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ACUTE ENCEPHALITIS SYNDROME IN CHILDREN: A DESCRIPTIVE CROSS-SECTIONAL STUDY IN A RURAL BASED TERTIARY CARE HOSPITAL IN INDIA

Paediatrics

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ABSTRACT

Background: Acute Encephalitis Syndrome (AES) is a group of clinically similar neurologic manifestations due to encephalitis. AES is an important cause of mortality and morbidity in children in various parts of India. Most of the study has been done in adult population. So, I have done this study to evaluate clinical profile, short-term outcome and changing trends of etiologies of acute encephalitis in children.

Methods: This is an institution-based descriptive cross-sectional study including sixty children aged one month to twelve years conducted over a period of one and half years in the pediatric department of a rural based medical college in India. Data collected in predesigned case record proforma and analysed with SPSS software version 25.

Results: Incidence rate 4 per 1000 patients per year with 2 to 6 years age group with males predominating. Important presenting complaints were fever, convulsion, abnormal behavior, rash, vomiting, headache, lethargy, aphasia and quadriparesis. Poor Glasgow coma score (GCS), meningeal sign and raised intra cranial pressure were important examination findings. Dengue and scrub typhus were important emerging etiologies replacing Japanese encephalitis. Overall mortality is around 13%.

Conclusions: All febrile children with altered sensorium should be investigated for central nervous system (CNS) infection, unless clear evidence of another diagnosis. Viruses are the main culprit with Dengue and Scrub typhus being the important emerging etiology. Timely diagnosis and treatment can reduce morbidity and mortality significantly.

KEYWORDS

Acute encephalitis syndrome, Japanese encephalitis, Changing trends, India.

INTRODUCTION

Acute encephalitis syndrome is a group of clinically similar neurologic manifestations due to encephalitis which is an important cause of mortality and morbidity in children in India.

According to World Health Organization (WHO) AES is defined as "A person of any age at any time of year presenting with acute onset of fever and change in mental status (including signs and symptoms such as confusion, disorientation, coma, or inability to talk) and/ or new onset of seizures (excluding simple febrile seizures). (1) This definition includes not only viral encephalitis, but also all the etiologies of fever and altered sensorium, such as bacterial meningitis, tubercular meningitis, cerebral malaria, acute disseminated encephalomyelitis (ADEM) etc.

Duration of illness of 14 days is termed as "Acute" as per Indian Academy of Paediatrician; (2) & not more than 5 to 7 days as per National Vector Borne Disease Control Programme.[3] Considering the huge burden of acute encephalitis worldwide, WHO has introduced surveillance programme to identify AES cases rather than only JE cases; thereby enhancing sensitivity of case detection. This approach is more feasible given the limitations of public health resources.(4)

We have carried out this study with aim to describe the detailed clinical profile, disease course, etiology, risk factors, demographic profile, geographic and seasonal variation & outcome, for better understanding the pediatric AES cases; to provide clinical clues to the physicians to identify the acute encephalitis cases at the earliest and considering the important non-JE etiologies to provide appropriate management accordingly.

METHODS

This is an institution based cross-sectional descriptive observational study conducted over a period of one and half year-from March'2019 to Auguat'2020 at the department of pediatric medicine in Bankura Sammilani Medical College & Hospital, Bankura, West Bengal, India. Total eighty-three patients with features of acute encephalitis were admitted. As per WHO guideline the minimum sample size required was 57, derived from the formula n= $[(Z1-\alpha/2)/\varepsilon]^2$ with relative precision(ε)-0.26 & standard normal variate(Z)-1.96 at 95% confidence interval. (5). Total 60 patients satisfying the inclusion criteria were included in this study. Written consent obtained from guardian of the children and confidentiality maintained. Case history and examination findings recorded in predesigned case record proforma. Data analyzed using IBM SPSS software version 25.

INCLUSION CRITERIA

a. Bacterial meningitis cases based on clinical features + CSF analysis ± neuroimaging.
b. Tubercular meningitis cases based on clinical features + CSF analysis ± neuroimaging.
c. Cerebral malaria cases based on clinical features + malaria parasite in peripheral blood smear and rapid diagnostic test.
d. Cases of ADEM based on clinical features + neuroimaging ± CSF study.
e. Cases of probable viral and other etiologies based on clinical features+ CSF analysis+ neuroimaging.
f. Age: one month to twelve years

EXCLUSION CRITERIA –

a. Age less than 1 months & >12 years.
b. AES in immune-compromised children
c. Rabies encephalitis
d. Chronic viral encephalitis like Sub acute sclerosing pan encephalitis (SSPE) etc.
e. Febrile seizures-simple or complex.
f. Recurrent episodes.
g. Neurodegenerative disorders
h. Metabolic disorders
i. Major congenital anomaly
j. Cases left hospital against medical advice and consent not given.

RESULTS

Total sixty patients out of eighty-three were included and evaluated. The following observations were made and documented.

Table 1 Cases based on age group and gender: (N=60)

	AGE GROUP		
GENDER	1 Month-2Years (%)	>2Years-≤6Years (%)	>6Years – 12Years (%)
Male=37(61.66)	13 (21.66)	14 (23.33)	10 (16.66)
Female=23(38.33)	8 (13.33)	9 (15)	6 (10)
Total=60	21 (35)	23 (38.33)	16 (26.66)

Table 1 showing age and gender-based distribution of AES cases.

Majority (38.33%) of the cases belong to two to six years age group with male (61.66%) predominance. Mean age of the cases were 4.5 years, Mean ± Standard deviation 4.5 ± 3.5 years.

Majority of the AES patients from rural area - 55 out of 60 (91.66%) and only 5 patients from urban area. P-value<0.0001 and Chi-square value 41.667 at degree of freedom (df) 1 shows significantly higher occurrence of acute encephalitis in rural population.

47 out of 60 AES patients (78.34%) belong to lower class of socioeconomic status. Socioeconomic distribution has been done according to Kuppuswamy scale. P-value 0.008, Chi-square value 7.118 at df 1 demonstrates significant presence of acute encephalitis cases in lower socioeconomic population.

56.66% AES patients belong to non-tribal and 43.34% from tribal ethnicity, this ethnic variation is not statistically significant as P-value 0.302 and chi-square value 1.067 at df 1.

Table 2 Symptoms in AES patients (N=60)

Symptoms	No. of patients (N%)
Fever	58 (96.66%)
Convulsion	34 (56.66%)
Abnormal Behaviour	9 (15%)
Rash	8 (13.33%)
Headache	7 (11.66%)
Vomiting	7 (11.66%)
Lethargy	5 (8.33%)
Not Feeding Well	5 (8.33%)
Weakness Of Limbs	3 (5%)
Inability To Talk	2 (3.33%)
Excessive Cry	2 (3.33%)

Table 2 shows frequency of common symptoms in AES patients.

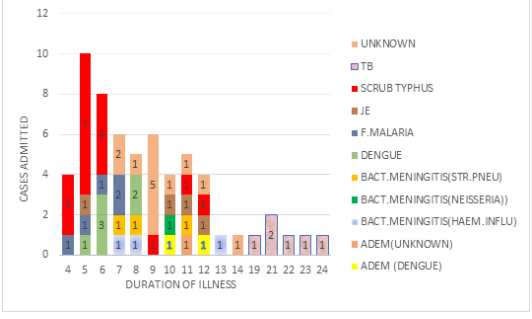

Figure 1 Duration of illness during hospital admission

Most of the AES cases with scrub typhus admitted in between 4th to 6th days of illness, only 3 cases admitted late in between 9 to12 days. Cerebral malaria cases admitted in between 4 to 7 days. JE cases came in 10th to 12th days, except 1 case who got admission on day 5 of illness. All the dengue cases admitted in between 5 to 8 days. The bacterial meningitis cases came by 8th to 14th days of illness. 3 ADEM cases took admission in between 12th to 14th days of illness and all the unknown causes of AES came in between 8th to 15th days. Tuberculosis patients came hospital very late, after 3rd weeks of illness.

76.66% children were immunised with measles containing vaccine and only 48.33% children were immunised with Japanese encephalitis vaccine as per National immunisation schedule. The information was verified seeing their immunisation card. No history of any recent immunisation in any of the viral AES cases found in this study.

Table 3 Glasgow coma score during presentation

Glasgow coma score gradation	Patients (N=60) (%)
Mild (13-15)	3 (5%)
Moderate (9-12)	24 (40%)
Severe (3-8)	33 (55%)
Mean ± SD	7.7 ± 2.15

Table 3 shows level of consciousness as per Glasgow coma score during hospitalisation.

Significant examination findings in AES were meningeal signs in 66.66% patients, raised intracranial pressure and hepatomegaly in 61.66% and 63.33% cases, splenomegaly and lymphadenopathy in 26.66% and 20% cases respectively. Indirect ophthalmoscopy was done to detect papilledema for assessment of raised intracranial tension.

Table 4 Different etiologies of AES (N=60)

Etiology	Patients Affected (N%)
Viral (Known & Unknown)	25 (41.66%)
Scrub Typhus	17 (28.33%)
Bacterial	7 (11.66%)
Tuberculosis	6 (10%)
Malaria	5 (8.33%)

Table 4 showing viral etiologies to be most common (41.66%) followed by scrub typhus (28.33%) causing AES in children.

Table 5 Viral etiologies in AES Patients (n=25) (N=60)

Etiology	No. of Patients (N%)
Japanese Encephalitis (Je)	5 (8.33%)
Dengue	8(13.33%)
Herpes Simplex (HSV)	3(5.00%%)
Mumps	2(3.33%)
Unknown	7(11.66%%)
Total	25(41.66%)

Table 5 showing Dengue as the most common viral etiology causing AES, even more than Japanese encephalitis. 7 viral encephalitis cases (11.66%) remained unknown due to lack of viral diagnostics.

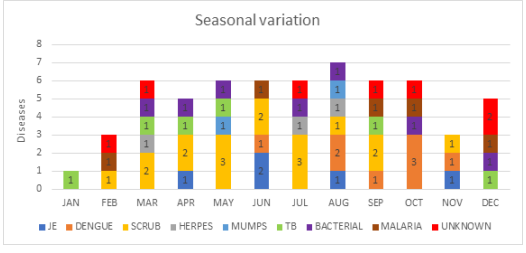

Figure 2 Seasonal variation of different etiologies causing AES

Most of the AES cases admitted in summer months (31.66%), followed by monsoon (28.33%) and autumn (25%) season. Least number of cases admitted in winter. Japanese encephalitis cases are seen in premonsoon, monsoon and post monsoon season, with higher cases (3 cases) in monsoon. Scrub typhus cases are seen round the year with more cases in the season as in JE.

Dengue cases are seen mainly in monsoon and with increased frequency in post monsoon season. Malaria, Tuberculosis, Bacterial and AES due to unknown etiologies are seen round the year without any seasonal preponderance. 3 herpes simplex encephalitis cases admitted, 1 in summer and 2 in monsoon. Mumps cases are seen sporadically, one in May and another in August.

56.1% of children with AES had leucocytosis. 16.4% children had leucocyte count within normal range- 4000 – 11000 cells/mm³ and only 9.5% children developed leucopenia. Mean± SD of leucocyte count 11807± 4500. 51.66% patients with AES due to various causes had thrombocytopenia. 21.6% patients showed raised total bilirubin level ≥1.5 mg/dl. 13.33% cases were seen with deranged renal function. 38.33% AES patients found abnormality in neuroimaging-CT or MRI brain, done during the period of hospital stay.

Table 6 Comparison of Mean values of basic laboratory parameters

Parameters (Mean)	Etiologies				
	Scrub	JE	Dengue	TB	Bacteria
Hemoglobin (gm/dl)	10.58	10.76	10.75	6.95	11.97
Leucocyte (Cells/mm³)	10381	13306	10312	15990	18543
Platelet (Cells/mm³)	1.48	2.02	0.81	2.1	3.23
Bilirubin (mg/dl)	1.39	0.94	0.88	1.43	0.86
Culture	Negative	Negative	Dengue	Positive	Positive
Serology	Positive	Positive	Positive	--------	Negative

On comparison of mean values of basic laboratory parameters of different etiologies of AES, severe anemia with hemoglobin below 7gm/dl has been noted only in TB encephalitis cases. Leucocytosis is evident in Tubercular and bacterial and Japanese encephalitis cases. Thrombocytopenia was significant in dengue encephalitis cases with mean platelet count 0.81 lakhs/mm³. Thrombocytopenia also detected in scrub typhus cases with mean platelet value 1.34 lakhs/mm³. Total bilirubin was within normal range in all the case, except in scrub typhus where 17.60% cases had total bilirubin ≥1.5mg/dl.

Table 7 Comparison of CSF study of the most important etiologies

Parameters	Japanese encephalitis	Dengue	Scrub typhus
Cell Count (cell/mm³)	20±6	34±21	24.53±9.01
Cell Type	All Lymphocytes	All Lymphocytes	All Lymphocytes
Protein (mg/dl)	48.8±9.44	48±10	53.82±11.84
Sugar (mg/dl)	88.6±11.79	90±10	89.59±12.30
Gram/AFB staining	Negative	Negative	Negative

Table 7 showing cerebrospinal fluid study in dengue, Japanese encephalitis and scrub typhus encephalitis cases revealed lymphocytic pleocytosis, mildly elevated protein, normal sugar; Gram and Acid-fast bacilli (AFB) staining were negative.

Magnetic resonance imaging of brain showed involvement of - basal ganglia and thalamus in all the 5 Japanese encephalitis cases; basal ganglia, thalamus and temporal lobes involvement in 3 dengue and non-specific findings in 3 scrub typhus encephalitis cases. 8 dengue and 14 Scrub typhus encephalitis patients showed normal neuroimaging. One ADEM case showed multifocal involvement in both cerebral hemisphere, cortical grey matter, thalamus, basal ganglia, brain stem and spinal cord while another patient showed normal neuroimaging. Central nervous system tuberculosis cases showed basal exudation and communicating hydrocephalus in 2 cases and only basal exudation in 4 cases.

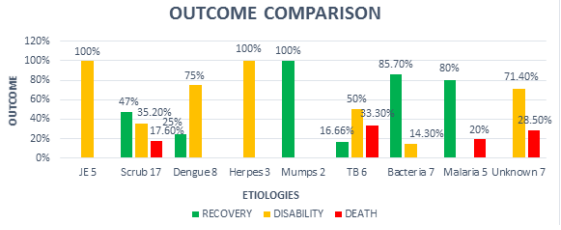

Figure 3 Outcome comparison of AES cases due to different etiologies

All the 5 JE cases survived but all of them discharged with cognitive, motor or neuropsychiatric disabilities. Same thing happened with all the 3 HSV cases. Among 17 Scrub typhus cases, 8 cases (13.33%) recovered completely, 6 cases (10%) discharged with disabilities and 3 cases (5%) died. In dengue encephalitis 2 out of 8 cases recovered completely and 6 cases including 2 ADEM cases have been discharged with disabilities. In our study 2 Mumps AES cases found with 100% recovery. Amongst 6 Tuberculosis cases, 1 case (1.66%) recovered completely, 3 cases (5%) recovered with disabilities and 2 cases (3.33%) succumbed to their disease. Bacterial meningoencephalitis showed complete cure rate in 85.7% and 14.3% (1 case) discharged with disability. No death occurred in bacterial encephalitis. In 5 cerebral malaria cases, 80% (4 cases) recovered fully with 1 death. Etiology of 7 cases couldn't be ascertained, of which 5 cases (71.4%) discharged with disabilities and 2 cases (28.5%) died.

DISCUSSION

Acute encephalitis syndrome is a medical and neurological emergency, require- immediate life support, identification of etiology and administration of specific therapy whenever possible.

The incidence rate (IR) of acute encephalitis syndrome ranges between 3.5 and 7.4 cases per 100,000 patient-years. An IR of 145-185 recorded during an epidemic in Nepal in 1997. A hospital-based study from Andhra Pradesh, India suggested IR 1. In this study, IR of AES detected 4 cases per 1000 patients- year. This higher IR may be due to being a hospital-based study in an endemic area.

In this study AES occurred mostly in age group of >2years-6years (38.33%) followed by 35% involvement in age group >1month – 2 years and >6 years – 12 yrs affected in 26.66% cases. Mean age estimated as 4.4±3.5years. Results of our study is consistent with study by Khinchi et.al in Nepal in 2010.

Male: female ratio 1.6 :1 is obtained. Male patients suffering from AES constitutes 61.66% and female 38.33%. p-value 0.071, Chi-square value 3.267 at degree of freedom 1. So statistically the gender difference was insignificant. Study by Bandyopadhyay et al in 2013 in Kolkata showed 59.92% males and 41.08% female, supports my study. (11) Another study conducted by Manish et.al in 2012 at kushinagar India showed 57% of male and Khinchi et.al also showed in 2010 a similar pattern of 55 % males suffering from AES.(4)(10)

Most of the AES patients are from rural (91.67%) area and the difference in geographical distribution is statistically significant with p-value <0.0001, Chi-square value 41.6 at the degree of freedom 1. Our findings are consistent with reports by Anuradha et al, Benakappa et al and Reuben et al.(12)[13][14]

78.34% of acute encephalitis patients belong to lower socioeconomic class and 43.34% of them are from tribal population, and this is statistically significant with p-value-0.008, Chi-square value 7.118 at degree of freedom 1.

Immunization coverage for Measles containing vaccine and Japanese encephalitis vaccine was in 76.66% and 48.34% cases respectively. No history of recent immunization noted in any of the known or unknown viral AES cases.

The commonest presenting complaint was fever (96.66%) and convulsion (56.66%). Other important presenting complaints were abnormal behavior, rash, vomiting, headache, lethargy, aphasia and quadriparesis etc. GCS score at the time of admission was in 3-8 range in 55% and 9-12 in 40% AES cases. Mean GCS estimated as mean±SD 7.75±2.15. Meningeal signs and signs of raised intracranial pressure noted in 66.66% and 61.66% cases. Study by Kakoti G et.al in 2013 showed fever in all AES cases followed by convulsion in 82% of cases. (15) Gupta et.al showed convulsion in 79% cases of AES.(16)

Viral etiology detected in 41.66% cases followed by Rickettsial infection in 28.33% cases. Occurrence of bacterial mening oencephalitis found more prevalent (11.66%) than central nervous system tuberculosis (10%) and cerebral malaria (8.33%). Dengue virus (13.33%) identified as the most predominant viral causative agent of AES. Japanese encephalitis, Herpes simplex, Mumps and unknown causes comprises 8.33%, 5%, 3.33% and 11.66% cases respectively. Rayamajhi et.al showed viral etiology in 78% cases with 23% Japanese encephalitis and 56% viruses were remained unidentified, which is much higher than our study. In 2014 report published by Parul Jain et. al from north India showed JE in 16.2% and HSV in 9.3% of cases which is similar to our findings.(17)[18]

In our study thrombocytopenia recorded as a consistent feature in dengue and scrub typhus cases.

Cerebrospinal fluid study in dengue, Japanese encephalitis and scrub typhus encephalitis cases revealed lymphocytic pleocytosis with mildly elevated protein in majority and other parameters were normal.

Magnetic resonance imaging of brain in Japanese encephalitis showed basal ganglia and thalamic changes which were supportive for diagnosis; but in dengue and scrub typhus- findings were non-specific. One ADEM case showed diffuse multifocal involvement of brain parenchyma, brain stem and spinal cord while another patient showed normal neuroimaging. Two tuberculosis cases showed communicating hydrocephalus, and basal exudation in all 6 cases.

Eight patients (13.33%) died during the hospital stay. Three died due to scrub typhus, two died of tuberculosis, two from unknown etiology and one due to cerebral malaria. Case fatality rate of scrub typhus 17.64%, Tuberculosis 33.33%, cerebral malaria 20% and unknown agents 28.57%. Khinchi et.al found mortality rate around 21.3% in AES. (10) Kakoti G et.al reported mortality in 14.7%, similar to our findings.(15)

Prospective follow up study is required to comment on long term

outcome. It would allow detection of persistent subtle deficits, such as cognitive and neuropsychological impairment, and their impact on scholastic and work performance, and this is an area for further research.

CONCLUSION

All febrile children with altered behaviour or decreased level of consciousness should be investigated for central nervous system infection, unless evidence of another diagnosis. Viral etiology is the main culprit, so virus diagnostics should be widely available. Dengue and Scrub typhus are the important emerging etiology with declining Japanese encephalitis cases. Central nervous system tuberculosis and cerebral malaria are still important cause of acute encephalitis. Timely diagnosis and treatment can reduce morbidity and mortality significantly. Coverage of primary immunisation is to be increased.

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