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Research Article

Clinical profile and outcome of patients with acute febrile encephalopathy: A prospective study from tertiary care teaching hospital

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Abstract: Acute febrile encephalopathy (AFE) is a common cause of hospital admissions in north Karnataka. It is a clinical term used to describe altered mental state that either accompanies or follows a short febrile illness and is characterized by a diffuse and nonspecific brain insult manifested by a combination of CNS manifestations. The objective of the study is to identify the etiological diagnosis and outcome in adult patients with AFE. A prospective observational study over a period of 1 year in patients aged 15 years or above who were admitted with AFE at a tertiary care center (Jan2012 to Dec 2012). AFE diagnosis was done after excluding the non-infectious causes of loss of consciousness. To determine the possible etiology Cerebrospinal fluid (CSF) analysis and imaging of brain was done. Of the total 100 patients studied, acute viral encephalitis (AVE) was the most common etiology (34%), followed by sepsis associated encephalopathy (SAE) (29%), pyogenic meningitis (PM)(22%). Cerebral malaria (CM) and tuberculous meningitis (TM) was diagnosed in 6%, and 5% of cases, respectively. In this study, acute viral encephalitis was the common etiology followed by sepsis associated encephalopathy and pyogenic meningitis. Our study demonstrates that acute febrile encephalopathy in adults is a heterogeneous syndrome with primary CNS infections being the commonest etiology
Keywords: Acute febrile encephalopathy, altered mentation, encephalopathy, fever, acute viral encephalitis, pyogenic meningitis, cerebral malaria

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INTRODUCTION

Acute onset fever with altered mentation is a common problem encountered by the physician in the emergency room. Acute febrile encephalopathy (AFE) is a used to describe patients with condition in which altered mental status either accompanies or follows a short febrile illness. Only a few studies have been done so far even though AFE is a common condition in India [1]. Central nervous system (CNS) infections are the most common causes of altered mental status in patients with non-infectious coma. The probable etiologies are virus, bacterium, or a parasite. Encephalopathy may be due to pathogenic mechanism directly affecting the nervous system or due to systemic complications like hypoglycemia, hyperpyrexia, hypotension, hypoxia, or electrolyte imbalance [2].

The profile of febrile encephalopathy varies across different geographic areas and in different seasons. Fever with altered mental state commonly results from bacterial meningitis, Japanese B encephalitis (JE), cerebral malaria (CM), and typhoid encephalopathy [3]. In tropical countries like India, CM, JE, and bacterial meningitis are the common causes of AFE, while tuberculous meningitis (TBM) can present with sub-acute or chronic history [3].

This study was carried out to evaluate the patients presenting with AFE in a tertiary care center in north Karnataka to understand the etiology and their outcomes over a period of 1 year.

EXPERIMENTAL SECTION

All patients above 15 years of age admitted with fever of less than 2 weeks duration with altered mentation, either at onset or following fever, and lasting at least 24 h were enrolled into the study. Exclusion criteria included patients in whom persistent altered mental state could be attributed to one or more deranged metabolic parameters such as hypoglycemia (<50 mg/dL), hypoxia (PaO_2< 60 mm Hg), hypercarbia ($PaCO_2$> 50 mm Hg), hyponatremia (<120 mg/dL), hypernatremia (>150 mg/dL), azotemia (serum creatinine>2.5 mg/dL), space-occupying lesion (ICSOL), or endocrinopathies. Patients having cerebrovascular diseases followed by fever were also excluded as structural lesion in the brain could be a reason for the altered mental state.

History and clinical examination was done in all the patients with fever with altered mental state of short duration. Investigations included: complete hemogram, metabolic profile, chest radiography, and electrocardiogram. Malaria card test and Peripheral smear for malarial parasite, dengue serology, weil-felix test, leptospira antibody was examined in all the patients. Samples for blood cultures and urine cultures were collected and any clinically obvious site of sepsis was investigated. Lumbar puncture was carried out in

all the patients at admission, and cerebrospinal fluid (CSF) was analyzed for cytology, protein levels, glucose to blood glucose ratio, gram stain, culture sensitivity for microbes, and adenosine deaminase levels. All patients underwent contrast-enhanced computed tomography (CT) of the brain. This was followed by a magnetic resonance imaging (MRI) scan of the brain using contrast, if required. Serological tests for other viral etiologies were not available in our institute at the time of this study.

The results were analyzed using SPSS statistical software. The values were expressed as mean with standard deviation for contiguous variable as percentage for the others.

RESULTS

Total of 100 patients were recruited during the study period. The age of patients ranged from 16 to 77 years with a mean of 33.2 ± 12.4 years. There were 58 males and 42 females. The most common complaints were fever (100%), headache (92%), and altered mental state (90%). The Glasgow Coma Scale (GCS) score at the time of presentation was ≤7 in patients. Seasonal variation was seen with clustering of cases from June to September. Of the 100 patients, acute viral encephalitis (AVE) (n = 34; 34%) was the most common etiology, followed by sepsis associated encephalopathy (SAE) (29%), pyogenic meningitis(PM) (22%) [Table1]. AVE included 16 patients with dengue, 2 patients with HSV encephalitis,1 had Japanese encephalitis and the etiology was not identified in remaining 15 patients. There were 6 patients with cerebral malaria, 5 with tubercular meningitis, 2 each of scrub typhus and enteric fever.

Among patients of AVE, the definite diagnosis of HSV encephalitis in 2 patients was based on MRI and CSF serology report. In the remaining 16 patients, definite diagnosis could not be made despite doing all possible investigations available in our institute and presumptive diagnosis of AVE was considered on the basis of clinical features and routine CSF studies. Among the cases of Pyogenic meningitis CSF culture was positive in only five patients we streptococcus was identified in 3 cases and staphylococcus in 2 cases. The reason for negative CSF culture may be because the cases were referred from primary or secondary care centers were they might have been given antibiotics.

CT scan brain as baseline imaging was done in all the patients of AFE. Only 31 patients had shown abnormalities on imaging, CT or MRI. Meningeal enhancement was seen in 45.5% patients with Pyogenic Meningitis. MRI brain was performed in patients with AVE. The bilateral T2 thalamic hyperintensity was seen in one patient with JE. MRI brain in two patients of HSV encephalitis showed characteristic T2-weighted hyperintensity corresponding to edematous changes in the temporal lobes.

There were 17 patients with co-morbid illness. 14 had uncontrolled diabetes mellitus, 2 had HIV infection and 1 had chronic kidney disease. In this study, 18 patients died during the hospital stay, 8 with AVE, 5 with sepsis associated encephalopathy, 3 due to pyogenic meningitis and 2 due to cerebral malaria.

Table 1: Characteristics of patients with acute febrile encephalopathy in different etiologies

characteristics	Acute viral encephalitis (34%)	Sepsis Associated Encephalopathy (29%)	Pyogenic Meningitis (22%)	Cerebral malaria (6%)
Age	32 ± 13.2	35 ± 11.8	29 ± 18.9	28.5 ± 11.5
Sex: M/F	20/14	16/13	12/10	4/2
Headache	33(97%)	29 (100%)	20 (90.9%)	5(83.3%)
Seizures	24(70.5%)	22(75.8%)	17(77.2%)	5(83.3%)
GCS < 7	11	16	14	4
CSF				
Total cells	45 ± 32.4	5 ± 2.4	2445 ± 32.4	-
polymorphs	8.2 ± 11.4	1.2 ± 1.4	78.2 ± 21.4	-
lymphocytes	90.4± 11.8	99.4± 6.8	29.4± 17.8	-
protein	69.7± 19.2	79.7± 9.2	169.7± 39.2	-
Sugar	67.2 ± 13.4	57.2 ± 10.4	27.2 ± 10.4	-
Radio-imaging CT/MRI	10	4	13	4

DISCUSSION

Fever with altered mentation is a common symptom complexes with large hospital admissions in our country. Various studies in children with non-traumaticcoma have shown that CNS infections are the commonest cause of non-traumatic coma. A study of non-traumatic coma in children has indicated that tubercular meningitis, pyogenic meningitis (PM), and encephalitis together constitute more than 90% of the cases [4]. In another study of 151 children, viral encephalitis was the most common etiology seen in 57 patients. A diagnosis other than viral encephalitis was reached in 94 (62.3%) patients. Pyogenic meningitis was the most frequent diagnosis (33.8%), followed by TBM (7.9%) and Cerebral malaria (5.2%) in the patient group of non-viral etiology [5].

TBM presents in adults in a more sub-acute/chronic form rather than the acute presentationand hence a lower prevalence of TBM in this study. In our study, male predominance was seen. In a study, Panagariaet al.has shown a similar trend of male predominance in HSV encephalitis [6]. Alteration in sensorium in a patient with CNS infection indicates an element of parenchymal involvement [5],[7]. The reason for altered sensorium is being spillage of inflammatory cells to the adjacent brain parenchyma and the resultant parenchymal involvement [7]. In Sepsis associated encephalopathy metabolic alterations and inflammatory cytokines play an important role in the pathogenesis of encephalopathy, rather than direct parenchymal involvement. HSV is a common cause of sporadic encephalitis around the world [8]. Post-monsoon JE has been reported from many parts of India. The less common varicella encephalitis tends to be fatal in immunocompromised patients.

Enterovirus, JE virus, and mumps are the important viral agents [5]. There were cases of viral encephalitis and cerebral malaria observed in our study. In endemic areas cerebral malaria remains an important differential diagnosis in patients presenting with acute fever and altered mental state [3]. Dengue hemorrhagic fever presents as a short febrile illness and thrombocytopenia and may present with altered sensorium. In a study, 62 of 265 patients with AFE from central India tested positive for dengue serology and only 39 met the criterion for definite dengue virus infection [9]. Sepsis associated encephalopathy (SAE) is associated with a wide range of manifestations from lethargy to overt delirium in sepsis patients. Patients with SAE have higher mortality at 6 months and has a serious prognostic implications, particularly who admitted to intensive care unit [10].

Due to a large number of patients presenting to emergency in a tertiary care hospital with sepsis, it becomes an important differential diagnosis of AFE in adults. In our study population SAE was an important cause of AFE in adults. CT scan brain was performed in all the patients with AFE. Enhancement of the meninges was seen on contrast-enhanced CT scan in cases of bacterial meningitis. Imaging studies performed in patients with acute meningitis may provide normal findings. Therefore, the results of an imaging study do not exclude or prove the presence of acute meningitis. MR imaging of brain was performed when the findings of CT scan and CSF were inconclusive and patients were not fitting into the criteria of either CM or SAE. MRI brain in patients with HSV encephalitis and JE may have characteristic findings as demonstrated in our patients with JE [11] and HSV encephalitis [12]. Bilateral T2 thalamic hyper intensities were the most common finding seen in patients with JE. MRI brain in patients with HSV encephalitis showed characteristic T2-weighted hyper intensities in the temporal lobes. Many acutely ill febrile patients with encephalopathy can make complete recovery once the underlying cause is treated. It is necessary to correctly diagnose the underlying etiology.

The majority of our patients made a complete recovery; however, a significant number of patients died and a small number of patients were also left with neurologic sequelae. Delayed neurologic recovery and sequelae are well described with meningoencephalitis [3, 12].The cause for maximum mortality was seen in patients with AVE and SAE signifies that diffuse cerebral involvement and multi-organ dysfunction in SAE might have contributed to a large extent in these patients. Raised intracranial pressure may also have contributed to mortality in patients with meningoencephalitis. Mortality was also high in patients in whom a definitive diagnosis could not be made.

Our study is limited by the facts that the complete serological screening for viral etiologies was not available to us, and hence we could not identify the culprit virus in many of our patients. To conclude, acute viral encephalitis was the most common etiology followed by sepsis associated encephalopathy in patients with AFE. The outcome in cases with AVE can be fatal if not identified and treated appropriately.

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