International Journal of Contemporary Pediatrics
*Singh D et al. Int J Contemp Pediatr. 2022 Jun;9(6):579-583*
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221377

**Original Research Article**

# Clinico-aetiological profile and outcome in children with acute febrile encephalopathy

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**Received:** 04 April 2022
**Accepted:** 30 April 2022

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## ABSTRACT

**Background:** Acute febrile encephalopathy (AFE) is a medical emergency as well as diagnostic and therapeutic challenge in children. Objective of this study was to assess clinico-aetiological profile and outcome in children with AFE.
**Methods:** This prospective observational study was carried out at tertiary care hospital Udaipur, from January 2020 to July 2021. Total 61 children aged 1 month to 18 years who were admitted in PICU with fever ≤2 weeks duration and altered sensorium either at onset or following fever were enrolled. Patient's detailed history and physical examination including detailed neurological examinations were recorded on pre-structured performa. The investigations included CBC with PBF, ESR, malarial parasite, dengue, scrub typhus, typhi-dot, blood sugar, KFT, electrolytes, LFT, calcium, CSF examination, urine examination, X-ray chest. ABG, serum ammonia, blood culture for bacteriological studies and CT/MRI brain were performed whenever required.
**Results:** 61 patients were admitted with fever and loss of sensorium. The most common clinical sign was the pallor (63.9%) and vomiting (55.7%) was the most common clinical symptom. Cerebral malaria was the commonest cause (31.1%) of AFE followed by suspected viral encephalitis (14.7%) and pyogenic meningitis 9 (14.7%). Out of total 61 patients, 45 (73.8%) patients were discharged and 16 (26.2%) patients were expired. Maximum mortalities were seen in Reye's syndrome (5 out of 6 cases) and was most in age group <5 years of age (26 cases).
**Conclusions:** Cerebral malaria was the leading cause of AFE followed by suspected viral encephalitis and pyogenic meningitis. While determining the aetiology of AFE in a malarial endemic area, cerebral malaria should be considered in all patients. Reye's syndrome should also be considered in patients of AFE should be evaluated to diagnose or rule out this entity.

**Keywords:** CNS infections, Encephalopathy, Acute febrile encephalopathy, Cerebral malaria

## INTRODUCTION

Encephalopathy is a nonspecific term, defined as diffuse disease of brain that changes its structure or function, can be caused by a variety of infective, metabolic, toxic, ischemic/hypoxic, nutritional causes or trauma.

AFE is a scientific term used to describe patients presenting with a short duration of febrile illness with altered mental condition.[1] It is a diagnostic and therapeutic challenge as well as medical emergency for pediatrician.[2] In febrile illness, encephalopathy results either from pathogenic mechanism directly affecting the central nervous system or due to any systematic complications like hypoglycemia, hyper-pyrexia, hypotension, hypoxia, electrolyte imbalance or release of systemic chemical mediators.[2]

In children, CNS infections are the commonest cause of altered mental condition with febrile non-traumatic coma in India as well as other developing countries but it can result from wide variety of aetiologies posing as a diagnostic challenge.[3-9] It can result from various CNS infections such as cerebral malaria (CM), Japanese B encephalitis (JE), bacterial meningitis.[10]

The occurrence of encephalitis in India is not known as there is problem in establishing viral analysis and the fact that a wide variety of both infectious and non-infectious CNS disorders, may mimic the illness. Most of the patient's acute febrile encephalopathy can make complete recovery once the underlying cause is identified and treated appropriately and timely.

The profile of AFE varies in the same country in the different geographical region and in different seasons. It is very clear that understanding the burden of these diseases in our respective regions becomes much more important in addressing patients with acute febrile encephalopathy to take proper steps in decreasing the mortality caused by it.

Hence this study was planned to evaluate children presenting with AFE in a tertiary care center to understand aetiology, prevalence, any seasonal variations, and their outcomes and risk factors associated with mortality, over a period of 1 year.

## METHODS

This prospective observational study was carried out in department of pediatrics Geetanjali medical college and hospital Udaipur, over a period of 1 year and 6 months from January 2020 to July 2021 after obtaining permission from ethical committee of institute.

### *Inclusion criteria*

All children of age 1 month to 18 years who were admitted in PICU with fever ≤2 weeks duration and altered sensorium (modified Glasgow coma scale ≤12) either at onset or following fever were included in this study.

### *Exclusion criteria*

Patients with space occupying lesion (SOL); cerebrovascular accidents; any CNS malformation; and febrile seizure were excluded from the study.

### *Method of collection of data (including sampling procedure)*

All eligible children with AFE who were consecutively admitted in PICU of Geetanjali medical college and hospital, Udaipur were included if they satisfied the case definition of AFE. Details of study were explained to each parent and written informed consent was obtained voluntarily from at-least, one of the parents, before child enters the study. Patient's detailed history and demographic data were recorded on pre-structured Performa. Physical examination including detailed neurological examination was recorded at admission and was followed throughout the course of illness in the hospital and outcome were assessed. Modified Glasgow coma scale for pediatric and infants was used to assess level of consciousness.

The investigations included were CBC with PBF, blood culture, random blood sugar, kidney function test, serum electrolyte, liver function test, serum ammonia, ESR, malarial parasite (card), NS1 antigen, IgM and IgG for dengue, typhoid (IgM, IgG), scrub typhus, CSF examination (for bio-chemistry, cytology, gram staining, ZN staining, bacterial culture, gene expert for TB), Mantoux Test, X-Ray chest, ABG, EEG and CECT/ MRI brain was done whenever required. Predefined criteria were used in the aetiological diagnosis of AFE (Table 1).

### *Statistical analysis*

Statistical analysis was performed using the statistical packages for social sciences (SPSS) version 21 IBM Corporation. Data was entered into MS Excel software. Statistical analysis of categorical variables was compared between patients using the chi-squared test. Quantitative data was analyzed using student t-test. A p value of 0.05 or less ($p \leq 0.05$) is considered to be statistically significant.

## RESULTS

Total 61 children were enrolled in this study who fulfilled the inclusion criteria. Data was collected for each subject in predesigned proforma.

In this study 39 males (63.9%) and 22 females (36.1%) were admitted. Males were affected more than females with male to female ratio of 1.7:1. Children were more from rural area (60.7%) as compared to urban residential area (39.3%) (Table 2).

**Table 1: Predefined criteria for different aetiologies of AFE.**

| Disease | Diagnostic criteria |
|---|---|
| **Cerebral malaria** | AFE+peripheral blood film positive for malarial parasite |
| **Pyogenic meningitis** | AFE+/-neck signs+CSF cytology (mainly polymorphs) and biochemistry |
| **Suspected viral encephalitis** | AFE+CSF normal or mild pleocytosis absence of bacteria on culture or direct microscopy+no other alternate diagnosis |

Continued.

| Disease | Diagnostic criteria |
|---|---|
| **Enteric encephalopathy** | AFE+blood culture positive±Typhi dot Igm positive |
| **TBME** | AFE+typical CSF picture (mainly lymphocytes) with or without abnormal neuroimaging studies |
| **Hepatic Encephalopathy** | AFE+icterus, raised liver enzymes (>3 fold), abnormal coagulogram and raised ammonia level |
| **Meningococcemia** | AFE+signs of meningeal irritation, petechial or purpuric rash and hypotension with shock with typical CSF picture |
| **Mumps meningoencephalitis** | AFE+bilateral parotid swelling with usually normal CSF picture. |
| **Acute disseminated encephalomyelitis** | AFE+characteristic MRI features with a preceding history of respiratory infection, exanthema or vaccination |
| **Dengue encephalopathy** | AFE+maculopapular rashes with Dengue IgM ELISA positive/ NS1 Antigen |

**Table 2: Demographic characteristics of study population.**

| Characteristics | No. of children (%) |
|---|---|
| **Gender** | |
| Male | 39 (63.9) |
| Female | 22 (36.1) |
| **Age group (years)** | |
| Less than 5 | 26 (42.6) |
| 6-10 | 22 (36.1) |
| 11-15 | 12 (19.7) |
| >15 | 1 (1.6) |
| **Area of residence** | |
| Rural | 37 (60.7) |
| Urban | 24 (39.3) |

**Table 3: Clinical profile of patients with AFE.**

| Clinical features | No. of children (%) |
|---|---|
| **Signs of meningeal irritation** | 13 (21.3) |
| **Sign of raised ICT** | 12 (19.7) |
| **CN involvement** | 3 (4.9) |
| **Vomiting** | 34 (55.7) |
| **Hepatomegaly** | 33 (54.0) |
| **Splenomegaly** | 26 (42.6) |
| **Lymphadenopathy** | 6 (9.8) |
| **Pallor** | 45 (73.7) |
| **Icterus** | 8 (13.1) |

In our study, pallor and vomiting were the most common presenting clinical features. The most common clinical sign was the pallor (63.9%) and vomiting (55.7%) was the most common clinical symptom. Other clinical features involve hepatomegaly (54.0%), splenomegaly (42.6%), sign of meningeal imitation (21.3%), sign of raised ICT (19.7%) and icterus (13.1%) as discussed in (Table 3).

The most common aetiology of AFE found in our study was cerebral malaria (31.1%) followed by suspected viral encephalitis (16.3%) and pyogenic meningitis in about (14.7%) cases (Table 4).

**Table 4: Aetiological profile of patients with AFE.**

| Aetiological profile | No. of cases (%) |
|---|---|
| **Cerebral malaria** | 19 (31.1) |
| **Typhoid encephalopathy** | 1 (1.6) |
| **Dengue encephalopathy** | 3 (4.9) |
| **Scrub typhus encephalopathy** | 6 (9.8) |
| **TBME** | 2 (3.2) |
| **Pyogenic meningitis** | 9 (14.7) |
| **Susp. viral meningitis** | 10 (16.3) |
| **Reye's syndrome** | 6 (9.8) |
| **ADEM** | 1 (1.6) |
| **Hepatic encephalopathy** | 2 (3.2) |
| **Mumps meningoencephalitis** | 1 (1.6) |
| **Meningococcemia** | 1 (1.6) |

**Table 5: Outcome in patients with AFE.**

| Outcome | No. of patients | % |
|---|---|---|
| **Discharged** | 45 | 73.8 |
| **Expired** | 16 | 26.2 |
| **Total** | 61 | 100 |

In our study, out of total 61 cases, 45 (73.8%) patients were discharged from the hospital after the treatment and 16 (26.2%) patients were expired (Table 5). Highest mortality rate was observed in Reye's syndrome (5 cases) followed by suspected viral encephalitis (3 cases) (Table 6). Mortality was most in age group <5 years and least in >15 years of age which is statistically significant ($p<0.05$) (Table 7). Poor GCS, mechanical ventilatory requirement, and age <5 years were found to be risk factors associated with mortality.

## DISCUSSION

In the present study total 61 children of age 1 month to 18 years with fever ≤2 weeks duration and altered sensorium either at onset or following fever were included.

Maximum children were in the age group of <5 years followed by 6-10 years. Similar results were observed by Gupta et al and Sharma et al.[11,12] In contrast to our study, Tripathy et al found maximum children from age group of 5-15 years.[11-13] These differences were mainly due to different sample size and different population group.

**Table 6: Outcome in relation to the aetiology.**

| Aetiological profile | Discharge | Expired | Total cases |
|---|---|---|---|
| **Cerebral malaria** | 17 | 2 | 19 |
| **Typhoid encephalopathy** | 1 | 0 | 1 |
| **Dengue encephalopathy** | 2 | 1 | 3 |
| **Scrub typhus encephalopathy** | 6 | 0 | 6 |
| **TBME** | 2 | 0 | 2 |
| **Pyogenic meningitis** | 7 | 2 | 9 |
| **Suspected viral encephalitis** | 7 | 3 | 10 |
| **Reye's syndrome** | 1 | 5 | 6 |
| **ADEM** | 1 | 0 | 1 |
| **Hepatic encephalopathy** | 0 | 2 | 2 |
| **Mumps Meningo-encephalitis** | 1 | 0 | 1 |
| **Meningococcemia** | 0 | 1 | 1 |

**Table 7: Outcome in relation to age group.**

| Age group (years) | Outcomes | | Total | P |
|---|---|---|---|---|
| | Discharged N (%) | Expired N (%) | | |
| **Less than 5** | 15 (57.6) | 11 (42.3) | 26 | 0.035 |
| **6-10** | 19 (86.4) | 3 (13.6) | 22 | |
| **11-15** | 10 (83.4) | 2 (16.6) | 12 | |
| **>15** | 1 (100) | 0 | 1 | |
| **Total** | 45 | 16 | 61 | |

In the present study, males (63.9%) were affected more than females (36.1%) with male to female ratio of 1.7:1. Similar results were found in study done by Khinchi et al, Biswas et al, Tripathy et al and Rajarshi et al.[13-15]

In the present study, AFE was more common in rural residential area (60.7%) as compared to urban residential area (39.3%). In the study conducted by Gupta et al they found that 40% children were from urban areas, 25.6% were from urban slum and 34.4% were from rural areas.[11]

In our study, the main presentation was fever and altered sensorium present in all 61 patients. Vomiting (55.7%) was the most common clinical symptom and pallor (73.7%) was the most common clinical sign. In the study done by Biswas et al most common presenting complaints were convulsion and vomiting and in study by Singh et al, most common presenting complaints were headache and vomiting.[7,15]

In our study, cerebral malaria was the commonest cause (31.1%) of AFE in children followed by suspected viral encephalitis (16.3%) and pyogenic meningitis (14.7%). Results were different in study done by Singh et al where pyogenic meningitis (42%) was commonest cause followed by viral encephalitis and cerebral malaria.[7]

In this study, out of total 61 cases, 26.2% patients were expired and 73.8% patients were discharged after the treatment. In the study done by Karmarkar et al they found that 19.01% patients expired and 80.9% were discharged.[3] In contrast to our study Karthika et al observed that only 12.5% patients expired out of total 56 patients in their study.[18] This difference was mainly due to difference in aetiological pattern seen in our area.

As per the analysis of current study, maximum number of mortalities was seen in Reye's syndrome where out of 6 patients 5 were expired, followed by cases of Suspected viral encephalitis in which 3 patients expired out of total 10 cases. On the other hand, CM which was most common aetiology in this study showed only 2 deaths out of total 19 cases. In contrast to our study, Khinchi et al observed maximum case fatality for Japanese encephalitis (16.6%) and in study by Kuntal et al maximum mortalities were seen for viral aetiology (dengue) 29%.[14,19]

In the present study, 26 patients were <5 years of age, out of them 42.3% patients were expired. Only 1 patient was of >15 year of age and discharged. Mortality was most in age group <5 years and least in >15 years of age ($p<0.05$).

***Limitations***

Due to financial constraints of the families and non-availability of all investigations within the hospital, some important investigations could not be performed like Viral panel studies on CSF, Auto-immune encephalitis panel, etc. and the children were not followed up for long-term complications and sequelae.

## CONCLUSION

In this study, cerebral malaria was the leading cause of acute febrile encephalopathy in children followed by, suspected viral encephalitis and pyogenic meningitis. Cerebral malaria needs special consideration and a high index of suspicion, especially in the post-monsoon period in the endemic areas. Larger systemic studies on AFE in children are required for systemic data generation as AFE is associated with significant morbidity and high mortality particularly in developing country like India.

And this can be significantly reduced by early diagnosis of disease and institution of aggressive supportive care may be able to decrease mortality and long-term morbidity.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Singh D, Bamnawat S. A study of clinico-aetiological profile and outcome in children with acute febrile encephalopathy. Int J Contemp Pediatr 2022;9:579-83.