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Clinico- Etiological Profile Of Adult Patient Presenting With Febrile Altered Sensorium To A Tertiary Care Hospital Of Eastern U.P.

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Abstract

Background: The objective of this study is to identify the clinical and etiological pattern of febrile altered sensorium among the Adult patient admitted in a tertiary care centre of eastern Uttar Pradesh.

Methods: This was an observational, prospective study conducted in a government tertiary care centre, Gorakhpur Uttar Pradesh. A total of 206 patients of age 17 years and above admitted with a history of fever of any duration with clinical feature of encephalopathy (change in behaviour or sensorium for more than 24 hours with onset of fever or during the course of fever) with or without headache and or vomiting, were enrolled into this study. Personal data, clinical profile and laboratory data were analysed after that aetiology was established in patient with febrile altered sensorium.

Result: Out of all patients admitted, the most common aetiology in patients of febrile altered sensorium were CNS infections (92%).The most common infection was scrub typhus (12.6%), Japanese encephalitis(JE) (9.7%)and co-infection of JE and scrub typhus was (2.9%), followed by neurotuberculosis (7.3%), sepsis associated encephalopathy SAE (4.9%) and etiology remain unknown in 62.6% cases.

Key words: Fever, altered sensorium, scrub typhus, JE.

Introduction

Fever with altered sensorium is a very common entity encountered by every physician/hospital in day to day practice. It is posing a challenge in the North Eastern part of India, as in monsoon and post monsoon season,[1] there is outbreak of febrile encephalopathy cases causing a great social, economic concern. Febrile encephalopathy is an important cause of case fatality and morbidity in the form of post encephalopathy sequelae not only in children's but in adults also.

Central nervous system (CNS) infections are the most common causes of altered mental status in patients with non - traumatic coma. The various aetiologies are virus, bacterium, or a parasite. In febrile illnesses, altered sensorium may result from pathogenic mechanism directly affecting the nervous system or it may be due to systemic complications like hypoglycaemia, hyperpyrexia, hypotension, hypoxia, or electrolyte imbalance.[2]

The profile of fever with altered sensorium varies across different geographical areas and in different seasons. Fever with altered mental status; commonly result from bacterial meningitis, JE, cerebral malaria, typhoid encephalopathy, scrub typhus, leptospirosis, dengue, tubercular meningitis (TBM).[3] once the underlying cause is identified, early and treated promptly, complete or near complete neurological recovery can be achieved.

The list of differential diagnosis of the clinical syndrome of fever with altered sensorium is long, and timely differentiation between the disorders is very important because correct diagnosis and treatment have a significant impact on morbidity and mortality. These diagnostic challenges especially important in dealing with patients with multiple chronic medical conditions.[4]

Even in the absence of infection, there can be uncontrolled rise in body temperature due to mechanisms like overproduction of heat, impaired dissipation of heat or due to non-infective CNS diseases or hypothalamic lesions.[6]

While various such studies were done in paediatric age groups in various centres, there are few studies done for the adult population[5].

In this study we tried to evaluate the aetiology of fever of any duration with encephalopathy in a tertiary care centre in Gorakhpur, Uttar Pradesh, India.

Methods

This was an observational, prospective study conducted in a tertiary care centre Baba Raghav Das Medical College Gorakhpur Uttar Pradesh. Total 206 patients with age 17 years or more admitted with a history of fever and clinical feature of encephalopathy (change in behaviour or sensorium for more than 24 hours with onset of fever or during the course of fever) with or without headache and or vomiting, were included in this study after taking written informed consent. Patients with recent history of head trauma/chemical or toxin exposure, recent neurosurgery within 3 months prior to admission, haematological malignancies, on immunosuppressant drugs or autoimmune disorder were excluded from our study.

Detailed history and clinical examination was done in all the patients with fever and altered sensorium. Following investigations were included: Haemoglobin, total leucocyte count, differential leucocyte count, platelet count, general blood picture, random blood sugar, renal function tests, liver function tests, serum electrolytes, and rapid diagnostic test for malaria parasite, chest radiography and electrocardiogram. Samples for blood cultures, The IgM testing against O. tsutsugamushi was done using ELISA kit (Scrub Typhus Detect; In Bios International Inc., Seattle, WA, USA) for both CSF/Serum (an optical density value >0.746 indicated IgM positivity in serum and >0.224 in CSF). Anti-JEV IgM antibodies were detected by IgM antibody capture-ELISA kit(P/N=5) (The National Institute of Virology JE MAC-ELISA kit version 1.4), Dengue NS1 antigen 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 analysed for cytology, protein levels, glucose to blood glucose ratio, gram stain, and culture sensitivity for microbes. All patients underwent non-contrast– and 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.

The results were presented in frequencies and percentages; The Chi-Square Test was used to assess the associations. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

Following table 1 is used to define diagnostic criterion for specific diseases.

Table 1: Diagnostic criterion for specific diseases

Pyogenic meningitis	Fever with altered sensorium (without focal symptoms/signs) ± neck signs + CSF cytology (predominantly polymorphs) + meningeal enhancement on either CT or MRI scan
Meningoencephalitis	Fever with altered sensorium (with focal symptoms/signs) ± neck signs + CSF cytology (predominantly lymphocytes) + EEG/MRI/CT evidence of parenchymal disease
ADEM	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
TBM	Fever with altered sensorium (with or without focal symptoms/signs) + CSF compatible with chronic meningitis + CSF ADA > 9/TB PCR positive
Cerebral malaria	Fever with altered sensorium (without focal symptoms/signs) with peripheral smear/HRP antigen test positive for malaria
Leptospirosis	Fever with altered sensorium (without focal symptoms/signs ± jaundice/renal dysfunction IgM ELISA for leptospira positive
Brain abscess	Fever with altered sensorium (with focal symptoms/signs) ± neck signs + CSF cytology (predominantly polymorphs) + Focal lesion on either CT or MRI scan
SAE	Underlying sepsis syndrome with normal CSF analysis, CT and MRI scan
CVT	Appropriate clinical setting+ fever with altered Sensorium (with focal symptoms/signs)+ evidence of CVT on MRI of the brain
NMS	Fever with altered sensorium (in the appropriate clinical setting) with normal CSF and imaging + raised total CPK
Heat stroke	Fever with altered sensorium (in the appropriate clinical setting) with normal CSF and imaging

Results

During the study period, a total of 206 patients admitted with febrile altered sensorium after applying exclusion criteria. The age of patients ranged from 17 to 76 years, about one fourth of patients were between 20-30 years (24.8%) followed by <20 (21.4%), 31-40 (16.5%), >60 (14.6%), 41-50 (12.6%) and 51-60 (10. 2%).There were 108 (52.4%) males and 98 (97.6%) females as shown in table 2

Table 2: Distribution of cases according to age and gender

Age in years	Male		Female		Total	
	No.	%		%	No.	%
<20	20	45.5	24	54.5	44	21.4
20-30	28	54.9	23	45.1	51	24.8
31-40	14	41.2	20	58.8	34	16.5
41-50	16	61.5	10	38.5	26	12.6
51-60	13	61.9	8	38.1	21	10.2
>60	17	56.7	13	43.3	30	14.6
Total	108	52.4	98	47.6	206	100.0

The most common complaints were fever (100%), headache (48.5%), and an altered mental state (100%). Seventy-six (55.3%) of the patients had seizures at presentation as shown in table 3

Table 3 - Distribution of cases according to presenting symptoms.

Clinical symptoms#	No. (n=206)	%
Fever	206	100.0
Altered sensorium	206	100.0
Seizure	114	55.3
Headache	100	48.5
Vomiting	80	38.8
Cough	14	6.8
Pain abdomen	55	26.7
Paralysis	20	9.7
Swelling of body	8	3.9
Diarrhoea	3	1.5
Abdominal distension	9	4.4
Breathlessness	4	1.9

The Glasgow Coma Scale (GCS) score at the time of presentation was ≤7 in 8 (3.9%) patients, while 198 (96.1%) patients had a GCS of >7. The duration of fever was 1-7 days in 125 (60.7%) patients and 7-15 days was in 60(29.1%) patients, as shown in table 4.

Table 4: Distribution of cases according to duration of fever.

Duration of fever in days	No. (n=206)	%
1-7	125	60.7
7-15	60	29.1
15-30	9	4.4
30-45	6	2.9
45-60	2	1.0
>60	4	1.9

Out of 206 patients infectious etiology includes 193 (94.9%) patients, acute viral encephalitis (AVE) 123(59.8) being the most common etiology, it includes Japanese encephalitis (JE) 20 (9.75%), Dengue encephalopathy 3(1.55%), HSV encephalitis 2 (1%), and in the remaining 98 (59.8%) patients, the etiology was not identified as seen in figure 4. Scrub typhus encephalopathy found to be most common non-viral encephalitis 26(12. 6%).Scrub and JE co-infection found in 6 (2.9%) patients. A total of 15(7.3%) patients had tubercular bacterial meningitis (TBM), and 3 (1.5%) patients had acute bacterial meningitis. Brain abscess found to be etiology in 2(1%) patients. Ten patients (4.9%) had infection elsewhere and were diagnosed as SAE as shown in figure 5.

Non-infectious etiology includes a total of 13(5.4%) patients. Stroke/SAH being the most common cause 4(1. 9%).metabolic encephalopathy accounting for a total of 3(1.5%) patients followed by hepatic encephalopathy(HE) 2(1%) and heat stroke 2(1%) patients. Cortical venous thrombosis (CVT) was present in 1(0.5%) followed by acute disseminated encephalomyelitis (ADEM) in1 (0.5%) patient as shown in figure 5.

Most of the infectious etiology (n=185, 89.9%) was present among those patients who had a duration of fever 1-15 days. With the duration of more than 15 days, the most common infectious etiology was tubercular bacterial meningitis (TBM) in 15 patients.

Among patients of AVE, the definite diagnosis of JE in 20 patients was established by demonstrating antibodies against JE virus in CSF and serum. The diagnosis of HSV encephalitis in 2 patients was based on MRI and CSF serology reports. Dengue encephalitis diagnosis was established by demonstrating dengue NS1 antigen in serum of 3 patients.

In the remaining 98 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 one patient. As most of our cases were referred from primary or secondary care centres and they might have been given antibiotics, it could largely be the reason for negative CSF culture.

On imaging CT and/or MRI, only 30 patients had shown abnormalities. Meningeal enhancement was seen in 2 patients with PM. We did MRI imaging in 13 patients who were either not improving on treatment or having some focal neurological deficit. We found that MRI brain scans suggestive of JE in 4 patients and 3 patients shows features suggestive of HSV encephalitis, 3 patients were suggestive of ischaemic infarct and one was SAH.

The bilateral T2 thalamic hyper intensities on MRI brain, was the most common finding seen in JE. MRI brain in patients of HSV encephalitis showed characteristic T2-weighted hyper intensity corresponding to oedematous changes in the temporal lobes. Out of all CT head we found that scan of two patients showed focal areas of hypodensities with surrounding oedema suggestive of brain abscess.

In this study, total of 31 patients died during the hospital stay, 4,3,2,1,1,1 with SAE, scrub typhus, stroke, PM, CM,

TBM, dengue respectively and 18 in whom no diagnosis could be made.

Table 5: Association of infectious etiology with duration of fever.

Table-5 shows the association of infectious etiology with duration of fever. Most of the infectious etiology was present among those patients who had duration of fever 1-7 and 7-15 days.

Etiology	Duration of fever												Total (n=206)
	1-7 (n=125)		7-15 (n=60)		15-30 (n=9)		30-45 (n=6)		45-60 (n=2)		>60 (n=4)		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Japanese encephalitis (JE)	16	12.8	3	5.0	0	0.0	1	16.7	0	0.0	0	0.0	20
Scrub typhus encephalopathy	14	11.2	11	18.3	0	0.0	1	16.7	0	0.0	0	0.0	26
J.E.+ Scrub typhus	4	3.2	2	3.3	0	0.0	0	0.0	0	0.0	0	0.0	6
Acute bacterial meningitis	1	0.8	2	3.3	0	0.0	0	0.0	0	0.0	0	0.0	3
HSV	1	0.8	1	1.7	0	0.0	0	0.0	0	0.0	0	0.0	2
Cerebral malaria	5	4.0	3	5.0	0	0.0	0	0.0	0	0.0	0	0.0	8
Dengue encephalopathy	2	1.6	1	1.7	0	0.0	0	0.0	0	0.0	0	0.0	3
TBM	3	2.4	1	1.7	5	55.6	0	0.0	2	100.0	4	100.0	15
Sepsis associated encephalopathy	5	4.0	2	3.3	1	11.1	2	33.3	0	0.0	0	0.0	10
Brain abscess	0	0.0	2	3.3	0	0.0	0	0.0	0	0.0	0	0.0	2

Discussion

Fever with altered mentation is one of the most common presenting symptoms leading to hospital admissions in both adults and children in our country. Fever with altered mental status is commonly caused by bacterial meningitis, Japanese B encephalitis (JE), CM, typhoid encephalopathy, and fulminant hepatic failure due to viral hepatitis.[3] Various studies in children with non-traumatic coma haves shown that CNS infections are the commonest cause of non-traumatic coma.[7] However, very few studies have been conducted in adults in our country, none in our geographical area. In the present study, we have tried to evaluate the common aetiologies of febrile altered sensorium irrespective of the duration of fever encountered in adults in a tertiary care centre of Eastern Uttar Pradesh. According to this study, the most common diagnosis in patients with clinical syndromes suggested CNS infection. (92%).The most common infection was scrub typhus (12.6%), Japanese encephalitis(JE) (9.7%)and co-infection of JE and scrub typhus was (2.9%), followed by neurotuberculosis (7.3%), SAE (4.9%), Cerebral malaria, Dengue and Acute bacterial meningitis. A study done in Iran for Etiological spectrum of febrile encephalopathy in adult patients suggested CNS infection was SAE (23%), followed by bacterial meningitis, neurotuberculosis, toxic encephalopathy, and herpes simplex encephalitis.[8]

Total cases of febrile altered sensorium (206)

Infectious etiology	**Non Infectious etiology**
94.9% (193)	**5.4% (13)**
AVE 59.9%(123)	Stroke /SAH 1.9 % (4)
Scrub 12.6(26)	Metabolic encephalopathy 1.5% (3)
scrub + JE 2.9% (6)	HE 1% (2)
TBM 7.3% (15)	Heat Strok 1% (2)
ABM 1.5% (3)	
Brain Abscess 1% (2)	
SAE 4.9% (10)	

While other studies done in our area was mainly on AES i.e. fever with altered sensorium of 14 days in which etiologies were bit different, it may be due to geographical difference as acute encephalitis syndrome (AES) is a major public health problem in North Eastern Uttar Pradesh.[9-10] Study done by Sorabh et al, in acute encephalitis syndrome (AES) among adult patients, found that most common etiology of AES is JE virus (20%) in our geographical area.[14] and there study found that majority of AES had unknown etiology (57%) as compared with other studies.[5,15,20,31] and we found that specific etiology remain unknown in 67.2 % despite of best effort. Most of the studies done in adult population, were considered the duration of fever<14 days.[15] We considered the etiology irrespective of the duration of fever, but in our study most of the etiology presented with fever <15 days of duration (90%), this difference may be again due to fact that AES is a major public health problem in North Eastern Uttar Pradesh.

In our study the most common etiology was scrub typhus (12.6%) followed by JE (9.7%) showing that scrub typhus is one of the most common infectious etiology of febrile altered sensorium in our geographical area as contradicting study done by sorabh et al. Tubercular meningitis appears to be the most common infectious etiology for >15 days duration of fever which is similar to a study done on tubercular meningitis previously.[25]In our study, most of the etiology of febrile altered sensorium involves younger population and scrub typhus being the most common etiology followed by tubercular meningitis and JE. We noted a male predominance in our study with males constituting around 52% of the study population, and a very similar male predominance was noted in a study in HSV encephalitis by Panagaria et al.[26] None of the CNS infections are known to have a male predominance, yet this apparent male predominance can be attributed to the male-dominated social system where a sick male gets preferential medical attention. Moreover, males in our society indulge in outdoor activities more often due to work making them more susceptible to vector borne infectious diseases.

A specific etiology could be established only in 32.8 %(n=63) and the remaining were unknown. All the patients with this syndrome did not undergo the PCR tests for herpes simplex virus, Adenovirus, Epstein Barr virus, Enterovirus or Varicella-zoster virus due to various reasons. Even after all the available investigations (serology, CSF, CT, and MRI), we could not arrive at a definite diagnosis. This figure is slightly higher than that reported in the literature.[7, 14] Non-CNS infectious etiology consist of total 13(6.7%) of all the cases. The etiological spectrum of febrile encephalopathy varied across different geographic regions, as well as on the basis of the age range of the participants and the study population[4]. Several studies have investigated the etiological spectrum of febrile encephalopathy and the appropriate threshold for urgent diagnostic evaluation to either verify or rule out CNS infection in the paediatric age group .[21,22]

However, there are few similar studies in the case of adults. A literature review found several studies that reported CNS infections to be the most common causes of changes in mental status in children with non-traumatic coma[11,12,13], however, this finding has not been observed in all studies.[23] Moreover, it is unclear whether this is also true in adult patients with similar clinical presentation or not. In a large study performed in China, [24] infectious syndromes, including CNS infections, accounted for only 13.1% of all 1934 adult patients with undifferentiated altered mental status at a single centre tertiary care emergency department.

Several other studies on the etiological spectrum of febrile encephalopathy in adults have been published. In two of

them that provided information about patients with an average age of 30 to 40 years, bacterial meningitis, viral encephalitis and SAE, followed by tuberculous meningoencephalitis, cerebral malaria, leptospirosis, and brain abscesses, were reported as the most common causes of febrile encephalopathy.[5, 18]

In another study in which one-third of the participants were elderly, meningitis was responsible for more than half of the cases with acute encephalitis syndrome, followed by metabolic encephalopathy, alcoholic encephalopathy, cerebral malaria, brain abscesses, and SAE.[19]

It is postulated that alteration in sensorium in a patient with CNS infection indicates an element of parenchymal involvement.[15] This can explain the altered mentation in meningoencephalitis patients.

HSV is a common cause of viral encephalitis around the world.[32] Post-monsoon JE has been reported from our area. The less common Varicella encephalitis tends to be fatal in immune compromised patients. Among the other identifiable viruses, enter virus, JE virus, and mumps are important agents[15]. In our study, the most commonly identifiable viral encephalitis was Japanese encephalitis followed by dengue and herpes simplex encephalitis. The complete virology screen was not available to us and hence, we could not identify the culprit virus in a substantial number of our patients. Cerebral Malaria (CM), the potentially fatal complication of P. Falciparum malaria is an important cause of unarguable coma in febrile patients in endemic areas. In the endemic areas, CM remains an important differential in patients presenting with fever and altered sensorium.[33] The post-monsoon surge in malaria cases coincides with that of viral encephalitis and the common symptomatology may be confusing to the physicians. We encountered a total of (3.9%) of CM cases in our study group.

Though dengue was earlier thought to be a non neurotropic virus, now a days dengue encephalopathy is a well-recognized and common entity, the incidence ranging from 0.5% to 6.2%.[34]In our study group dengue encephalopathy incidence was 1.5%.The possible mechanism of encephalopathy are liver failure (hepatic encephalopathy), cerebral hypo perfusion (shock), cerebral edema (vascular leak), deranged electrolytes, and intracranial bleeding due to thrombocytopenia or coagulopathy, which is secondary to hepatic failure.[28]

There are subsets of patients in whom the cause for neurological injury remains unclear, even after excluding the above-mentioned indirect mechanisms. Dengue neurotropism has been suggested as the possible mechanism in such cases because evidence of dengue virus [29] and dengue IgM antibodies[16] has been discovered in CSF of encephalopathy patients, which suggests that the dengue virus is capable of CNS infection.

Sepsis associated encephalopathy (SAE) though is not a primary CNS infection presented with this syndrome in 4.9 % of patients. SAE is a poorly-understood CNS condition that is associated with a wide range of manifestations from lethargy to overt delirium in sepsis patients. Our study demonstrated that SAE is more common in older population, this outcome is similar to a study done in USA suggested that upto 60% of severe sepsis cases were from population aged=>65 yrs of age.[35]

SAE has serious prognostic implications and it is an important predictor of higher 6 months mortality.[17] Since a large number of patients present to the emergency room in a tertiary care hospital with sepsis, it becomes an important differential diagnosis of febrile altered sensorium in adults. In our study population, we did encounter SAE as an important cause of febrile altered sensorium in adults.

Conclusion & Summary

Febrile Altered sensorium is a challenging clinical entity for the physicians in the emergency department because of the wide spectrum of etiology causing it and the high mortality and morbidity associated with it.

In this study we found scrub typhus was the most common aetiology of febrile altered sensorium in younger population, while sepsis associated encephalopathy was found to be the most common etiology in elderly.

We also observe scrub typhus being the most common infectious etiology among the patients presenting with febrile altered sensorium within 15 days of duration however with the duration fever of more than 15 days, tubercular meningitis was found as the most common cause.

In Spite of best efforts and limited resources, aetiologies among 67.2% Febrile Altered sensorium cases could not be ascertained. Further research and analysis is required to analyse aetiology of Febrile Altered sensorium cases.

Conflict of Interest and funding

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Contributor

SM was involved in data collection and data interpretation and writing of results and discussion including figures and tables. PKS combined all the data and did proof reading. RKS was involved in critical analysis of data and manuscript.