Original Article

# Changing Clinical Profile and Predictors of Mortality in Patients of Acute Febrile Encephalopathy from North India

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## Abstract

**Introduction:** Acute encephalitis syndrome (AES) or acute febrile encephalopathy is a clinical condition characterized by altered mental status occurring after or along with a short febrile illness. In developing countries, infections are the predominant cause of AES. Prominent infections known to cause AES include viruses (such as herpes simplex virus [HSV], Japanese Encephalitis [JE] virus, dengue, enteroviruses [EVs]), bacteria, fungus, and parasites. In the present study, we aim to analyze the etiology, clinical features, and predictors of mortality in patients presenting with acute febrile encephalopathy or acute encephalitic syndrome. The present study was a prospective observational study conducted at Post Graduate Institute of Medical Education and Research a tertiary care center in Chandigarh, India. **Methods:** A total of 105 patients with ≥18 years of age with fever (body temperature >101° F for duration ≤14 days) and altered sensorium (Glasgow coma scale [GCS] score ≤10) lasting for more than 24 h, either accompanying the fever or following it were enrolled. Demographic and clinical details were recorded on pro forma. Cerebrospinal fluid (CSF) analysis was performed for all the enrolled patients at admission for cytology, CSF glucose to blood glucose ratio, protein levels, gram stain and culture sensitivity, adenosine deaminase levels, polymerase chain reaction for HSV/EV/mycobacterium tuberculosis (TB) and immunoglobulin M Enzyme-linked immune assay for JE. Computed tomography of the brain was done in all patients while magnetic resonance imaging (MRI) of the brain was carried out in 75 patients. **Results:** Among the 105 patients, tubercular meningitis was seen in 27 (25.7%) patients followed by acute pyogenic meningitis in 18 (17.1%) patients. Probable viral encephalitis was present in 12 (11.4%) cases. Septic encephalopathy ($n = 10$) and scrub typhus encephalitis ($n = 8$), HSV encephalitis ($n = 6$), dengue encephalitis ($n = 4$), leptospirosis ($n = 3$) were the other infections causing acute febrile encephalitis in our study. In addition to fever and altered sensorium common symptoms observed were headache (52.4%), vomiting (35.2%), and seizures (29.5%). The factors predicting increased mortality were female gender, fever of more than 38°C at admission, GCS <7, MRI showing disease-related findings like altered signal intensity bilateral medial temporal and insular area in herpes simplex encephalitis, etc., changes, and the group of patients where a definite diagnosis could not be established during the hospital stay. **Conclusions:** Tubercular meningitis/central nervous system TB is the predominant cause of acute febrile encephalopathy in developing countries. Scrub and dengue encephalitis are emerging as an important cause of acute febrile encephalopathy and occur predominantly in postmonsoon seasons. Acute febrile encephalopathy remains an important cause of mortality in patients presenting to Emergency Department (ER). The strongest predictors of mortality are low GCS and undiagnosed cases of AES.

**Keywords:** Acute encephalitis syndrome/acute febrile encephalopathy, acute pyogenic meningitis, dengue encephalitis, herpes simplex virus encephalitis, Japanese encephalitis, sepsis-associated encephalopathy, tuberculous meningitis

## Introduction

Acute fever with encephalopathy (AFE) is a syndrome of altered sensorium following a short febrile illness or accompanying it. As per the World Health Organization, a case of acute encephalitis syndrome (AES) is defined as a person of any age, at any time of year with the acute onset of fever (usually <14 days) and a change in mental status (including symptoms such as

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confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures).[1] AFE is most commonly caused by an infection of the central nervous system (CNS) which could be a virus, bacterium or parasite, etc., but sometimes infection outside the CNS may play a role, for example, septic encephalopathy. Many times, etiology remains undiagnosed even with extensive workup.[2]

Most of the organisms have their own spectrum of brain involvement.[3] The presence of focal signs and seizures is usually suggestive of encephalitis, but the complete distinction is usually not possible and investigations such as cerebrospinal fluid (CSF) and neuroimaging are required for confirmation. If untreated, cases of acute febrile encephalitis have high mortality and those who survive may be left with moderate-to-severe disabling neurological sequelae. In the present study, we aim to analyze the etiology, clinical features, and predictors of mortality in patients presenting with acute febrile encephalopathy or acute encephalitic syndrome to ER.

## Methods

The present study, a prospective observational study was done at Post Graduate Institute of Medical Education and Research, Chandigarh, India, over 15 months from March 2017 to May 2018. One hundred and five patients who were ≥18 years of age with fever (body temperature >101° F for duration ≤14 days) and altered sensorium (Glasgow Coma Scale [GCS] score ≤10) lasting ≥24 h; either accompanying the fever or following it were enrolled. A total of 105 patients were included in the final analysis after taking written and informed consent. This study excluded patients who presented with metabolic encephalopathy because of hypoglycemia (random blood sugar <50 mg/dl), hypoxia ($PaO_2$ <60), hypercarbia ($PaCO_2$ >50), hyponatremia (<120 mg/dl), hypernatremia (>150 mg/dl), and creatinine (>3 mg/dl). Patients with a cerebrovascular accident, pregnancy or postpartum period, and patients whose parents or next to kin refused to give consent were also excluded. Demographic and clinical information was recorded on prescribed pro forma. Hemogram, biochemistry including metabolic profile, malaria parasite examination, chest X-ray, and electrocardiography was done in all patients. Lumbar puncture was done in all the enrolled patients on admission and the CSF examination was sent for cytology, CSF glucose to blood glucose ratio, protein levels, gram stain and culture sensitivity, adenosine deaminase (ADA) levels, polymerase chain reaction (PCR) for herpes simplex virus (HSV), enterovirus (EV), tuberculosis (TB), and immunoglobulin M (IgM) ELISA for Japanese encephalitis (JE).

CSF ADA ($n$ = 100), PCR for HSV and EV analysis was done in 99 and 100 patients, respectively. For carrying out TB-PCR on CSF samples, DNA was extracted from 500 µL of CSF using QIAamp DNA blood mini kit (250) (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's instructions. Further testing was done as per the standard protocol. TB-PCR was done in all the enrolled patients however multiplex PCR was done in 103 patients only. Scrub PCR in CSF and blood was done in 100 and 105 patients, respectively. JE IgM ELISA in CSF and blood was done in 92 and 94 patients respectively. Leptospira and scrub IgM were done in 99 and 103 patients, respectively. Computed tomography of the brain was done in all patients while magnetic resonance imaging (MRI) of the brain was done in 75 patients out of 105.

All the enrolled patients were treated as per the standard protocols and were followed up until discharge from the hospital. A telephonic follow-up was also done after 28 days in all the 105 enrolled patients. A standard set of criteria's was used for the diagnosis of various acute encephalitic syndromes [Table 1].[4] A new category was added after data analyses. This was named as probable viral encephalitis (patients with typical history and imaging s/o viral encephalitis but having a negative HSV/Dengue/JE/EV microbiological test).

### Statistical analysis

Data were recorded on preprinted pro forma. The data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Inc. New York city, New York, USA.). Descriptive statistics including frequency, mean, median, minimum, maximum, and standard deviation were calculated for the demographic data and laboratory parameters. Categorical variables were presented as percentage and continuous variables were presented as mean/median along with 95% confidence limit. The association between categorical variables was tested using Chi-square or Fisher's exact tests. The comparison of continuous variables between groups was done by Student's *t*-test or one-way analysis of variance. A *P* value (two-tailed) of <0.05 was considered statistically significant.

## Results

### Baseline characteristics

Males outnumbered females with ratio of 1.187. The mean age of the patients was 39.58 ± 17.40 years. The number of patients belonging to age group ≤45 years was statistically significantly higher than that of the age group >45 years (72.4% compared to 27.6%) with $P < 0.001$. Most of the patients, i.e., 48 (45.7%) were referred or belonged from Punjab; Chandigarh, Haryana, and Himachal Pradesh accounted for another 48 (45.7%) of the enrolled patients. On combining the referred patients from neighboring states accounted for more than 90% of the patients with AES. Most of the patients who were enrolled in the study were during May, June, July, and August (summer to monsoon season) accounting for 73 cases (69.6%) [Figure 1]. 16 (15.2%) patients were diabetics, 3 HIV and one patient postrenal transplant [Figure 1].

### Clinical characteristics

The most common symptoms observed after fever and altered sensorium were headache in 52.4% ($n$ = 55), seizures in 29.5% ($n$ = 31), and vomiting in 35.2% ($n$ = 37) of cases. The most common finding was neck rigidity (53.3%). Papilledema was found in 5.7% and rash was present in 3.8%, eschar was

**Table 1: Criteria for diagnosis of acute encephalitic syndromes[4]**

| Disease | Diagnostic criteria |
|---|---|
| Pyogenic meningitis | Fever with altered sensorium±neck signs (without focal symptoms/signs) + CSF cytology (predominantly polymorphs; ranges from 10/µL to 10,000/µL) + meningeal enhancement on either CT or MRI scan |
| Viral encephalitis | Fever with altered sensorium (with focal symptoms/signs) ± neck signs+CSF cytology (predominantly lymphocytes) + EEG/MRI/CT evidence of parenchymal disease+CSF serology/PCR |
| HSV encephalitis | Fever+altered sensorium±focal deficits±CSF with normal to raised pressure, lymphocytic pleocytosis (10–200 cells/mm$^3$), normal glucose, and raised protein (0.6–6 g/L) + CSF HSV PCR (+) and/or suggestive MRI changes involving temporal and frontal lobes |
| JE | Fever±altered sensorium±focal deficits±CSF with normal or raised pressure, lymphocytic pleocytosis (usually 10–60 lymphocytes/mL) with normal glucose level+CSF JE antigen (+) or IgMAb (+) or JE PCR (+) and/or suggestive MRI changes involving thalamus and basal ganglia |
| EV encephalitis | Fever+altered sensorium±focal deficits+CSF pleocytosis with lymphocyte predominance, raised protein and normal sugar + CSF EV PCR (+) and/or suggestive MRI changes involving medulla oblongata and pons |
| Scrub encephalitis or meningoencephalitis | Fever+headache±altered sensorium±neck signs+CSF cytology (predominantly lymphocytes) with moderate elevation of protein and low to normal glucose with or without PCR CSF positivity+positive serum IgM serology positive and/or blood/eschar PCR (+) |
| Leptospiral meningitis | Fever with altered sensorium±neck signs±raised CSF pressure with CSF cytology showing predominantly lymphocytes, with raised protein and low to normal glucose+serum or CSF serology (+) by MAT or ELISA |
| TBM | Fever with altered sensorium (with or without focal symptoms/signs) + CSF compatible with chronic meningitis+CSF ADA >9/TB PCR positive/positive Gene Xpert |
| Cerebral malaria | Fever with altered sensorium (without focal symptoms/signs) with peripheral smear/HRP antigen test positive for malaria[4] |
| Septic encephalopathy | Underlying sepsis syndrome with normal CSF analysis, CT and MRI scan |
| ADEM | Fever with altered sensorium±headache±neck signs±focal deficits with CSF cytology showing predominantly lymphocytes, moderately raised protein and normal sugar+diffuse white matter changes in the MRI consistent with ADEM |
| NMS | Fever with altered sensorium + muscle rigidity with history of neuroleptics within 1–4 weeks+normal CSF (protein may raised) and imaging+raised CPK |
| Indeterminate | If none of the above criteria for diagnosis are met |

CT: Computed tomography, MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, EEG: Electroencephalogram, HSV: Herpes simplex virus, EV: Enterovirus, JE: Japanese encephalitis, MAT: Microagglutination test, ADA: Adenosine deaminase, HRP: Histidine rich protein, ELISA: Enzyme linked immunosorbent assay, CPK: Creatinine protein kinase, PCR: Polymerase chain reaction, IgM: Immunoglobulin M, ADEM: Acute disseminated encephalomyelitis, NMS: Neuroleptic malignant syndrome, TBM: Tuberculous meningitis, TB: Tuberculosis

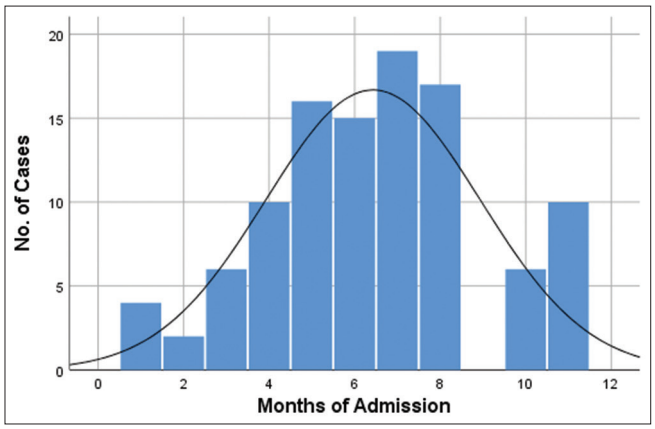


**Figure 1:** Distribution of the study population according to time of admission (Season) ($n$ = 105)

not found in any of the patients. The mean duration of fever was 8.21 ± 4.09 days with a median of 7 days. The mean duration of the altered sensorium was 81.83 ± 59.78 h with median of 72 h. The average temperature recorded was 101.2 ± 1.27 F respectively. The average systolic blood pressure was 112.7 ± 20.98 mm of Hg. 61% of patients were in systemic inflammatory response syndrome at the time of presentation. Shock (systolic blood pressure <90 mm of Hg) was present in only 19% of patients at the time of presentation. Most of the patients who are enrolled in study had GCS of between 7 and 9, collectively accounting for 77.1% of cases. The mean duration of hospital stay was 8.89 ± 7.83 days. Among the discharged patients, the mean duration of hospital stay was 9.02 days. Out of 105 patients, 29 patients (27.6%) died. Seventy-five patients (71.4%) improved with treatment and were discharged whereas in one patient outcome was not known [Table 2].

## Laboratory investigations

The mean hemoglobin was 11.63 ± 2.09 g/dL; total leukocyte count of 11,819.43 ± 5719.4 cell/µL and platelet count of 202.56 ± 92.92 × 10$^3$ cells/µL. The mean CSF leucocyte count was 409.1 ± 1345.95 per hpf. The mean CSF protein seen in the study was 221.06 ± 500.9 mg%. The mean ADA was 9.7 ± 14.20/µL. The mean neutrophil percentage in CSF was 41.66 ± 43.56. The mean lymphocyte percentage was 24.8 ± 36.64. PCR for CSF was positive in 21 patients for TB and 4 for HSV [Table 2].

## Etiology

The most common diagnosis was CNS TB or tubercular meningitis, observed in 27 (25.7%) patients followed by acute pyogenic meningitis in 18 (17.1%), probable viral encephalitis (non-HSV, non-Dengue, non-JE, and non-EV) ($n$ = 12), septic encephalopathy in ($n$ = 10), scrub AES meningoencephalitis ($n$ = 8), and HSV encephalitis ($n$ = 6)

**Table 2: Demographic profiles, clinical features and laboratory investigations among patients of fever and encephalopathy (by Chi-square statistics using cross tab analysis in Statistical Package for Social Sciences)**

| | CNS TB | Pyogenic meningitis | Probable viral encephalitis | Septic encephalopathy | Scrub encephalopathy | HSV encephalitis | *P* |
|---|---|---|---|---|---|---|---|
| Age ≤45 | 21 (77.8) | 13 (72.2) | 11 (91.7) | 5 (50) | 8 (100) | 4 (66.7) | 0.048 |
| Age >45 | 6 (22.2) | 5 (27.7) | 1 (8.3) | 5 (50) | 0 | 2 (33.3) | 0.048 |
| Male | 17 (63.0) | 10 (55.6) | 8 (66.7) | 5 (50) | 3 (37.5) | 1 (16.7) | 0.629 |
| Female | 10 (37) | 8 (44.4) | 4 (33.3) | 5 (50) | 5 (63.7) | 5 (83.3) | 0.629 |
| Fever>7 days | 17 (63.0) | 7 (38.9) | 4 (33.3) | 5 (50) | 4 (50) | 1 (16.7) | 0.344 |
| Fever≤7 days | 10 (37) | 11 (61.1) | 8 (66.7) | 5 (50) | 4 (50) | 5 (83.3) | 0.344 |
| Altered sensorium ≥72 h | 15 (55.6) | 9 (50) | 6 (50) | 7 (70) | 3 (37.5) | 5 (83.3) | 0.293 |
| Altered sensorium <72 h | 12 (44.4) | 9 (50) | 6 (50) | 3 (30) | 5 (62.5) | 1 (16.7) | 0.293 |
| HIV infection | 3 (11.1) | 0 | 0 | 0 | 0 | 0 | 0.000 |
| DM | 2 (7.4) | 4 (22.2) | 0 | 5 (50) | 0 | 1 (16.7) | 0.000 |
| Headache | 19 (70.4) | 14 (77.8) | 5 (41.7) | 2 (20) | 3 (37.5) | 5 (83.3) | 0.014 |
| Seizures | 7 (25.9) | 2 (11.1) | 7 (58.3) | 2 (20) | 2 (25) | 5 (83.3) | 0.021 |
| Vomiting | 11 (40.7) | 7 (38.9) | 2 (16.7) | 5 (50) | 4 (50) | 3 (50) | 0.758 |
| Shock | 3 (11.1) | 4 (22.2) | 1 (8.3) | 5 (50) | 3 (37.5) | 1 (16.7) | 0.407 |
| Tachycardia (>90/min) | 15 (55.6) | 10 (55.6) | 9 (75) | 8 (80) | 6 (75) | 3 (50) | 0.442 |
| Tachypnoea (>20/min) | 2 (7.4) | 6 (33.3) | 2 (16.7) | 5 (50) | 3 (37.5) | 1 (16.7) | 0.226 |
| SIRS | 12 (44.4) | 14 (77.7) | 9 (75) | 9 (90) | 7 (87.5) | 2 (33.3) | 0.046 |
| Meningeal signs | 20 (74.1) | 13 (72.2) | 4 (33.3) | 2 (20) | 6 (75) | 3 (50) | 0.027 |
| GCS (>7) | 21 (77.8) | 14 (77.8) | 9 (75) | 7 (70) | 5 (62.5) | 4 (66.7) | 0.671 |
| GCS (<7) | 6 (22.2) | 4 (22.2) | 3 (25) | 3 (30) | 3 (37.5) | 2 (33.3) | 0.671 |
| WBC count (>11,000/mm$^3$) | 10 (37) | 10 (55.6) | 7 (58.3) | 7 (70) | 4 (50) | 4 (66.7) | 0.766 |
| Thrombocytopenia (<150,000/mm$^3$) | 4 (14.8) | 6 (33.3) | 3 (25) | 5 (50) | 2 (25) | 1 (16.7) | 0.070 |
| CSF (neutrophils >50%) | 12 (44.4) | 16 (88.9) | 3 (25) | 0 | 4 (50) | 4 (66.7) | 0.001 |
| CSF protein (>100 mg %) | 20 (74.1) | 13 (72.2) | 1 (8.3) | 1 (10) | 5 (62.5) | 1 (16.7) | 0.000 |
| Abnormal MRI findings | 20 (74.0) | 7 (38.8) | 7 (58.3) | 1 (10) | 3 (37.5) | 5 (83.3) | 0.236 |

MRI: Magnetic resonance imaging, WBC: White blood cell, GCS: Glasgow coma scale, SIRS: Systemic inflammatory response syndrome, CNS: Central nervous system, HSV: Herpes simplex virus, CSF: Cerebrospinal fluid, DM: Diabetes mellitus, TB: Tuberculosis, HIV: Human immunodeficiency virus

patients, respectively. Co-infections were seen in five patients. Leptospira and malignancy-related encephalopathy was seen in three and two patients, respectively. Dengue encephalitis was seen in four patients whereas fungal, immune-mediated encephalitis, and central venous thrombosis were found in one patient each. In 10 patients, a diagnosis cannot be reached and they were categorized into the indeterminate group [Figure 2 and Table 2].

## Radiological investigations

Computed tomography of the brain was reported normal in 74 (70.5%) patients. Among the remaining, 6 (5.7%) patients had cerebral edema and ring lesions each, meningeal involvement and hydrocephalus were seen in 5 (4.8) and 4 (3.8%) patients, respectively. Contrast-enhanced brain MRI was done in 75 patients (71.4%) and was abnormal in 57.1% ($n$ = 60). The most common abnormality was parenchymal involvement seen in 35 patients followed by meningeal involvement in 21 patients, i.e., 12 patients had both parenchymal and meningeal involvement. Secondary lesions such as infarct and other findings (e.g., hydrocephalus) were seen in two and four patients, respectively. The most common MRI finding was parenchymal changes in 21.9% of cases such as ring lesions, meningovasculitic changes, or cerebral edema. Meningeal enhancement was seen in 9 cases. 11.4% of cases had both meningeal and parenchymal involvement. Hydrocephalus was present in 4 cases. Two cases had secondary infarcts. In patients with proven Tubercular meningitis on PCR; MRI was done in 23 out of 27 patients. Among these, 10 patients had both parenchymal and meningeal involvement in the form of ring lesions, meningovasculitis and cerebral edema; 1 patient had infarcts, 3 had only meningeal enhancement, 2 had basal exudates; 2 had hydrocephalus and only ring lesions were present in 4 cases. MRI was done 7 cases out of 18 patients of pyogenic meningitis. In this 3 had meningeal enhancement, two had cerebral edema, and one had brain abscesses. MRI suggestive of HSV encephalitis with altered signal intensity in medial temporal, frontal, and insular area was found in 5 cases. In scrub typhus infection, two patients had meningeal involvement.

## Predictors of mortality

In our study, 29 (27.6%) patients died of total of 105 patients. Seventy-five patients (71.4%) improved with treatment and were discharged; and outcome of one patient was not known. The predictors of mortality were assessed by comparing the variables between survivors and nonsurvivors. The variables which predicted the mortality in our study with a significant statistical difference were: (1) Female Gender, (2) Persistent fever on presentation, (3) Abnormal MRI at admission, (4)

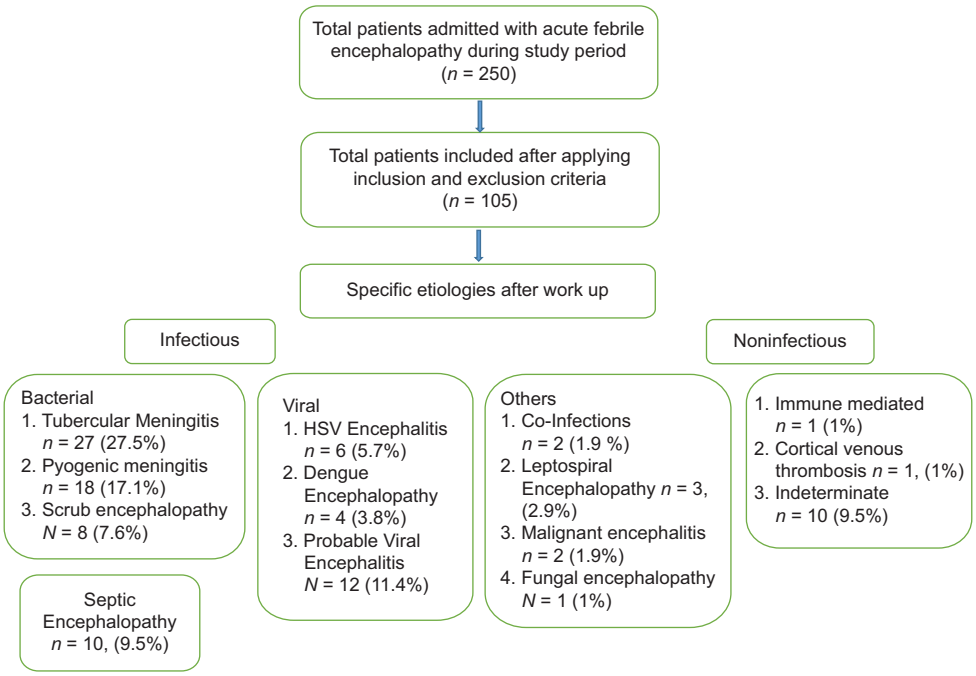


**Figure 2:** Study design and etiologies of various causes of acute encephalitic syndromes (Total number of cases = 105)

GCS score ≤7, (5) Indeterminate/Undiagnosed cases [Table 3]. The strongest predictors of outcome were poor GCS and the cases where the diagnosis was not established with a $P = 0.001$ and 0.002 respectively.

## Discussion

Acute encephalitic syndrome remains an important cause of morbidity and mortality in tropical countries. Majority of cases of AES reported in literature from India/South East Asia have their etiology as JE, acute pyogenic meningitis, cerebral malaria, dengue encephalitis, scrub meningoencephalitis, and HSV encephalitis. Tubercular meningitis usually has subacute to chronic course.

The cases of AES see show some seasonal preference, with most of the cases of AES usually occurring in summer and postmonsoon seasons. Most of the patients in our study were admitted during summer and monsoon seasons (69.6% collectively) whereas winter and spring accounted for 15.2% of cases each. A large study by Lee *et al*. done over 10 years in Vietnam showed, the peak of cases of AES occurring from July to August.[5] Most of the admissions occurred in hot and wet seasons in the study by Sajadi and Naderi[6] Singh *et al*. found a slight inclination during rainy season.[7] However, in contrary Jain and Goyal observed peak of cases of AES during post-monsoon season, a possible reason could be that their study was conducted in the western Indian desert state of Rajasthan in India where drug-resistant malaria is prevalent and the major etiology in their study was cerebral malaria which is typically found more prevalent in the postmonsoon period.[8]

The mean duration of fever was 8.21 ± 4.09 days in our study. Contrary a far less mean duration of fever was seen in a study by Mueller *et al*. from Cambodia and the possible explanation was that this study was conducted among outpatients in a community setting while ours was a in-patient study conducted at a tertiary care hospital.[9] Similar results were observed in a study among pediatric AES cases from Nepal by Singh *et al*.[10] The mean duration of altered sensorium in our study was 81.83 ± 59.78 h with most the 54.3% of cases admitted after 72 h of onset of altered sensorium. This is contrary to the study done by Reza and Sareh where the mean duration of altered sensorium was much less 46.8 ± 5 h, similarly Singh *et al*. from Eastern Nepal reported a <72 h duration of altered sensorium for 96.3% children they studied.[10,11] The possible cause in our study as PGIMER, Chandigarh, India, being a tertiary care hospital and most of our patients were referred from other hospitals. 65.7% of cases were referred after being treated outside in our study.

The most common clinical symptoms in our study apart from fever and altered sensorium were headache observed in 52.4%. Seizures and vomiting were found in 29.5% and 35.2% of cases. Like in our study headache and seizures were found in 40.86% and 30.43% of cases respectively by Singh *et al*.[7] Bhalla *et al*. also reported seizures in 26% of cases however headache was seen in 94% of cases.[4]

The most common clinical sign observed in this study was neck rigidity in 53.3% of cases followed by pallor (16.2%), sluggishly reacting pupil (6.6%), and papilledema (5.7%). Neck rigidity was present in 26% of cases by Bhalla *et al*.[11] In our study, the mean GCS was 8.14+/–1.3 with median of 8 and 27.6% of patients had GCS below or equal to 7. Similarly, Modi *et al*. observed that 82.5% of patients had GCS above 7% and 17.5% had GCS below or equal to 7 at the time of

**Table 3: Predictors of mortality and comparison of parameters in survivors and nonsurvivors of patients with of fever and encephalopathy (by Chi-square statistics using cross-tab analysis in Statistical Package for Social Sciences)**

| | Died (*n*=29), number of cases (%) | Improved (*n*=75), number of cases (%) | *P* |
|---|---|---|---|
| Demographic profiles | | | |
| Age ≤45 years | 18 (62.1) | 57 (76) | 0.155 |
| Age >45 years | 11 (37.9) | 18 (24) | 0.155 |
| Female | 18 (62.1) | 30 (40) | 0.043 |
| Male | 11 (37.1) | 45 (60) | 0.043 |
| Fever (>7 days) | 14 (48.3) | 35 (46.7) | 0.883 |
| Fever (≤7 days) | 15 (51.7) | 40 (53.3) | 0.883 |
| Altered sensorium (≥72 h) | 14 (48.3) | 43 (57.3) | 0.405 |
| Altered sensorium (<72 h) | 15 (51.7) | 32 (42.6) | 0.405 |
| Hospital stay (>7 days) | 10 (34.5) | 35 (46.7) | 0.261 |
| Hospital stay (≤7 days) | 19 (65.5) | 40 (53.3) | 0.261 |
| Type 2 DM | 7 (24.1) | 15 (20) | 0.643 |
| Signs and symptoms | | | |
| Headache | 15 (51.7) | 39 (52) | 0.980 |
| Vomiting | 9 (31) | 27 (36) | 0.633 |
| Seizures | 8 (27.6) | 23 (30.7) | 0.758 |
| Febrile on presentation (>38°C) | 17 (59) | 59 (78.7) | 0.039 |
| Tachycardia (>90 per min) | 21 (72.4) | 42 (56) | 0.125 |
| Tachypnoea (>20 per min) | 8 (27.6) | 16 (21.3) | 0.497 |
| Laboratory investigations | | | |
| Anemia (<8 g/dL) | 2 (6.9) | 2 (2.7) | 0.314 |
| Thrombocytopenia (<150,000/µL) | 12 (41.4) | 22 (29.3) | 0.240 |
| WBC (>11,000/µL) | 14 (48.3) | 35 (46.7) | 0.883 |
| CSF (neutrophils >50%) | 14 (48.3) | 30 (40) | 0.444 |
| CSF (lymphocytes >50%) | 3 (10.3) | 20 (26.7) | 0.072 |
| CSF protein (>100 g %) | 17 (58.6) | 29 (38.7) | 0.066 |
| MRI brain findings present | 16 (55.2) | 44 (58.7) | 0.049 |
| Organ dysfunction | | | |
| Shock (SBP <90 mm of Hg) | 7 (24.1) | 13 (17.3) | 0.430 |
| GCS ≤7 | 15 (51.7) | 13 (17.3) | 0.001 |
| SIRS | 17 (58.6) | 47 (62.7) | 0.704 |
| Renal failure (serum creatinine >1.5 mg %) | 6 (20.7) | 11 (14.7) | 0.456 |
| Etiological diagnosis | | | |
| CNS TB | 6 (20.7) | 21 (28) | 0.446 |
| HSV encephalitis | 2 (6.9) | 4 (5.3) | 0.759 |
| Indeterminate/undiagnosed | 7 (24.1) | 3 (4.0) | 0.002 |
| Pyogenic | 6 (20.7) | 11 (14.7) | 0.456 |
| Scrub | 2 (6.9) | 6 (8.0) | 0.850 |
| Septic | 1 (3.4) | 9 (12.0) | 0.185 |
| Dengue encephalitis | 0 (4) | 4 (5.3) | 0.205 |
| Non-HSV meningoencephalitis | 1 (3.4) | 11 (14.7) | 0.108 |
| Co infections | 1 (3.4) | 1 (1.3) | 0.481 |

SBP: Systolic blood pressure, GCS: Glasgow Coma Scale, SIRS: Systemic inflammatory response syndrome, Type 2 DM: Type 2 diabetes mellitus, HSV: Herpes simplex virus, WBC: White blood cell, CNS: Central nervous system, CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, TB: Tuberculosis

presentation.[12] In contrast, 91% of patients had GCS below 7 in the study done by Kashikunti *et al*.[13]

Similar radio-imaging findings were observed in a study by Kashikunti *et al*. in their study where 31 of the 100 patients enrolled had an abnormal MRI or computed tomography (CT). They observed a meningeal enhancement in 45% of cases of pyogenic meningitis, MRI suggestive of JE or HSV was seen in one and two patients, respectively.[13] In another study by Modi *et al*. only 34 patients out of 120 had abnormal neuroimaging (CT or MRI) in which meningeal enhancement was seen in 41% of pyogenic cases. MRI suggestive of HSV encephalitis and JE were present in two and five patients, respectively.[12]

CNS TB had shown 100% association with HIV in this study. Berenguer *et al*. in their study showed that an HIV-positive individual with TB has 5 times more likely to involve CNS

in comparison with HIV-negative individuals.[14] In this study, diabetes was more commonly associated with septic encephalopathy ($P < 0.001$).[14]

The most common etiology in our study was tubercular meningitis although various other studies have reported pyogenic meningitis to be the predominant cause of AES and there is increase in number of cases of dengue and scrub meningoencephalitis.[7,11,12,15] Earlier study done from the same Institute by Bhalla *et al*. showed viral meningoencephalitis in 29.9% of case followed by pyogenic meningitis in 25.2% of cases and 7.8% of cases of tubercular meningitis, 12.7% into septic associated encephalopathy, leptospirosis for 3.14% of cases. In 11% of cases, the diagnosis could not be achieved.[11] The proportion of patients with no definitive etiological diagnosis in our study (9.5%) is lower than that seen in a study by Mueller *et al*.[8] and Bhalla *et al*.[11] Possible explanations could be better diagnosis with the CSF TB-PCR and PGIMER being a tertiary care center with a large number of referred patients.

In this study, the duration of prolonged hospital stay and co-morbid conditions were neither found to be associated with mortality nor was found to associate with any specific etiology except HIV which was associated with CNS TB. Similar findings were also seen from the study done in Iran by Reza and Sareh, Singh *et al*. from Uttarakhand.[6,10]

The poor predictors of outcome in our study were female gender, presence of fever (more than 38°C) at presentation, positive MRI findings, GCS ≤7 and patients with no clear-cut diagnosis. The strongest predictors of outcome were poor GCS and the cases where the diagnosis was not established with a $P = 0.001$ and 0.002 respectively. In study by Khan *et al*. poor prognostic markers were age >60 years; shock at presentation, duration of illness >7 days; GCS <7 days at presentation; focal neurological deficit at presentation; etiological diagnosis of septic encephalopathy, acute meningoencephalitis, or no diagnosis; and CT/MRI findings suggestive of thalamic lesions.[15] Similarly, Feng *et al*. showed poor GCS, focal neurological deficits at presentation and prolonged hospital stay were associated with poor outcomes.[16] The mortality observed by Bhalla *et al*. was 16.5% with the maximum mortality being seen among patients with septic-associated encephalopathy and again those patients who remained undiagnosed even after extensive investigations.[11]

## Conclusions

Our study suggests that tubercular meningitis or CNS TB constituted the majority of febrile encephalopathy cases with a definite diagnosis. Acute febrile encephalopathy remains the predominant cause of mortality. The presence of seizures has a better correlation with the diagnosis of viral meningoencephalitis. There is shift in etiology of AES with rise in cases of scrub and dengue encephalitis especially in postmonsoon season. The strongest predictors of outcome were poor GCS and the cases where the diagnosis was not established.

### Research quality and ethical statement

This study was approved by the Institutional Ethics Committee of PGIMER, Chandigarh, India INT/IEC/2018/000905. The authors followed applicable EQUATOR network (http://www.equator-network.org/) guidelines during the conduct of research project.

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### Conflicts of interest

There are no conflicts of interest.

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