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Cause of Encephalopathy Short Febrile Illness in Patients: A Case Study of Tertiary Care Hospital in Kumaon Region of Uttarakhand

Jainendra Kumar, Basant Chaurasia
SR Medicine , Government Doon Medical College, Dehradun,Uttrakhand, India
Departkment of Medical Science, NIT, kurukshetra, Haryana, India

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Abstract
A dominance of males was seen in our study. Maximum numbers of patients were seen in age group of 20-40 years. No correlation between the age and etiology could be established. No significant difference in clinical features on the basis of the geographical distribution of patients could be established in our study. All the patients in our study were having infective/inflammatory pathology of central nervous system.
In our study the incidence of mosquito borne diseases (mosquito borne encephalitis and cerebral malaria) was significant. This finding was in contrast to the popular belief that there are fewer incidences of mosquito borne diseases is low in hilly areas. Few studies from Nepal and other hilly areas also had similar finding. Total viral serology was not established in all the viral encephalitis cases. Similar findings were seen from studies in developed countries.

1.Introduction

Acute febrile encephalopathy is a clinical term used to describe patients manifesting with a short and febrile illness(less than 15 days), characterized by diffuse and non specific brain insult manifested by a combination of seizures and decereberation [1]. CNS infections are the most common causes of altered mental status in patients with febrile non-traumatic coma[2]. Most acutely ill febrile patients with encephalopathy can make complete neurological recovery once the underlying cause is identified and treated promptly and appropriately.

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 tubercular meningitis (TBM) can present with subacute or chronic history. The profile of acute febrile encephalopathy varies across different geographical regions and in different seasons in the same area.

In febrile illness, encephalopathy may result either from pathogenic mechanism directly effecting the nervous system or it may be due to systematic complications like hypoglycemia, hyperpyrexia, hypotension, hypoxia, electrolyte imbalance or release of systemic chemical mediators[3] .In India, fever with altered mental state commonly results from bacterial meningitis, viral encephalitis, tubercular meningitis, cerebral malaria and enteric encephalopathy along with several unrecognized entities.

2.Review of Literature

The term Pyrexia is derived from the Greek word pyr meaning fire. Term Febrile is derived from the Latin word Febris, meaning fever, and archailly known as ague. One of the first known written references to fever was found in Akkadian inscriptions from about the sixth century BC. These appear to have been interpretations of ancient Sumerian hieroglyphics depicting fever. In the fifth century BC, written works of Hippocrates presented thoughts on the pathogenesis of fever. During that time health was described as the delicate balance among the 4 corporeal humors; blood, phlegm, black bile, and yellow bile. An excess of Yellow bile was thought to cause fever. By the 1700 new information on blood circulation and microbiology brought other hypothesis that fever was caused by fermentation occuring in the blood.

Temperature is regulated by hypothalamus which sets the target temperature or set point, for the body. The hypothalamus receives feedback through different pathways. Peripheral nerves provides one pathway by directing cool/warm sensation to the brain. The hypothalamus provides another feedback pathway by sensing heat from the surrounding brain tissue.17

Thermoregulatory center is located in the anterior portion of hypothalamus. When the vascular bed surrounding the hypothalamus is exposed to certain exogenous pyrogens (bacterial, viral) or endogenous pyrogens (interleukin1, interleukin6, tumor necrosis factor etc); arachadonic acid metabolites are released from the endothelial cells of the vascular network. These metabolites such as prostaglandin E2 cross the blood brain barrier and diffuse into the thermoregulatory area of the hypothalamus triggering the cascade of events that ultimately increases the set point. When the higher set point gets established, the hypothalamus sends sympathetic signals to peripheral blood vessels, causing vasoconstriction and decreased heat loss through the skin. Increased sympathetic activity also initiates piloerection which thickens the body insulating shell. If these adjustments do not salvage enough heat to match the new set point, shivering is triggered through the spinal and supraspinal motor system to cause an increase in heat production. The goal of the body is to reach the new set point.18The final phase called defervescence is characterised by flushing, diaphoresis and feeling warm as the body tries to dissipate heat.

3.Material and Methods

Method of collection of data- All patients with history a of fever of less than 15 days duration and with altered sensorium who presented in Medicine OPD, Emergency or Medicine wards were included in the study.

A pre-designed questionnaire was used to obtain a data which incorporated personal information such as name, age, sex, address, clinical profile, associated risk factors and investigations. This was done after explaining the purpose of this study and obtaining written informed consent.

All patients were subjected to complete routine haematological, biochemical investigations. Other special investigations which were relevant to our study such as malaria (card+smear), dengue card, widal (paired sera), ultrasound were done wherever needed. Routine Cerebrospinal fluid (CSF) analysis was done in all the subjects. In cases wherever needed, CSF was sent outside for Adenosine Deaminase (ADA) analysis and or analysis of viral serology. Plain Computed Tomography (CT scan) head was done in all patients. Magnetic resonance imaging head or contrast enhanced computed tomography head was also done in selective cases whenever the condition warranted it. Electroencephalography (EEG) was also done in patients wherever required. Majority of the investigations were done in our hospital. ADA analysis of CSF and viral serology of CSF was not available in our hospital laboratory and these were evaluated elsewhere.

3.1 Inclusion criteria

***Corresponding Author,**
E-mail address: jainendrakumar70@gmail.com

1. Fever of less than 15 days duration.
2. Altered mentation either at onset or following fever and lasting for at least 24 hours.

3.2 Exclusion criteria

The patients excluded were those who at the time of presentation hadAltered mentation due to

1. Deranged metabolic parameters
   - A. 1.Hypoglycemia (Blood sugar <50mg/dl)
   - B. 2.Hypoxia (Pao_2 < 60 mmHg)
   - C. 3.Hypercarbia ($Paco_2$ >50 mmHg)
   - D. 4.Hyponatremia (serum sodium<120mEq/lt)
   - E. 5.Hypernatremia
   - F. 6.Azotemia (S.creatinine >5 mg/dl)
   - G. 7.Diabetic ketoacidosis
   - H. 8.Hyperosmolar coma
   - I. 9.Hepatic encephalopathy
2. SOL (space occupying lesion)
3. Cerebrovascular accidents followed by fever as lesions in brain could be reason for alteration in mentation.
4. Any past history of CNS disorder.

All the patients were asked about the following details

1. Smoking
2. Alcohol
3. History of hypertension- amongst the study group patient having blood pressure greater than or equal to 140/90 mm Hg and having history of similar increased blood pressure or on antihypertensive medications were taken as hypertensive.
4. Diabetes Mellitus-- Diabetes mellitus (DM) was diagnosed on the basis of following criteria (Modified from American Diabetes Association, 2011)

Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes mellitus plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL) *or*
- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) *or*
- Hb_1Ac > 6.5% *or*
- Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[147]

5. History of tuberculosis in past.

3.3 Investigations done

Haemoglobin-was measured by Acid haematin method using Sahli's Haemoglobinometer

TLC- by Thoma-Zeiss haemocytometer with improved Neubar Counting chamber

DLC by studying peripheral blood film stained with Leishman's stain

Serum Creatinine modified Jaffe's reaction, initial rate assay

Blood urea was done with GLDH kinetic method

Blood glucose GOD-POD method, end point assay and kinetic assay methods were used

Bilirubin- Mod. Jendrassik and Grof's method.

SGPT-ALAT KIT Mod IFCC method (range 5-35U/L)

Alkaline phosphatase- DEA KIT pNPP kinetic method (UPTO 270U/L)

Albumin test kit by bromocresol green, end point assay (3.5-5.5gm/dl).

3.4 Dengue card test

Dengue card test for IgM/IgG antibodies tests the IgM/IgG antibodies in patients sera. The testing card is coated with anti-human IgM/IgG antibodies. Reaction between sera antigen and antibodies gives the result.

Similar principle is used for Dengue NS1 antigen test.

3.4.1 Widal paired sera- The widal test is an antigen-antibody reaction, where the commercially avaible antigen (obtained from salmonella cells) is added to serially diluted serum. The highest dilution at which the agglutination reaction takes place is termed as antibody titre of the patient's serum, Thus the highest the amount of antibody present in the sample, higher is the titre.

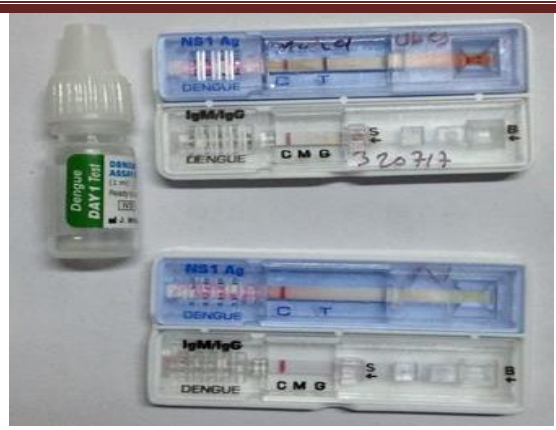

Fig. 1 Dengue card

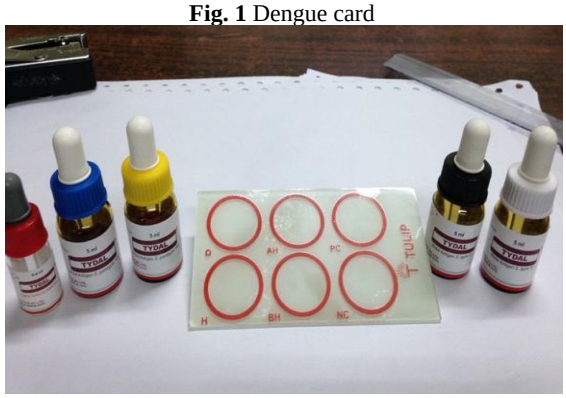

Fig. 2 Apparatus for widal test

3.5 Malaria (Card+smear)

Malaria Card is an immunoassay based on the "Sandwich principle". Colloidal gold is conjugated to *Plasmodum falciparum* specific monoclonal anti-HRP-2 antibody and monoclonal anti-pan specific pLDH (plasmodium lactate dehydrogenase) antibody. The test uses monoclonal anti-Pf HRP-2 antibody (test line F) & monoclonal anti-*Plasmodium vivax* specific pLDH antibody (test line V) immobilized on a nitrocellulose strip. The test sample is added to the device. On addition of assay buffer, the red blood cells get lysed. If the sample contains *P. falciparum* or *P. vivax* or both, the colloidal gold conjugate complexes the HRP-2 (histamine rich protein-2) / P.vivax specific pLDH in the lysed sample. This complex migrates through the nitrocellulose strip by capillary action. When the complex meets the line of the corresponding immobilized antibody, the complex is trapped forming a purplish pink band which confirms a reactive test result. Absence of a coloured band in the test region indicates a negative test result. To serve as a procedural control an additional line of anti-mouse antibody has been immobilized on the strip as control.

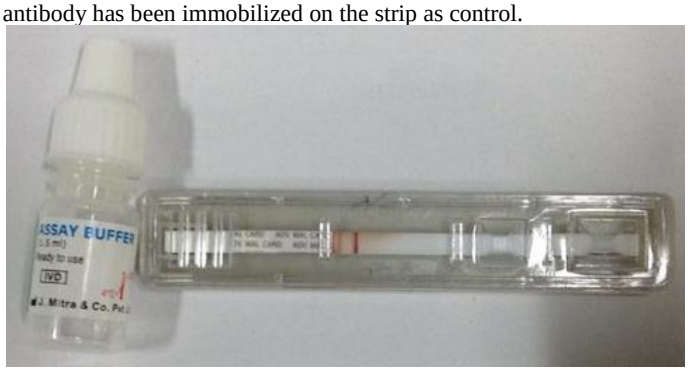

Fig. 3 Malaria card

3.6 Cerebrospinal fluid analysis

CSF was done in all our patients with using completely aseptic technique with the conventional method where the patient lies on his or her side, with knees pulled up toward the chest, and chin tucked downward.

Normal values for spinal fluid examination are as follows:148

- Protein (15-45 mg/dl)
- Glucose (50-75 mg/dl)
- Cell count (0-5 mononuclear cells)
- Initial pressure (70-180 mm)

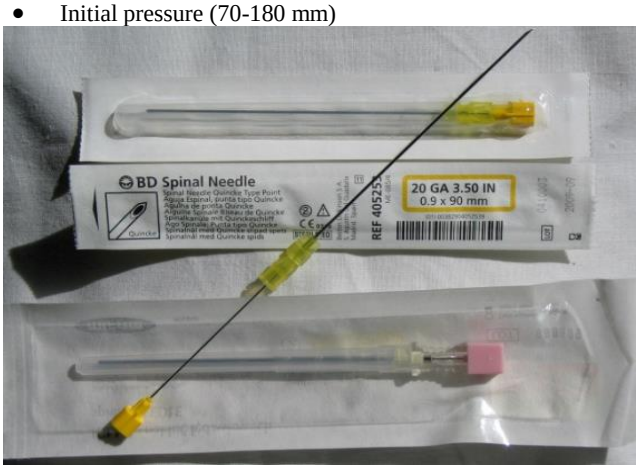

Fig.4 Lumber puncture needle

3.6.1 Computed Tomography Scan

CT scan was done in all the patients in the study group.

3.6.2 **Magnetic resonance imaging**

MRI was done in patients wherever warranted.

4.Observations and Results

On the basis of duration of fever patients were distributed in 3 groups. One group with very short history of fever of 1-4 days, second group of 5-9 days and third of 10-15 days. Maximum number of patients, 72 (62.6%) presented with history of fever of 5-9days.Thirty one patients (26.9%) were in the group of 10-15days and Twelve patients (10.43%) were in the group of 1-4days.

In group of very short febrile illness i.e. 1-4 days, maximum number of cases were of pyogenic meningitis (50%); followed by meningoencephalitis (33%) and tubercular meningitis (8.3%).

It was seen that as the duration of fever was increasing there was rising trend in number of case of tubercular meningitis. Also there was fall in number of cases of pyogenic meningitis and viral meningitis. Total number of cases of other etiologies were so less that their relation with age could not be ascertained.

Table-1 Duration of fever in various etiologies

Duration (days)	Etiology							
	APM	AVM	TBM	CM	SAE	EE	Cryp.M	DE
1-4 days	6 (50%)	4 (33.4 %)	1 (8.3%)	0	0	0	0	0
5-9 days	33 (53.2%)	14 (22.5 %)	8 (12.9 %)	6 (9.6 %)	0	1 (1.6 %)	0	2 3.2 %)
10-15 days	9 (29.03 %)	6 (19.3 %)	10 (32.2 %)	1 (3.2 %)	5 (16.1 %)	1 (3.2 %)	2 (6.4%)	0

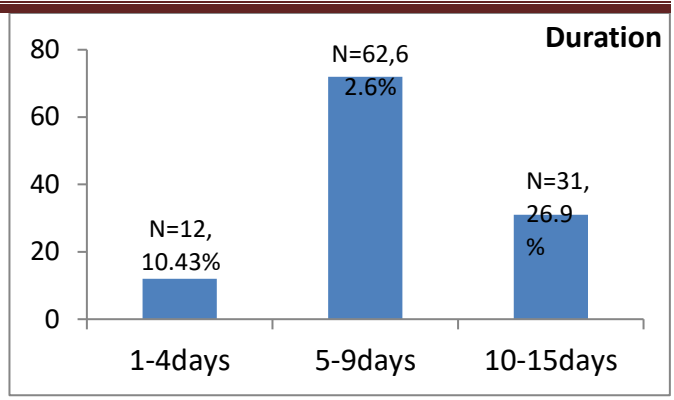

Fig.5 Distribution of patients according to duration of fever Duration of fever and etiology

5.Conclusions

In study by Bhalla et. al there were total 127 patients. Twenty one (16.5%) deaths were reported. The maximum mortality (33%) was seen in patients with SAE.Of the total number of 38 patients with meningoencephalitis, 7 (18.42%) succumbed to their illness. One patient each died due to pyogenic meningitis cerebral malaria and leptospirosis. Five (35.7%) patients out of 14 in whom no definitive diagnosis could be established succumbed to their illness.

On comparing the mortality of other etiologies, in present study mortality rate of cerebral malaria was 42.8% which was higher in comparison to study of Bhalla et al (25%) Modi et al (11.5%). Only 7 number of cases of cerebral malaria were seen in present study. No definite inferences can be made as number of patient was very low.

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