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Clinicoetiological profile and outcome of patients of acute febrile encephalopathy in a tertiary care hospital in New Delhi - A prospective observational study

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ABSTRACT

Background: Acute febrile encephalopathy (AFE) in spite of being a common clinical condition is less known to the general population thereby resulting in delay in seeking medical attention with detrimental consequences. The causes can range from infectious central nervous system (CNS) and systemic diseases to non-infectious conditions such as neuroleptic malignant syndrome, poisoning, and drug overdose. Early diagnosis and prompt medical management can result in good clinical outcome in terms of morbidity and mortality. **Aims and Objectives:** The aims and objectives are to study the clinical profile, etiology, seasonal variation, and outcome in patients admitted as case of AFE in a tertiary care hospital. **Materials and Methods:** All patients of AFE fulfilling the inclusion and exclusion criteria admitted in the departments of neurology and general medicine in Batra Hospital and Medical Research Centre (BHMRC) New Delhi, a tertiary care hospital were subjected to study analysis. The patients underwent detailed history, examination, baseline, and special investigations such as cerebrospinal fluid and magnetic resonance imaging brain whenever needed. Patients of AFE were studied according to the prevalence, etiological diagnosis, and seasonal variations. The final outcome at discharge was based on modified Rankin scale (mRs). **Results:** About 122 serially admitted patients diagnosed with AFE were found eligible and included in the study. About 47 (45%) patients had acute pyogenic CNS infection while as 36 (35%) had non-pyogenic CNS infection followed by malarial, tubercular, and cryptococcal CNS infection. We found maximum number of cases (n = 61, 50%) of AFE during monsoon followed by 36 patients (30%) in post-monsoon, 15 patients (12%) were in summer, and only 10 cases (8%) during winter. We found higher and statistically significant disability in CNS infection group, patients with delayed hospitalization (P = 0.001), and lower Glasgow coma scale (0.00001). **Conclusion:** AFE being a condition with serious consequences, we conclude that clinical suspicion, sensitization, and swift response from the treating physicians are required to avoid worse outcomes associated with the delayed diagnosis and late hospitalization of these patients.

Key words: Acute febrile encephalopathy; Central nervous system; Modified Rankin scale; Outcome; Mortality; Monsoon

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INTRODUCTION

A short febrile illness with an altered mental state ranging from confusion to impaired wakefulness, stupor, and coma is referred to as acute febrile encephalopathy (AFE).[1] In spite of being common in India, AFE is less known to the general population which leads to delay in seeking medical attention[1,2] Although the presence of

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fever generally points toward infective etiology, other mechanisms such as overproduction of heat, impaired dissipation of heat, non-infective central nervous system (CNS) diseases, hypothalamic lesions, neuroleptic malignant syndrome, poisoning or drug overdose must be ruled out to avoid catastrophic results[3,4] The clinical and etiological spectrum of febrile encephalopathy can vary across different geographic areas and in different seasons. In tropical countries like India, pyogenic meningitis (PM), cerebral malaria (CM), and Japanese encephalitis (JE) are the common causes of AFE, while tubercular meningitis (TBM) mostly presents with subacute or chronic history.[5] Enterovirus, herpes simplex virus (HSV), varicella-zoster virus, and mumps are important causes of viral encephalitis[6,7] Prompt identification and immediate treatment of HSV can be lifesaving.[8,9] We conducted a study to evaluate clinical features, etiology, and the seasonal variation of AFE patients admitted to a tertiary care hospital in New Delhi.

Aims and objectives

The aims and objectives are to study the clinical profile, etiology, and seasonal variation in patients admitted as case of AFE in a tertiary care hospital in New Delhi.

MATERIAL AND METHODS

Study design

This hospital-based prospective, observational study was conducted in the Department of General Medicine and Neurology at Batra Hospital and Medical Research Centre (BHMRC), New Delhi. About 122 sequentially admitted patients, who fulfilled the selection criteria over a period of 1 year from January 2021 to December 2021 were included in the study.

Inclusion criteria

(1) All patients between 14 and 40 years of age with no previous history of neurological disorder, (2) fever with temperature ≥100 F lasting more than 24 h but of <2 weeks duration, (3) altered mental state, presenting either with or following fever and lasting at least 24 h, (4) altered mental state in terms of distinguishable change in level of alertness, i.e., Glasgow coma scale score of 14 or less ranging from confusion, drowsiness, stupor to coma.

Exclusion criteria

(1) Hypoglycemia (blood glucose ≤50 mg/dL), (2) hypoxia (PaO_2 ≤60 mm Hg), (3) hypercarbia ($PaCO_2$ ≥50 mm Hg), (4) hyponatremia (Na ≤120 mg/dL), (5) hypernatremia (Na ≥150 mg/dL), (6) azotemia (serum creatinine ≥3.5 mg/dL), (7) hepatic disease (deranged LFT's, cirrhosis on ultrasound), (8) intracranial space-occupying lesion on magnetic resonance imaging (MRI) brain or non-contrast computerized tomography brain, (9) epileptic disorders and patients having cerebrovascular diseases followed by fever were excluded.

All the eligible patients were worked up with detailed history, general physical and systemic examinations. The patients were subjected to biochemical investigations which include complete blood count with differential count, renal function tests, liver function tests, thyroid function tests, chest radiography, urine routine examination, urine culture, and blood culture. Other relevant biochemical investigations, lumbar puncture, radiological investigation (MRI brain/CT scan brain), and Electroencephalogram (EEG) were done after explaining the purpose and procedure of the study and obtaining proper consent. Special tests were ordered when appropriate, for HSV I and 2, Chikungunya virus, dengue virus, JE virus, leptospira species, tests for HIV, HBsAg, and anti-HCV. Peripheral smears for malaria parasites and other hemoparasites were examined in all the patients with clinical suspicion. All patients with abnormal cerebrospinal fluid (CSF) picture were classified as CNS infection, while those with normal CSF were considered as having systemic infection (non-CNS). Based on abnormal CSF picture, patients were grouped as CNS pyogenic infection, non-pyogenic/aseptic CNS infection, tubercular CNS infection, malarial illness, etc. Further analysis of CSF was carried to identify etiological agents. In some cases, etiology could not be found despite extensive work up, and these cases were labeled probable/presumed bacterial CNS infection or probable/presumed viral CNS illness, as done in previous studies[7,10,11] CSF analyses and interpretation were used to define cases based upon previous studies.[10,12]

Patients of AFE were studied according to the prevalence, etiological diagnosis, and the seasonal variations on the basis of history, clinical examination, laboratory investigation, and radiological testing. Final outcome at discharge was based on a modified Rankin scale (mRs) which had been used elsewhere also.[10] mRs score of 2 or less was taken as slight disability to no symptom while as mRs score of 3–6 was taken as significant disability to death.

Statistical analysis

Statistical analysis of observation was done using standard statistical methods after compiling the results of all patients included in study. Descriptive statistics computed for all the numerical data. Frequency tables were constructed for categorical data. The study was compared with similar type of studies in the literature and analyzed statistically. For all the statistical analysis, a P≤0.05 was considered to indicate a significant difference at 5% level of significance. All statistical analyses were performed by using software SPSS version 16.0.

RESULTS

About 122 serially admitted patients diagnosed with the cases of AFE were found eligible and included in the study. In our study, mean age was 32.54±5.23 years. Males (n=74, 60.7%) outnumbered the females (n=48, 39.3%). Majority of our patients (n=64, 52.50%) belonged to the rural areas, urban patients were 58 (47.50%). Most of the patients presented with fever and altered sensorium followed by neck stiffness and headache as shown in Figure 1.

All patients were febrile with mean temperature of 101.48±1.54 F. Minimum temperature was 100.5 F while maximum temperature was 104 F. Out of 122 cases, 56 (45.90%) cases had Glasgow coma scale (GCS) of ≤7, while 66 (54.10%) cases had GCS of more than 7. Among the 122 patients, 44 (36%) presented within 3 days of the onset of symptoms, while 78 patients (64%) presented later than 3 days of the onset of symptoms to the hospital. Table 1 shows the CSF pattern of the studied population admitted with AFE.

Seventeen patients had normal CSF results so they were not included in the group of primary CNS infections. They were evaluated for locating site of infection. Out of them, 4 patients had enteric fever, rest 13 patients were labeled as sepsis associated encephalopathy.

While evaluating the seasonal trend of febrile encephalopathy patients, we found that maximum number of cases (n=61, 50%) of AFE were seen during monsoon followed by 36 patients (30%) in post-monsoon, 15 patients (12%) were admitted in summer while only 10 cases (8%) were admitted during winter.

In our study, we found that 38 patients had CSF picture of meningoencephalitis out of which 16 cases (42%) had probable viral CNS infection, 3 patients (8%) each had acute pneumococcal CNS infection, tubercular CNS infection, probable bacterial CNS infection, 2 patients each of JE, herpes simplex encephalitis, dengue encephalitis, malarial CNS infection, 1 patient each of chikungunya CNS illness, acute staphylococcal CNS illness, acute *Escherichia coli* CNS illness, acute meningococcal CNS illness, and crytococcal CNS illness. Among 122 patients, positive blood culture was seen in 13 patients of which 8 patients had primary CNS infection (all had PM) while 5 patients had sepsis outside CNS (pneumonia).

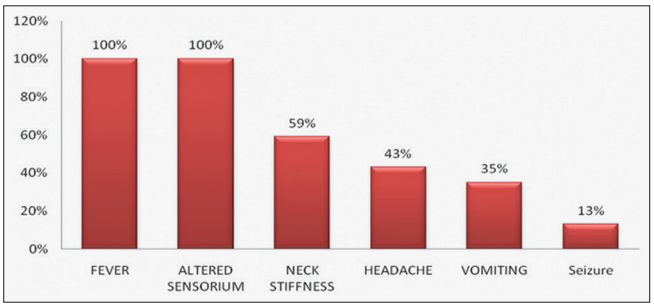

Figure 1: Symptom wise distribution of patients

Among 122 patients, 42 patients had normal EEG. Out of the remaining 80 patients with abnormal EEG, 16 cases had seizures clinically. The EEG findings were statistically associated with morbidity and mortality. Table 2 shows the different EEG findings and associated mortality in studied population.

Among the 122 patients, 2 groups, i.e., with CNS infections (n=105) or with systemic/non-CNS (n=17) were studied for the degree of disability burden. Fifty-three cases with CNS infection had mRs of 3 or more, while 52 cases had mRs of 2 or less. Among cases with non-CNS infections, 4 cases had mRS of 3 or more while 13 cases had mRs of 2 or less (P=0.03). Higher and statistically significant disability was seen in CNS infection group. Similarly delayed hospitalization was associated with increased morbidity (mRs 3 or more) as among 78 cases who had duration more than 3 days preceding the hospitalization, 33 cases had mRs of 2 or less while 45 cases had mRs of 3 or more (P=0.001). Based upon Glasgow coma scale at admission (weather more than 7/15 or <7/15), patients were compared for disability on mRs scale. Among 66 cases, who had GCS more than 7, total of 56 patients had mRs of 2 or less while 10 cases had MRS of 3 or more (0.00001). Lower GCS score at admission was statistically significantly associated with higher disability burden at discharge (Table 3).

In our patients, CNS infection group and those with delayed hospitalization had higher mortality as shown in Table 4.

DISCUSSION

In our study, among 122 patients studied, majority belonged to the rural areas (64 cases, 52.50%) despite the fact that the study center is a tertiary care center at National capital of India, possibly because majority of Indian population resides in rural areas and have easy access to New Delhi. Majority of our patients in the study were having agriculture (n=48, 39%) as the main occupation followed by transport (drivers) (16%) and private business (14%). In our study, male (n=74, 60.7%) patients exceeded females (n=48). Although none of the CNS infections are known to have a male predominance, yet the similar apparent male predominance seen in different studies can be attributed

Table 1: Etiological pattern of the patients with abnormal CSF

Abnormal CSF	Type of infection	Number (n)	Percentage
Acute pyogenic CNS infection	Probable Bacterial CNS Infection	34	32
	Pneumococcal CNS Infection	7	7
	Acute Staphylococcal CNS Infection	3	3
	Acute *Escherichia coli* CNS Infection	2	2
	Acute Meningococcal CNS Infection	1	1
	Total	47	45
Non pyogenic CNS infection	Probable viral CNS infection	20	19
	Chikungunya illness	5	5
	Dengue illness	4	4
	Japanese encephalitis illness	3	3
	Herpes simplex illness	3	3
	Leptospiral CNS infection	1	1
	Total	36	35
Malarial CNS infection		9	8
Tubercular CNS infection		12	11
Cryptococcal CNS infection		1	1

CNS: Central nervous system, CSF: Cerebrospinal fluid

Table 2: Comparison of mortality with EEG abnormalities in study population

Comparison of mortality with EEG findings in different study groups	Number (n)	Mortality (%)		P-value*
		Deaths	No deaths	
Normal	n=42	1 (2.38)	41 (97.62)	-
Seizure	n=16	5 (31.25)	11 (68.75)	0.03
Diffuse slowing	n=42	3 (7.14)	39 (98.86)	0.99
Focal slowing	n=7	0	7	0.99
Spikes and slow waves	n=8	0	8	0.99
Sharp waves	n=3	0	3	0.99
Periodic discharges	n=4	0	4	0.99

EEG: Electroencephalogram, *P-value is calculated by using Chi-square/fisher exact test

Table 3: Assessing disability on the modified Rankin scale (at the time of discharge) based upon various characteristics

Parameters	Modified Rankin scale		P-value*
	mRs ≤2 (n=65)	mRs ≥3 (n=57)	
Etiology			
Systemic (non-CNS) infections (n=17)	13	4	0.03
CNS infections (n=105)	52	53	
Duration of symptoms before hospitalization			
<3 days (n=44)	32	12	0.001
More than 3 days (n=78)	33	45	
Glasgow coma scale score at admission			
<7 (n=56)	9	47	0.0001
More than 7 (n=66)	56	10	
EEG			
Normal EEG (n=42)	32	10	0.002
Abnormal EEG (n=80)	33	47	
Magnetic resonance imaging			
Normal imaging (n=40)	40	0	0.0001
Abnormal imaging (n=82)	0	82	

*P-value is calculated by using Chi-square/Fisher exact test. CNS: Central nervous system, EEG: Electroencephalogram

to the male-dominated social system where a sick male gets preferential medical attention.[1] Some studies say that males are more prone to develop these infections, by virtue of their outdoor work activities being earning members of the family[1,7] Fever and altered mental state which were the mandatory inclusion criteria were seen in all of the 122 (100%) patients. Neck stiffness was seen in 59% headache in 44% while vomiting was present in 36% and seizure was seen in 13.11%. The classic textbook symptoms and signs of meningitis such as headache, fever, neck stiffness, and decreased level of consciousness were not present in all our patients which as per several studies[13,14]

Table 4: Assessing mortality in patients based upon various characteristics

Parameters	Mortality figures		P-value
	Deaths (n=9)	No death (n=113)	
Etiology			
CNS infections (n=105)	6	99	0.22
Systemic (Non-CNS) infections (n=17)	3	14	
Duration of symptoms before hospitalization			
<3 days (n=44)	0	44	0.029
More than 3 days (n=78)	9	69	
Glasgow coma scale score at admission			
<7 (n=56)	8	48	0.016
More than7 (n=66)	1	65	
EEG			
Normal EEG (n=42)	1	41	0.23
Abnormal EEG (n=80)	8	72	
Magnetic resonance imaging			
Normal imaging (n=40)	3	37	0.99
Abnormal imaging (n=82)	6	76	

CNS: Central nervous system, EEG: Electroencephalogram

can be absent in as many as two-thirds of the patients. Among 122 patients, 105 (86%) cases had abnormal CSF results and they were labeled as primary CNS infection. Other studies have reported varying but similar percentage of CNS infection cases. Remaining 17(14%) cases had normal CSF and they were labeled as non-CNS infection including sepsis and enteric encephalopathy causing AFE like in previous studies.[1,15]

Based on CSF analysis, we found that probable acute pyogenic CNS infection was the most common diagnosis in 45% cases, followed by 34% cases of non-pyogenic (mildly elevated CSF cell count) CNS infection, 11% cases of tubercular CNS infection, 9% cases of malarial illness, 1 patient of leptospiral CNS illness, and 1 patient of fungal (*Cryptococcus*) CNS infection. Different studies[1,11,15] have given different results, with most of studies documenting the presence of bacterial meningitis, Japanese B encephalitis, CM, typhoid encephalopathy in a percentage not too different from our observation. Khan et al.,[11] and Bhalla et al.,[1] reported more than 30% of AFE cases in their studies due to PM as their major group, while other studies. Karmakar et al.,[7] reported viral encephalitis as their most common etiology. Etiological search was done in all 105 cases with abnormal CSF finding. In 32% cases having pyogenic CSF picture, no specific etiology was found and they were labeled as presumed acute bacterial CNS infections, 7% had pneumococcal CNS infection, 3% had staphylococcal CNS infection, 2% had *E. coli*-related CNS infection while 1% had meningococcal CNS infection. Modi et al.,[10] Khan et al.,[11] Bhalla et al.,[1] have given varying but somewhat similar results.

In our study, among 19% cases having viral CNS illness, no specific etiology was found and they were labeled as presumed viral CNS infection, 5% had chikungunya illness, 4% had dengue illness, 3% had herpes simplex-related CNS illness, 3% patients had JE CNS illness while one case had leptospirosis. Viral CNS illness as an important cause of AFE is supported by number of studies with contribution ranging from 30% by Bhalla et al.,[1] to 28% by Modi et al.,[10] and 37% by Karmakar et al.[7] Our 8% cases with abnormal CSF results had malaria. Malaria with variable contribution to the population of AFE was reported in different studies ranging from 21.7% by Modi et al.,[10] to 3.15% by Bhalla et al.[1] Furthermore, 11% cases in our study had tubercular CNS infection, the percentage was lower than PM like in many other studies, possibly because tubercular infection generally presents as chronic infection. Sengupta et al., recently found viral encephalitis in 16 (32%) patients, sepsis-associated encephalitis in 14 (28%), bacterial meningoencephalitis in 8 (16%), and tuberculosis meningoencephalitis in 5 (10%) in their study.[16] Khan et al.,[11] reported TBM in 6.7% cases of AFE, while 7.8% was reported by Bhalla et al.[1] One patient had AIDS and one patient had cryptococcal CNS infection. Patients with AIDS and opportunistic infection can present in variable ways including altered mental state as reported by Mitchell and Perfect.[17] Among 13 patients with sepsis-associated encephalopathy, 30% (n=4) cases had urinary tract infection, 46% (n=6) cases had pneumonia, 1 case (8%) had intra-abdominal abscess, 1 case (8%) had retropharyngeal abscess while one patient (8%) had only isolated leukocytosis with unidentified septic foci. Out of these 13 cases, 8 had comorbidities such as diabetes mellitus or hypertension. In our study population, we did encounter SAE as an important cause of AFE in adults reported by other studies.[1,10,11]

Out of 122 cases, 34.42% patients had normal EEG, 13.11% had seizures, 40.16% cases had non-epileptiform changes (which included 34.42% cases with diffuse slowing and 5.73% with had focal slowing. Different EEG patterns are expected due to heterogeneous nature of diseases presenting as AFE ranging from normal to severe abnormalities, including seizures, epileptiform changes, periodic changes, asymmetric dysrhythmia, etc., as seen in other studies.[18]

Mortality was seen in 3 groups based on EEG finding and was maximum in seizure group (n=5, 31.25%), followed by diffuse slowing (n=3, 7.14%) and was least in normal group (n=1, 2.38%). As can be seen that mortality was maximum and statistically significant in seizure disorder (P=0.03). Zoons et al.,[19] had reported about 3 times higher mortality in bacterial meningitis with seizures, it was associated with radiographic abnormalities in one-third of the patients.

Among the patients with seizures (n=16), 15 cases had mRs of 3 or more and it was statistically significant (P=0.00007) while 1 patient had mRs of 2 or less. Seizure indicates parenchymal damage and is associated with poor outcome as mentioned by other studies also.[19] We observed higher mortality and morbidity which was Statistically significant in CNS infection group patients which correspond with the study conducted by Modi et al.[10] We found that increased duration of symptoms before hospitalization, lower GCS score at admission and abnormal EEG records were significantly associated with higher disability burden at disharge.[5,20] We also recorded increased mortality with CNS infection group, delayed hospitalization, and lower GCS score at admission.

India is a country with diverse climate and precipitation but in general, four seasons are recognized in many parts of the country including North India.[21] Among the admitted cases, maximum number of cases (n=61, 50%) of AFE were seen during monsoon followed by 36 patients (30%) in post-monsoon, 15 patients (12%) in summer while only 10 cases (8%) during winter. Most cases seen in the hot and wet months between July and October had been supported by previous studies,[22-24] this is the season where all the vector-borne diseases are abundant as the weather is conducive for the growth and survival of mosquitoes, which are important vectors for transmission of infections such as herpes, JE, malaria, and dengue.[24] Out of 122 patients, 8 patients died during hospitalization while 4 patients left against medical advice. Among all deaths, 4 (45%) had SAE, 2 (22%) patients had CM, and 1 (11%) patient each had dengue and pneumococcal meningitis. The presence of seizure activity was statistically associated (P<0.005) with number of deaths. Functional disability was assessed by mRs. Moderate-to-severe (mRs 3–5) disability was more among the cases with seizure activity.

Limitations of the study

Although one of the easily affordable hospitals of New Delhi with diverse patients attending the hospital, some of the patients belonging to the very poor socioeconomic status could not get enrolled in our study which was our limitation.

CONCLUSION

Acute febrile encephalopathy being a common clinical condition associated with adverse clinical complications if not treated in time. We conclude that clinical suspicion, sensitization and swift response from treating physicians is required to avoid detrimental consequences associated with delayed diagnosis and late hospitalization of these patients.

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Authors Contribution:
MAD- Concept and design of the study; prepared first draft of the study; interpreted the results and reviewed the literature and manuscript preparation, statistically analyzed and interpreted; **EAB**- Review of literature; **AK**- Review of literature and manuscript preparation; **MSHZ-** Review of literature and manuscript preparation; **OHD-** Review of literature.

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