Section: Miscellaneous

Original Research Article

CLINICO-ETIOLOGICAL PROFILE OF ACUTE ENCEPHALITIS SYNDROME BEYOND JAPANESE ENCEPHALITIS: A HOSPITAL-BASED STUDY IN ASSAM, NORTH EAST INDIA

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ABSTRAC

Background: Annual outbreaks of Acute Encephalitis Syndrome (AES) continue to pose a challenging public health issue in Assam. While Japanese Encephalitis (JE) accounts for a significant proportion of cases, an appreciable number of AES cases still remain of unknown aetiology. This study aims to **identify the aetiology** and clinical profile of acute encephalitis cases beyond Japanese Encephalitis cases.

Materials and Methods: This study was prospective and observational, conducted in the Microbiology department including all AES patients (as per WHO case definition) admitted to the Medicine and Paediatrics departments of Tezpur Medical College, Tezpur, Assam in between January 2019 to December 2021. Under strict aseptic conditions, both cerebrospinal fluid (1–2 mL) and serum (2 mL) samples were collected. Samples from all cases were tested for JE. Based on reagent availability, subsets of samples were tested for Scrub typhus, Chikungunya, Leptospira and West Nile virus.

Results: Out of 475 AES cases, 252 (53.05%) were male and 223 (46.94%) female. All 475 cases were tested for JE, with 133 (28%) testing positive. Among the remaining cases West Nile: 2 out of 73 tested positive (2.7%), Scrub Typhus: 39 out of 276 positive (14.1%), Chikungunya: 12 out of 203 positive (5.9%), Leptospira: 26 out of 263 positive (9.88%). Thus aetiology could be established in 212 (44.63%) cases and the rest of samples of 263 cases (55.36%), the aetiology could not be established. Incidence of AES cases among paediatric age group (1-15 yrs.) is found to be 39.3% while JE incidence is 48.12%. Fever and change in mental status was the presenting symptom for all cases. Followed by headache 52.2%, seizure 35.3%, and neck rigidity 25.8%. Unconsciousness 22.1%. Most of the cases were seen from June to October with peak incidence in July(AES 39.78% and JE 63.15%). Majority of the cases are from rural areas (87.5%). Mortality among JE positive cases was higher (15.06%) while among Non JE cases was 8.18% and overall mortality was 10.1%. Vaccination coverage among AES and JE cases is 42.5% and 50.7% respectively.

Conclusion: A significant proportion of AES cases in Assam still remain of unknown aetiology. Strengthening diagnostic capabilities and expanding testing for emerging pathogens is crucial to better understand and manage AES.

Keywords: Acute Encephalitis Syndrome, Japanese Encephalitis, AES, JE.

INTRODUCTION

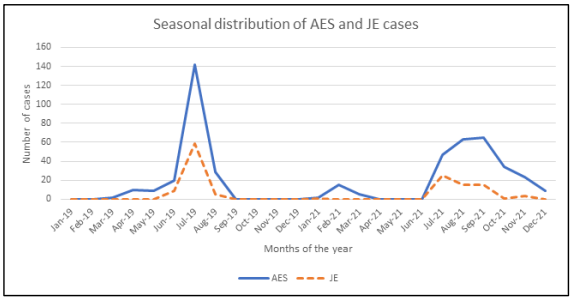
Acute Encephalitis Syndrome (AES) is a clinical condition characterized by inflammation of the brain, with a rapid onset of fever and altered mental status. Symptoms may include confusion, disorientation, and coma with or without convulsions (as per the WHO definition of AES.[1] The condition can be

caused by a wide range of pathogens.[2] including viruses such as Japanese Encephalitis (JE), Herpes Simplex Virus, Enteroviruses, Dengue, West Nile Virus, and Chikungunya, as well as non-viral agents like Scrub Typhus, Leptospirosis, malaria, bacterial meningoencephalitis, fungi, and even toxins (e.g., toxins from litchi fruit). In India, Japanese Encephalitis (JE) remains the most significant viral cause of AES, accounting for 20% to 50% of cases in various studies.[4,7,11,12,16,17] particularly in endemic regions like Assam. The first major JE outbreak in Assam was recorded in 1978 in Lakhimpur district.[3] and the outbreak has been occurring intermittently since then. JE is a Flavi viral infection primarily transmitted by Culex species mosquitoes. The virus's life cycle is maintained between mosquitoes and amplifying hosts such as pigs and certain birds (e.g., herons and sparrows), while humans are accidental, dead-end hosts.[1] JE affects predominantly the children and young adults in the age group of 5 to 15 years.[1] Specific treatment for AES is still to be identified. Management typically requires hospitalization, intensive care and supportive therapy. The disease is a significant public health issue due to its high morbidity and mortality, with case fatality rates ranging from 10% to over 30%,[1] and the potential for long-term neurological sequelae. The National Vector Borne Disease Control Programme (NVBDCP) has been actively monitoring AES cases since the early 2000 with Assam consistently reporting a substantial burden. For instance, between 2014 and 2018, Assam reported between 10,867 and 13,672 AES cases to the NVBDCP with JE accounting for approximately 14% to 18% of these cases.[4] The tropical climate, high mosquito density, rural agrarian lifestyle, and pig-rearing practices in Assam contribute to sustained transmission. JE vaccination (SA 14-14-2) campaign was launched in 2006 in Siva sagar district in Assam for the first time and introduced into the Universal Immunization Programme (UIP) in 2011 in Assam.[18] Outbreaks continue to occur indicating gaps in vaccine coverage, public awareness, and vector control. This necessitates an improved surveillance, early diagnosis, and effective case management. The aim of this study is to assess the epidemiological and clinical characteristics of AES in Assam beyond Japanese Encephalitis, and to find out outcomes, risk factors, and preventive strategies in the affected population.

MATERIALS AND METHODS

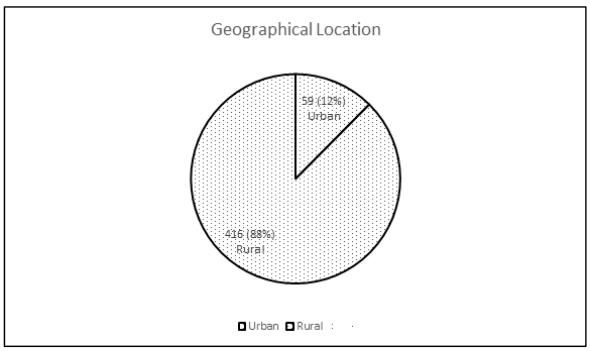
This prospective hospital based observational study was carried out in the Department of Microbiology Tezpur Medical College in collaboration with the Department of Paediatrics and Medicine. The period of Study was from January 2019 to December 2021 but study could not be done during 2020 due to Covid19 pandemic. The study included all AES patients of different age groups admitted to the Medicine and Paediatrics department. The case definition of Acute Encephalic Syndrome (AES) is taken as per WHO guideline i.e acute onset of fever and change of mental status including symptom such as confusion, disorientation and inability to talk and /or new onset of seizure excluding febrile convulsions in a person of any age at any time of the year. Exclusion criteria were known cases of space occupying lesion, head injuring and repetitive AES cases and bacterial meningitis. Cases were enrolled using standard case investigation form after obtaining informed consent from patients. In minor patient's, consent was obtained from parents or guardians. Institutional ethics committee clearance was taken. Both CSF (1-2 ml) and serum sample (2ml) were collected under strict asepsis. In whom lumber puncture was not possible or was contra indicated, only serum samples were collected. Blood samples were left at room temperature for 30 min for clot formation then serum was separated by centrifugation. Both were stored at 4-8-degree C if tested within 48 hrs. If not tested within the above period, they were kept in a deep refrigerator at -80C for a long time. All the samples were tested for JE and depending on availability of reagent, a different number of samples were tested for Scrub typhus, West Nile, Chikungunya and Leptospira. IgM antibody detection by enzyme linked immunosorbent assay (ELIZA) for above etiological agents was used. Samples were reported as positive, negative and equivocal. Data was compiled and analysed using Microsoft Excel 2016.

RESULTS



Graph 1: Seasonal distribution of AES and JE cases

Graph1 shows distribution of AES cases and JE cases around the year. In 2019 the majority of AES cases were from Jun to August and all JE cases were detected during those months only. In 2021 AES started late i.e from July and continued till November. Likewise, JE also detected most between July and September. Overall most of the cases were seen from the month of June to October. Highest incidence was in July (AES 39.78% and JE 63.15%) followed by August (AES 19.36% and JE 15.03%), September (AES 13.68% and JE 11.27%), Jun (AES 4.21% and JE 6.76%). A negligible number of cases were enrolled from November to April.



Graph 2: Geographical location

Graph 2 shows that the majority of the cases from rural areas 87.5% as compared to 12.4% were from urban areas.

Table 1: Positivity of Different Etiological Agents:

Test	No of sample	Positive	Positivity percentage
JE	475	133	28%
Scrub Typhus	276	39	14.1%
Chickungunya	203	12	5.9%
Leptospira	263	26	9.88%
West nile	73	2	2.7%

Table 1 shows the positivity percentage of different aetiological agents. 475 clinically suspected AES cases were enrolled in the study out of which 212 cases were included in 2019 and 263cases in 2021, due to COVID pandemic during 2020 no cases could be enrolled. All the cases were subjected to a test for JE and 133 (28%) cases were diagnosed as JE positive in the study period (Table 1).

Out of non JE 343cases, tests for West Nile, Scrub typhus, Chikungunya and Leptospira was done. Depending upon availability of reagents the number of samples were different for different pathogens. Out of 276 samples tested for Scrub Typhus 39were positive (14.1% positivity). Like that Leptospira was detected in 26 out of 263 samples (9.88%), Chikungunya in 12 out of 203 samples (5.9%) and West Nile in 2 out of 73 cases (2.7%) (Table1).

Table 2: Percentage of Identifiable Causes

Name of isolates	No	Total	Percentage
Je	133	212	44.63%
West Nile	2		
Scrub Typhus	39		
chickungunya	12		
Leptospira	26		
No aetiology found	263	263	55.36%

Table 2 is showing the percentage of identifiable causes. From here it is evident that aetiology could be established in 212 out of total 475 (44.63%) cases where JE 133, West Nile 2, Scrub typhus 39, chikungunya 12 and leptospira 26 in number. In the rest of the samples of 263 (55.36%), aetiology could not be established.

Table 3: Sex and Age Distribution of AES and JE Cases

Age in years	AES				JE			
	Male	Female	Total	percentage	Male	Female	Total	percentage
0-15	95	92	187	39.3%	31	33	64	48.12%
15-30	51	53	104	21.8%	10	9	19	14.28%
30-45	53	40	93	19.5%	13	9	22	16.54%
45-60	32	20	52	10.9%	9	3	12	9.02%
>60	21	18	39	8.2%	8	8	16	12.03%
Total	252	223	475	100%	71	62	133	100%

Table 3 is about the distribution of AES and JE cases. Out of total 475 AES cases 252 (53.05%) were male and 223(46.94%) were female. Likewise, among 133 JE positive cases 71 cases (53.3%) were male and 62cases (46.6%) were female. Regarding age distribution, among the 1-15yrs age group, the incidence of AES is found to be 39.3% while JE incidence is 48.12%. Likewise, among the 15-30yrs age group AES is 21.8% and JE is 14.28%, 30-45yrs age group AES 19.5% and JE 16.54%, 45-60yrs age group AES 10.9%. And JE 9.02%, among >60yrs group AES 8.2% and JE 12.03%.

Table 4: Clinical Presentation of AES Cases

Serial no	Clinical features	Total	Percentage
1	Fever	475	100%
2	Change in mental status	475	100%
3	Seizure	168	35.3%
4	Headache	248	52.2%
5	Paralysis	22	4.6%
6	Unconsciousness	105	22.1%
7	Neck rigidity	123	25.8%

Table 4 is showing clinical presentations of AES cases. From the table it is evident that fever with change in mental status were the presenting symptom for all the cases. Other symptoms were headache 52.2%, seizure 35.3%, and neck rigidity 25.8%. Unconsciousness 22.1% and paralysis 4.6%.

Table 5: Distribution of Cases from Different District

District	AES		JE	
	Number	Percentage	Number	Percentage
Sonitpur	301	63.36%	79	59.3%
Biswanath	83	17.47%	29	21.80%
Nagaon	39	8.21%	9	1.89%
Udalguri	32	6.73%	10	2.10%
Darrang	10	2.10%	2	0.42%
West kameng	5	1.05%	3	0.63%
Lakhimpur	3	0.63%	1	0.21%
Karbi angong	2	0.42%	0	0
Total	475	100%	133	100%

Table 5 shows distribution of cases from different districts. Most of the AES cases were from Sonitpur district (63.36%) where the medical college is situated and study was conducted, followed by neighbouring district Biswnath (17.47%), Nagaon (8.21%), Udalguri(6.73%) and Darrang 2.10% . Few number of cases were also coming from far away district like Lakhimpur(0.63%), Karbi angling(0.42%) and also from West Kameng district of Arunachal Pradesh(1.05%) Likewise, among JE positive cases incidence was in Sonitpur 59.3%, Biswath 21.80%, Udalguri 2.1% ,Nagaon 1.89%, Darrang0.42%,,Lakhimpur 0.21%, West Kameng 0.63% and both the two cases from Karbi Anglong are JE negative.

Table 6: Mortality among JE and NON JE Cases

Year	Non JE cases			JE positive cases			All AES cases		
	No of cases	No of death	Percent	No of cases	No of death	percent	No	No of death	percent
2019	139 (54)	10 (8)	7.19%	73 (36)	11 (4)	15.06%	212 (90)	21 (12)	9.90%
2021	203 (81)	18 (11)	8.86.2%	60 (31)	9 (3)	15%	263 (112)	27 (14)	10.2%
Total	342 (135)	28 (19)	8.18%	133 (67)	20 (7)	15.03%	475 202	48 (26)	10.1%

Table6 shows mortality percentage among JE and non JE cases. Mortality among JE positive cases was higher which was 15.06% while among Non JE cases was 8.18% and overall mortality of AES was 10.1%.

Table 7: JE Vaccination Status among AES (JE and Non JE Cases)

Year	Non JE cases		Non JE death		JE Positive cases		JE positive death	
	No of cases	Vaccinated	No of cases	vaccinated	No of cases	vaccinated	No of cases	vaccinated
2019	139	54	10	8	73	36	11	4
2021	203	81	18	11	60	31	9	3
Total	342	135	28	19	133	67	20	7

Table 7 shows vaccination status among AES. Out of 133 JE positive cases JE vaccine was taken by 67 (50.3%) and among Non JE cases vaccination was for 135 (39.47%). Among 48 cases of AES death, 20 were JE positive while the other 28 were JE negative. Among JE negative death vaccination was 19 (67%) while among 20 JE positive cases 7 were vaccinated (35%).

DISCUSSION

Japanese Encephalitis (JE) remains the commonest cause of Acute Encephalitic Syndrome (AES) in this region. In this study, JE accounted for 28% of cases, which is comparable to findings by [4]Ravi V. et al. (17.7%) and [12]Tiwari A.K. et al (22.04%). However, some other studies have reported higher incidences

such as [7]Medhi M. et al (40.7%) [15]Dihingia et al (50%), [16]Ahmed R.A. et al. (54.39%), and [11]Phukan A.C. et al. (53.7%). This reduction in positivity for JE may be related to improved preventive measures including increased public awareness, use of mosquito nets, vector control efforts, and widespread vaccination. The aetiology of AES appears to be multifactorial. In our study, a definitive aetiology was established in 44.63% of cases, while 55.36% remained undiagnosed. This is consistent with findings by [4]Ravi et al who identified causes in 40.3% of cases. In contrast, [5]Jain P. et al. were able to determine the aetiology in 58.4% of cases. Besides JE, Scrub Typhus was identified in 14.1% of cases, similar to the 18.5% reported by [4]Ravi V. et al although [13]Khan et al. reported a lower prevalence of 8.6%. West Nile virus was identified in 2.7% of cases compared to 0.7% in the study by [4]V.Ravi et al. and 11.6% reported by [20]Khan S.A et al. Leptospira was detected in 9.88% of our cases, [4]Ravi et al. found in 2.4% and [10]Khan SA et al (4.06%)whereas [18]Sen S.S et al reported a much higher rate of 39%. Chikungunya was identified in 5.9% of our cases, aligning closely with the 4.8% reported by 4Ravi V et al. Differences in diagnostic yields across studies may be accredited to the availability and use of various testing methods and variations in regional pathogen prevalence. In our study, no significant difference in the incidence of Acute Encephalitic Syndrome (AES) was observed between sexes. Males constituted 53.05% of cases, while females for 46.94%, which is comparable to findings of other studies such as [12]Tiwari AK et al. (male: 56.4%, female: 43.5%) and [6]Das B.R. et al. (male: 55.7%, female: 44.3%). However, some other studies have reported a clear male preponderance, including [14]Rathore S.K. et al. (61.9% male), [7]Medhi M. et al. (62.04% male), [16]Ahmed R.A. et al. (61.8% male). In terms of age distribution, our study found that 37.8% of AES cases occurred in the paediatric age group (below 15 years), which aligns with [16]Ahmed R.A. et al (25.8%) but contrasts with studies like [6]Das B.R. et al. (84%) and [14]Rathore S.K. et al. (72.2%), which reported much higher paediatric involvement. However, positivity of Japanese Encephalitis (JE) was highest (48.12%) among children under 15 years in our study which is in contrast to the findings of 19Patgiri S.J. et al who reported a JE positivity rate of 28.6% in this age group. Clinically 100% of the cases presented with fever and change in mental status similar to [6]Das BR et al and [7]Mehdi M at al. This is followed by headache 52.2%, ([7]Medhi M 65.6%), Seizure 35.3 %([7]Medhi M et al 45.4%, [6]Das BR et al 56.4 %), Neck frigidity 25.8 %,([6]Das BR et al 69.3%, [7]Medhi M et al 56.5%), Unconsciousness 22.1%. [7]Medhi M et al 48.9%) and paralysis is seen in only 4.6% similar to [19]Patgiri SJ et al 4.2%, [6]Das BR et al 2.9% and [7]Medhi M et al 11.06%. The study showed a clear clustering of Acute Encephalitic Syndrome cases during the monsoon season beginning in June with a peak in July and August, may continue till September-October. This pattern is similar with findings from other studies conducted in Assam like [7]Medhi M, 11Phukan A.C., [6]Das B.R., and [19]Patgiri S.J. With the onset of winter, the number of AES cases declined. Although the incidence of AES persisted during the winter months, Japanese Encephalitis were not reported from December to June. This suggests that AES cases coming during this period are likely of non-JE origin. The outbreaks AES/JE coincide with monsoon post monsoon period because during this season the vector density goes up. In our study we found that 87.5% cases were coming from rural areas which was like other studies [6]Das B R et al (94.3%), [11]Phukan AC et al (96.3%). This rural predominance is likely because of the abundance of paddy fields and water-logged environments that facilitate mosquito breeding. Additionally, rural pig farming often occurs in close proximity to human dwellings and poor usage of mosquito nets and repellents also contributes to higher infection rates in rural population. The overall mortality rate in AES cases in our study was 10.1%, while the mortality rate among JE cases was higher at 15.06%. These findings are consistent with other studies: [7]Medhi M. (13.58%), [9]Kalita D. (13.2%), [5]Jain P. (15%), and [6]Das B R. (14%). However, higher mortality rates have been reported in regions like Sivasagar [16]Ahmed RA et al (13–45% between 2011–2020) as well as by [12]Tiwari A.K. (AES: 35%, JE: 22%), 17Dihingia P. (24.3%), and [19]Patgiri S.J. (AES: 34.6%, JE: 29.9%). In the study vaccination coverage among AES and JE cases is 42.5% and 50.7% respectively but vaccination among dead AES and JE cases is 54.1% and 35% respectively. Das Br et al reported vaccination only in 4.1% cases in dead JE positive cases indicating vaccination coverage is improving in our study.

CONCLUSION

AES is still a leading cause of mortality and morbidity in public health. Among AES, non JE cases are more than JE cases. Overall incidence of AES among paediatric age is reducing, vaccination needed to improve, mortality among JE positive cases are higher than non JE cases.

Limitation of the study: Since the study is hospital based, the true picture of the community may not be reflected. Further study is needed with a large sample size including a wider diagnostic facility.

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