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A study on etiology, clinical profile and outcome of acute febrile encephalopathy in children: A prospective study at a tertiary care center of Eastern India.

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ABSTRACT

Background: Acute febrile encephalopathy (AFE) is defined as fever associated with acute alteration of consciousness, with or without seizure, motor and/ or sensory deficit and total duration of illness one week or less. It is associated with significant morbidity and mortality in children. Various etiologies have been implicated in its causation and differ as per geographical. Efforts to promptly identify the underlying etiology and institute appropriate treatment early and adequately should be our goal so as to avoid any long-term sequelae and death. **Aims and Objectives:** To evaluate the clinical profile and aetiology of children presenting with fever and altered sensorium and to assess the predictors of morbidity & mortality related to Acute Febrile Encephalopathy. **Materials and Methods:** In this prospective, hospital-based study, a total of 282 children, between 1month to 12 years, presenting to the department of Pediatric Medicine, Calcutta National Medical College, Kolkata, West Bengal, India with fever and altered sensorium were clinically evaluated and investigated. Each patient was examined for vital signs, detailed systemic examination with focus on neurological examination. The etiology of AFE was evaluated based on detailed history, a meticulous clinical examination and relevant investigations. **Results:** The incidence of AFE was 5% of the total hospital admissions. Demographic profile showed 166 (58.8%) males, 116 (41.2%) females and 48% of the study population less than 5 years of age. The most important presenting complaints apart from fever and altered sensorium, were convulsion and vomiting. Raised Intracranial tension (58%), low GCS (58%) and shock (48%) were commonest presenting signs. CNS infections were the most common cause of AFE encountered. Low GCS, refractory seizures, multi-organ failure respiratory failure were significantly associated with death ($p<0.005$). **Conclusions:** CNS infections are the leading cause of febrile encephalopathy. Toxic- metabolic and unknown etiologies contributed maximum to the mortality. Low GCS, shock, refractory seizures, multi-organ failure and respiratory failure are associated with higher risk of mortality. Most of the morbidities were observed in auto-immune encephalitis and ADEM and as most of them were curable, early institution of appropriate treatment will decrease morbidity.

Key words: Acute febrile encephalopathy; Viral encephalitis; Glasgow Coma Score; Tertiary care hospital; Eastern India

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INTRODUCTION

Acute febrile encephalopathy is defined as fever associated with acute alteration of consciousness, with or without seizure, motor and/ or sensory deficit and total duration of illness one week or less. Acute febrile encephalopathy is a common problem in children leading to hospital admissions.[1]

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Although AFE is one of the major causes of hospital admissions of children and adults in India, only a few studies have been done so far.[2] Amongst the studies that have been done, most have focused on the varying etiologies of AFE and lesser ones on the predictors of outcome.[3]

Despite much epidemiological investigation, the presentation with acute onset fever and altered sensorium has often remained mystery, especially in Indian states of Uttar Pradesh, Bihar and West Bengal.[1] Most acutely ill patients with febrile encephalopathy are capable of making a complete neurological recovery once the underlying cause is identified and treated promptly, appropriately and adequately.

Majority of the studies revealed etiology of AFE, but very few studies emphasized on predictors of mortality. The objectives of our study were to know the etiology, presentation and outcome of acute febrile encephalopathy in terms of mortality, morbidity and recovery among children aged 1month to 12 years and to evaluate outcome in relation to etiology and Glasgow Coma Score at the time of presentation.

MATERIALS AND METHODS

This was a descriptive and prospective hospital-based study conducted in the Pediatric Department of Calcutta National Medical College and Hospital, Kolkata from 2017 to 2019 (a period of 24 months). A total of 5564 children aged between 1month to 12 years were admitted in the in-patient's department during the study period. Among these, 282 children presented with history of fever and altered sensorium of less than 7 days duration. The aim of the study was to evaluate the clinical profile and aetiology of children presenting with fever and altered sensorium and to assess the predictors of morbidity & mortality related to Acute Febrile Encephalopathy.

Inclusion criteria

All patients from 1 month to 12 years of age, after obtaining Informed consent from care- giver(s). An effort was made to enroll all consecutive patients. A case diagnosed to have acute febrile encephalopathy was based on the following criteria: (i) fever (ii) acute depression of consciousness or mental deterioration for more than 12 hours and iii) total duration of illness at the time of admission 1 week or less.

Exclusion criteria

Patients with traumatic coma, simple febrile convulsions, cerebral palsy and epilepsy were excluded from our study. Also, those patients excluded were from whom consent could not be obtained and those who left the hospital without completing treatment.

Data was collected in a pre-structured proforma. Detailed clinical history and examination was done for each patient and recorded at admission, followed throughout during the course of illness and the outcome was recorded. Immediate emergency management and specific treatment was started and changed as per the patient's course in the hospital. Patients were followed daily till discharge/death to study the outcome. The investigations included CBC, ESR, Malarial parasite, blood sugar, renal function test, liver function test, serum electrolytes, CSF examination including search for viral etiology, urine examination, X-ray chest PA view, blood culture & sensitivity and CT/ MRI brain were performed whenever required. Patients were classified in to various broad categories like CNS infections (viral/bacterial/tubercular, etc), Toxic-Metabolic Encephalopathy, Auto-immune Encephalitis, ADEM, Intracranial SOL, etc. Patients were also divided into three groups as per age: 1month-5 years,6years -9 years and 10 years -12 years. Management was given according to standard protocol. Depth of coma was evaluated with reference to modified Glasgow coma scale. Outcome was evaluated in terms of complete recovery, morbidity (recovery with sequelae) and mortality (death). Preceding the study, approval for the study was obtained from the Institutional Ethics Committee of CNMC & Hospital, Kolkata.

Statistical analysis

Descriptive statistics were expressed as number and percentages. Data was analysed using SPSS statistical software. Fisher's exact test was performed to test for differences in proportions of categorical variables between two groups. A p value of 0.05 or less was considered as statistically significant.

RESULTS

A total of 282 children were admitted with the diagnosis of AFE during the 2year study period. Most of the children 135(48%) were below 5 years of age, 105(37%) between 6-9 years and rest 42(15%) between 10-12 years. Male to female ratio was 1.43:1. The incidence of acute febrile encephalopathy was 5%. The average duration of hospital stay was 14.26 days, with a minimum stay of 4 days and maximum duration of 26 days. Apart from fever and altered sensorium, most common presenting complaints were convulsion (77%), followed by vomiting (37%). Raised intracranial tension(58%), GCS<8(58%) and shock were important clinical signs.Table 1 shows frequency of various clinical symptoms and signs. The mean duration

of fever was 4.62 ±3.27 days with maximum of 25 days and a minimum of 2 days. Fever was present for less than 72hrs in 43% of children and 88% children had altered sensorium for less than72 hrs. Low GCS (<8) was found to be more common in 6 to 9yearrs age group (44%) while raised ICT was found more commonly in the youngest group of 1month to 5 years (38%). Average GCS at the time of admission was 10.24±2.5 with a lowest of 5 and highest GCS of 12, median 12. Various etiologies leading to causation of AFE in our study have been summarized in Table 2. The most common cause of AFE was CNS infections across all three age groups and the age wise breakup is shown in Table 3. Other common etiologies encountered were toxic- metabolic encephalopathies (summarized in Table 4). Autoimmune encephalitis, ADEM (Acute demyelinating encephalomyelitis) and intracranial SOL. In about 66(23%) cases no cause could be identified with our limited resources and hence were classified as being "Inconclusive".

Table 1: Distribution of cases according to frequency of clinical symptoms and sign (n=282)

Sl. No	Clinical Features	Number	Percentage (%)
1.	Fever	282	100
2.	Convulsion	197	70
3.	Headache	59	21
4.	Vomiting	104	37
5.	Skin rash	17	6
6.	Signs of meningeal irritation	62	22
7.	Cranial nerve palsy	17	6
8.	Involuntary movements	11	4
9.	Icterus	20	7
10.	Raised intracranial tension	164	58
11.	Shock	135	48
12 a.	GCS<8	163	58
12 b.	GCS≥8	119	42
13.	Organomegaly	95	34

Among the infectious causes (n=119) of AFE, viral encephalitis(n=59,49.6%) was the most common diagnosis across all age groups, followed by bacterial meningo-encephalitis (n=38,31.9%) and tubercular meningitis (n=22,18.5%). Among the viral etiologies, only Japanese Encephalitis (JE), Herpes Simplex Virus (HSV) and Dengue virus were identified. We could not isolate other viral etiologies as our institution did not have the facility for viral PCR or culture in our institute. Scrub typhus encephalitis was the commonest cause of bacterial meningo-encephalitis. Amongst the 38(64.4%) cases of JE, maximum children (n=20,53%) were of 6-9 years age group, 10 (26%) of 1month to 5 years age group and 8 (21%) were older than 9year.JE vaccine were received by only 42% cases. The duration of symptoms off ever, convulsion, altered sensorium in these cases were comparable to the non-JE cases. CSF analysis was conducted in total 235 patients as per indication of lumbar puncture. CSF study was abnormal in 69% children. Neuro-imaging was done in 248(88%) children. Table 5 shows the etiological distribution across various ages. Apart from etiology, outcome was analyzed on the basis of GCS scoring, presence of shock, refractory seizure, MODS and respiratory failure. Maximum recovery was found in case of CNS infections (68.3%) and lowest in Auto-immune encephalitis. Highest mortality was noted in case of toxic-metabolic causes (30.9%) and 27.8% cases death occurred where no etiology was found. Sequelae were noted to be maximum in Auto-immune encephalitis (38.8%) and ADEM (38.4%) followed by unknown etiology (26.3%). Table 6 shows outcome in relation to etiology. In the present study, we found highest risk of mortality in patients who had multiorgan failure (odds ratio:6.88, CI=3.56-13.30) followed by patients had refractory seizure (odds ratio:5.49, CI=2.8-10.78) and shock (odds ratio:4.34, CI=2.32-8.13). Table 7 revealed that subjects with GCS <8 had 2.75 times higher risk of death (Odds' ratio 2.75,

Table 2: Etiological distribution of patients across various age groups (n=282)

Sl. No	Diagnosis	1 month to 5 years (n=135)	6 years to 9 years (n=105)	10 years to 12 years (n=42)
1.	CNS infections	57 (42.2)	46 (43.8)	16 (38)
2.	Toxic-metabolic	21 (15.6)	16 (15.2)	6 (14.3)
3.	ADEM	3 (2.2)	5 (4.8)	5 (12)
4.	Autoimmune encephalitis	5 (3.7)	9 (8.6)	4 (9.5)
5.	Intracranial SOL	6 (4.4)	5 (4.8)	1 (2.4)
6.	Febrile status	11 (8.2)	-	-
7.	Inconclusive	32 (23.7)	24 (22.8)	10 (23.8)

Table 3: Distribution of CNS infections among various age groups

Type of CNS infection	Age group 1month-5 years (%) (n=57)	Age group 6 years- 9 years (%) (n=46)	Age group 10 years- 12 years (%) (n=16)
Viral	26 (45.6)	24 (52.2)	9 (56.3)
Bacterial	18 (31.6)	15 (32.6)	5 (31.3)
Tubercular	13 (22.8)	7 (15.2)	2 (12.4)

Table 4: Distribution of Toxic-Metabolic Encephalopathies among various age groups

Types of toxic- metabolic	Age group 1month- 5 years (%) (n=21)	Age group 6 years- 9 years (%) (n=16)	Age group 10 years- 12 years (%) (n=6)
DKA	3 (14.3)	2 (12.5)	1 (16.6)
Hepatic encephalopathy	4 (19)	3 (16.7)	2 (33.4)
Poisoning	3 (14.3)	4 (25)	-
Secondary to sepsis	11 (52.4)	7 (43.8)	3 (50)

Table 5: Etiological distribution of patients across various age groups (n=282)

Sl. No	Diagnosis	Age group 1 month-5 years (n=135)	Age group 6 years- 9 years (n=105)	Age group 10 years- 12 years (n=42)
1.	CNS infections	57 (42.2)	46 (43.8)	16 (38)
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5.	Intracranial SOL	6 (4.4)	5 (4.8)	1 (2.4)
6.	Febrile status	11 (8.2)	-	-
7.	Inconclusive	32 (23.7)	24 (22.8)	10 (23.8)

Table 6: Outcome in relation to etiology

Type of sequelae	CNS infection (n=126)	Auto- immune enceph alitis (n=18)	Toxic- metabolic (n=42)	ADEM (n=13)	Intracr anial SOL (n=11)	Inconclusive (n=61)
Discharged without sequelae (n=156)	86 (68.3)	7 (38.8)	22 (52.4)	6 (46.1)	7 (63.6)	28 (45.9)
Discharged with sequelae (n=50)	13 (10.3)	7 (38.8)	7 (16.7)	5 (38.4)	2 (18.2)	16 (26.3)
Death (n=65)	27 (21.4)	13 (30.9)	13 (30.9)	2 (15.5	2 (18.2)	17 (27.8)

Table 7: Outcome of Acute Febrile Encephalopathy(AFE) and Predictor variables

Variables	Present/absent	Discharge (%)	Death (%)	Confidence Interval	Odds' Ratio	p value
GCS	<8 (N=163)	130 (81.7)	30 (18.4)	1.25-6.05	2.75	0.01
	≥8(N=119)	110 (92.4)	9 (7.6)			
Shock	Yes (N=137)	89 (65)	48 (35)	2.32-8.13	4.34	<0.0001
	No (N=145)	129 (89)	16 (11)			
Refractory seizure	Yes (N=112)	75 (67)	37 (33)	2.80-10.78	5.49	<0.0001
	No (N=170)	156 (92)	14 (8)			
MODS	Yes (N=86)	52 (60.5)	34 (39.5)	3.56-13.30	6.88	<0.001
	No (N=196)	179 (91)	17 (9)			
Respiratory failure	Yes (N=87)	57 (65.5)	30 (34.5)	1.55-5.00	2.78	<0.001
	No (N=195)	164 (84)	31 (16)			

CI=1.25-6.05) as compared to subjects who had GCS ≥8. This was found to be statistically significant(p=0.01).

DISCUSSION

In this hospital based prospective study, we analyzed the clinical profile, etiology and outcome of 282 children admitted in PICU with AFE. Acute Febrile Enephalopathy was an important cause of hospital admissions constituting 5 % of all hospital admissions, although it constituted 17.9% of all PICU admissions. Male to female ratio in our study was 1.4:1 and majority of patients belonged to age group 1month to 5 years (48%); most the patients (72%) had presented within the first week of illness. The previous Indian studies have almost always demonstrated a male preponderance, as ours and the age group commonly affected also remained the same.[1,4]

The average duration of fever was comparable to the study done by Sharma et al.[5] They found mean duration of 4.4±3.57. In our study, convulsion (77%) and vomiting (37%) were most common clinical presentation after fever and altered sensorium. Study done by Bhupesh et al[6] at a hospital in South Rajasthan also showed convulsion in 64.7% and vomiting in 45.88% cases. They also found headache in 16.47%, raised ICT in 21.17%, cranial nerve palsies in 4.7%, hepatomegaly in 55.29 % and clinical icterus in 7% cases.[6] In our study headache, raised ICT,

cranial nerve palsies, organomegaly and icterus were 21%,58%,6%,34% and 7% respectively. The median GCS found in our study was comparable to the median GCS found by Sharma et al and Anga et al.[5,7] In our study high number of cases of raised ICT and low GCS may be due to high referral from periphery to our center. In the present study, CNS infections (42%) were the most common etiology implicated in causing AFE. Bansal et al.,[1] also found infections as the most common cause of non-traumatic coma. Viral encephalitis was the most common infectious etiology in our study, comparable to study by Sharma et al.,[5] which was 63% of viral encephalitis and 22.2% bacterial meningo-encephalitis. In our case, it was 49.0% and 31.9% respectively. Astudy by Bokade et al.,[8] from Central India, also found, out of 176 subjects 46.59% were diagnosed as viral encephalitis, 22.15% as pyogenic meningitis and 15.34% as tuberculous meningitis.

We found maximum children (55.9%) with viral encephalitis were within 6-12 years of age and 52.6% cases with bacterial meningo-encephalitis were in the youngest age group. These findings were similar with the study done by Sharma et al.[5] JE virus was the most common virus we could isolate. In our study, JE encephalitis was found in 13.5% cases which was similar to study done by Kumar et al.,[9] Singh et al.,[10] conducted a study shows non-JE viral encephalitis in 25% and JE in 18% cases.

We found mortality of 23% cases and 17.7% subjects had developed sequelae. Bokade et al.,[8] also found death and sequelae in 19.31% and 26.7% respectively. Another study from North India reported mortality of 33.9% and sequelae of 32.7% cases.[11] A study done in Malaysia revealed mortality and sequelae of 35.7% and 29.3% cases respectively.[12] This difference in mortality can be explained by the difference in aetiology, diagnostic and treatment facilities. In our study, higher mortality 27(41%) was seen in the age group of 1month to 5 years. We found higher mortality in females (58.5%) and it was similar to previous study. However, Wong CP et al.,[13] found no significant sex difference in mortality.

Our study showed a death of 27(21%) out of total 126 infectious cases. In a similar study done by Bansal et al.,[1] found 26.7% mortality in infectious causes and 63% mortality in toxic-metabolic causes. In our study too, toxic-metabolic etiology was leading cause of death (30.9%). In the present study, presence of multi-organ failure (MODS), refractory seizure, respiratory failure, shock and low GCS correlated significantly with mortality. Study done by Sahin et al.,[14] showed refractory seizures were significantly associated with mortality. They stated outcome of severe refractory seizure in 22 children aged 45 months to 18 years and found a mortality of 39%. Another study done by Bokade et al.,[8] also found a GCS <8 had 4.32 times higher risk of death as compared to our study where the risk of death was 2.75 times higher (OR-2.75, CI 1.25-6.05) and p-value <0.001. They also found out that refractory seizures (OR 3.4,CI 1.46- 7.96), shock(OR 2.46,CI 1.04-5.3) and MODS (OR 2.33,CI 1.01-5.3). In our study, MODS had higher risk of death (OR 6.85, CI 3.56-13.3), followed by refractory seizure (OR 5.49, CI 2.0- 10.78).

CONCLUSION

Acute onset febrile encephalopathy is a common problem encountered by a pediatrician. Viral encephalitis was the most common cause of AFE in our study followed closely by pyogenic meningitis. The leading cause of mortality in our study was toxic- metabolic cause and maximum recovery was seen in CNS infection. Presence of multi organ dysfunction, refractory seizure, shock and low GCS were associated with poor prognosis. However, finding of this study cannot be generalized though they are in relevance with present scenario in resource poor set up and in developing countries where infective etiology predominates for AFE.

Limitations of the study

Being a hospital-based study done in a tertiary care center; the incidence observed in this study may not reflect the actual incidence of acute febrile encephalopathy of the entire population. 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.

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Author's contribution:
RB- Concept and design of the study, prepared first draft of manuscript; **KB-** Interpreted the results, reviewed the literature and manuscript preparation; **IT-**Concept, coordination, review of literature and manuscript preparation; **SKR-** Statistically analyzed and interpreted, preparation of manuscript and revision of the manuscript.

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