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"REYE'S SYNDROME – OFTEN MISSED IN PATIENTS OF ACUTE FEBRILE ENCEPHALOPATHY"

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ABSTRACT

1. Background and Objective: - Acute Febrile Encephalopathy (AFE) defined as fever associated with acute depression of consciousness or mental deterioration with or without seizure, motor and/ or sensory deficit and total duration of illness one week or less. Reye's syndrome, an encephalopathy with fatty infiltration of the viscera is an acute illness, characterized by profound disturbance in consciousness, fever, vomiting, convulsion, hypoglycemia with fatty infiltration of the viscera. This study was conducted to find out clinical and etiological profile & outcome of Acute Febrile Encephalopathy in south Rajasthan. **2. Methods:-**This study was Hospital based prospective study from July 2015 to Dec. 2015. All patients of AFE with raised liver enzymes (>3 fold), raised serum ammonia (>50 µmol/L), abnormal coagulogram, anicteric and usually a history of fever in recent past were diagnosed as Reye's syndrome. **3. Results: -** A total of 85 patients of AFE were admitted, 14 cases (16.47%) were diagnosed as Reye's syndrome. Clinical profile of patients of Reye's Syndrome include Fever and altered sensorium 14 (100%), Generalized convulsions 13 (92.85%), raised ICT 9 (64.28%), Protracted vomiting 14 (100%). Most of the patients {12 (85.71%)} had hypoglycemia. All patients of Reye's syndrome had SGPT level >1000 IU/L, anicteric and raised Ammonia level. Seven patients show cerebral edema on neuroimaging. Four patients had raised CSF pressure. Case fatality rate (78.57%) was high in patients of Reye's syndrome compared to Suspected viral encephalitis, Cerebral Malaria and Pyogenic Meningitis. **4. Conclusion: -** Reye's syndrome was seen in 14 patients (16.47%) of AFE. Increasing awareness of this syndrome and a high index of suspicion are important for timely diagnosis. This is important because management has to be energetic, if the mortality from this disease is to be reduced.

KEYWORDS: Acute Febrile Encephalopathy; Reye's syndrome; Cerebral Malaria; Suspected viral encephalitis; Pyogenic Meningitis.

INTRODUCTION

Acute encephalopathy refers to a state of rapid deterioration of brain function, usually presenting as an alteration in state of consciousness, with or without seizure and focal neurological signs. Acute Febrile Encephalopathy (AFE) defined as fever associated with acute depression of consciousness or mental deterioration with or without seizure, motor and/ or sensory deficit and total duration of illness one week or less.[1] In febrile illnesses, encephalopathy may result from pathogenic mechanisms affecting nervous system directly or systemic complications like hypoglycemia, hypovolemia, hyperpyrexia, hypoxia, anemia, hepatic / renal failure and bleeding may contribute to its pathogenesis.[2]

Several unrelated disorders such as bacterial and viral infections of the CNS, Reye's syndrome (RS), Cerebral Malaria and Electrolyte imbalance may present as AFE in children. Often no definitive cause can be assigned and a provisional diagnosis of 'viral encephalitis' is made.

Reye's syndrome, an encephalopathy with fatty infiltration of the viscera is an acute illness that was first described in 1963. This disease is now recognized throughout the world as a significant metabolic cause of neurological morbidity and mortality following viral illnesses in children. In India Reye's syndrome was first reported in 1969. It is characterized by profound disturbance in consciousness, fever, vomiting, convulsion, altered muscle tone and reflexes with fatty infiltration of the viscera. It is now recognized to be one of the commonest neurological complications of viral infection in childhood. Varicella in sporadic cases and influenza B infection in epidemic outbreaks of Reye's syndrome are particularly common. Mycotoxins, hypoglycins, salicylates, phenothiazenes and insecticide

poisoning have been implicated.[3] The hallmark of the disease is universal mitochondrial damage and triglyceride accumulation. Epidemics of this syndrome have been reported from Bihar, Delhi, Uttar Pradesh and Maharashtra and sporadic cases have been reported from Vellore, Nagari, Chandigarh, Bombay and Delhi.

There is paucity of systemic study from our country for establishing diagnosis in patient with AFE. Hence this study was conducted to find out- 1.Clinical and etiological profile of patients with AFE 2. Outcome of patients with AFE of different etiology.

METHODS

This study was Hospital based single centre prospective study from July 2015 to Dec. 2015. All Children (> 1 month & < 18 year) presenting with fever, altered sensorium with or without seizure, motor and/or sensory deficit and total duration of illness 1 week or less were admitted in Balchikitsalay of RNT Medical College, Udaipur (Rajasthan). Neonates and patients of simple febrile seizures were excluded from the study. The clinical and the demographic information were recorded based on a pre-structured proforma, together with the detail history & physical examination at the time of admission with informed consent. The investigations included CBC with PBF, ESR, Malarial parasite {card, slide, MP (QBC)}, blood sugar, kidney function test, electrolytes, liver function test, calcium, CSF examination, urine examination, X-ray chest PA view. ABG, serum ammonia, blood culture for bacteriological and virological studies and CT/ MRI brain were performed whenever required.

All patients presenting with abrupt onset of protracted vomiting followed by delirium, combative behavior, rapidly deteriorating sensorium, stupor/coma with or without seizures and focal neurological signs with raised liver enzymes (>3 fold), raised serum ammonia (>50 μmol/L), usually a history of fever in recent past and usually anicteric were diagnosed as Reye's Syndrome.

All patients were examined daily till discharge from the hospital or death & the surviving patients were examined weekly for 1 month & outcome at the end of 1 month was recorded.

RESULTS

A total of 85 cases with the diagnosis of AFE were admitted. Cerebral Malaria was the commonest cause (37.64%) of AFE followed by Pyogenic Meningitis (18.82%), Suspected Viral Encephalitis (17.64%) and Reye's syndrome (16.47%). Etiological profile of AFE is shown in Table 1**.**

Table-1 Etiological Profile of Acute Febrile Encephalopathy

Disease	Total Patients (%)
Cerebral Malaria	32 (37.64%)
Pyogenic Meningitis	16 (18.82%)
Suspected Viral Encephalitis (SVE)	15 (17.64%)
Reye's Syndrome	14 (16.47%)
TBME	02 (2.35%)
Hepatic Encephalopathy	02 (2.35%)
Meningococcemia	01 (1.17%)
Mumps Meningoencephalitis	01 (1.17%)
ADEM	01 (1.17%)
Dengue Encephalopathy	01 (1.17%)
Total	**85 (100 %)**

Reye's syndrome was diagnosed in 14 cases (16.47%) of AFE. Most of the children 9 (64.28%) were in the age group of 1-5 year followed by 5-10 year 3 (21.42%). Male to Female ratio was 3:1. The most common stage of Encephalopathy at the time of admission was stage 4 (50%) followed by stage 3 (35.71%). Clinical profile of patients with Reye's syndrome is given in Table 2.

Table 2: Clinical Profile of Patients with Reye's syndrome

S. No.	Clinical features	No. of cases (%)
1	Fever	14 (100%)
2	Loss of sensorium	14 (100%)
3	Convulsion (Generalized)	13(92.85%)
4	Vomiting	14 (100%)
5	Signs of raised ICT	09 (64.28%)
6	Hepatomegaly	08 (57.14%)
7	Splenomegaly	03 (21.42%)
8	Anemia	05 (35.71%)

Most of the patients {12 patients (85.71%)} had hypoglycemia (blood sugar < 50 mg/dl). All patients of Reye's syndrome had SGPT level >1000 IU/L, anicteric and had raised Ammonia level. Other investigations revealed leucocytosis (TLC count > 11000/mm^3) in 14 (100%), urea > 50 mg/dl in 10 (71.42%), creatinine > 1.5 mg/dl in 3 (21.42%), hyponatremia (Sodium level < 135 Meq/L) in 11 (78.57%) patients. Seven patients show cerebral edema on CT Brain. CSF examination was done in 9 patients and four patients had raised CSF pressure.

Mortality rate of patients of AFE was 28.23%. Case fatality rate was high in patients of Reye's syndrome (78.57%) compared to SVE (20%), Cerebral Malaria (6.66%). One patient was neurological abnormal at the time of discharge.

DISCUSSION

In our study Cerebral Malaria was the commonest cause (37.64%) of Acute Febrile Encephalopathy followed by Pyogenic Meningitis (18.82%). Suspected Viral Encephalitis (17.64%) and Reye's syndrome (16.47%).

In another study of 151 children by Karmarkar *et al*[1], viral encephalitis was the most common etiology seen in 57 patients.[1] The diagnosis of Reye's syndrome was made in three patients aged 3, 5 and 6 years on the basis of clinical features, more than three times elevated liver enzymes and CT scan head showing diffuse cerebral edema in all. Serum bilirubin was within normal limits in all three patients, which is consistent with the fact that Reye's syndrome mostly causes anicteric hepatitis. In our study, results were a bit different. Cerebral malaria was the most common cause (37.64%) followed by Bacterial meningitis (18.82%). No specific etiology was found in 17.64% cases included in the present study, these were labeled as suspected viral encephalitis. It is possible that a more detailed diagnostic work up such as serology and antigen detection by PCR for viruses could have picked more etiologies.

Another study by Kalra V., Sachdev H.P.S., Menon P.S.N.[4] on twelve patients of histopathologically proven Reye's syndrome seen over a span of three years at the All-India Institute of Medical Sciences between 1977 - 1980. Reye's syndrome was diagnosed in about 15% of cases of encephalopathy syndrome admitted in hospital. Hypoglycemia, considered a hallmark of the disease, was an uncommon observation particularly in patients beyond one year of age (8.5%). Transaminases were more useful than hypoglycemia for suspecting this syndrome (raised in 80% of cases). Progression of the disease was very rapid. 11 out of 12 cases died. A high order of suspicion in a patient who presents with vomiting, hepatomegaly and sensorial obtundation is proposed for early diagnosis.

Benakappa D.G. conducted a study on children seeking admission to Vanivilas Children's Hospital, Bangalore, formed the study group. During the period October 1983 to December 1986 (38 months) there were 269 cases of acute encephalopathy and of these 124 were diagnosed as having Reye's syndrome. Patients had Vomiting (80%), Convulsion (42%), Hepatomegaly (17%), raised Ammonia level (100%), increased SGPT level (88.7%), Hypoglycemia (64.5%). Mortality rate was 78% which was quite similar to present study.

Role of aspirin in producing mitochondrial dysfunction in virus primed liver is proved beyond doubt and body of evidence favours aspirin as the most important co-factor for production of Reye's syndrome.[5-7] In our study we could not get any history of aspirin use for prodromal fever.

To conclude, while determining the etiology of AFE in a malaria endemic area, Cerebral Malaria should be consider in all patients. As death in Reye's syndrome is usually secondary to increased intracranial pressure and herniation, increasing awareness of this syndrome and a high index of suspicion are important for timely diagnosis. This is important because management has to be energetic, if the mortality from this disease is to be reduced. Reye's syndrome often missed in patients of AFE so there remains a need for systematic round the year studies to establish the etiology, epidemiology and clinical feature to rationalize the management.

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