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ACUTE ENCEPHALITIS SYNDROME: A HOSPITAL-BASED CROSS-SECTIONAL STUDY OF THE ETIOLOGY AND OUTCOMES FROM THE NORTH INDIAN STATE OF UTTARAKHAND

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ABSTRACT

Acute encephalitis syndrome (AES) has a diverse etiology and Japanese encephalitis virus (JE) is the most common etiological agent implicated in its causation. However, AES in different geographical locations have distinct etiological agents that may have seasonal variability, miscellaneous presentations and outcome. We wished to study the demographical profile, etiology and clinical parameters of AES in a tertiary referral center of Uttarakhand as data from this newly created state is lacking. An observational cross-sectional study was conducted where various demographic and clinical profile, etiology and laboratory parameters in 111 patients of AES were studied and comparison was made between the two outcome groups (improved and expired). In the present study, tuberculous meningo-encephalitis was the most common etiology (22.5 %) of AES followed by scrub typhus (19.8 %). Statistically significant (p-value < 0.05) difference was observedbetween patients who expired from those who improved in terms of hematological parameters (mean leucocyte and platelet counts), renal function (mean creatinine, pH, bicarbonate) and liver functions (liver enzymes and albumin levels).This study highlights the fact that AES can have different etiologies depending upon various factors like difference in geographic location, season, agent and vector prevalence. Identification of the specific etiological agent is important for management, understanding the prognosis, instituting timely prophylaxis and public health interventions.

KEYWORDS: Acute Encephalitis Syndrome, Japanese Encephalitis, TBM, Scrub Typhus.

INTRODUCTION

Acute Encephalitis Syndrome (AES) encompasses cluster of several diseases with acute onset of fever, and altered mentation and/or new onset of seizures associated with wide-ranging etiologies such as bacteria, fungus, spirochetes, parasites, viruses, chemicals, toxins etc. (1) The incidence of AES varies globally and etiologically, from 0.9 per 100,000 adult population in Nigeria to 185 per 100,000 adults in rural Nepal. (2) AES is endemic in 171 districts of 17 states of India and pose a potential infectious risk to 375 million people residing here. (1) In India, as per the National Vector-Borne Disease Control Program (NVBDCP), Japanese encephalitis virus (JEV) is the major cause of AES (ranging from 5%-35%), and nearly 75,000 AES cases were reported from 22 states and Union Territories between 2007 and 2016, with a case fatality ratio of 15% (NVBDCP 2017). (1) During 2018, 10485 AES cases and 632 deaths were reported across 17 states. The north Indian state of Uttar Pradesh (UP), the parent state of Uttarakhand, has been the epicentre of this syndrome bearing approximately 70 % of the disease burden of India. (3) While the mortality due to AES for the year 2012 alone was more than 16%, data regarding morbidity attributable to it is scarce. (4)

Although viruses are the most commonly incriminated etiological agents in AES, bacteria, parasites, fungus, toxins etc. may also be causal. As most of the agents are arthropod-borne and transmitted, stagnant water in the rice fields cultivated along the foothills of lower Himalayan belt in eastern UP and neighbouring areas favour their proliferation. (5) Japanese encephalitis (JE) virus has been the most important etiologic agent in UP responsible for 10-15% AES annually and contributing to the bulk of mortality and morbidity associated with it. (3) In India, the history of AES has paralleledthat of JE, especially in northern, north-eastern and southern India. For several decades, based on confirmed outbreak reports, JE has been considered as the only major cause of AES in India. (6)The importance of JE is evident fromthe guidelines of the clinical management of AES whichare centred around JE and require the categorization of all patients of AES

as laboratory-confirmed JE, probable JE, AES due to agent other than JE or AES due to unknown agent. Besides JEV, other viruses that have or may contribute to the large number of AES cases in India include herpes simplex virus (HSV), Chandipura virus, Dengue virus, enterovirus, measles virus etc. However, the etiology is elusive in almost three quarter of patients with AES. (7)

It is also important to establish the significance of contagious agents isolated beyond CNS as they can presumablycause neurological symptoms indirectly without colonizing the central nervous system. (5) Also, differentiation of infectious, post-infectious and post-immunization encephalitis or encephalomyelitis like acute disseminated encephalomyelitis (ADEM) is essential. (7) Likewise, non-contagious CNS diseases viz. collagen vascular disorders, vasculitis, paraneoplastic syndromes may mimic infectious encephalitis and can be included in differential diagnosis. (7)

Optimum management is delayed or denied to these patients due to scarcity of region wise epidemiological data, variable etiologies, erratic availability of appropriate and economical laboratory and radiological investigations and/ or intensive care facilities, and non-availability of specific treatment for viral encephalitis. Inappropriate response during epidemics and delay in seeking health care also contribute significantly to morbidity and the mortality caused by the disease process itself. (8)

Although specific treatment guidelines for managing AES exist, recognition of specific etiological agent is essential for determining the prognosis, instituting prophylactic measures, formulation of public health interventions and surveillance. Data pertaining to AES is virtually non-existent from the newly created state of Uttarakhand and the JE-centric guidelines borrowed from the parent state of Uttar Pradesh (9), are usually applied with variable success. We studied the causes and epidemiology, and the factors precluding mortality in patients of AES presenting to the largest tertiary referral centre of Garhwal region of Uttarakhand.

MATERIALS AND METHODS

Study Setting : Uttarakhand is situated in the laps of Shivalik range of Himalayas in north India. It is bestowed with exquisite biodiversity, from snowclad peaks to moist alpine, and sub-alpine vegetations to temperate and deciduous forests. More than two-third of its population resides in rural areas. The largest tertiary care centre of the state caters to the population of Garhwal division of Uttarakhand, few districts of Kumaon division and adjoining areas of Uttar Pradesh.

Patient Selection: Ours was a hospital-based observational cross-sectional study approved by institutional research and ethics committees. All adult patients over 18 years of age fulfilling the inclusion criteria of AES in the 1-year study period, were included after obtaining informed written consent.

Data collection: Demographic characteristics, namely the residence (rural/ urban), exposure to insects, use of repellants/ mosquito nets, kutcha/ pucca house, dirt/ garbage disposal methods, etc. were noted. Clinical characteristics of the included patients were noted at the time of hospitalization and they were followed-up till discharge from the hospital. All laboratory and radiological parameters utilized in the diagnostic evaluation and treatment of the patients were noted.

Data Management & Statistical Analysis: Descriptive statistics were utilized in the interpretation of the categorical variables compiled. Mean/ median was used as the measure of central tendency of continuous variables. Chi square test was used to determine the association between categorical variables whereas unpaired T-test was used for analyzing the difference in the means of continuous variables. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 111 patients of AES (mean age 50.4 ± 17.7 years; range 18-87 years) were included over the 1-year study period. Maximum (43.4%) patients were aged between 41and 60 years; 4.5 % were over 80 years old. The male to female ratio was 2.8:1. Three-fifth (60.3%) patients hailed from urban areas and majority (72.1 %) resided in pucca houses. While 53.2 % patients did not have proper dirt/garbage disposal at home or the neighbourhood, 54.1 % patients used mosquito repellents regularly. Cases of AES were clustered during the spring and winter months. Majority of the cases presented with improved outcomes were presented with fever (58%), altered sensorium (51.04%), neck stiffness(58.6%), seizure (58.6 %), and vomiting (58.6 %).The presence of icterus (62.1%), Kernig's sign (61.1%), Brudzinski's sign (61.1%), was almost double in the group with improved clinical outcome whereas oedema (61.8%), Anisocoria (55.6%) and cyanosis (100%) were the worst clinical outcome variables found in the patients expired due to AES.

Leucocytosis (52.2%), neutrophilia (94.5%), thrombocytopenia (54.9%), high ESR (49.4%), metabolic acidosis (51.3%), hypoalbuminemia (74.7%), elevation of transaminases (66.6%), and hyperbilirubinemia (47.7%) were the prominent laboratory abnormalities observed in these patients.

Significant haematological differences between the two groups include leucocyte count which was more in the expired patients (16.1%) as compared to the patients with improved clinical outcome (11.7%). Also, a greater lymphocyte (18.4%) and neutrophil (74%) count was also seen in patients with improved clinical outcome. Main radiological abnormalities encountered were consolidation (32.4%),pleural effusion (14.4%), hepatomegaly (16.2%), ascites (10%) on chest x-ray and ultrasonography respectively; hydrocephalus (13.5%) and meningeal enhancement (10.8%) were observed on neuroimaging.

All the three key liver enzymes Alanine Transaminase, Aspartate Transaminase& Alkaline Phosphatase are elevated in patients with worst clinical outcome as compared to the improved patients. However, only Aspartate Transaminase was significantly elevated in the worst clinical outcome patients (897.6) as compared to the improved patients (114.9).

Tuberculous meningo-encephalitis was found to be the most common aetiology (22.5%) in patients of AES in our study, followed by scrub typhus (19.8%) and sepsis(18%) (see figure 1). Anisocoria (8.1%) reflecting raised intracranial pressure was universally associated with tuberculous meningo-encephalitis.

Overall, 52.3 % (n=58) of AES patients had a favourable outcome; 60% and 54.5% cases with AES due to tuberculosis and scrub typhus improved with treatment. Outcome was unfavourable in 55 % cases of septic encephalopathy and in 68.7% of AES due to undetermined cause. Table shows comparison of demographic, clinical features, haematological and biochemical parameters according to the outcomes in patients with AES. The survivors and the non-survivors differed significantly in relation to mean leucocyte and platelet counts, and mean serum aspartate transaminase, albumin, potassium, creatinine, pH, pCO_2 and bicarbonate levels at the time of admission.

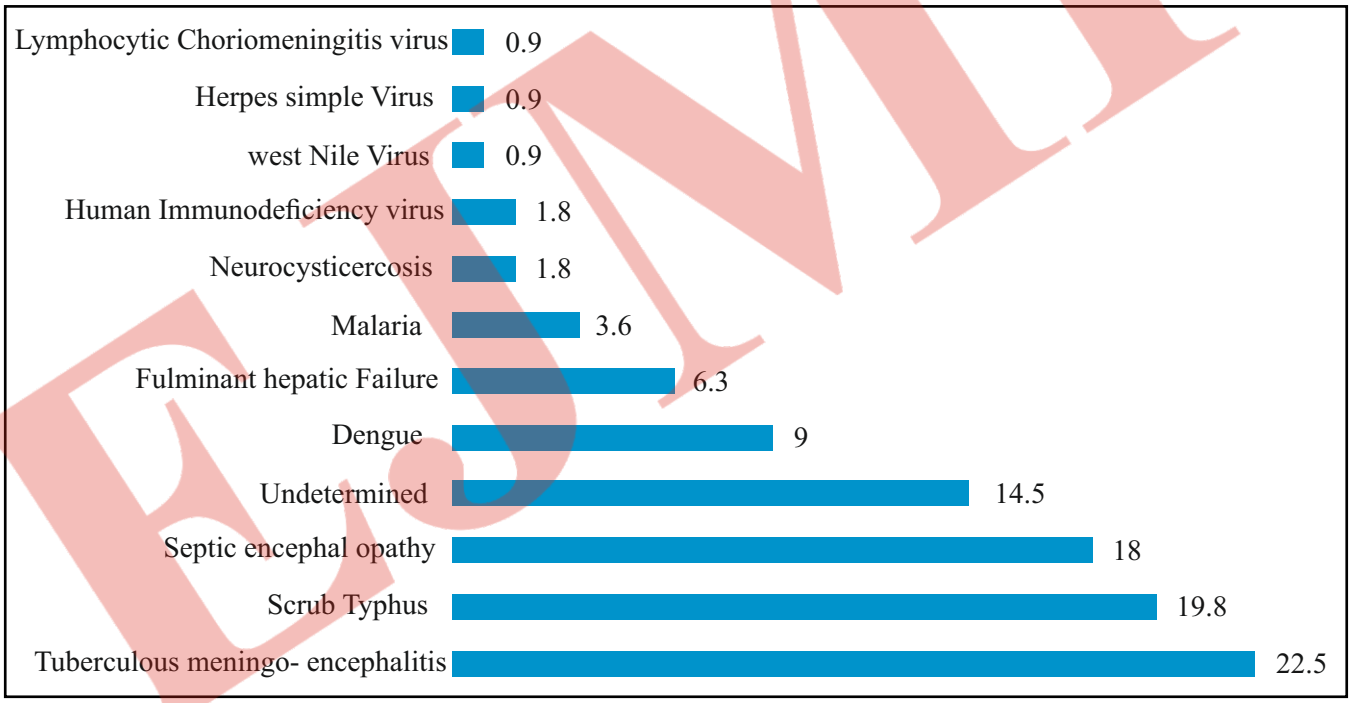

Fig 1: Etiology of Acute Encephalitis Syndrome (Figures Mentioned are Percentage of 111)

Parameters	Improved (n=58)	Expired (n=43)	p-value
Demographic			
Age (years)	48.3 ± 18.9	52.6 ± 16.3	0.197
Male/female	45/13	37/16	0.352
Rural/Urban	25/33	19/34	0.435

Table 1: Comparison of Demographic, Clinical Features, Hematological and Biochemical Parameters According to the Outcomes in Patients with AFE (n=111)

Kutcha/Pucca	21/37	10/43	0.042
Proper dirt/garbage disposal at home/ neighbourhood (Yes/No)	31/27	21/32	0.145
Use of mosquito repellents (yes/no)	28/30	32/21	0.201
Symptoms			
Fever	58	53	
Duration of hospitalization	6.7 ± 6.8	5.5 ± 5.8	0.014
Altered sensorium	51.04 %	49.0 %	0.518
Headache	62.5 %	37.5 %	0.169
Seizure	58.6 %	41.4 %	0.424
Neck stiffness	58.6 %	41.4 %	0.424
Jaundice	62.1 %	38.0 %	0.218
Cough	7 %	0 %	0.013
Photophobia	1 %	0 %	1.000
Signs			
Febrile	51.0 %	49.0 %	0.562
Oedema	38.2 %	61.8 %	0.003
Pallor	44.2 %	55.8 %	0.176
Neck rigidity	58.6 %	41.4 %	0.424
Icterus	62.1 %	37.9 %	0.218
Kernig's sign	61.1 %	38.9 %	0.411
Brudzinski's sign	61.1 %	38.9 %	0.411
Anisocoria	44.4 %	55.6 %	0.734
Clubbing	66. 7 %	33.3 %	0.681
Cyanosis	0 %	100 %	0.106
Hematological Parameters			
Haemoglobin (g/dL)	12.4 ± 2.5	11.9 ± 2.9	0.215
Total leucocyte count (x 10^3/ cumm)	11.7 ± 6.(10.1)	16.1 ± 9.8 (14.1)	0.004
Neutrophil (%)	74.0 ± 14.9 (77)	81.9 ± 16.9 (87)	0.009
Lymphocyte (%)	18.5 ± 13.1 (14)	11.8 ± 10.3 (9)	0.001
Monocyte (%)	6.2 ± 4.1 (5.5)	4.5 ± 4.5 (3)	0.042
Eosinophil (%)	1.3 ± 2.5	0.7 ± 1.3	0.150
Platelets (x 10^3/cumm)	193.6 ± 157.6 (164.8)	136. 8 ± 127 (100)	0.031
ESR (mm in1st hour)	31.6 ± 25.7 (24)	30 ± 23.9 (22)	0.816
Biochemical Parameters			
Random blood sugar (mg/dL)	135.5 ± 52.3	157.1 ± 96.7	0.141
Total Bilirubin (mg/dL)	2.5 ± 2.8 (1.1)	2.8 ± 4.15 (1.3)	0.577
Indirect Bilirubin (mg/dL)	1.4 ± 1.4 (0.9)	1.3 ± 1.6 (0.8)	0.573
Alanine Transaminase (IU/L)	74.1 ± 98.0 (45)	326.2 ± 836.4 (62)	0.112
Aspartate Transaminase (IU/L)	114.9 ± 223.1 (54)	897.6 ± 3059.9 (89)	0.024

Cont. Table 1: Comparison of Demographic, Clinical Features, Hematological and Biochemical Parameters According to the Outcomes in Patients with AFE (n=111)

Alkaline Phosphatse (IU/L)	153.1 ± 124.4 (100)	170.5 ± 156.80 (119)	0.432
Albumin (gm/dL)	2.8 ± 0.8 (2.8)	2.4 ± 0.9 (2.2)	0.004
Sodium (mmol/L)	134.7 ± 9.2 (135.4)	137.7 ± 7.9 (137.2)	0.074
Potassium(mmol/L)	4.2 ± 1.0 (4.1)	4.7 ± 1.1 (4.6)	0.020
Creatinine (mg/dL)	1.4 ± 1.9 (0.9)	3.3 ± 2.6 (2.7)	<0.001
pH	7.3 ± 0.1 (7.33)	7.2 ± 0.1 (7.2)	<0.001
pO2 (mmHg)	95.1 ± 27.1 (92)	102.1 ± 56.2 (88)	0.076
pCO2 (mmHg)	34.8 ± 8.2 (35)	31.6 ± 13.9 (28)	0.004
Bicarbonate (mmol/L)	21.0 ± 5.4 (21)	14.5 ± 6.7 (14.6)	<0.001

Cont. Table 1: Comparison of Demographic, Clinical Features, Hematological and Biochemical Parameters According to the Outcomes in Patients with AFE (n=111)

DISCUSSION

Non-JE etiologies are responsible for acute encephalitis syndrome in the state of Uttarakhand, tuberculosis and scrub typhus being responsible for 42.3% cases of AES. National vector borne disease control programme (NVBDCP) has categorized all AES cases as laboratory confirmed JE, probable JE, AES due to agents other than JE and AES due to unknown agents. (9) Not even a single case of laboratory-confirmed or probable JE-associated AES was found during the 12-month study period. This might be because of non-prevalence of JE in Garhwal region of Uttarakhand. Overall, 85.5 % cases of AES in our study had non-JE ethology whereas remaining 14.5 % had AES due to undetermined cause.

Also, virtually all ages were affected in contrast to mainly the children (less than 14 years of age) as mentioned in earlier studies. (10, 11) This disparity appears to be due to differences in patient selection, geographical differences in disease prevalence and non-inclusion of the pediatric population in our study group. In contrast to other studies observing AES mainly in rainy season predominantly during the monsoons, with a peak during August and September, subsequently declining in later half of November (12), we observed clustering of cases in rainy season and during winter. This appears because proportion of vector borne etiologies were less in the present study. High mosquito repellants usage at home maybe partly responsible, however, the impact of the same on the incidence of AES is questionable, especially in this part of the world with high prevalence of dengue like vector borne diseases. AES, long considered a rural phenomenon (2), appears to affect those residing in poor sanitary conditions prevalent even in the urban localities of India. More than 50% of our cases didn't dispose their garbage properly; proper individual disposal is nullified by poorly performing government agencies mainly responsible for the same.

Bacterial or tuberculous meningo-encephalitis are treatable and a few etiologies of AES are potentially vaccine-preventable (e.g. JEV). Scrub encephalitis, prevalent in Himalayan regions, poses a big diagnostic challenge but has an established treatment. Likewise, enteric encephalopathy and cerebral malaria are not uncommon but a credible database for the same is lacking. (13)

A survey from UP (India) implicated different viruses in 58% cases while 42% cases had an undetermined etiology. Among the viruses, JE (16%), dengue (11%), HSV (9%), mumps (9%), measles (9%) and varicella zoster (4%) were incriminated. A countrywide database on other viruses viz. Chandipura virus, West Nile virus, Nipah virus, Kyasanur Forest Disease Virus, enteroviruses, adenoviruses, Parvovirus B19 and Parvovirus 4 that have been responsible for regionally-limited outbreaks of AES (13), is lacking. Surveillance in the present scenario focusses more on untreatable and unknown causes of AES.

Scrub typhus, caused by *Orientia tsutsugamushi* is emerging as a leading cause of AES in India especially along the Himalayan belt. This is evident from the fact that 28 % of cases of scrub typhus in pediatric age group showed clinical or laboratory features of meningoencephalitis in one study group (14) and was responsible for one-fifth of all our cases. Dengue virus implicated in 10.8 % cases of AES (13) is known to cause encephalopathy as part of multi-organ dysfunction as well as by direct neurotropic effect; 9% of cases of AES in our study group had dengue infection. Our observations emphasize that identification of the specific etiological agent is important for understanding the natural history of disease and for proper management. The present study highlights the necessity of formulating region-specific guidelines of AES in order to improve the diagnostic efficacy, outcome and to capitalize on available sanctioned funds.

The limitation of our study was the short period of case inclusion resulting in an inherent selection bias attributed to environmental and climatic factors prevalent over a single year leading to non-identification of a few etiologies. The results of this small study group might not be extrapolatable to the entire population. Moreover, most of our diagnosis of non-tuberculous AES was serology-based and inconclusive to suggest direct neurotropic effect of these etiological agents. Nevertheless, this study has identified the major non-JE etiologies of AES in the state of Uttarakhand. Also, serology remains the mainstay diagnostic tool for the population on which the treatments and the outcomes are based. This study may initiate further research on the topic to validate or negate our observations contributing to the non-existent literature from the region. The strength of this study was inclusion of all cases based on WHO case definition of AES. Thorough diagnostic work-up led to a definitive diagnosis in 85% cases, and could challenge the JE-centricity of AES guidelines of our national agency.

Non-JE AES etiologies should also be sought in areas endemic for JE and given due credit as they constitute a significant number of AES cases and maybe responsible for the cases categorised as AES of undetermined etiology. This will ensure proper and specific management, reduce morbidity and mortality, formulate better health programmes, identify the at-risk population that may benefit from immunization, lay down strategies for disease prevention and implementation of appropriate control measures, especially during an outbreak.

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