above 14 years of age) in the Department of General Medicine, Gandhi Medical College, and associated Hamidia Hospital, Bhopal, between December 2017 and May 2019.

The Institutional Ethics Committee approval was obtained before starting the study. Patients with persistent alteration in mentation with one or more deranged parameter such as hypoglycemia (blood sugar <50 mg/dl), hypoxia, hypercarbia (carbon dioxide > 50 mm of Hg), hyponatremia (serum sodium <120 mg/dl), hypernatremia (serum sodium >150 mg/dl), and serum creatinine >3 mg/dl were excluded from the study. Patients having cerebral vascular accidents followed by fever and patients with head injury were also excluded from the present study.

All the patients were subjected to detailed evaluation with clinical history and systemic examination and investigations, including routine investigations (complete blood count and urine routine microscopy), radiological investigations (X-ray chest), cerebrospinal fluid (CSF) analysis, non-contrast and contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI), and PS for malaria parasite and malaria antigen. All patients also undergone renal and liver function tests, serum electrolyte (sodium and potassium), electrocardiogram, blood sugar and HIV, HBsAg, and HCV viral markers.

Statistical Analysis
All the data analyses were performed using SPSS ver. 20 software. Frequency distribution and cross-tabulation were performed to prepare the tables. Qualitative data were expressed as a percentage and were analyzed statistically using the Chi-square test. The level of significance was assessed at 5%.

RESULTS
Male preponderance was observed (54.63%). The majority of the females were diagnosed with TM (44.8%) followed by BM (25.7%). Similarly, most male populations were diagnosed with TM (41.6%) followed by BM (25%).

Out of 507 patients, 108 (21.3%) died, 250 (49.3%) were discharged without any complications, and 149 (29.4%) were discharged with some complications.

The majority of the patients who died had TM (57.4%) followed by BM (21.3%) and malarial encephalitis (8.3%). Similarly, those who were discharged without any complications majority were diagnosed with TM (38.8%) followed by viral meningitis (VM) (30%) and malarial encephalitis (10%). Similarly, most of those discharged with some complications were diagnosed with BM (54.4%) followed by TM (34.9%). This means that mortality was higher among the patients diagnosed with TM and BM (P<0.001).

Out of 108 patients who died, 89 (82.4%) had age <45 years, whereas 19 (17.6%) had age ≥45 years. Out of 250 patients who were discharged with no complication, 104 (41.6%) had age ≥45 years.

Table 1: Comparing different predictors of outcome in patients with AFE

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Outcome</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>TM CSF protein&lt;90</td>
<td>39 (62.9)</td>
<td>75 (50.3)</td>
<td>114 (54)</td>
</tr>
<tr>
<td>CSF protein≥90</td>
<td>23 (37.1)</td>
<td>74 (49.7)</td>
<td>97 (46)</td>
</tr>
<tr>
<td>BM CSF protein&lt;90</td>
<td>0 (0)</td>
<td>6 (5.8)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>CSF protein≥90</td>
<td>23 (100)</td>
<td>98 (94.2)</td>
<td>121 (95.3)</td>
</tr>
<tr>
<td>TM CSF glucose&lt;35</td>
<td>29 (46.8)</td>
<td>70 (47)</td>
<td>99 (46.9)</td>
</tr>
<tr>
<td>CSF glucose≥35</td>
<td>33 (53.2)</td>
<td>79 (53)</td>
<td>112 (53.1)</td>
</tr>
<tr>
<td>BM CSF glucose&lt;35</td>
<td>18 (78.3)</td>
<td>89 (85.6)</td>
<td>107 (84.3)</td>
</tr>
<tr>
<td>CSF glucose≥35</td>
<td>5 (21.7)</td>
<td>15 (14.4)</td>
<td>20 (15.7)</td>
</tr>
<tr>
<td>TM CSF cells&lt;60</td>
<td>41 (66.1)</td>
<td>79 (53)</td>
<td>120 (66.9)</td>
</tr>
<tr>
<td>CSF cells≥60</td>
<td>21 (33.9)</td>
<td>70 (47)</td>
<td>91 (33.1)</td>
</tr>
<tr>
<td>BM CSF cells&lt;60</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CSF cells≥60</td>
<td>23 (100)</td>
<td>104 (100)</td>
<td>127 (100)</td>
</tr>
<tr>
<td>TM ADA CSF&lt;15</td>
<td>36 (58.1)</td>
<td>94 (63.1)</td>
<td>130 (61.6)</td>
</tr>
<tr>
<td>ADA CSF≥15</td>
<td>21 (33.9)</td>
<td>47 (31.5)</td>
<td>68 (32.2)</td>
</tr>
<tr>
<td>BM ADA CSF&lt;15</td>
<td>20 (87)</td>
<td>84 (80.8)</td>
<td>104 (81.9)</td>
</tr>
<tr>
<td>ADA CSF≥15</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are expressed as number of patients (percentage). AFE: Acute febrile encephalopathy, TM: Tuberculous meningitis; BM: Bacterial meningitis, CSF: Cerebrospinal fluid, ADA: Adenosine deaminase.
182 (72.8%) had age <45 years, and 68 (27.2%) had age ≥45 years. Similarly, out of 149 patients who were discharged without any complication, 114 (76.5%) had age <45 years and 35 (23.5%) had age ≥45 years. The outcome distribution among the different ages of the patients was not significant, as revealed by the insignificant with P=0.146, which means that the outcome was similar across the age groups.

The prevalence of papilloedema was 53.1%. Out of 17 patients with papilloedema, one patient died (14.3%). The distribution was highly significant with P<0.01.

In the present study, 67 TM patients on antitubercular drugs (ATTs) had abnormal CSF; 26 (38.8%) died. The distribution was highly significant, with P<0.001.

Out of 57 patients with TM who died, 35 (27.6%) had abnormal imaging findings. The distribution was significant with P=0.0026. Hence, it means if the patients have abnormal imaging in tubercular meningitis, the chances of death are more, whereas out of 19 patients with BM who died, 8 (12.7%) had abnormal imaging findings. However, the distribution was insignificant, with P=0.217 (Table 1).

**DISCUSSION**

AFE is a leading cause of hospitalization in India, characterized by fever with altered mentation. Fever with altered mental status results from BM, JE, CM, typhoid encephalopathy, and fulminant hepatic failure due to viral hepatitis. Evidence on the predictors of the outcome of AFE is limited in the Indian population. Hence, the present study evaluated the factors associated with AFE to make an early diagnosis.

In the present study, majority of the patients with AFE were males. Bhalla et al., and Panagariya et al., also found male preponderance (78.1%). Singh et al., reported that almost two-thirds (64.5%) of the subjects with AFE were male. Although no documented CNS infection has a male preponderance, this apparent male predominance can be attributable to the male-dominated social structure in which a sick male receives preferential medical attention.

In the present study, out of 507 patients, the majority were diagnosed with TM (41.6%), followed by BM (25%), VM (16%), and CM (8.9%). In line with that, Bhalla et al., analyzed the cause of AEF following a short febrile illness in 127 patients with fever of fewer than 2 weeks duration along with alteration in mentation. The author reported that 127 patients (70%) had primary CNS infection as the etiology of AFE. Most common were acute pyogenic meningitis (25.2%) and TM (7.87%). The most common cause of primary CNS infection reported by Bhalla et al., was meningoencephalitis (29.9%), followed by CM, leptospirosis, and brain abscess. Bansal et al., reported that 90% of the non-traumatic coma cases had TM, PM, and encephalitis. A study from Lucknow by Kumar et al., (n=740) reported that 18% and 12% of the cases had PM and JE. Mehrotra et al., found PM in 49.1% and VM in 11.4%.

TM is the most prevalent form of central nervous system tuberculosis and is associated with a high morbidity and mortality rate. In the present study, the majority of the patients who died had TM (57.4%) followed by BM (21.3%) and malarial encephalitis (8.3%). Of the 127 patients studied by Bhalla et al., mortality was reported in 21 (16.5%); most of them had SAE followed by PM and CM and leptospirosis. Five patients out of 14 (35.7%) in whom no definitive diagnosis could be established succumbed to their illness.

While CSF abnormalities support the diagnosis of a meningoencephalitis syndrome, the changes in the CSF constituents are often non-specific. They frequently do not assist in establishing a particular etiological diagnosis. CSF has a similar electrolyte composition to plasma, except that the former contains less K+, a lower pH, and a greater Cl- content. CSF has a protein content of around 250 mg/L. In general, the CSF is devoid of antibodies and complements. Significant amounts of proteins in CSF either breach the blood–brain barrier through facilitated diffusion through particular transporters or are synthesized within the CNS. All serum proteins are present in the CSF by simple diffusion at least trace amounts despite the tight junction barriers. Protein concentrations are higher in lumbar CSF than in cisternal CSF because the lumbar barrier which is more permeable. CSF is an essential diagnostic window into the central nervous system. A lumbar puncture is a preferred method of obtaining CSF.

There is an increase in protein concentration in patients with TM and PM in the previous studies performing biochemical analysis. Higher protein concentration is observed in TM than PM due to breaches in the blood–brain barrier and increased local synthesis of gamma globulins. In the present study, out of 211 patients diagnosed with TM, 114 (54%) had CSF protein <90, whereas 97 (46%) TM patients had CSF protein ≥90. The liver principally produces albumin. Thus, its level in CSF gives some integrated information about changes in the permeability of the blood-CSF barrier and CSF turnover. The TM group has decreased albumin with increased severity. A low level of CSF albumin has been observed in
similar studies on CSF analysis patients with TM. The culture of CSF is the gold standard for confirming the diagnosis of BM. In the present study, out of 127 patients diagnosed with BM, 6 (54%) had CSF protein <90, whereas 121 (95.3%) had CSF protein ≥90. In a similar series by Karmarkar et al., the mean CSF protein concentration was 32.23±20.105 (range: 10–89). The CSF protein levels were raised in only 15 patients (26%).

In the present study, survival was more among the patients having CSF protein <90 (50.3%) as compared to those with CSF protein ≥90 (49.7%), as revealed by the highly significant P=0.012. In the present study, out of 23 patients who died were diagnosed with BM, all of which had CSF protein ≥90 (100%). This was highly significant, as revealed by P<0.001.

CSFs low glucose concentration is also reported in bacterial, fungal, parasitic, or neotropical meningoencephalitis. Because CSF lymphocytosis is common in both conditions and the yield for smear positivity of Mycobacterium tuberculosis in the CSF is poor, it may be challenging to distinguish VM from TM in endemic areas. Serial CSF samples and contrast-enhanced CT/MRI may be the sole methods for differentiating TM from viral encephalitis. In the present study, out of 211 patients diagnosed with TM, 99 (46.9%) had CSF glucose <35, whereas 112 (53.1%) TM patients had CSF glucose ≥35. In the present study, out of 127 patients diagnosed with BM, 107 (84.3%) had CSF glucose <35, whereas 20 (15.7%) BM patients had CSF glucose ≥35. In a similar series by Karmarkar et al., the mean CSF sugar level was 76.46±28.987 (18–148). The previous study reported that a raised CSF protein occurs in most tuberculosis patients, and CSF glucose will be reduced by 70%.

In the present study, mortality was more among the patients who had CSF glucose ≥35 (53.2%) as compared to those who had CSF glucose <35 (46.8%). In the present study, out of 23 patients who died who were diagnosed with BM, the majority had CFS glucose <35 (78.3%), and 5 (21.7%) had CFS glucose ≥35. This means that mortality was more prevalent among the BM patients with CSF glucose levels <35.

Karmarkar et al., reported that the mean CSF cell count in the patients was 27.40±70.885 (range: 0–520), a median of 10 cells. In line with that, in the present study, out of 211 patients diagnosed with TM, 120 (56.9%) had CSF cells <60, whereas 91 (43.1%) TM patients had CSF cells ≥60. Out of 127 patients diagnosed with bacterial meningitis, all 100% had CSF cells ≥60. A higher number of polymorphonuclear leukocytes in the CSF after the first 48 h indicate BM as the likely etiology.

Approximately 20% of patients with AFE have an excess of red blood cells (>500/mm³) in the CSF without a traumatic tap. This is typically associated with necrotizing and hemorrhagic encephalitis listerial and primary amoebic meningoencephalitis. Bonsu and Harper predicted a model based on CSF pleocytosis, which used age, CSF white cell count (WBC) count, CSF protein concentration, and CSF neutrophil percentage to indicate BM in 80% of cases. However, Meligy et al excluded CSF with low WBC in their model. The normocellular BM is observed among critical patients. Freemont Smith also presented in his study that 1% of patients with bacterial meningitis had CSF cells lower than 100 cell count.

Typically, the CSF shows a high CSF WBC, predominantly lymphocytic, with a high protein and low CSF to blood glucose ratio. However, total CSF WBC can be normal in those with TM and depressed cell-mediated immunity, such as elderly and HIV-infected individuals. A low CSF cell count has also been associated with poor outcomes. All 23 patients who died had CFS cells ≥60 (100%) in the present study. Mortality was more among the patients who had CSF cells ≥60 (8.2%) as compared to those who had CSF cells >60 (1.7%). However, the distribution was insignificant, with P=0.652.

In the present study, survival was more among the TM patients with CSF cells <60 (53%) as compared to 70 (47%) patients who had CSF cells ≥60 (P=0.012). Neutrophils can predominate, especially early in the disease. A high proportion of neutrophils in the CSF has been associated with an increased possibility of a bacteriological diagnosis and improved survival.

In the present study, out of 211 patients with TM, we performed ADA estimation in 198 patients. It was found that, out of 198 patients, 130 (61.6%) had CSF ADA <15, whereas 68 (32.2%) TM patients had CSF ADA ≥15. Out of 127 patients diagnosed with BM, ADA was done in 104 (81.9%) patients, and none had ADA ≥15. Furthermore, survival was more among the TM patients with CSF ADA <15 (63.1%) as compared to 47 (31.5%) patients who had CSF ADA ≥15. The comparison was highly significant, with P<0.0001.

In the present study, 67 TM patients on ATT had abnormal CSF; 26 (38.8%) died. Karmarkar et al., in line with present study findings, reported that a normal CSF picture was seen in 15 patients (26%).

Brain imaging is an essential part of patient evaluation. Diagnosis of TM can be helped by neuroimaging. Classic neuroradiologic features of TM are basal meningeal enhancement and hydrocephalus. Hypodensities due to
cerebral infarcts, cerebral edema, and nodular enhancing lesions may also be seen. In the present study, out of 57 patients who died with TM, 35 (27.6%) had abnormal imaging findings. Hence, it means if the patient has abnormal imaging in TM, the risk of death is more. More recently, a study examining the radiological features of TM showed that the most common abnormalities seen on cerebral MRI were basal meningeal enhancement and hydrocephalus. Tuberculomas developed in 74% of patients during TB treatment, and the basal ganglia was the most common site of infarction. In the present study, out of 19 patients who died with BM, 8 (12.7%) had abnormal imaging findings. However, the distribution was insignificant, with \( P=0.217 \).

In the present study, out of 232 abnormal imaging findings, 46 (19.8%) died. Karmarkar et al., reported that of the 39 patients, MRI was abnormal in 14 patients. Meligy et al., reported that CT imaging was normal in 67 (69.8%) of cases, while 23 (24.0%) revealed brain edema. The author also reported more mortality among the patients with abnormal imaging. In a CT study of 60 cases of TBM in adults and children, only three had normal brain scans.

**Limitations of the study**

Small sample size and cross sectional nature are the few limitations of the present study due to that findings cannot be applied to whole population. There is a need of a large randomized clinical trial to provide more strength to present study findings.

**CONCLUSION**

AFE was more prevalent in males. TM was more prevalent, followed by BM, VM, and CM. TM followed by BM is the most common form of CNS TB and has very high morbidity and mortality. Mortality was more common among the TM and BM patients who had elevated CSF protein, increased CSF cells, and low glucose. Low CSF ADA levels can also be a marker for the abnormal outcome among patients with AFE. Brain imaging is an essential part of patient evaluation. Mortality was more in patients with abnormal imaging profiles. Treatment for TM and BM should be initiated as soon as initial CSF studies support clinical suspicion. To conclude, CSF analysis could be important for predicting the outcome and should be done as soon as possible after the clinical judgment of the AFE.

**ACKNOWLEDGMENT**

Nil.

**REFERENCES**


