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A STUDY ON ETIOLOGICAL PROFILE IN ADULTS WITH ACUTE FEBRILE ENCEPHALOPATHY IN A TERTIARY CARE CENTRE IN EASTERN INDIA

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Abstract

Background: Acute febrile encephalopathy is a common clinical syndrome across the globe with the principal cause and manifestations differing according to the demographics. In developing nations like India primary central nervous system infections is the chief culprit.

Aim: To identify the etiology of acute febrile encephalopathy and to document the clinical manifestations on presentation. The patients were followed up till discharge and outcome was analyzed in relation with etiology.

Materials & Methods: This observational prospective study was done among 50 patients presenting with fever and altered mental status. History, clinical examination, biochemical investigations including cerebrospinal fluid analysis and neuroimaging was done to diagnose the cases individually. The statistical software SPSS version 2.0 was used for the analysis Categorical variables were expressed as number of patients or percentage of patients and compared across the groups using Pearson's Chi Square test for independence of attributes. Continuous variables was expressed as mean and standard deviation and compared across the groups using Kruskal Wallis Test. An alpha level of 5% was taken, i.e. if any p value is less than 0.05 it was considered as significant.

Results: Out of these 50 patients 70% were due to CNS infections among which viral meningoencephalitis were the commonest cause. The other causes were leptospirosis, brain abscess, cerebral malaria, sepsis associated encephalopathy, acute disseminated encephalomyelitis, neuroleptic malignant syndrome. 14% of patients had sepsis associated encephalopathy and these patients had the highest mortality

Conclusion: Acute febrile encephalopathy is a clinically heterogeneous syndrome with a number of causes. It is an important public health issue due to its steep mortality rate.

Keywords: acute febrile encephalopathy, meningoencephalitis, mortality, sepsis associated encephalopathy

Introduction:

Acute febrile encephalopathy is a commonly encountered clinical problem in the hospitals of tropical countries like India. Acute febrile encephalopathy is defined as fever with acute depression of consciousness or detoriation of mental status for more than 12 hours with or without motor, sensory or other neurological deficits and total duration of illness at time of admission should be 1 week or less. There is myriad number of causes leading to this clinical syndrome but the commonest culprit is central nervous system infections. In fact about 60% of cases with nontraumatic coma have an infectious etiology. [1] The infectious agent may be bacteria, virus or parasite and in rare cases fungus, spirochete. There are a number of non infectious causes also like acute disseminated encephalomyelitis, cortical vein thrombosis, neuroleptic malignant syndrome, septic encephalopathy, cerebral abscess, chronic subdural haematoma etc.

The epidemiological profile of the causative agent varies with the geographical region and even in the same locality there are seasonal variations.

The importance of acute febrile encephalopathy as a public health problem lies in the fact that untreated cases have a poor survival rate. [2, 3]However prompt diagnosis and early initiation of therapy has a favorable outcome with no long term neurological sequel. [4-6]Many a time however even a detailed diagnostic work up may not reveal the specific causative agent and empirical therapy is warranted in such cases.

A number of studies have been carried out to identify the clinical profile of acute febrile encephalopathy in different parts of the world but the emphasis had been on pediatric population [7-9] except for some isolated study in north-west India and one in Iran [10-11]. So this study was carried out in a tertiary care hospital in eastern India to identify the etiology and clinical manifestations of acute febrile encephalopathy in adult patients.

Materials and Methods:

This prospective observational study was carried out in the medicine department of a tertiary care hospital in Eastern India. Over the proposed study period of 12 months all patients with fever and altered mental status who were admitted in the department were screened by pretested and predesigned questionnaire. Among them all consecutive patients with fever greater than duration of one week along with altered mental status, seizures or any other focal neurological deficit during initial presentation or developed subsequently were enrolled in the study.

The patients with metabolic encephalopathy due to conditions like hypoglycemia (capillary blood glucose <50 mg/dl), hypoxia (partial pressure of oxygen <60 mm of Hg), hypernatremia

(Na>150 mg/dl), azotemia (serum creatinine >3mg/dl) were excluded because fever was suspected to be an associated factor not the cause for encephalopathy. Patients having cerebrovascular accident followed by fever were also excluded as structural lesion in the brain or raised intracranial pressure could be a reason for altered mental status and fever might be due to causes like urinary tract infection, aspiration pneumonia or trophic ulcers.

The detailed history of the patients was recorded with emphasis on nature of fever, features of raised intracranial tension, detailed neurological symptoms, immune status, and drug history. Then a detailed clinical examination was done with emphasis on general survey, neurological system, liver, spleen, lymph node examination. Complete haemogram, metabolic profile, liver function tests, chest radiography and electrocardiogram were done in all patients. An immunochromatographic card test for falciparum and vivax malaria was also performed. A sample for blood culture and urine culture was also collected in all cases and any other clinically suspicious source of sepsis was investigated in selected cases like jugular venous catheter tip culture. Lumbar puncture was carried out in all cases during admission and

cerebrospinal fluid (CSF) was analyzed for cytology, protein levels, glucose, gram stain, Zeihl-Neelsen stain and CSF adenosinedeaminase levels. Prior to lumbar puncture all patients underwent computed tomography scan of brain. In all cases magnetic resonance imaging (MRI) scan of the brain using contrast were done. Serology for herpes simplex and Japanese encephalitis virus was performed in 15 cases. Also for confirmation of the diagnosis serum CPK and electromyogram and nerve conduction velocity of all 4 limbs was done in 1 case. After diagnosis of the patients based on these parameters they were classified into clinical syndromes on the basis of predesignated diagnostic criteria [Table 1] The patients were followed up till discharge or death and their clinical parameters noted at that time.

The data was analyzed using SPSS statistical software version 2.0. The continuous variables were expressed as mean with standard deviation and percentages and compared across groups using Kruskal Wallis test. Categorical variables was expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for independence of attributes.

Results:

During the study period of one year a total of 72 patients were admitted with complaints of fever and altered sensorium among whom 12 had fever later in course of illness so were excluded. 10 patients were excluded as complete information was not available. So 50 patients were finally included in the study, data was analyzed and the following results came out. The mean age of the patients was 35.06 years with the most represented falling in the age group of 31-40 years. There was male preponderance in the study with 32 males and 18 females. The maximum cases 32 occurred during the monsoon season in the months of June to September. When analyzing the etiology of the cases primary central nervous system infections was the chief culprit with 30 cases amounting to 60%.On further differentiation 15 patients had viral meningoencephalitis, 11 had acute pyogenic meningitis, and 4 had tubercular meningitis. 7 patients had evidence of infection elsewhere and were diagnosed as sepsis associated encephalopathy (SAE). The other causes were 5 patients with cerebral malaria, 3 with brain abscess, 2 with leptospirosis, 2 with acute disseminated encephalomyelitis (ADEM) and 1 patient with neuroleptic malignant syndrome. [Table2]

The 50 cases were also analyzed based on their clinical features at presentation with etiological diagnosis. The mean temperature at presentation was 102.13 degree Fahrenheit. Fever and headache were the most common presenting complaints with 100% of patients having fever and 92% patients having headache. Seizure which can be considered a red flag sign in febrile encephalopathy was present in 52% patients with 28% having focal seizure and 24% having generalized tonic clonic seizure. Level of consciousness was evaluated on admission and 52% were in confused state, 6% were semiconscious and 8% were comatose.

All patients were assessed thoroughly on admission with emphasis on general survey and neurological examination. The mean pulse rate was 91.64 beats/minute. The mean systolic blood pressure was 112.84 mm of mercury and mean diastolic blood pressure was 74.64 mm of mercury. 52% patients had meningeal signs like neck rigidity, positive Kernig's sign, Brudzinski's sign. In patients with pyogenic meningitis it was maximally seen with 10 patients having features among 11. Similar high frequency was seen in patients with tubercular meningitis with 3 among 4 having meningeal signs. In 15 patients with viral meningoencephalitis 7 patients had prominent features. 19 patients had features of raised intracranial tension like papilloedema. As for other neurological signs 72% had no focal neurological signs, 16% had cranial nerve palsy, 2% had hemi paresis, and 10% had ataxia. They were evaluated for signs in other systems among them 8% had evidence of hepatospelomegaly.

18% had coarse crepitations on auscultation of the chest. Routine blood examination was carried out on admission. The salient observations were 88% had normal platelet count and 46% had leucocytosis. Cerebrospinal fluid (CSF) analysis was done in all patients, with 58% having increased cell count and 42% having normal level. Among the patients with CSF pleocytosis 24% had polymorphs and 34% had lymphocyte predominance. As for the CSF biochemical parameters 72% had sugar >40 mg/dl and 28% had sugar<40 mg/dl. 80% patients had CSF protein between 40-100 mg/dl and 20% patients had protein greater than 100 mg/dl. Prior to CSF analysis non contrast Computed Tomography scan of brain was done in all patients among which 52% had radiological findings and 48% had normal study. Due to the high frequency of lesions on CT scan of brain contrast enhanced Magnetic Resonance Imaging of brain was performed in all patients. There 38% had normal study, temporal lobe hyperintensity was found in 6% patients, periventricular and subcortical white matter hyperintensity in 4% patients, meningeal enhancement in 46% cases and cerebral abscess in 6% patients. Other relevant investigations as required were done among which 3 patients had Herpes Simplex virus antibody in CSF, 2 patients had IgM leptospira antibody, 5 patients had malaria parasite dual antigen positive for falciparum malaria, 2 patients had dengue IgM antibody, 3 patients had positive urine culture and 1 patient had a consolidation on chest skiagram.

The patients were followed up till discharge from the hospital. 24% patients succumbed to their illness, among the 76% who survived 18% had residual neurodeficits, like 6% with cranial neuropathy, 2% with hemiparesis, 8% with involuntary movement and 2% with cognitive impairment. Among the patients who died 4 patients had viral meningoencephalitis, 3 patients were of sepsis associated encephalopathy, 2 had acute pyogenic meningitis, 2 had cerebral malaria, and 1 had cerebral abscess. Among the 12 patients who died 4 patients had initial presentation of haemodynamic instability like systolic blood pressure less than 90 mm of mercury and tachycardia. Among the patients who succumbed to their illness none was fully conscious, oriented at presentation, 5 were confused, 4 were semiconscious and 3 were comatose.

Table 1: Diagnostic criterion for specific diseases

1	Pyogenic meningitis: Fever with altered sensorium (without focal symptoms/signs) ± neck signs + CSF cytology (predominantly polymorphs) + meningeal enhancement on either CT or MRI scan
2	Meningoencephalitis: Fever with altered sensorium (with focal symptoms/signs) ± neck signs + CSF cytology (predominantly lymphocytes) + EEG/MRI/CT evidence of parenchymal disease
3	Acute Disseminated Encephomyelitis: Fever with altered sensorium (with focal symptoms/signs) + compatible CSF (raised CSF protein + normal CSF sugar + normal CSF cytology + diffuse white matter changes in the MRI
4	Tubercular Meningitis: Fever with altered sensorium (with or without focal symptoms/signs) + CSF compatible with chronic meningitis + CSF ADA > 9/TB PCR positive
5	Cerebral malaria: Fever with altered sensorium (without focal symptoms/signs) with peripheral smear/ Antigen test positive for malaria
6	Leptospirosis: Fever with altered sensorium (without focal symptoms/signs ± jaundice/renal dysfunction IgM ELISA for leptospira positive

7	Brain abscess: Fever with altered sensorium (with focal symptoms/signs) ± neck signs + CSF cytology (predominantly polymorphs) + Focal lesion on either CT or MRI scan
8	Sepsis associated Encephalopathy: Underlying sepsis syndrome with normal CSF analysis, CT and MRI scan
9	Neuroleptic malignant Syndrome: Fever with altered sensorium with normal CSF analysis and neuroimaging with raised creatinine phospokinase
10	Cerebral Venous Thrombosis: Appropriate clinical setting+ fever with altered sensorium (with focal symptoms/signs)+ evidence of CVT on MRI of the brain

Table 2: Etiology of acute febrile encephalopathy

Etiology	Frequency	Percent
Viral meningoencephalitis	15	30.0
Acute pyogenic meningitis	11	22.0
Tubercular meningitis	4	8.0
Cerebral malaria	5	10.0
Leptospira	2	4.0
Brain abscess	3	6.0
Sepsis associated encephalopathy	7	14.0
Neuroleptic malignant syndrome	1	2.0
Acute disseminated encephalomyelitis	2	4.0

Table 3: Table showing association of meningeal signs with etiological diagnosis

		Meningeal Sign		Total		
		Present	Absent		p Value	Significance
Etiology	ADEM	0(0)	2(7.69)	2(4)	0.003	Significant
	APM	10(41.67)	1(3.85)	11(22)		
	BRAIN ABCESS	0(0)	3(11.54)	3(6)		
	CEREBRAL MALARIA	2(8.33)	3(11.54)	5(10)		
	LEPTOSPIRA	0(0)	2(7.69)	2(4)		
	NMS	1(4.17)	0(0)	1(2)		
	SAE	1(4.17)	6(23.08)	7(14)		
	TBM	3(12.5)	1(3.85)	4(8)		
	VIRAL ME	7(29.17)	8(30.77)	15(30)		
Total		24(100)	26(100)	50(100)		

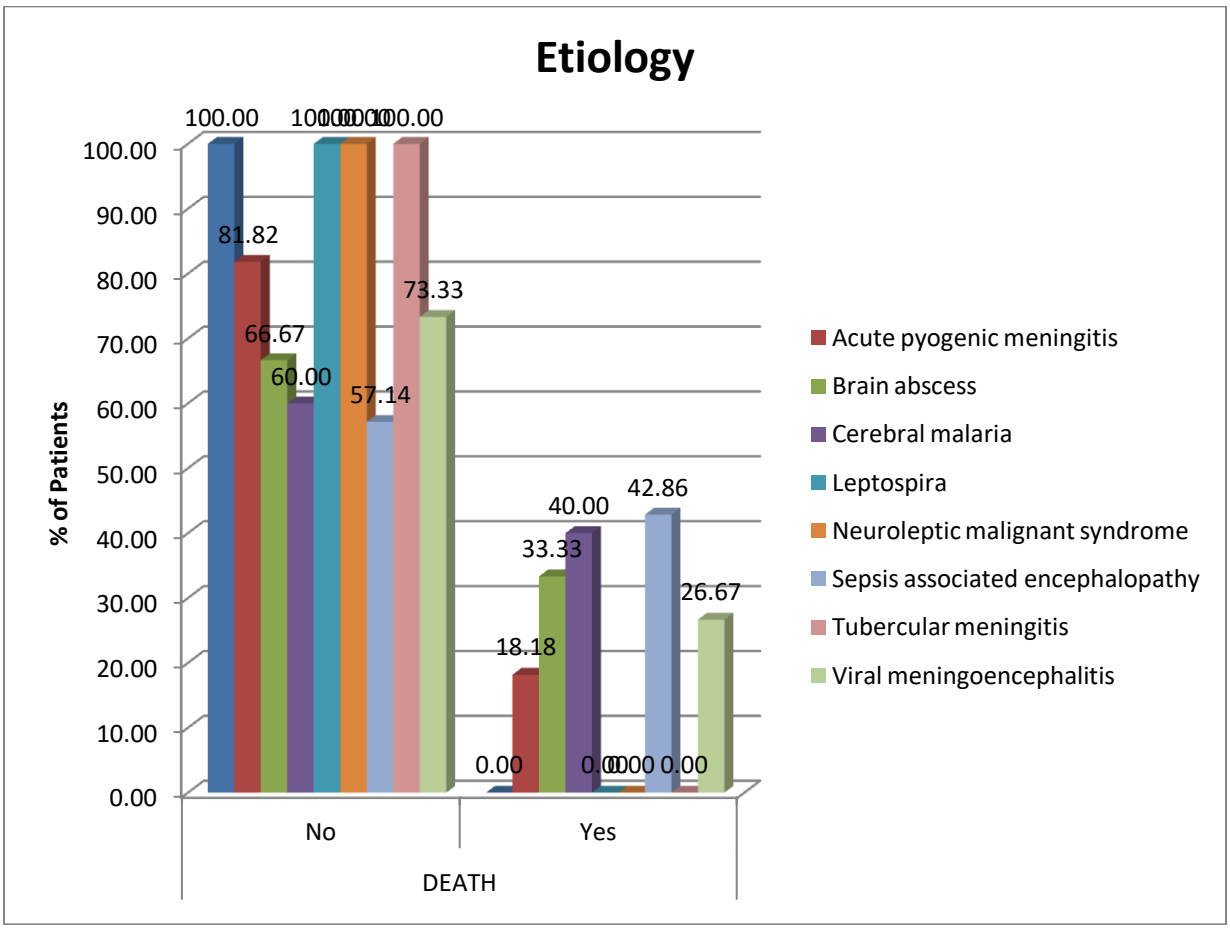

Figure 1: Bar diagram showing outcome in percentage according to etiology

Discussion:

Fever with altered mental status is a common and important syndrome leading to hospitalization and significant morbidity and mortality. The etiology differs according to age, socio-economic factors, immune status, and demography even according to seasons. The most common cause is CNS infections worldwide. In a study from India in pediatric population (age<18 years) commonest cause of acute febrile encephalopathy was viral encephalitis accounting for 40% cases and among non viral causes were the bacterial meningitis (33.8%), tubercular meningitis (7.9%) and cerebral malaria (5.2%). [12] The prominent infectious causes are encephalitis, meningitis, cerebral malaria, brain abscess, subdural or epidural empyema, sepsis associated encephalopathy, sepsis with disseminated intravascular coagulation. The pathogens are DNA viruses like herpes simplex virus, other herpes virus (HHV6, Ebstein Barr virus, Varicella zoster virus, cytomegalovirus) Adenovirus serotype 1,6,7,12,32 and RNA viruses like influenza virus serotype A, enterovirus, arbovirus and retrovirus. Apart from the causative organisms of acute pyogenic meningitis other bacteria are Listeria monocytogenes, leptospira, legionella, Salmonella typhi and most significantly Mycobacterium tuberculosis. The important species of Rickettsia are Rickettsia typhi and Rickettsia prowazekii. Fungus may also cause encephalitis like Cryptococcosis, histoplasmosis and candidiasis. The important parasites are Plasmodium, Toxoplasma gondii, Naegleria fowleri, Schistosomiasis**.** This study was carried out in a tertiary care hospital among adult population in Eastern India. Different studies have been carried out in different parts of India both in adult and pediatric population

but there has no study depicting the etiological profile in this region. In this study the main cause of acute febrile encephalopathy is primary CNS infections with viral meningoencephalitis the most prevalent type. Among the 15 patients of viral meningoencephalitis, 3 patients were found to be due to HSV infection. 2 patients were diagnosed to be a case of dengue viral encephalitis. In rest of the patients, the causative proper viral agent could not be identified as neurotrophic viral panel was not available. 4 patients had tubercular meningitis. Although tuberculosis is a major prevalent disease in our country but the reason for the lower prevalence of TBM as an etiology for acute febrile encephalopathy in adults as compared with children could be the subacute/chronic presentation of TBM in adults. In this study 10 % of cases was due to cerebral malaria, which was in concordance with a study done in North West part of the country by Yatendra et al where a total 6.15% was due to cerebral malaria. The majority of patients in this study were young individuals. Average age of the patients was 35.06 years. Similar study results were found by Bhalla et al. [2] Younger patients is more prone to develop febrile encephalopathy because of lack of cumulative immunity due to natural infection.

In the present study, proportion of male cases is higher than the female cases. Male patients were 64 %, while female patients were 36%. Very similar findings were noted in a study done by Panagaria et al [13]. This apparent male predominance can be attributed to the fact that skin acquiescent to mosquito bites is higher in men as compared to women in India. However there was no correlation between etiology and sex. The incidence peaked to nearly 60 % in between the months of June to September i.e. during the monsoon period. The incidence of arboviral infections as well as malaria increases in this period due to coincidental increase in population density of mosquito vector. A similar type of results was shown in a study on acute encephalitis syndrome by Rakesh kumar et al. [14] Duration of febrile episodes correlated with the etiology. It was seen that, most of the viral meningoencephaliits and acute pyogenic meningitis patients presented with less than 7 days duration of fever. Similar types of result were obtained in a study done on pediatric age group patients by Jones et al [15] and on adult patients by Yatendra Singh et al. [16] Most of the patients of cerebral malaria, and all patients of tubercular meningitis, sepsis associated encephalopathy, leptospirosis presented with febrile episodes more than 7 days.

It is postulated that alteration in sensorium, seizure, vomiting in a patient with CNS infection indicates an element of parenchymal involvement. High intracranial pressure may also contribute to distorted mental status. The reason behind for altered mental status in meningitis may be due to the spillage of inflammatory cells to the adjoining brain parenchyma and the resultant parenchymal involvement.

Most of the patients were admitted in haemodynamicaly stable condition. Mean pulse rate 91.64 beats per minute with standard deviation 17.978 and mean SBP is 112.84 mm hg with standard deviation 13.143. Mean diastolic BP is 74.64 mm hg with standard deviation is 9.497. However 4 patients had SBP <90 mm Hg and pulse >100 beats per minute. All these patients had septic associated encephalopathy so these alterations of vital parameters may be due to sepsis itself. Among the 50 patients, 24 patients (48%) had meningeal signs due to irritation of the lining of brain and spinal cord. It correlated well with the etiological diagnosis as depicted in Table 3. Most of the acute pyogenic meningitis patients and tubercular meningitis patients had neck stiffness during admission. However this was less among viral meningoencephaltis patients. This finding is analogous with previous studies. [17] On neurological examination, 8 patients had cranial nerve palsy. Among them, 5 patients had 6th cranial nerve palsy. And 3 patients had 3rd cranial nerve palsy. Meningitis with basal exudate collection is often related with cranial nerves involvement. Cranial nerve palsies are likely to

occur when the cranial nerve are sheathed by exudates (perineuritis) within the arachnoidal sheath. Cranial nerves may also be affected by compressible pressure of brain in general. Abducens (VI) nerve with its longest intra cranial route adjacent to brain stem is most prone to raised ICP and exudates (perineuritis) related compression. Other cranial nerves like III, IV, and VII may also be affected. 4 patients in this study group presented with abnormal movement in the form of chorea and tremor during hospital stay. And all of these patients were subsequently diagnosed as a case of viral meningoencephalitis. Movement disorders have been reported in association with herpes simplex virus (HSV) encephalitis in adults and children. The cause of this complication is unclear, although a number of proposed etiologies have been suggested, including inadequate antiviral therapy, a side effect of anticonvulsants, or a possible post infectious mechanism. [18, 19] One patient of viral meningoencephalitis had developed ataxia. Post viral encephalitis specially HSV virus, Varicella zoster virus, EBV virus may present with ataxia. [20, 21] One patient of acute pyogenic meningitis in this study developed hemiparesis. This may occur from vasculitis, cortical vein or sagittal sinus thrombosis, cerebral artery spasm, subdural effusion or empyema, hydrocephalus, cerebral infarct or abscess, or cerebral edema.

38 patients (76%), during admission had normal haemoglobin value.10 patients (20%) had mild pallor. (Hb% 9-12 gm/dl). And 2 patients of sepsis associated encephalopathy had moderate and severe pallor (Hb % 6-9 gm/dl), (Hb% <6gm/dl). Anemia in sepsis may be due to a number of causes. It may be due to associated anemia of chronic disease, associated DIC, and alteration of mechanical properties of red blood cell impairing the microcirculatory blood flow. Among the patients of febrile encephalopathy, 25 patients (50%) had normal total leucocyte count (4000-10000/microlitre). Leucocytosis was present in 23 cases (46%). Leucocytosis can be due to acute pyogenic meningitis, leptospirosis but most importantly sepsis associated encephalopathy. Thrombocytopenia (<1.5 lakhs/microlitre) was present in 6 patients. And this thrombocytopenia might be due to viral infections causing meningoencephalitis, leptospirosis, dengue and sepsis. Among the biochemical parameters, altered liver function test results was present in 7 patients (14 %) and altered renal function test was present in 12 cases (24%). This can be because of sepsis associated multi organ dysfunction, complicated cerebral malaria, leptospirosis. Similar patterns of altered biochemical parameter was also noted in a study by Rakesh Kumar et al. [14] During the CSF microscopical analysis , it was seen that polymorphonuclear lymphocytosis is present in 12 cases(24%) and this is due to acute pyogenic meningitis cases and leptospiraemic meningitis. Lymphocytic predominance in CSF analysis was present in 17 cases (34%) and this may be due to tubercular meningitis and viral meningoencephalitis.[22] On CSF biochemical analysis , increased CSF protein (>100 mg/dl) was found to be elevated in 10 cases (20%) representing the viral meningoencephalitis patients ,indicating disruption of the blood brain or the blood-CSF barrier. Decreased CSF sugar was present in 14 cases. Decreased CSF glucose results from changes in the physiological functioning of the choroid epithelium as well as from consumption by bacterial pathogens and leukocytes. [23] CSF ADA was found to be elevated in 4 patients (8%) and this was seen in patients with tubercular meningitis. [24]

On analyzing the neuroimaging results, there was abnormality in CT scan in 26 (52%) cases. On doing MRI brain, meningeal enhancement is noted in 23 % of cases suggesting meningeal involvement. However, meningeal enhancement is a nonspecific sign and may also be caused by other different etiologies like carcinomatous meningitis, reactive meningitis, and inflammatory vascular diseases of CNS. 3 patients had shown hyperintensity in temporal lobe in T2 FLAIR, suggesting diagnosis of HSV encephalitis. Also in 2 cases, extensive white matter lesions' involving cortex and basal ganglia

was noted suggesting diagnosis of ADEM. On analyzing the prognosis of the patients, it was seen that 29 patients (58%) had recovered completely. 9 patients had partial recovery with neurological sequel and 12 patients (24%) had died. Comparing the mortality with other studies, overall mortality in this study was higher (24%) than other similar studies like by Modi et al where the overall mortality was 13.4% or in study by Bhalla et al where 16.5% deaths were reported. As this hospital caters to a densely populated area of Kolkata and West Bengal, and many of these patients are referred here in critically ill conditions, mortality may be higher. On further analysis it was found that maximum mortality was due to SAE (sepsis associated encephalopathy) (42.86), followed by viral meningoencephalitis (26.67%), acute pyogenic meningitis (18.33 %). This mortality rate of etiology was similar with previous studies done by Bhalla et al and Modi et al. The fact that maximum mortality was seen in patients with SAE signifies that multiorgan dysfunction may have contributed to a large extent in these patients. Raised intracranial pressure may have contributed to mortality in patients with meningoencephalitis. Patients who had presented in a haemodynamically unstable condition (SBP <90 mm Hg+ pulse rate 100 beats per minute) had maximum mortality. And this finding was statistically important as a risk factor for presenting clinical findings of acute febrile encephalopathy. Patients who had presented in a comatose condition had maximum mortality (75 %). This might be due to more brain parenchyma damage and aspiration pneumonia. There was no significant statistical correlation between etiology and altered sensorium.

Conclusion:

There is a myriad of causes of acute febrile encephalopathy the commonest among them is primary CNS infections. The case fatality rate was highest in sepsis associated encephalopathy. In spite of India being a high prevalence zone for tuberculosis it generally follows a prolonged cause and is not significant as a cause of acute encephalopathy.

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