



ETIOLOGY AND OUTCOME OF ACUTE FEBRILE ENCEPHALOPATHY AMONGST ADULTS ADMITTED AT A TERTIARY CARE CENTER

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ABSTRACT

Background- The present study was conducted at a tertiary care centre to analyze the cause as well as outcome of encephalopathy following short febrile illness in adults (> 14 years old).

Methodology- The present study was conducted as a prospective observational study on patients presenting with fever and altered mental status at Department of General Medicine, Gandhi Medical College and associated Hamidia Hospital, Bhopal for a period of 18 months i.e. from 1st December 2017 to 31st May 2019. All the patients were subjected to detailed evaluation with clinical history and systemic examination and investigations. CSF analysis and neuroimaging was also conducted.

Results- A total of 507 patients were included and majority of patients had tubercular meningitis followed by bacterial meningitis. The present study documented significantly higher mortality in patients with tubercular meningitis who presented with abnormal finding in neurological imaging ($p < 0.05$). Conclusions

Conclusion- CNS infections are causes of acute febrile encephalopathy, and the most common infection was tubercular meningitis and bacterial meningitis. Mortality was significantly higher in tubercular meningitis and neurological imaging with abnormal finding also had significant impact on mortality.

KEYWORDS : Acute febrile encephalopathy, bacterial, viral, tubercular, outcome, complications

INTRODUCTION

Acute febrile encephalopathy (AFE) is a clinical term used to describe patients presenting with short febrile illnesses with altered mental state.^[1] AFE is characterized by fever with altered mental sensorium. The most common cause of acute febrile encephalopathy include CNS infections such as bacterial meningitis, Japanese B encephalitis (JE), cerebral malaria (CM), and typhoid encephalopathy. In tropical countries like India, CM, JE, and bacterial meningitis are the common causes of AFE, while tubercular meningitis (TBM) can present with subacute or chronic history.^[2]

Apart from common clinical manifestations like headache, vomiting, convulsion, patients may present with different complications like dyselectrolyemia, respiratory acidosis due to CNS depression accompanied by metabolic acidosis if there is shock.^[2] Many a times even a detailed diagnostic workup may not identify a specific organism.^[3] The physician is faced with challenge of establishing etiology and ensuring prompt treatment in the emergency not only to ensure survival but also to prevent long-term sequel in these patients.^[4] One has to be very meticulous while approaching such a patient because of the diversity of causes and equally large number of mimicking conditions. In untreated cases, mortality is very high and the survivors are often left with disabling neurologic sequelae.^[4]

Various studies in children with nontraumatic coma have shown that CNS infections are the commonest cause of nontraumatic coma.^[5] However still the data on Indian population is limited hence the present study was thus conducted at a tertiary care centre to analyze the cause as well as outcome of encephalopathy following short febrile illness in adults (> 14 years old).

Methodology

The present study was conducted as a prospective observational study on patients presenting with fever and altered mental status at Department of General Medicine, Gandhi Medical College and associated Hamidia Hospital, Bhopal for a period of 18 months i.e. from 1st December 2017 to

31st May 2019. All the patients belonging to age group of more than 14 years, presenting with fever of less than 2 weeks along with altered mentation were included in the study. Patient with persistent alteration in mentation with one or more deranged parameter like Hypoglycemia (<50 mg/dl), Hypoxia, Hypercarbia (> 50 mm of Hg), Hyponatremia (< 120mg/dl) or Hypernatremia (> 150 mg/dl) deranged Serum Creatinine (> 3 mg/dl); Patients having cerebral vascular accident followed by fever and patient with altered mentation following Head Injury were excluded from the study.

After obtaining ethical clearance from Institute's ethical committee, written consent was obtained from the spouse/parents of the patients. All the patients were subjected to detailed evaluation with clinical history and systemic examination. Investigations such as complete blood examination, urine examination, LFT, RFT, Chest Xray, Serum electrolytes, ECG and blood sugar were conducted for all the patients. PS for malaria parasite and viral markers such as HIV, HBsAG, HCV were advised when necessary. Cerebro Spinal Fluid Analysis under aseptic precautions were conducted for all the participants to determine the etiology of encephalopathy. Apart from this Non Contrast and Contrast Enhanced CT/ MRI were advised when necessary. All the patients were followed up during the hospital stay and their outcome was assessed in terms of discharge (with or without complication) and death.

Statistical analysis:

All the data analysis were performed by using SPSS ver. 20 software. Frequency distribution and cross tabulation was performed to prepare the tables. Qualitative data were expressed as percentage and were analysed statistically using Chi-square test. Level of significance was assessed at 5%.

Observations and results

The present study could enroll 507 patients with fever and altered mental status fulfilling the inclusion criteria during the study period. Majority of patients belonged to <45 years of age (75.9%) whereas remaining 24.1% belonged to >45 years of age.

Table-1: Distribution of Gender with diagnosis

Diagnosis	Sex		Total	P value
	Female	Male		
Bacterial meningitis	59(25.7)	68(24.5)	127(25)	0.408
Cryptococcal meningitis	4(1.7)	3(1.1)	7(1.4)	
Enteric encephalopathy	9(3.9)	18(6.5)	27(5.3)	
Cerebral malaria	21(9.1)	24(8.7)	45(8.9)	
Septic encephalopathy	2(0.9)	7(2.5)	9(1.8)	
Tubercular meningitis	103(44.8)	108(39)	211(41.6)	
Viral meningitis	32(13.9)	49(17.7)	81(16)	
Total	230(100)	277(100)	507(100)	

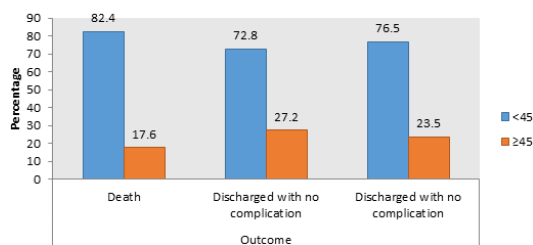
In present study majority of the patients were male (n=277 out of 507), on comparing the diagnosis distribution between genders it was found that majority of the females were diagnosed with tubercular meningitis (44.8%) followed by bacterial meningitis (25.7%) and viral meningitis (13.9%) similarly majority of the male population were diagnosed with tubercular meningitis (41.6%) followed by bacterial meningitis (25%) and viral meningitis (16%). However, the diagnosis was equally distributed among the genders as revealed by in the insignificant p value of 0.408.

Table-2: Distribution of Diagnosis with outcome

Diagnosis	Outcome Death Discharged with no complication			Total	P value
	Bacterial meningitis	23 (21.3)	23(9.2)		
Cryptococcal meningitis	2 (1.9)	4(1.6)	1(0.7)	7(1.4)	
Enteric encephalopathy	5 (4.6)	17(6.8)	5(3.4)	27(5.3)	
Cerebral malaria	9 (8.3)	27(10.8)	9(6)	45(8.9)	
Septic encephalopathy	2 (1.9)	7(2.8)	0(0)	9(1.8)	
Tubercular meningitis	62(57.4)	97(38.8)	52(34.9)	211(41.6)	
Viral meningitis	5 (4.6)	75(30)	1(0.7)	81(16)	
Total	108(100)	250(100)	149(100)	507(100)	

Out of 507 patients, mortality was documented in 108 (21.3%) patients whereas 250 (49.3%) were discharged without any complication and 149 (29.4%) were discharged with some complications. Maximum mortality was observed in patients with tubercular meningitis (57.4%) followed by bacterial meningitis (21.3%) and malarial encephalitis (8.3%) similarly those who were discharged without any complications majority were diagnosed with tubercular meningitis (38.8%) followed by viral meningitis (30%) and malarial encephalitis (10%). Similarly those who were discharged with some complications majority were diagnosed with Bacterial meningitis (54.4%) followed by tubercular meningitis (34.9%). The diagnosis was significantly distributed among the outcomes revealed by in the highly significant p value of <0.001.

Graph 1: Comparing Age with outcome



In present study, out of 108 patient who died, 89 (82.4%) had age <45 years whereas 19 (17.6%) had age ≥45 years. Out of

250 patients who Discharged with no complication, 182 (72.8%) had age <45 years and 68 (27.2%) had age ≥45 years. Similarly out of 149 patients who Discharged without any complication, 114 (76.5%) had age < 45 years and 35 (23.5%) has age ≥45 years. The outcome distribution among the different ages of the patients was not significant as revealed by the insignificant with p value of 0.146, that means outcome was similar in different age groups.

Table 3- Imaging findings in various etiologies

Etiology	Outcome	Normal imaging	Abnormal Imaging	Total	P value
Bacterial	Death	11 (21.6)	8 (12.7)	19 (16.7)	0.217
	Survived	40 (78.4)	55 (87.3)	95 (83.3)	
Tubercular	Death	22 (42.3)	35 (27.6)	57 (31.8)	0.026
	Survived	30 (57.7)	92 (72.4)	122(68.2)	
Viral	Death	2 (9.5)	2 (5.1)	4 (6.7)	0.759
	Survived	19 (90.5)	37 (94.9)	56 (93.3)	

The present study observed a statistically highly significant mortality in tubercular cases with abnormal imaging as compared to patients with normal imaging (p<0.05). However, no significant association between death and imaging findings was documented in bacterial and viral meningitis (p>0.05).

DISCUSSIONS

Fever with altered mentation, is a common symptom complex leading to hospital admissions in both adults and children in our country and is also known as acute febrile encephalopathy. Fever with altered mental status is commonly produced by bacterial meningitis, Japanese B encephalitis, cerebral malarial, typhoid encephalopathy, and fulminant hepatic failure due to viral hepatitis.^[2]

In present study majority of the patients were male (n=277 out of 507), on comparing the diagnosis distribution between genders it was found the etiology was statistically similar among males and females (p>0.05). In a similar series by Bhalla et al, male preponderance (78.1%) was observed.^[1] In another study in by Panagaria et al, the authors documented slight male predominance which could be due to male dominated social system in India i.e. a sick male gets preferential medical attention.^[6]

In present study, most common cause of acute febrile encephalopathy was tubercular meningitis (41.6%) followed by bacterial meningitis (25%), viral meningitis (16%) and cerebral malaria (8.9%). In line with that Bhalla A et al analyzed the cause of encephalopathy following short febrile illness in 127 patients with fever of less than 2 weeks duration along with alteration in mentation and found that of the total 127 patients, 70% had primary CNS infection as the etiology of febrile encephalopathy. A total of 42 patients had meningitis with 32 patients (25.2%) having acute pyogenic meningitis and 10 patients (7.87%) having tubercular meningitis (TBM). Thirty-eight patients (29.9%) had evidence of mening oencephalitis, which was followed by cerebral malaria, leptospirosis, and brain abscess as a cause of primary CNS infection.^[1]

A study of nontraumatic coma in children by Bansal et al indicated that TBM, pyogenic meningitis, and encephalitis together constitute more than 90% of the cases.^[5] Singh et al observed that the most common illness presenting as fever with altered sensorium was viral encephalitis seen in 49 (45.8%) cases. The cause of viral encephalitis was established as Japanese encephalitis in 19 (17.7%) patients and herpetic encephalitis in 4 (3.7%) patients. Pyogenic meningitis was second most common diagnosis responsible for 45 (42%) cases. Cerebral malaria was documented in 8 (7.5%) children and tubercular meningitis in 4 (3.7%) children presenting as acute febrile encephalopathy.^[7]

In present study, mortality was observed in 108 (21.3%) cases, of them, majority of the patients who died had tubercular meningitis (57.4%) followed by bacterial meningitis (21.3%) and malarial encephalitis (8.3%) similarly those who were discharged without any complications majority were diagnosed with tubercular meningitis (38.8%) followed by viral meningitis (30%) and malarial encephalitis (10%). Those who were discharged with some complications majority were diagnosed with Bacterial meningitis (54.4%) followed by tubercular meningitis (34.9%). The observed association between mortality and diagnosis was statistically highly significant ($p < 0.001$). Reports of Bhalla et al showed mortality in 16.5% cases. The maximum mortality was seen in patients with Sepsis Associated Encephalitis with as many as 33% patients dying (6/18). Of the total number of 38 patients with meningoencephalitis, 7 succumbed to their illness (18.42%). One patient each died due to pyogenic meningitis and cerebral malaria and leptospirosis. Five patients out of 14 (35.7%) in whom no definitive diagnosis could be established succumbed to their illness.⁽¹¹⁾

While cerebrospinal fluid abnormalities support the diagnosis of a meningoencephalitic syndrome, the changes in the cerebrospinal fluid constituents are often non-specific and may not be helpful in securing a specific aetiological diagnosis in many cases. There is considerable urgency to establish an efficient diagnostics for these patients. Irreversible brain damage may result while waiting for confirming the diagnosis. Delay in diagnosis and treatment are regarded as a major contributing factors to the morbidity and mortality.⁽⁸⁾

Brain imaging is frequently an essential part of patient evaluation. Diagnosis of TBM can be helped by neuroimaging. Classic neuroradiologic features of TBM are basal meningeal enhancement and hydrocephalus.⁽⁹⁾ Hypodensities due to cerebral infarcts, cerebral edema, and nodular enhancing lesions may also be seen. In present study, Out of 57 patients who died with tubercular meningitis, 35 (27.6%) had abnormal imaging findings. The distribution was significant with p value of 0.026. So it means if the patients has abnormal imaging in tubercular meningitis, chances of death is more. More recently, a study examining the radiological features of TBM showed that the most common abnormalities seen on cerebral magnetic resonance imaging (MRI) were basal meningeal enhancement and hydrocephalus. Tuberculomas developed in 74% of patients during the course of TB treatment and the basal ganglia were the most common site of infarction. Karmarkar et al conducted MRI brain in 39 patients, of them, MRI was abnormal in 14 patients.⁽¹⁰⁾ Basant M et al documented that mortality was more among the patients with abnormal imaging.⁽¹¹⁾

CONCLUSIONS

Based on the finding of present study, CNS infections are causes of acute febrile encephalopathy, and the most common infection was tubercular meningitis and bacterial meningitis. Mortality was significantly higher patients with abnormal neurological imaging findings especially in tubercular meningitis.

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