Epidemiology of Acute Encephalitis Syndrome in India: Changing Paradigm and Implication for Control

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Abstract

The burden of Acute Encephalitis Syndrome (AES) and its potential implication on human health cannot be overemphasized. Conceptualization of its changing epidemiology particularly in the context of its varied aetiology, introduction of new genotype of Japanese encephalitis (JE), expansion to newer areas, occurrence of JE cases in older population, trend of occurrence of JE following mass vaccination campaign, clinical spectrum of the disease, trend in case fatality rate, socio- economic context, seasonality and environmental factors and associated risk factors like under- nutrition in children have been dealt with. Based on the current understanding, the review highlights its implication in addressing strategies for prevention and control of AES in India.

Keywords: **Japanese Encephalitis (JE), Acute Encephalitis Syndrome (AES), Aetiology, Case Fatality Rate, Implication.**

Introduction

Japanese Encephalitis (JE), the leading cause of viral neurologic disease is of public health concern. The virus was first described in Japan in 1871, and subsequently characterized for the first time in the year 1943. The disease at present is reported from South Asia, South- East Asia, East Asia and the Pacific region.[1] At least three billion people live in countries where JE virus is endemic.[2] As per conservative estimate 50,000 to 175,000[4] cases are reported every year with 10,000 to 15,000 deaths annually[1,3].

The history of Acute Encephalitis Syndrome (AES) in India over decades has been considered to be parallel to that of JE. Large numbers of cases have increasingly been reported with isolated confirmation of JE. In India, JE Virus was first isolated in humans in Vellore (previously North-Arcot) district of Tamil Nadu in 1955.[5]Since the large outbreak in the districts of Bankura and Burdwan in West Bengal in 1973[6], JE Virus has been reported from different parts of the country.[7, 8]

Uttar Pradesh in Northern India experienced outbreak of JE for the first time in 1978. In the same year, Japanese Encephalitis Virus (JEV) was reported from the State of Assam. In 1982, the disease occurred for the first time in the western coastal region of Goa.[9] Japanese Encephalitis Virus was found in Andhra Pradesh in 1997.[10] A major outbreak occurred in 2005 in Uttar Pradesh affecting 5737 persons including 1344 deaths.[11] In 2006, an outbreak of viral encephalitis was reported from April to October from predominantly Gorakhpur and five adjoining districts of eastern Uttar Pradesh viz., Maharajganj, Kushinagar, Sant Kabir Nagar, Siddharthnagar, and Deoria, and two adjoining districts of Gopalganj and West Champaran in Bihar where JE was known to be endemic. 1,912 cases of viral encephalitis occurred in these areas, and 411 (21.5%) people died during the outbreak.[12]

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There was no regular reporting of JE positive cases in India till 2005; it was mainly outbreak-based surveillance. After 2005, since the major outbreak in Gorakhpur and adjoining districts of Eastern Uttar Pradesh, regular reporting of AES and JE positive cases through routine sentinel site based surveillance system was thought to be the utmost necessity and therefore, National Vector Borne Disease Control Programme (NVBDCP) as the national nodal agency took up the challenge of establishing 51 sentinel sites across 15 endemic states during 2006- 2007. This major initiative undertaken by the programme helped surveillance sites to carry out laboratory diagnosis of JE based on IgM antibody captured ELISA technique, which were made available to the surveillance sites in the country for regular reporting of JE cases. This system started reporting AES and laboratory confirmed JE cases to segregate separately the total AES and JE cases. The number of laboratory based sentinel sites has increased over the years from 51 to 85 till June 2014.

Change in etiologic understanding of AES: the Agent

AES is considered to be a group of disease condition characterized by onset of an acute febrile illness and a change in mental status (such as confusion, disorientation, inability to talk, and coma) with or without new onset seizures, excluding simple febrile seizures.

Figure 1.AES/ JE cases from 2008- 2013 in the country

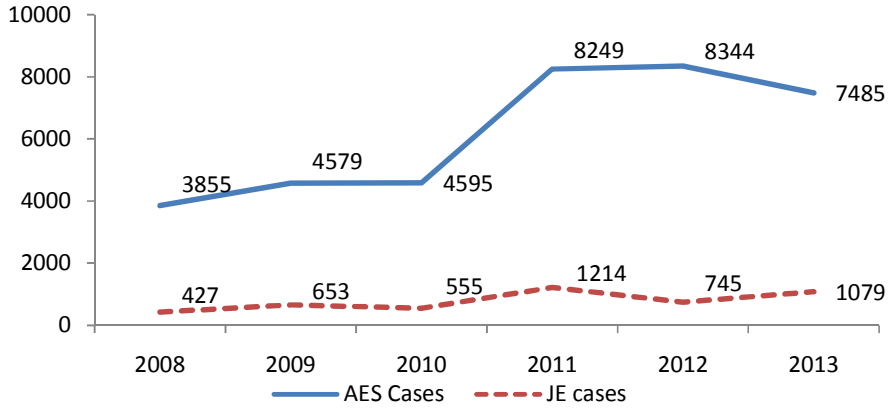


Fig. 1 represents the number of AES and JE positive cases in India since 2008 collected, collated and analysed through this established routine surveillance system between 2008 to 2013.[13] It is observed that there is a gap between the total AES and JE positive cases over the years; the percentage of JE cases as proportion of total AES varied from 8.93% to 14.72%. This represents a shift in understanding of the spectrum of aetiology of AES in India, which in contrast to the earlier belief that the most of the AES cases were due to JE, has been observed to be contributed largely by non- JE aetiology in the country.

Thus, the disease spectrum of AES seems to be much wider, and may be caused by a wide variety of viruses, bacteria, protozoa, fungi, or may even be non- infectious in aetiology; most AES are, however, considered to be of viral aetiology. The virus identified as causing Acute Encephalitis include Herpesvirus, Influenza A virus, West Nile virus, Chandipura virus, Mumps, Measles, Rubella, Varicella- Zoster, Nipah and others. The isolation of Enterovirus amongst cases of AES outbreak of eastern Uttar Pradesh in 2006 by National Institute of Virology, Indian Council of Medical Research, field station at Gorakhpur, Uttar Pradesh is considered to be a landmark development in the etiologic understanding of AES. Attempts to identify etiologic agents in cerebrospinal fluid of AES cases using RT–PCR showed positivity to Enterovirus (EV) in 66 of 306 (21.6%) patients. [12]

CSF samples collected from patients of AES in the vicinity of Lucknow, Uttar Pradesh referred to a viral diagnostic laboratory during January 2011 - December 2012 were tested for IgM antibodies against Japanese Encephalitis virus (JEV), Dengue virus (DV), Herpes Simplex virus (HSV), Measles virus, Mumps virus, Varicella- Zoster virus (VZV), and Enterovirus using Enzyme Immuno-Assays. The most common causative agent for AES was observed to be JEV (16.2%) followed by DV (10.8%), HSV (9.3%), Measles virus (8.9%),

Mumps virus (8.7%) and VZV (4.4%); however, no Enterovirus was detected.[14]

The task force study on aetiology of AES conducted by Regional Medical Research Centre, Dibrugarh between September 2011 to September 2013, isolated JE virus in 351 of 784 (44.8%) blood and CSF samples collected from different parts of North- Eastern region of India; Chikungunya, Leptospira, Scrub typhus, Rubella, Measles, Mumps, HSV-1 and HSV-2 were also identified in this series.[15] Furthermore, since 2006 West Nile (WN) virus emerged as an important cause of AES in this part of the country.[16]

No etiologic agents including JE, Nipah, West Nile and Chandipura virus were identified in the clinical samples of cases presenting with AES in Muzzaffarpur, Bihar during June 2011.[17, 18]

Genotype of JE virus

Currently four distinct genotypes of JEV are believed to be circulating, genotypes I to IV[19], although some studies support the existence of a fifth JEV genotype[20], all of which are thought to have arisen from a common ancestor virus present in the Indonesian- Malaysian region[19] .

Until 2007, all known JEV strains isolated in India belonged to genotype III. [21] The prevalence of genotypes III and I among the JE cases of West Bengal was reported in 2012.[22] Studies from Gorakhpur also indicate the presence of genotypes I and III isolates among the AES cases.[21] Understanding of the implications of JE virus serotype in the severity of the disease is still premature.

Spread to newer areas

From the surveillance data it has also been observed that more than 90% of the total AES cases have been reported from 5 endemic states in the country viz., Assam, Bihar, Uttar Pradesh, Tamil Nadu, and West Bengal. JE cases are being reported from areas, which were not known to be endemic; this might possibly be due to taking up of mass vaccination campaigns since 2006 in known endemic districts of the country and establishment of new sentinel sites.

JE cases are increasingly being reported from northern districts of West Bengal particularly Jalpaiguri and Coochbehar districts since 2011[23] where mass vaccination campaign was conducted only in late 2013.

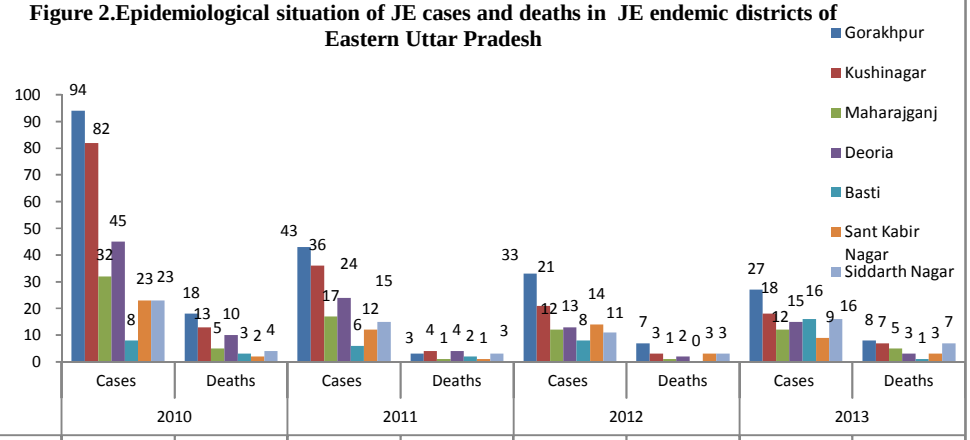
There are reports of occurrence of JE cases in the north eastern states of Arunachal Pradesh, Meghalaya, and Manipur.

JE positive cases have also been reported from Jharkhand in 2011 where vaccination campaign was not done earlier. Occurrence of JE has been established in Tripura in 2013. Migratory birds might possibly play an important role in the spread of JE virus to the newer areas. Reported occurrences of JE in Rourkela, Odisha in 1989[24] and also recently from some parts of the state critically urge confirmation of JE infection in Odisha based on eco- epidemiologic profile.
Thus, there is spread of JE to newer areas, which were earlier not known to be endemic.

Trend of occurrence of JE cases following mass vaccination campaign

The trend of occurrence of JE cases following mass vaccination campaign can be exemplified with the situation in eastern Uttar Pradesh. Since the major outbreak of JE during 2005, seven most endemic JE districts in Eastern UP were taken up on priority basis for JE vaccination in 2006. This resulted in significant reduction of JE cases from 312 cases reported during 2010 to 136 (56.4% decrease) during 2013. Similarly, JE deaths were reduced from 55 to 36, a significant decline of 34% as reported during corresponding period of 2013. The trend of JE cases in the seven districts of Uttar Pradesh since 2010 is shown in fig 2.

Figure 2.Epidemiological situation of JE cases and deaths in JE endemic districts of Eastern Uttar Pradesh



	2010		2011		2012		2013	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Gorakhpur	94	18	43	3	33	7	27	8
Kushinagar	82	13	36	4	21	3	18	7
Maharajganj	32	5	17	1	12	1	12	5
Deoria	45	10	24	4	13	2	15	3
Basti	8	3	6	2	8	0	16	1
Sant Kabir Nagar	23	2	12	1	14	3	9	3
Siddarth Nagar	23	4	15	3	11	3	16	7

It has also been observed that as compared to the period of 2012, JE cases have increased from 139 as reported during 2012, to 263 (an increase of 47.1%), from districts of Lucknow and Devipatan divisions, in 2013. This is primarily due to the increased incidence of JE in districts like Unnao, Sultanpur, Sitapur, Lakhimpurkhiri, Rae Bareilly and Pilibhit which did not report any case during previous years. It is pertinent to mention here that all the above districts have been covered under JE vaccination from 2006- 2010 except district Pilibhit; however, in most of these districts Routine Immunization (RI) is very poor. Poor coverage of JE vaccination under RI and limited vector control measures can be contributory factors for increase number of JE cases in these 7 districts in 2013.

Host Factors: Age

AES is typically acknowledged to be a disease in children below 15 years of age. There is, however, increasing evidence of occurrence of JE in older age group. Analysis of surveillance data received from the sentinel sites shows that a large number of JE cases occur in the adult population. About 77% of the JE cases in Assam and nearly half of the JE cases in West Bengal are contributed by population above 15 years of age. Furthermore, more number of JE cases in population above 15 years of age have been reported in areas where JE vaccination has not been conducted earlier - majority of the JE cases (9 out of 14) reported from Tripura for the first time in 2013 are in adult population; most of the JE positive cases reported from the North Bengal districts of West Bengal viz., Jalpaiguri and Coochbehar in 2011 to 2013 were in older age group where mass vaccination campaign was carried out in late 2013. In Uttar Pradesh, any significant change in the occurrence of adult JE cases in consideration of mass vaccination campaign since 2006 followed by routine JE immunization has not been observed. Thus, it is too premature to conclude any shift in modal age.

Trend in Case Fatality Rate

The Case Fatality Rate (CFR) due to AES has been below 20% in recent years, which was around 30- 40% during the previous decades. Fig. 3 shows the number of AES cases, deaths, and case fatality rate in India since 2006. Marginal decrease in case fatality rate in JE cases has also been observed in year 2013 (18.60%) as compared to 2012 (18.79%); however, there is a wide variation as reported by different states. There is also variation in CFR in different districts. Analysis to distinguish variation in CFR in relation to geographic location of accessibility of health care facility and performance of health facility would be useful for designing more effective disease control strategies.

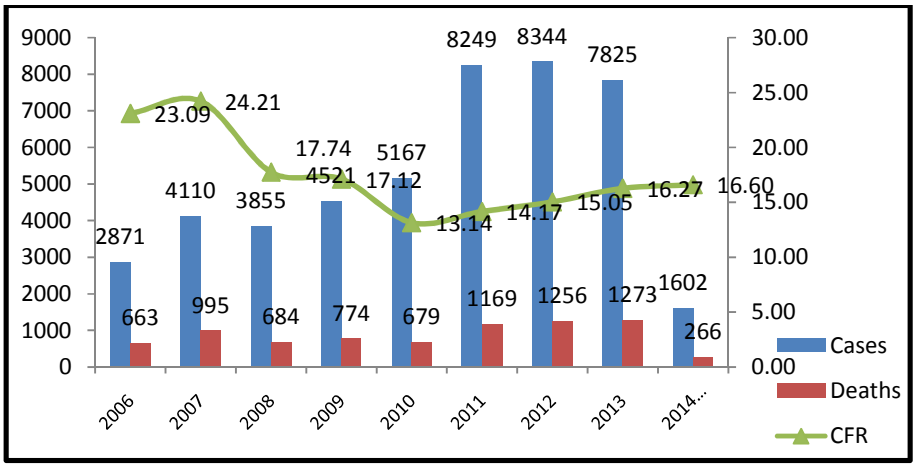


Figure 3.AES Cases, Deaths, and CFR since 2006 in India

Spectrum of clinical presentation

Onset of an acute febrile illness and a change in mental status (such as confusion, disorientation, inability to talk, coma) with or without new onset of seizures, excluding simple febrile seizures define an AES case, although clinical presentation of AES cases is very much variable due to its varied aetiology. In AES cases from eastern Uttar Pradesh, hepatomegaly, splenomegaly and decreased tone were reported in non JE AES cases, while in JE cases increased tone, neck rigidity, superficial abdominal reflexes were predominant symptoms. In JE, the clinical presentation includes a nonspecific prodrome and frequent seizures. Atypical clinical presentation such as moderate grade fever, hypotonia, and hepatosplenomegaly along with electrocardiographic findings suggestive of myocarditis have been observed in enteroviral encephalitis in Uttar Pradesh. Generalized convulsions along with altered sensorium were the significant findings in patients with non- JE Viral encephalitis in western Uttar Pradesh.[25] Jacob John and his co- worker reported clinical features in children with AES in Muzaffarpur, Bihar as sudden onset without prodromal phase, inconsistent presence of fever, brain oedema, absence of inflammatory cell response in cerebrospinal fluid (CSF) and hypoglycaemia; children are quite well until evening, but early next morning they are found seriously ill with brain function derangement and seizures; under-nutrition has been observed to be a consistent associated factor. [26] Co- infections with other arboviral diseases like dengue or chikungunya may further complicate the presentation.

Under- nutrition: risk factor of AES

Under- nutrition has been identified as an important risk factor of developing AES. Children suffering from AES in Muzaffarpur, Bihar have been found to be associated with under- nutrition (short and underweight for age). [26]

Seasonality and Environmental Factors

Although AES cases other than JE continue to be reported throughout the year, there is an overall increase of total AES cases since the month of June, peak during July- August and decline in September- October.

In Assam, JE cases start increasing in the month of June, reaches its peak in July then decline in October. In Uttar Pradesh, AES cases other than JE continue to be reported throughout the year with an increase in number of AES cases during the rainy season from the month of July, and then decline in November. Very hot and humid temperature also favours precipitation of AES cases during months of April- June, which was reported in North Bihar.[15] The presentation, seasonal distribution and climatic conditions suggest evaluation of the effect of El Niño phenomenon in occurrence of AES cases in Bihar. In West Bengal, most of the JE cases are reported in monsoon and post- monsoon season, which might be due to increased prevalence of the *Culex* vector mosquitoes, which breed abundantly in the paddy fields covered with stagnant water during the rainy season.[27] However, increasing number of AES cases have been reported from Malda district of West Bengal in the month of June during hot climate, when many of the children have history of visiting litchi orchards.

The AES cases in Muzaffarpur and adjoining litchi producing districts have been observed mostly during April to June particularly in children who are undernourished with a history of visiting litchi orchards; many of the cases are hypoglycaemic. In view of the seasonality with spatial and temporal coincidence with litchi cultivation, presence of hypoglycaemia, together with reported occurrence of AES in Bac Giang Province in north Vietnam is found to coincide with litchi harvesting season[28] the possible association with some toxin in litchi or in environment need to be documented. Methylenecyclopropyl-glycine (MCPG) which has been known to be a content of litchi fruit has been shown to cause hypoglycaemia in experimental animals. [26, 30] National Centre for Disease Control (NCDC) has taken up epidemiologic study on AES in Muzaffarpur.

For the last few decades, Gorakhpur district has undergone ecological changes in the form of construction of irrigation canals and small dams. The habitats have been modified for development of agriculture in the region, which has resulted in the vast expansion of water bodies, which support mosquito breeding. These environmental changes probably have triggered JE in the region.[31]

In- depth study on changing vector population, bionomics, susceptibility to insecticides and applicability of integrated vector management is a growing necessity, which might have direct implication for control, particularly for JE.

Socio- economic context

Social and economic factors play an essential role in occurrence of AES. People of lower socio-economic background are primarily engaged in pig rearing, thus susceptible to JE. People living in rural areas have the highest risk of JE because the vector mosquitoes breed in rice fields and large water bodies rich in aquatic vegetation. Change in agricultural practice from dry land to wet land cultivation of rice has been observed to be directly associated with the incidence of JE. Poor access to safe drinking water, practice of open field defecation and poor environmental sanitation are some of the important contributory factors in the transmission of enteroviral encephalitis in children from lower socio- economic background. AES in Muzaffarpur has mostly been observed amongst the children with low socio- economic background.

Implications for control

Implication of changing paradigm of epidemiologic understanding of AES on its prevention and control strategies cannot be overemphasized. JE mass vaccination campaign in endemic regions using a single dose of live-attenuated vaccine SA-14-14-2 in children between 1- 15 years of age followed by routine immunization to protect the new cohorts was introduced in 2005 considering a high endemic burden of JE, together with frequent and explosive epidemics in different parts of the country. Furthermore, the implication of the trend for increased incidence of JE in adults from the point of its prevention by vaccination of adult population is an important consideration particularly in Assam. The recommendation of the National Technical Advisory Group on Immunization (NTAGI) Standing Technical Sub-Committee in context of areas where protection is already likely to be very high, that adult JE vaccination campaigns will have to be comprehensive enough to cover the small proportion of susceptible population in these endemic areas and, therefore, vaccination could be taken up in districts where a reliable disease burden data indicates a substantial adult disease burden, is important from programme point of view.

The implication of JEV genotypes on occurrence and severity of disease is still little understood. However, the efficacy of the live attenuated SA14–14–2 vaccine imported from China derived from Genotype III currently in use in India must be carefully evaluated to protect against Genotype I. Futhermore, it would be prudent to closely monitor the protective efficacy of India's first indigenously developed JE vaccine using JEV strain isolated from Karnataka's Kolar district in this context.

Identification of Enterovirus as an etiologic agent of AES has been a basis for new dimension for prevention and control of AES incorporating strategies to provide safe drinking water to the highly endemic districts. Considering the complexity of AES problem and the urgency of addressing the adverse consequences of the growing incidence of AES, a multi- pronged strategy recommended by a Group of Ministers was adopted with convergence of different concerned ministries (details may be found in the article by Dhariwal et al. Inter- Ministerial Convergence towards Prevention and Control of Japanese Encephalitis and Acute Encephalitis

Syndrome (JE/AES) – An Integrated Multi-pronged Public Health Approach in this issue). In view of spread of the disease to newer areas, surveillance was strengthened with the establishment of new sentinel sites. Initiative is being taken to develop a network of laboratories to identify the agents causing AES.

High CFR has led to adoption of strategies for early detection of AES cases by the grass- root level ASHAs; incentive has been provisioned for early identification and transportation of cases to the nearest district health facility. IEC/BCC has been incorporated as an integral part of the programme for prevention and control of AES with extensive social mobilization campaign. Strengthening of case management has been given utmost importance hence, establishing paediatric intensive care units in identified 60 high priority districts is being given top priority. Capacity building of clinicians and nursing personnel has already been started. To address under- nutrition, provision has been incorporated to provide Take Home Ration (THR) to moderately and severely undernourished children under Integrated Child Development Services (ICDS) scheme of Women and Child Development Ministry.

The changing epidemiologic understanding together with population growth, changing landscape, agricultural practices, human behavioural patterns, ecological issues and complex interplay of factors between agent, host, and environment implicate human vulnerability for addressing strategies for prevention and control of AES, aetiology and epidemiology of which still are largely unknown, and critically challenge the scientific community with growing public health concern.

Acknowledgement

Information presented in this paper was collected from the official reports/ statements given by various Ministries of Government of India and State Governments. Authors would like to acknowledge the contribution and efforts of all stakeholders including concerned State Governments in putting together the National Programme for Prevention and Control of JE/AES. The authors owe a debt of gratitude to all of them.

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Journal of Communicable Diseases
Official Publication of Indian Society for Malaria and Other Communicable Diseases
Published by: ADR Publications