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Research Article

CLINICAL AND ETIOLOGICAL SPECTRUM OF ACUTE FEBRILE ENCEPHALOPATHY IN ADULT PATIENTS: A PROPSPECTIVE STUDY FROM ODISHA, INDIA

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ABSTRACT

Objectives: Acute febrile encephalopathy (AFE) is a medical emergency and might be an indicator of numerous systemic and central nervous system pathologies. In this backdrop, the present study was carried to evaluate the etiology and clinical features of encephalopathy succeeding short febrile illness in adults approaching to a tertiary care center.

Methods: A prospective study was done up to 2 years in 110 patients beyond 14 years. The demographic variables were documented and along with routine examinations, cerebrospinal fluid analysis and radioimaging studies were performed.

Results: The most common etiology of AFE was cerebral malaria (CM) that constitutes 39.1% (43 of 110) of total cases, followed by acute viral encephalitis (AVE), tuberculous meningitis (TBM), acute bacterial meningitis (ABM), sepsis associated encephalopathy (SAE), and enteric encephalopathy (EE) with 24 (21.8%), 20 (18.2%), 13 (11.8%), 5 (4.5%) and 2 (1.8%) cases, respectively. Death rate was 30.20% in CM, 23.07% in ABM, 20.83% in AVE, and 20% in TBM. Two cases of SAE and one case of EE also succumbed.

Conclusion: CM found to be the furthermostcommunalsource of AFE followed by AVE, TBM, and ABM.

Keywords: Altered mentation, Encephalopathy, Fever, Meningoencephalitis.

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INTRODUCTION

Encephalopathy is relatively acute decline in cognition that changes over periods [1]. Acute febrile encephalopathy (AFE) refers to encephalopathy that accompanies or monitors a short febrile disorder [2]. It is a communal complaint leading to hospital admittances, very often to emergency department in both adults and children. It may be due to pathogenic mechanisms affecting the nervous system straightly or due to systemic impediments [3]. Central nervous system (CNS) infections are the furthermost common source of non-traumatic coma [4]. It may be due to a bacterium, virus, parasite, or fungus. The systemic complications include hypoglycemia, hypoxia, hypotension, hyperpyrexia, and electrolyte imbalance [3]. When there is no infection also, it may be due to uncontrolled augmentation of body temperature by overproduction or decreased degeneracy of warmth such as heat stroke, non-infectious CNS disorders, or hypothalamic lesions [5]. The profile of fever with altered mentation differs not only with geographical variation but also with seasonal variation. In India, very few studies have been done so far on AFE and rarely a study was done in Western Odisha. Therefore, considering the problem of diseases in our respective regions becomes significant.

The diseases commonly constituting AFE are cerebral malaria (CM), pyogenic meningitis (PM), viral encephalitis, tubercular meningitis (TBM), sepsis associated encephalopathy (SAE), and enteric encephalopathy (EE).The virus includes herpes simplex virus (HSV1,HSV2), other herpes viruses (EBV, VZV, and CMV), arbovirus (JE), adenovirus, retrovirus (HIV). The present study was carried out to understand the etiology, scientific management, and biochemical profile of AFE by outcome in terms of mortality and recovery in a tertiary care hospital in Western Odisha.

METHODS

A hospital-based prospective and observational study was performed on the adults admitted to the Department of Internal Medicine, Veer Surendra Sai Institute of Medical Sciences And Research during the period of November 2015–October 2017.

Inclusion criteria

Adults more than 14 years of age presenting with fever <15 days with changed sensorium each at start or subsequent fever and long-lasting at least 24 h were enrolled.

Exclusion criteria

Patients having altered metabolic parameters like hypoglycemia (blood glucose <50 mg/dL), hypoxia (PaO_2<60 mmHg), hypercarbia ($PaCO_2$>50 mmHg), hyponatremia serum sodium <120 mEq/L), hypernatremia (serum sodium>150 mEq/l), azotemia (serum creatinine >3 mg/dL), hyperbilirubinemia (serum bilirubin >2.5 md/dL), diabetic ketoacidosis, hyperosmolar coma were excluded. AFE due to intracranial space occupying lesion, cerebrovascular accident, hypertensive encephalopathy, endocronopathies, and drugs were also excluded from the study. An effort was done to consist of every consecutive case. Control were not included and selected in the study.

An informed consent was received from patient party. After the case was admitted, a thorough history was documented and clinical investigation was done cautiously. Consciousness levels were assessed using Glasgow coma scale (GCS). Investigations included both routine and specific tests. It involved whole blood count, plasma sugar, renal, and liver function examinations. Specific tests relevant to presentation included peripheral smear and histidine-rich protein based immune chromatographic card test for malaria, cerebrospinal fluid analysis for cytology, protein. glucose, gram stain, adenosine deaminase level, culture, viral serology available in hospital and cartridge-based nucleic acid amplification test, radioimaging studies of brain like computed tomography (CT) and magnetic resonance imaging (MRI), widal test for enteric fever, plasma culture and urine culture, and suspected site of sepsis was examined, chest X-ray, dengue non-structural protein

1 (NS1) and Immuno globulin M (IgM), and IgM for HSV. Serological tests for other virus were unavailable in the hospital. Patients were categorized into broad groups on the basis of predesigned diagnostic criteria [2].

Statistical analysis

The variables were analyzed using SPSS software and the variables were denoted in mean value with standard deviation and categorical data were denoted in percentages.

RESULTS

Among the 110 cases, 61 (55.50%) males and 49 (44.50%) females with male to female ratio of 1.24:1 were observed. The least age was 16-years-old and the oldest was 74 years old. Regarding age wise distribution, majority of the patients were in the age group of 20–29 years (32/110), followed by 30–39 years (22/110). The mean age in the present study was 36.95±15.40 years (Table 1). The etiology of AFE along with the percentage description is shown in Table 2.

The most common etiology of AFE was CM that constitutes 39.1% (43 of 110) of total cases (Table 3). It was followed by acute viral encephalitis (AVE), TBM, acute bacterial meningitis (ABM), SAE, and EE with 24 (21.8%), 20 (18.2%), 13 (11.8%), 5 (4.5%), and 2 (1.8%) cases, respectively. Three (2.7%) cases could not be diagnosed with the possible amenities available in this hospital. Among cases of AVE, four cases were diagnosed of herpes encephalitis and two cases that of dengue encephalitis. No causative agent could be ascertained in rest of AVE due to unavailability of complete viral panel.

Excluding fever and altered sensorium which were a part of inclusion criteria, headache was the most common symptom. It was found in 63.6% cases followed by vomiting, chills, and rigors and convulsion in 43.6%, 40%, and 33.6% cases, respectively (Table 4). CM cases presented most commonly with chills and rigors and headache with 27 (62.8%) cases in each followed closely by vomiting in 26 (60.5%) cases and then convulsions in 12 (27.9%) cases. Most cases presented with headache (16 of 24 cases that is 66.7%) followed by vomiting, convulsion and chills and rigors in (37.5%), 8 (33.3%), and 7 (29.25%) cases, respectively, in AVE. TBM cases also had headache as prominent symptom and was seen in 15 (75%) cases. Convulsions and vomiting were also reported in 11 (55%) and 8 (40%) cases correspondingly. ABM showed headache, chills and rigors, vomiting, and convulsions in 9 (69.2%), 6 (46.2%), 2 (15.4%), and 2 (15.4%), respectively. SAE showed convulsions, vomiting and chills, and rigors in 2 (40%) cases and 1 (20%) case had headache. Headache was the only associated symptom in both EE cases. Neck stiffness was associated with 54 (49.09%) cases. It was seen most commonly seen in ABM with 12 out of 13 cases (92.3%). It was also associated with 15 (75%) cases of TBM and 15 (62.5%) cases of AVE. This sign was also seen in 11 (25.6%) cases of CM.1 (20%) case of SAE also had stiffness of neck.

Systolic blood pressure <90 was found in 11 (10%) cases. The mean oral temperature was 99.8±1.2 F. Most cases had a fever of short duration (5–9 days). Eighty-one out of 110 cases (73.6%), Longer duration (10–14 days) and very short duration (1–4 days) were seen in 14.54% and 11.81% of patients, respectively. About 30.77% of ABM presented with very short duration whereas 50% of TBM cases presented with a longer duration. In summer and rainy season, maximum reports were observed, that is, from May to September, with 73 (66.36%) cases. It was due to high incidence of CM and AVE in this period with 39 cases and 17 cases, respectively. Case distribution was highest in July (19 cases) and lowest in December (2 cases). GCS >7 was seen in 79 (71.81%) cases and that of ≤7 was seen in 31 (28.12%) cases. Sixteen (37.21%) cases of CM, 4 (30.77%) cases of ABM, 6 (30%) cases of TBM, 4 (16.67%) cases of AVE, and 1 (20%) cases of SAE had GCS ≤7. There was a wide distribution of level of consciousness with confusion, drowsiness, stupor and coma having 34 (30.90%), 24 (21.82%), 33 (30%), and 19 (17.27%) cases, respectively.

Table 1: Age-wise distribution of the study participants

Age (years)	Number of cases	Percentage
14–19	12	10.90
20–29	32	29.09
30–39	22	20.00
40–49	17	15.45
50–59	14	12.72
>60	13	11.81
Total	110	100

Table 2: Etiology of acute febrile encephalopathy

Etiology	No. of patients	Percentage
ABM	13	11.8
AVE	724	21.8
CM	2743	39
EE	02	1.8
SAE	25	4.5
TBM	220	18.2
UD	03	20.7

ABM: Acute bacterial meningitis, AVE: Acute viral encephalitis, CM: Cerebral malaria, EE: Enteric encephalopathy, SAE: Sepsis associated encephalopathy, TBM: Tuberculous meningitis

Table 3: Etiology of cases with AFE and gender distribution

Etiology	Male (n=61)	Female (n=49)	Total (n=110)	Percentage
ABM	9	4	13	11.8
AVE	9	15	24	21.8
CM	24	19	43	39.1
EE	2	0	2	1.8
SAE	3	2	5	45
TBM	12	8	20	18.2
UD	2	1	3	2.7

ABM: Acute bacterial meningitis, AVE: Acute viral encephalitis, CM: Cerebral malaria, EE: Enteric encephalopathy, SAE: Sepsis associated encephalopathy, TBM: Tuberculous meningitis

Table 4: Symptoms and signs with etiology among the cases

Etiology	Chills and Rigors	Headache	Convulsion	Vomiting	Neck Stiffness
ABM	6	9	2	2	12
AVE	7	16	8	9	15
CM	27	27	12	26	11
EE	0	1	0	0	0
SAE	2	1	2	2	1
TBM	2	15	11	8	15
UD	0	1	2	1	0
Total	44	70	37	48	54

ABM: Acute bacterial meningitis, AVE: Acute viral encephalitis, CM: Cerebral malaria, EE: Enteric encephalopathy, SAE: Sepsis associated encephalopathy, TBM: Tuberculous meningitis

Most cases at the time of presentation were confused and stuporous with 34 (30.90%) and 33 (30%) cases, respectively. Twenty-four (21.82%) cases were drowsy and 19 (17.27%) cases were comatose. Most of the CM cases, that is, 46.51% were stuporous followed by drowsiness, coma, and confusion in 23.25%, 18.60%, and 11.62%, respectively. Confusion was seen in 54.17% cases of AVE which was relatively more than that of other etiologies. Confusion and stupor was seen in equal proportion, that is, 35% cases of TBM. The results are shown in Table 5.

In this study, 18 (16.36%) cases had comorbidities with 10 cases having diabetes mellitus, six cases having hypertension and two cases having both of the above (Table 2). Cerebrospinal fluid (CSF) analysis formed

the backbone of etiological diagnosis excluding CM. The mean cell count was highest in ABM with 2311±398.77 cells/mm^3 with neutrophil predominance. It was followed by TBM and AVE with mean cell count 188.50±29.86 cells/mm^3 and 50.04±17.29 cells/mm^3 with lymphocyte predominance. EE and SAE cases had counts raised marginally which was insignificant.

Biochemical parameters showed low mean glucose (36.92±8.64 mg %) and high mean protein (191.31±37.86 mg %) level in ABM whereas TBM showed normal mean glucose (54.30±13.30 mg %) and raised protein (173.50±23.15 mg %) level. There was mild rise of protein with mean value of 69.33±7.53 mg% and normal glucose level in AVE. Mean Adenosinedeaminase level was 20.60±6.39 U/L in TBM.

Based on staining and culture of CSF in ABM, six cases were confirmed pneumococcal meningitis and two cases that of meningococcal meningitis. In other cases of ABM, no causative agent was ascertained which may be due to prior treatment at peripheral hospitals with antibiotics.

Radiological finding were evident in 28 (25.5%) cases. It was seen in seven cases of AVE, six cases of TBM and four cases of CM. Two cases of AVE had T2 hyperintensity in temporal lobe suggesting herpes simplex encephalitis in MRI of brain. Meningeal enhancement was seen in five cases and ventriculomegaly was seen in one case of ABM on CT scan of brain. Basal exudates were seen in two cases of TBM in MRI. Two cases of CM showed diffuse cerebral edema with cerebellar hypointensities on CT brain while other two showed thalamic infarcts on MRI brain.

Out of 110 patients, 28 (25.45%) patients died. Majority of death was due to CM (13 cases). Death rate was 30.20% in CM, 23.07% in ABM, 20.83% in AVE, and 20% in TBM. Two cases of SAE and one case of EE also succumbed. The results were shown in Table 6.

There was significant death rate seen in cases having GCS ≤7 (38.70% cases died) compared to that of GCS >7 (20.25% cases died). The association was found to be significant at p=0.046 (<0.05).

DISCUSSION

Fever with transformed mental state is a communal scenario which leads to increased number of hospitalization and also elicits significant morbidity and mortality. The etiology spectrum varies based on the age, immune status, sociodemographic factors, and also due to seasonal variations. An overall of 110 patients admitted throughout the research period with the above complaint. Among them, 61 (55.45%) cases were male and 49 (44.54%) cases were female with male to female ratio 1.2:1. In our study, we have observed a male preponderance and likewise in a study done by Peidaee *et al*., [6] 60.8% were males and 39.2% were females with a male to female ratio of 1.54. Similarly in another research, reported by Sen *et al*., [7] in India 64% were males and 36% were females. Although no CNS infections are identified to require predilection toward every gender and the male preponderance in the present study might be due to male subjugated social organization with male getting privileged medical consideration.

Table 5: Etiology with level of consciousness at admission

Level of consciousness	ABM	AVE	CM	EE	SAE	TBM	UD	TOTAL
Confused	4	13	5	1	1	7	3	34
Drowsy	2	6	10	0	2	4	0	24
Stuporous	3	1	20	1	1	7	0	33
Comatose	4	4	8	0	1	2	0	19

ABM: Acute bacterial meningitis, AVE: Acute viral encephalitis, CM: Cerebral malaria, EE: Enteric encephalopathy, SAE: Sepsis associated encephalopathy, TBM: Tuberculous meningitis

Table 6: Etiology and final outcome of the study

Etiology	Outcome	
	Survived	Death
ABM	10	3
AVE	19	5
CM	30	13
EE	1	1
SAE	4	1
TBM	16	4
UD	2	1
TOTAL	82 (74.54)	28 (25.45)

ABM: Acute bacterial meningitis, AVE: Acute viral encephalitis, CM: Cerebral malaria, EE: Enteric encephalopathy, SAE: Sepsis associated encephalopathy, TBM: Tuberculous meningitis

The most commonly affected age groups were 20–29 years with 32 (29.09%) cases followed by 30–39 years having 22 (20%) cases. Similarly in a study done by Murali *et al*., [8] further most communal age group exaggerated with AFE was 21–35 years 72 (32.88%). In our study, mean age of the study participants was 36.95±15.40 years. Similar to our report another study reported by Siddiqui *et al*., [9]. The mean age of the patients was 37.2 years and in Khan *et al*., [10] also the mean age was 33.89±17.31 years. Thus, it has been shown that young adults are more susceptible to AFE.

In this present report, the chief cause of AFE is mainly due to the primary CNS infection in 87 out of 110 (79.09%) of the cases. Wide range of studies analyzed the etiological spectrum of specific syndromes of CNS infections, containing encephalitis syndrome in several countries [11,12]. In addition, a large, retrospective, and cohort study (n=2583) displayed the etiological profile of community acquired CNS infections in 20 countries [13]. In corroboration with our report Job *et al*., [14] performed the research in South India reporting 70.5% of AFE is mainly due to CNS infection, in which bacterial constitute 17.7%, mycobacterium (17%), viral (28.9%), unknown etiology (22.7%), and sepsis (5.7%), respectively.

In our study, CM came out to be the most common etiology with 43 (39.10%) cases followed by AVE, TBM and ABM having 24 (21.80%), 20 (18.20%), and 13 (11.82%) cases, respectively. There are 5 (4.5%) cases of SAE and 2 (1.8%) cases of EE. Likewise, in a study done by Bhalla *et al*., [2] 42 patients had meningitis and among these 32 (25.2%) had acute pyogenic meningitis (APM) and 10 (7.87%) had TBM. In another study done by Sen *et al*., [7] the major etiology was viral meningoencephalitis in 30% of the cases, followed by APM in 22% of cases, CM in 10% of the cases and SAE in 14% of the patients.

In our study, the major etiology was CM and this due to high endemicity of malaria in this part of country. Odisha contributes to highest number of malarial cases that is 25% of total and that of malarial deaths too that is 40% of total deaths due to the disease. Geographical distribution, poor sanitation, and low standard of living in this part of state might be playing a contributory role to it. The main biological mechanism involves parasite sequestration in cerebral microvasculature is assumed to be a significant factor in pathogenesis and the resulting pathophysiological deviations in tissue round the sequestered parasites, which may elucidate why an intravascular parasite may grounds neural dysfunction [15]. Sequestration due to the adherence of pRBC's in endothelial lining (cytoadherence) by parasite-derived proteins exposed on erythrocyte surface [16]. In addition, parasite sequestration also leads to the neuronal release of pro-inflammatory cytokines and causes neurological manifestations.

In our study, the incidence of TBM was 18.20%. A document reported by Peidaee *et al*., [6]. A great occurrence of admissions was pragmatic in febrile encephalopathy syndrome patients with neurotuberculosis and also it is one of the common etiologies of febrile encephalopathy syndrome.

Out of 24 cases of AVE, diagnosis was possible in six cases; four cases were due to HSV and two cases were due to dengue virus. HSV is one of the recurrent categories of viral encephalitis reported worldwide [17].

HSV viruses can spread at any time in the year and the peak incidence occurs among the age group of 5–30 years. If it is not properly managed, it can lead to fatality and nearly 70% of the cases with HSV elicit neurological deficits [18]. Neuronal injury mechanism of HSV is either by direct action of virus and/or immune-mediated cell injury. HSV can encourage apoptosis of the involved cells disturbing involuntary cell death. Another documented retrospective study revealed that on imaging temporal lobe involvement as 60%, pure temporal lobe 20%, pure extratemporal 15%, and normal imaging 25% [19]. In a review study of dengue fever related with neurological disease in 2012, encephalopathy was observed to be the mostly reported complication in general to all aspects [20]. The previous reports shows that brain edema, anoxia, hemorrhage, intense hyponatraemia, liver or kidney failure, release of toxic substances, metabolic acidosis, and direct organ invasion are commonly reported precursors of encephalopathy in patients with serious dengue fever [21]. The most common symptom associated with fever and altered mentation was headache which was seen in 70 (63.6%) cases. Headache was associated with 62.82% of CM, 66.67% of AVE, 75% of TVM, 69.23% of AVM, 50% of EE, and 20% of SAE. Similar to our report, in a study by Khan *et al*., [10] the headache was present in PM (100%), common etiology (CM) (91.7%), SAE (79.4%) acute meningoencephalitis (95.5%), and TBM (100%). In another study done by Murali *et al*., [8] separately from different sensorium (100%), lethargy (84%), headache (83%), and vomiting (76%) were the greatest history in most cases presented with AFE.

In our study, majority of the cases were hemodynamically stable at presentation. About 25% of SAE and 16.2% of CM had hypotension. In Bhalla *et al*., [2] the study more cases were hemodynamically unstable. About 50% of SAE and 16.2% of CM were hypotensive. Eighty-one (73.6%) cases with altered sensorium had a fever of 5–10 days. Thirteen (11.8%) cases and 16 (14.5%) cases in our study had fever of 1–5 and 10–15 days, respectively. Our results are in line with Singh *et al*., [6] study where approximately two-third of the cases belonged to that of 5–10 days duration.

In our study, most of the cases (66.36%) were observed during the period between May and September, with a high incidence of CM (39 cases) and AVE (17 cases), respectively. However, in Bhalla *et al*., [2] study where AVE predominates in this season our study showed CM as the most common etiology in these seasons. In our study, a GCS≤7 was seen in 31 (28.25%) cases of which CM constitute half of the cases. In Modi *et al*., [5] study GCS <7 was seen in 17.5% of the cases.

Meningeal enhancement was seen in 46.2% of ABM, 30% of TBM, and 29.2% of AVE. Two cases showed bilateral T2 temporal lobe hyperintensity in MRI brain suggestive of HSV encephalitis. In Modi *et al*., [5] study 28.33% had radio imaging abnormalities. In the present study, four cases of CM had abnormal findings with two cases showed diffuse cerebral edema with cerebellar hypointensities on CT brain and other two cases on MRI brain had unilateral thalamic infarct.

The complete rate of mortality rate in this outcome is 25.45% and majority of death was observed in CM cases (30.25%, 13 cases). Further, the mortality rate was higher among the cases GCS ≤7 (38.70%) as compared to GCS >7 (20.25%). Likewise in another document done by Peidaee *et al*., [6] Overall mortality among CNS infection cases was 21.2%. In Job *et al*., [14] study, the overall mortality rate at the period of discharge was 10.2% then subsequently 1 month of discharge is 20.1%. In addition, they have reported that based on univariate and multivariate analysis for the predictors of 1 month mortality, GCS score <8 was significantly affected with mortality (p<0.01).

CONCLUSION

AFE is a heterogeneous disorder. Numerous agents can result in a very comparable kind of appearance. There were several constraints to our study with unavailability of complete serological screening for viral etiologies and lack of polymerase chain reaction for various viral encephalitis. To conclude, CM found to be the utmost communal source of AFE in this region followed by AVE, TBM, and ABM.

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AUTHORSHIP CONTRIBUTIONS

Dr. Ayaskanta Kar and Dr. Pravin Kumar Mishra–Design and Data collection or processing, editing the manuscript. Dr. Pravin Kumar Mishra and Dr. Parsuram Jena-analysis or interpretation, literature search, manuscript writing, and submission.

CONFLICTS OF INTEREST

Nil.

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