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Study of clinico-etiological profile of acute febrile encephalopathy

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Abstract
Background: The profile of febrile encephalopathy varies on the basis of different demographic and geographical characteristics of the study population. It is important to determine the etiologic spectrum of febrile encephalopathy syndrome, with an emphasis on the CNS infection by focusing on epidemiology and age groups.
Aims and objectives: To study the clinical and etiological profile of patients presenting with Acute Febrile Encephalopathy and correlate it with lab parameter in various etiological categories.
Materials and Methods: Three hundred and ninety eight patients were studied in the Medicine Department attached to the Gandhi Medical College Bhopal and affiliated Hamidia Hospital Bhopal, over a period of 12 months. After detailed history and clinical examination, patients were classified into six broad groups of categories as pyogenic meningitis (PM), acute viral encephalitis (AVE), cerebral malaria (CM), sepsis associated encephalopathy (SAE), enteric encephalopathy (EE) and tubercular meningitis (TBM).
Results: Majority of the patients were diagnosed with CM (29.4%) followed by SAE (17.1%) and AVE (16.6%), PM (13.8%), TBM 913.6%) and EE (9.5%). AVE and CM were more prevalent in working age group while EE, TBM and PM were more prevalent in young age group subjects. Patients having fever, vomiting, serizers, fundus abnormality and hepatosplenomegaly can be suspected for having CM, PM and TBM as these symptoms were more prevalent among these patients. Seizers were more common among the patients with AVE and PM. Brain imaging (CT/MRI) evaluation revealed that Cerebral Oedema was most common among CM patients (66.7%), meningeal enhancement was mainly observed in PM (50.5%) and TBM patients (38.5%). EEG findings revealed that AVE (45%), CM (35%), PM (12.5%), SAE (1.2%) and TBM (6.2%) had generalized seizures respectively, whereas all patients affected with temporal lobe spikes were of AVE (100)].
Conclusion: Etiology of acute febrile encephalopathy is varied. Cerebral malaria was the most common cause of acute febrile encephalopathy from this region followed by Sepsis Associated Encephalopathy, Acute Viral Encephalitis, Pyogenic Meningitis and Tubercular Meningitis.

Keywords: acute febrile encephalopathy, meningeal enhancement, electroencephalography

Introduction
Acute onset fever with altered mentation is a problem commonly encountered by the physician in the emergency. "Acute febrile encephalopathy" is a term commonly used to identify this condition. It is a common condition leading to hospital admissions of adults in India [1].
Central nervous system (CNS) infections are the most common cause of nontraumatic coma. The etiologic agent may be a virus, bacterium, or a parasite. There is no systematic study available to define the etiology and the extent of this problem in adults [2, 3].
The profile of febrile encephalopathy varies on the basis of different demographic and geographical characteristics of the study population [4]. It is important to determine the etiologic spectrum of febrile encephalopathy syndrome, with an emphasis on the CNS infection by focusing on epidemiology and age groups [4, 5].
The knowledge of these data is essential for protocol development at the regional level in order to appropriately manage patients. While such studies are commonly performed in the pediatric age group, there are few data for the adult population. This study was conducted to determine the clinicoetiological profile of acute febrile encephalopathy in hospitalized patients of a tertiary care hospital in central India.
The present study is an attempt to study the clinico-etiological profile of cases of febrile encephalopathy presenting at tertiary care centre in central india. As such a study has not been undertaken for Bhopal and its surrounding areas, it will help in furthering our knowledge on this subject and hopefully lead to better management.

Material and Methods
Present study was carried out on 398 patients in the Medicine Department attached to the Gandhi Medical College Bhopal and affiliated Hamidia Hospital Bhopal, Over a period of 12 months.
We screened all the patients presenting to our emergency with fever and altered mentation and enrolled all consecutive patients older than 14 years, who presented with fever of less than 14 days duration with altered mentation, either at onset or following fever, and lasting at least 24 h.
As we were trying to look at the clinical-etiological profile of the patients presenting with short febrile illness and altered mentation, an effort was made to enroll all consecutive patients, there were no controls selected.

All the Patients >14 years of age presenting with fever (>38°C) of less than 2 weeks duration with altered sensorium with/or without seizure and with or without focal neurological deficit were included.

Patients in whom the persistent alteration in mentation is due to deranged metabolic parameters, rather than fever (Hypoglycemia, Electrolyte imbalance, Azotemia, Hepatic Failure) and patients with altered mental status followed by fever were also excluded as structural lesion in the brain could be a reason for alteration in mentation.

The detailed history of the patients was recorded and the patients then underwent a detailed clinical examination. The investigation included were Complete Blood Picture, Renal Function Test, Liver Function Test, Urine Routine Microscopy in all patients. A Histidine-rich protein-based immunochromatographic card test for falciparum malaria was performed in all patients. Widal test was performed in all the cases of Acute Febrile Encephalopathy. The agglutination test for H and O antigens was done, and an O titre of >1:160 or more was taken as diagnostic. Samples for blood cultures were collected and any clinically obvious site of sepsis was investigated. Lumbar puncture was carried out in all the patients at admission and cerebrospinal fluid (CSF) was analyzed for cytology, protein levels, glucose, gram stain and CSF Adenosine deaminase levels. All patients, underwent computed tomography (CT) of the brain. This was followed by a magnetic resonance imaging (MRI) scan of the brain with or without contrast only if needed. Electroencephalography Was done in all patients, to aid in diagnosis, it was done on an 24 channel EEG machine in hamidia hospital Bhopal.

The patients were classified into six broad groups of categories meningitis, meningoencephalitis, cerebral malaria, sepsis associated encephalopathy, enteric encephalopathy and other clinical syndromes on the basis of predesignated diagnostic criteria:

Pyogenic Meningitis (PM)

Fever with altered sensorium +/- neck signs/nuchal rigidity +/- seizures, focal neurologic deficits (including cranial nerve palsies), and papilledema +/- positive blood culture +/- csf cytology predominantly polymorphs /percentage of neutrophils usually greater than 80 percent, protein of 100 to 500 mg/dl, and glucose < 40 mg/dl (with a csf: serum glucose ratio of ≤0.4& gram stain+/-meningeal enhancement.

Acute Viral Encephalitis (AVE)

Fever with altered sensorium (with focal symptoms/signs+/- seizures) ± neck signs + csf cytology wbc count, usually less than 250/mm^3 (predominantly lymphocytes), protein less than 150 mg/dl, glucose usually normal occasionally moderatory reduced + imaging findings suggestive of involvement of the temporal lobe, thalamus or basal ganglia, brainstem, and cerebellum.

Cerebral Malaria (CM)

Fever with altered sensorium (with or without focal symptoms/signs), convulsions with anemia, thrombocytopenia and hepatomegaly, and/or splenomegaly with malarial antigen test positive.

Sepsis Associated Encephalopathy (SAE)

Underlying sepsis syndrome with normal csf analysis, ct and mri scan.

Enteric Encephalopathy (EE)

Fever With With Altered Consciousness, Delirium, And Confusion, Positive Blood Cultures, Rose Spots, positive Widal Titre

Tubercular Meningitis (TBM)

Fever With Altered Sensorium (With Or Without Focal Symptoms/Signs) + Csf Compatible With Tubercular Meningitis Elevated Protein And Lowered Glucose Concentrations With A Mononuclear Pleocytosis (+ CSF ADA> 9), CT Or MRI Evidence Of Basilar Meningeal Enhancement Combined With Any Degree Of Hydrocephalus.

Clinical presentation and lab parameters were correlated with underlying etiology, The data were analysed using SPSS statistical software. The values were expressed as mean with standard deviation and percentage.

Results

In present study majority of the patients were diagnosed with CM (29.4%) followed by SAE (17.1%) and AVE (16.6%), PM (13.8%), TBM 913.6%) and EE (9.5%).

In present study AVE [21(31.8%)] and CM [38 (32.4%)] was significantly higher in age group of 31-40 years. Patients of EE were higher in age group of 21-30 years [16 (42.1%)]. PM was equally distributed between age group of ≤20 and31-40 years [24 (43.6%) in each age group]. SAE was significantly higher in >50 years age group of [37 (54.4%)]. Majority of the TBM patients were in the age group of 21 -30 years [34 (63%)]. The comparison was higher significant between all the diagnosis ($p<0.001$).

In present study AVE [40 (20%)], SAE [42 (61.8%)] and TBM [30 (55.6%)] was significantly higher among male patients ($p=0.01$) whereas CM [59 (50.4%)], EE [24 (63.2%)] and PM [39 (70.9%)] were significantly higher among the female population ($p=0.01$).

Majority of the patients of AVE [38 (57.6%)] and CM [88 (75.2%)] were having GCS score of more than 13, Majority of the EE patients EE [22 (57.9%)] had between 9-12 whereas maximum patients of, PM [33 (60%)] and SAE [44 (564.7%)] and TBM {37 (68.5%) had GCS score of≤8. The comparison was highly significant ($p<0.001$).

Distribution of symptoms among diagnosis revealed that headache was the main symptoms among patients with CM [112 (29.71%)] followed by TBM [68 (18.04%)] and PM[54 (13.32%)]. Vomiting was the main symptoms of PM [95 (32.09%)] patients followed by CM [56 (18.92%)] and TBM[54 (18.24%)]. Seizerswere more in AVE [77 (31.56%)], CM [66 (27.05)] and PM[42 (17.2)]. Fundus Abnormality was mainly seen in CM [117 (29.40%)], SAE [68 (17.09%)] and AVE [66 (16.58%)]. Meningial signs were most common among TBM [66 (28.2%1)] followed by PM [55 (23.50%)] ($p<0.001$). Hepatosplenomegaly was mainly reported in CM [81(78.64%)] followed by TBM patients [10 (9.71%)] ($p<0.001$). Neurological deficits were comparable between all diagnosis ($p=0.143$).

Majority of the patients of AVE [49 (74.2%)] and CM[70 (59.8%)]had Duration of fever between ≤3days. Whereas majority of the patients with PM[40 (72.7%)] and SAE[40 (58.8%)]had Duration of fever 4-7 days. Majority of patients of EE [29 (65%)] had Duration of fever between 7-14 days. The comparison was highly significant ($p<0.001$).

Mean HB, TLC, Platelet blood urea, serum creatinine and bilirubin in patients of AV was 11.27±1.92, 7437.11±4950.75, 20.38±35.88, 31.45±21.82, 1.23±0.72 and 2.17±1.74 respectively. Mean HB, TLC, Platelet blood urea, serum creatinine and bilirubin in patients of CM was 10.56±1.95, 7623.09±4431.82, 70.51±27.98, 71.98±110.64, 1.99±0.98 and 3.20±1.87respectively.Mean HB, TLC, Platelet blood urea, serum creatinine and bilirubin in patients of EE was 9.37±2.08, 9854.21±5665.21, 2.43±0.61, 23.95±9.66, 1.00±0.28 and 1.41±0.49 respectively. Mean HB, TLC, Platelet blood urea, serum creatinine and bilirubin in patients of PM was 10.75±0.84, 8129.60±3515.62, 2.57±1.24, 20.22±8.85, 1.10±0.44 and 1.30±0.45 respectively. Mean HB, TLC, Platelet blood urea, serum creatinine and bilirubin in patients of SAE was 10.29±1.08, 23548.35±10067.13, 40.04±31.31, 86.65±127.64, 2.25±1.04 and 3.16±1.93respectively.Mean HB, TLC, Platelet blood urea, serum creatinine and bilirubin in patients of TBM was 10.15±2.57, 6543.44±2022.84, 2.20±1.07, 19.37±7.20, 0.92±0.28 and 1.38±0.40respectively.

In present study CSF cell count was higher in PM patients followed by AVE. Minimum cell count was observed in patients with EE followed by SAE and CM. CSF proteins were higher in TBM patients followed by PM whereas CSF proteins were minimum among EE and CM patients.

CSF Glucose was higher among patients of CM followed by EE and minimum CSF glucose values was reported in patients with PM and TBM. CSF Gram staining revealed that patients with EE [9 (13.6%)], PM [55 (83.3%)] and SAE [2 (3%)] had positive gram staining. Predominant cell type in CSF among patients of AVE[66 (21.5%)], CM [20 (6.5%)], EE[21 (6.8%)], SAE[7 (2.3%)] and TBM[78 (24.4%)] was lymphocyte whereas among PM[28 (70)] it was polymorph. Patients with AVE [38 (15.7%)], CM [103 (42.6%)], EE [38 (15.7%)], PM[13 (5.4%)] and SAE[50 (20.7%)] had ADA ≤9 whereas TBM[40 (100%)] patients had ADA ≥10.

Positive blood Culture was reported in 26 (18.6%), 50 (35.7%), 54 (38.6%) and 10 (7.1%) patients of EE, PM, SAE and TBM respectively. Whereas none of the patients of AVE and CM showed positive blood Culture. Positive urine CS culture was reported in 22 (32.4%), 7 (10.3%) and4 (5.9%) patients in SAE, PM and TBM respectively. The comparison was highly significant ($p<0.001$).

Table 1: Showing CT/MRI findings in study cohort

CT/MRI	AVE	CM	EE	PM	SAE	TBM	Total
Cerebral Oedema	23 (36.5)	42 (66.7)	17(27)	21(33.3)	5(7.9)	14 (22.2)	63 (100)
Meningial Enhancement	0 (0)	0 (0)	12 (11)	55 (50.5)	0 (0)	42 (38.5)	109 (100)
Fronto-temporal lobe Enhancement	37(100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (100)
Intra cranial space occupying lesion/tuberculoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	12 (100)	27 (100)
White Matter Hypodensities	10 (27.7)	9 (25)	2 (5.6)	4 (11.1)	5 (13.88)	0 (0)	12 (100)
No Significant Abnormality	14 (9.9)	53(37.6)	24 (17.1)	0 (0)	50 (35.5)	0 (0)	141 (100)
Total	66 (16.6)	117 (29.4)	38 (9.4)	55 (13.8)	68 (17.1)	54 (13.6)	398 (100)

Table 2: EEG findings

Diagnosis	Generalized Seizures	Temporal Lobe Spikes	Normal	Total
AVE	36 (45)	28(100)	2	66
CM	28 (35)	0 (0)	89	117
EE	0 (0)	0 (0)	38	38
PM	10 (12.5)	0 (0)	45	55
SAE	1 (1.2)	0 (0)	67	68
TBM	5 (6.2)	0 (0)	49	54
Total	80	28	290	398

Discussion

In present study we found that prevalence (in sequence) of cerebral malaria was more prevalent as compared to sepsis associated encephalopathy, acute viral encephalitis, pyogenic meningitis, tubercular meningitis and enteric encephalopathy. We noticed that AVE and CM were more prevalent in working age group while EE, TBM and PM were more prevalent in young age group subjects. Hence in present study younger patients were more affected most probably because of lack of cumulative immunity due to natural infection.

Patients having fever, vomiting, serizers, fundus abnormality and hepatosplenomegaly can be suspected for having CM, PM and TBM as these symptoms were more prevalent among these patients. Seizers were more common among the patients with AVE and PM. Patients with TBM had the meningial signs as the most common symptoms in present study. Neurological deficits were comparable between all types of diagnosis. Similar results were reported by previous studies [6, 7].

Duration of fever is an important criterion for diagnosis. Duration of fever for more than three days can be suspected for AVE and CM. However, longer duration of fever of 4-7 days is an important clue for identification of patients with PM and SAE. Patients with EE should be judged on the bases of fever persisting for more than 7 days.

When we compared the blood parameters among the different types of diagnosis we found that hemoglobin level was comparable between all type of diagnosis whereas higher TLC level gave a clue for SA, PM and EE. It may be due to the fact that patients with SA, PM and EE have higher infection rates as compared to other diagnosis. Platelet count is another important tool for diagnosis of AVE as these patients had lowest platelet count in present study. Patients with SAE and CM also had lower platelet count, all these patients should be given immediate intervention for maintaining normal platelet count. Blood urea was significantly higher among the patients with SAE and CM patients. Similar results were reported by previous studies [8, 9].

In present study CSF cell count was higher in PM patients followed by AVE. Minimum cell count was observed in

patients with EE followed by SAE and CM. CSF proteins were higher in TBM patients followed by PM whereas CSF proteins were minimum among EE and CM patients. Similar results were reported by previous studies [10, 11].

CSF Glucose was higher among patients of CM followed by EE and minimum CSF glucose values was reported in patients with PM and TBM.

CT/ MRI is another important tool for the confirmation of CM and PM as Cerebral Oedema and Meningial Enhancement were the most common findings among these patients in present study. Enhancement in Fronto-Temporal lobe can be taken as suspicion of AVE diagnosis whereas Tuberculoma was significantly higher in TBM patients. Generalized seizures was significantly higher among the patients of AVE, CM and PM. We recommend EEG for all such patients for the confirmation. Similar results were reported by previous studies [5, 12, 13].

Based on the findings we found that etiology of acute febrile encephalopathy varies. Cerebral malaria was the most common cause of acute febrile encephalopathy from this region followed by SAE, AVE, PM and TBM. Similar results were reported by previous studies [6, 8, 11]. The causes and risk factors for high prevalence of cerebral malaria need to be urgently explored in order to initiate preventive strategies. Although, viruses have been traditionally thought to cause most cases of encephalitis, pyogenic meningitis and even tubercular meningitis form a sizeable number of cases, especially in our country. Cerebral malaria needs special consideration, and a high index of suspicion.

Conclusions

Based on the findings we found that etiology of acute febrile encephalopathy is varied. This study shows Cerebral malaria was the most common cause of acute febrile encephalopathy from this region followed by Sepsis Associated Encephalopathy, Acute Viral Encephalitis, Pyogenic Meningitis and Tubercular Meningitis. Cerebral malaria needs special consideration, and a high index of suspicion. This study concludes duration of fever is important for distinguishing various categories of Febrile Encephalopathy. In present study deep jaundice and acute kidney injury is very prevalent in cerebral malaria and sepsis associated encephalopathy. Meningial signs and focal neurological deficit are most common in Tubercular Meningitis Patients. While the seizures are mainly associated with cerebral malaria and viral encephalitis. The study compared the blood parameters among the different types of Febrile Encephalopathy. In present study the CSF cell count was higher in Pyogenic Meningitis patients followed by Tubercular Meningitis. Cerebral Oedema and meningial enhancement are most common findings in cerebral malaria and meningitis patients. While fronto temporal lobe enhancement was more common in patients with viral encephalitis. So this study shows correlation between various clinical lab and radiological parameters in the patient of acute febrile encephalopathy.

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