

Review Article

Changing landscape of acute encephalitis syndrome in India: A systematic review

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ABSTRACT

Background. Seasonal outbreaks of acute encephalitis syndrome (AES) occur with striking regularity in India and lead to substantial mortality. Several viruses, endemic in many parts of India, account for AES. Although Japanese encephalitis virus (JEV) is a key aetiological agent for AES in India, and has attracted countrywide attention, many recent studies suggest that enteroviruses and rhabdoviruses might account for outbreaks of AES. We did a systematic review of published studies to understand the changing landscape of AES in India.

Methods. Data sources: Electronic databases (PubMed, Web of Science and BIOSIS) from the start of the database to 2010. We also hand-searched journals and screened reference lists of original articles, reviews and book chapters to identify additional studies. **Study selection:** We included studies only on humans and from three time-periods: pre-1975, 1975–1999 and 2000–2010. **Data extraction:** Independent, duplicate data extraction and quality assessment were conducted. Data extracted included study characteristics, type of study and aetiological agent identified. **Data synthesis:** Of the 749 unique published articles screened, 57 studies met the inclusion criteria (35 outbreak investigations and 22 surveillance studies).

Results. While most studies from 1975 to 1999 identified JEV as the main cause of AES, many studies published after 2000 identified Chandipura and enteroviruses as the most common agents, in both outbreaks and surveillance studies. Overall, a positive yield with respect to identification of aetiological agents was higher in outbreak investigations as compared to surveillance studies.

Conclusion. The landscape of AES in India has changed in the previous decade, and both outbreak investigations and surveillance studies have increasingly reported non-JEV aetiologies. Because of these findings, there is a need to explore additional strategies to prevent AES beyond vector control and JEV vaccination.

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INTRODUCTION

Acute encephalitis syndrome (AES) is defined as the acute-onset of fever and a change in mental status (including signs and symptoms such as confusion, disorientation, delirium or coma) and/or new-onset of seizures (excluding simple febrile seizures) in a person of any age at any time of the year.¹ Also known as ‘acute febrile encephalopathy’, ‘viral encephalitis’, ‘infectious encephalitis’, and ‘brain fever’, the concept of AES was introduced to facilitate surveillance for Japanese encephalitis (JE), a mosquito-borne viral encephalitis. Although the definition of AES is broad and includes illnesses caused by many infectious as well as non-infectious causes, most AES are considered to be due to a viral encephalitis.²

For decades, JE has been considered to be the leading cause of AES in Asia^{3,4} with over 50 000 cases and 10 000 deaths reported each year.⁵ The history of AES in India has paralleled that of JE, with the virus first being reported from southern India (Vellore, Tamil Nadu) in 1955.⁶ Various subsequent studies confirmed that most AES in India are due to JE, which has been considered as the only major cause of AES in India.⁶ A high endemic burden of JE, together with frequent explosive epidemics, has led to adoption of mass vaccination strategies in endemic regions in India⁷ using a live-attenuated vaccine shown to provide more than 90% protection.⁸ However, several recent studies have reported that novel viruses such as enteroviruses (ENV),^{9,10} Chandipura virus (CHPV),^{11–13} and Nipah virus (NV) may account for AES in the regions endemic for JE.^{14,15} This change may reflect either a true epidemiological effect or the use of improved diagnostic tests for non-JEV aetiologies.¹⁶

The aetiology and transmission of AES have been studied in various human, animal, entomological and laboratory-based studies. Although these studies have enhanced the understanding of AES, we have limited this review to population-based studies that have focused on outbreak investigations and surveillance of AES. Outbreaks are usually investigated when a large number of cases are reported over a short period of time or cases occur in several healthcare facilities. Surveillance studies, on the other hand, typically involve a more wide-ranging diagnostic evaluation of consecutive AES cases presenting to a health facility over an extended period of time. This study aims to review the epidemiological features of AES in India, both in outbreak and surveillance settings.

METHODS

Study definitions

We defined AES as a clinical syndrome characterized by the acute-onset of fever and altered mental status of <7 days' duration, with or without seizures or a focal neurological deficit in a person of any age at any time of the year.¹ A study was defined as an 'outbreak investigation' if (i) the occurrence of AES cases was sudden, unexpected, (ii) more than the usual number seen in the same area in the same season in previous years, and (iii) all cases presented over a period of a few days to a few months. A study was defined as a 'surveillance study' if it was planned *a priori* to include consecutive cases presenting with AES from a specified population-base and over a period of one year or longer. We used author-defined age cut-points for paediatric age group, which varied from 12 to 18 years. We defined viral diagnostic studies as investigations conducted on any human sample, including but not limited to the serum, cerebrospinal fluid (CSF), brain tissue, throat swab, stool, urine, tissue aspirates and biopsies. We excluded from this review viral diagnostic studies on animal, and entomological or environmental samples.

Search strategy

We searched electronic databases (PubMed, Web of Science and Biosis) from the start of the database to December 2010, to identify relevant articles for this review. We used medical subject heading (MeSH) key words 'encephalitis' and 'India' for the initial search, and study selection criteria to identify the most relevant articles. In addition, we hand-searched all volumes of two journals—the *Journal of Communicable Diseases* (published by the Indian Society for Malaria and other Communicable Diseases) and the *Indian Journal of Medical Research* (published by the Indian Council of Medical Research)—from 1973 to 2010, to identify additional articles. We chose these two journals because they publish most of the research on encephalitis from India. We also screened reference lists of original articles, reviews and book chapters on encephalitis to identify additional studies.

Study selection and data abstraction

One investigator (RJ) screened the title, abstracts and full text of identified articles. The following criteria were used to identify relevant studies:

Inclusion criteria

1. Original research on human AES cases
2. Cases of AES occurring within the geographical boundaries of India
3. Inclusion of clinical or demographic data describing human cases

Exclusion criteria

1. Case reports, review articles and conference abstracts
2. Secondary laboratory studies on viruses
3. Studies on samples collected from normal human subjects, or human subjects who had symptoms not suggestive of AES.

The full text articles of all relevant studies were obtained and data were abstracted by RJ. The studies were classified as either an outbreak investigation or a surveillance study. Abstracted data included study characteristics (outbreak investigation or surveillance study), year and location of the study, AES characteristics (number of cases, case-fatality proportion and

proportion of children) and laboratory characteristics (type and number of samples collected from cases, diagnostic tests and their results that helped in determining the aetiologies).

Analysis

We described the results of the review using frequencies and proportions. Outbreak investigations and surveillance studies were separately tabulated. To evaluate whether recent studies differed from older ones, we divided the studies into three time-periods: pre-1975, 1975–1999 and 2000–2010. These three periods also broadly correspond to advances in diagnostic technologies.¹⁷ Studies were classified, based on size, as small (<100 cases), intermediate (100–999 cases) and large (≥ 1000 cases). Case-fatality proportion and proportion of presumptive or definite positive cases were analysed for study size subgroups. Human samples were considered definitely positive if they tested positive for a viral aetiology by cell line inoculation or nucleic acid amplification techniques; and presumptively positive if they tested positive by CSF, serological testing (haemagglutination inhibition [HI] or enzyme-linked immunosorbent assay [ELISA]) or immunocytology. We pooled the definite and presumptive positives to generate overall positivity.

We expected the studies to show wide heterogeneity, for they were reported from different populations and at different points in time. In addition, the body sites and timing of obtaining human samples, the laboratory techniques, and the range of viral aetiologies investigated were also heterogeneous over time. We, therefore, did not calculate pooled estimates for demographic characteristics or aetiological agents and have provided only a descriptive analysis of the results.

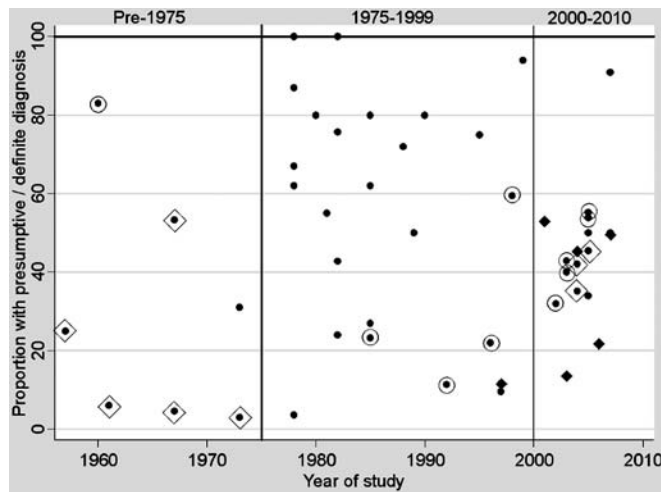
RESULTS

We identified 749 articles (721 from PubMed, 394 from BIOSIS, 498 from Web of Science and 29 from other sources) and included 57 unique studies (35 outbreak investigations and 22 surveillance studies). Fifty studies (30 outbreak investigations and 20 surveillance studies) reported diagnostic testing of human samples. Overall 37 (74%) of all studies were predominantly, and 26 (52%) exclusively, among children. Most studies had a high case-fatality proportion (median 37% [interquartile range IQR 24%–54%]). The overall landscape of these studies with respect to their temporal distribution and diagnostic yield is presented in Fig. 1.

Outbreak investigations

Two studies were published before 1975, 21 during 1975–99 and 12 after 2000 (median year 1989; IQR of years 1980 to 2003). The first AES outbreak investigation was from eastern India in 1973;^{18,19} and subsequently 24 more outbreak investigations were reported between 1975 and 1999 (Fig. 2). Most studies reported epidemics during summer or raining (between May and October), and mostly from northern and eastern parts of India. Of these 25 studies, 13 were small,^{20–32} 10 intermediate,^{19,33–41} and two large^{42,43} in size (Table I). Case-fatality proportions were higher in the small studies (median 52.9%, IQR 37%–60%), compared to intermediate (median 34.5%, IQR 23.5%–44%) and large (median 31%, 21.5%–32.8%). Of 18 studies which reported demographic data, 12 (66.6%) were predominantly among children (56%–100% cases were in children).

Of 22 studies that did viral diagnostic testing, 18 (82%) tested for JEV alone; three studies tested for other arboviruses in addition to JEV. Most studies found a high positivity among the samples analysed for JEV (median 67%, IQR 31%–80%).



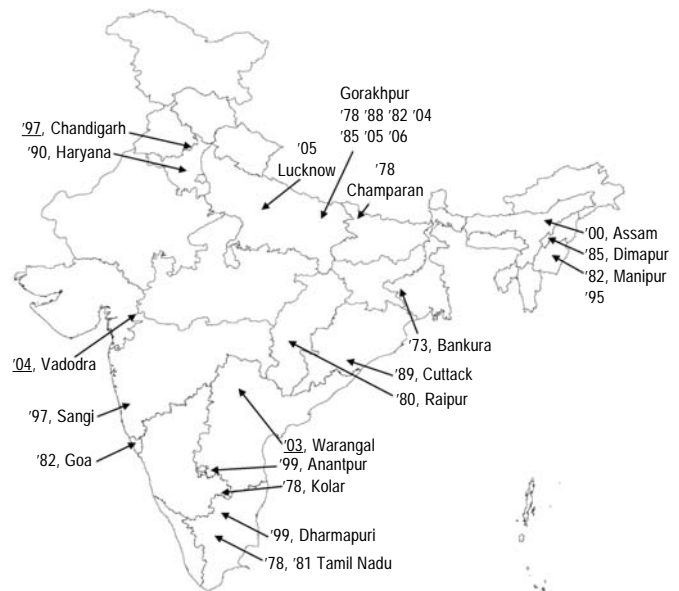
Outbreak investigation • JEV as a key aetiology ◉ Non-JEV as a key aetiology
 Surveillance study ◊ JEV as a key aetiology ◊ Non-JEV as a key aetiology

FIG 1. Landscape of published outbreak investigations and surveillance studies of acute encephalitic syndrome from India. Each symbol in the graph represents a unique study, across three time-periods (pre-1975, 1975–1999 and 2000–2010). Pre-1975 period includes surveillance studies, and first outbreak, reported in 1973, which was attributed to Japanese encephalitis virus (JEV). Between 1975 and 1999, a number of outbreaks and surveillance studies were due to JEV. In 1997, an AES outbreak was attributed to measles virus. Between 2000 and 2010, a number of outbreaks have been attributed to non-JEV aetiologies (Chandipura, Nipah and enteroviruses). Three surveillance studies have also reported Chandipura and enteroviruses as predominant aetiologies.

Among the more recent epidemics, the one reported from Sangli district in Maharashtra in 1997³⁰ was an exception, with <10% of sera being positive for IgM antibodies against JEV. A total of ten^{9,11,13,14,44–49} outbreak investigations were reported between 2000 and 2010, and eight of these evaluated human samples for viral causes. Three of these (two reporting on a 2005 outbreak in Gorakhpur, and one reporting on a 2007 outbreak in Assam) were attributed to JEV.^{44,48,49} However, others were attributed to Nipah (Siliguri, 2001),¹⁴ Chandipura (Warangal 2003, Vadodra 2004, Nagpur 2007),^{11,13,46} and enteroviruses (Gorakhpur, 2006).⁹ These outbreaks also had a high case-fatality proportion, and mainly affected children (except the 2001 outbreak in Siliguri, which affected adults). All samples obtained from these epidemics tested negative for JEV. Because the researchers failed to find JEV in these outbreaks, they did diagnostic tests for multiple viral families (arboviruses, paramyxoviruses, herpesviruses, entero-viruses and rhabdoviruses). The 2001 outbreak in Siliguri was initially attributed to JEV, but after Nipah virus (a paramyxovirus, with a respiratory–zoonotic route of transmission) was reported to cause AES in Malaysia and Bangladesh, the stored samples from the Siliguri outbreak were re-analysed using reverse transcriptase-polymerase chain reaction (RT-PCR) and serology, and Nipah virus was confirmed as the causative agent.¹⁴ Unlike all previous AES epidemics in the same district, in the 2006 outbreak in Gorakhpur, JEV was not isolated from any of the human samples tested. Instead, this epidemic turned out to be caused by enterovirus-71.⁹

Surveillance studies

We found 22 surveillance studies,^{10,12,50–69} all but one of which were prospective, hospital-based evaluations of consecutive patients suspected to have AES. Most studies were limited to children (Table II, Fig. 3). Seven of the surveillance studies were



Numbers indicate year of outbreak. Example '73 means 1973.

FIG 2. Location of published acute encephalitis syndrome outbreaks from India (1973–2010). Underlined years indicate when Japanese encephalitis was not ascribed as the cause of outbreak. These outbreaks were 1997, Chandigarh (measles); 2001 Siliguri (Nipah); 2003 Warangal and 2004 Vadodra (Chandipura); and 2006 Gorakhpur (enterovirus).

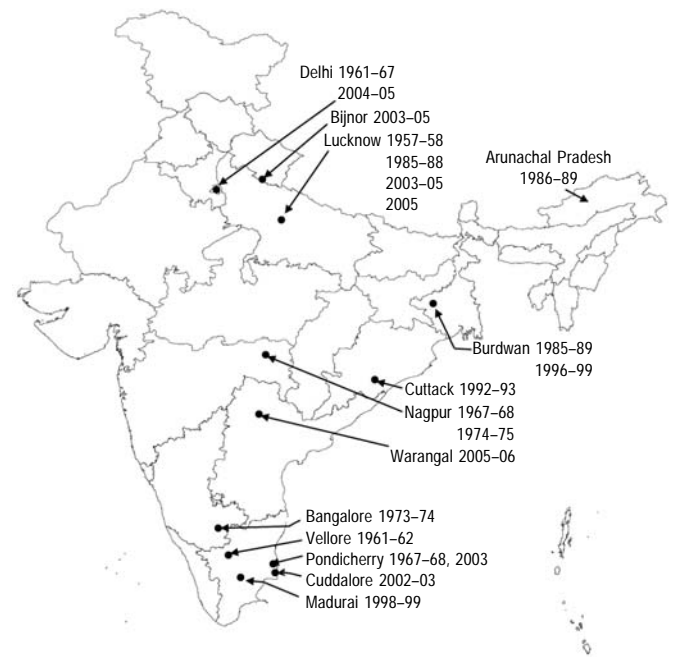


FIG 3. Published surveillance studies of acute encephalitis syndrome in India (1957–2010). Numbers indicate years when surveillance studies were conducted.

TABLE I. Outbreak investigations of acute encephalitis syndrome (AES) in India

First author, year	District, State	Number of AES (CFP)	Per cent children	Human samples evaluated (number)	Diagnostics performed	Aetiological agents detected
Chatterjee, 1973 ¹⁹	Bankura, West Bengal	324 (45.9)	44.7*	None	na	na
Banerjee, 1973 ²¹	Bankura, West Bengal	na	na	Serum (29), brain tissue (4)	HI for JEV, mouse brain inoculation	31% sera positive for JEV, JEV isolated from one brain tissue
Bhardwaj, 1978 ²²	Deoria, Uttar Pradesh	78 (na)	30†	Serum (78)	HI for Gp B arboviruses: Chik/JEV/WNV/DEN2	62% positive for one or more arbovirus, 10% positive for JEV
Mathur, 1978 ³⁴	Gorakhpur, Uttar Pradesh	647 (23)	42.5‡	Serum (322), CSF (12), brain tissue (5)	HI for JEV, mouse brain inoculation	JEV isolated in 4/5 brain tissue samples, 87% of paired sera positive for JEV
Loach, 1978 ²⁵	Champanan, Bihar	na	na	Serum (4)	HI for JEV	All JEV-positive
Rao, 1978 ³⁷	Tamil Nadu	298 (33.2)	84.6*	Serum (70), CSF (29)	Mouse brain inoculation	JEV isolated from 11 cases
Prasad, 1978 ²⁹	Kolar, Karnataka	71 (25.3)	na	Serum (33)	HI for JEV	Presumptive/compatible diagnosis of JEV in 21 (67%) cases
Mathur, 1980 ²⁶	Raipur, Madhya Pradesh	33 (54.5)	100†	Serum (10)	HI for Gp B arboviruses: 2 JEV/WNV/DEN	80% positive for an arbovirus
Rao, 1981 ³⁶	Tamil Nadu	607 (24.0)	92.3*	Serum (125), CSF (90), brain tissue (9)	HI for JEV, mouse brain inoculation	55% of paired sera JEV-positive, no virus could be isolated
Chaudhury, 1982 ²⁴	Goa	35 (37.1)	34.2*	Serum (10), brain tissue (1)	HI for JEV, mouse brain inoculation	100% seropositive, JEV isolated from brain tissue
Mohan Rao, 1982 ²⁷	Goa	26 (42.3)	38.4*	Serum (14), CSF (7), brain tissue (2)	HI for JEV, mouse brain inoculation	42.8% presumptive JEV, JEV isolated from brain tissue
Chakraborty, 1982 ²³	Manipur	99 (53.5)	31.3*	Serum (46)	HI for JEV	24% JEV-positive
Kar, 1982–88 ⁴²	Gorakhpur, Uttar Pradesh	1680 (32.8)	71.7*	Serum (70)	HI for Gp B arboviruses and JEV	75.7% Gp B arbovirus-positive, 24.5% JEV-positive
Chakraborty, 1985 ³³	Gorakhpur, Uttar Pradesh	831 (33.3)	64.5*	Serum (8)	HI for Gp B arboviruses	62% positive for arbovirus group
Angami, 1985 ²⁰	Dimapur, Nagaland	50 (60)	56*	Serum (10)	HI for JEV, Gp B arboviruses, WNV	80% positive for arboviruses, 30% positive for WNV
Mukherjee, 1985–89 ³⁵	Dimapur, Nagaland	220 (14.0)	na	Serum (37), CSF (1)	JEV IgM ELISA	27% serum and single CSF sample positive for JEV
Narsimhan, 1988 ⁴³	Gorakhpur, Uttar Pradesh	4544 (31.0)	78	None	na	na
Rathi, 1988 ³⁹	Gorakhpur, Uttar Pradesh	875	100*	Serum (670), CSF (25)	IgM ELISA for JEV, HI for JEV	JEV IgM CSF 18/25 (72%), JEV IgM Blood 27/53 (51%), HI IgG serum 498/670 (74.3%)
Vajpayee, 1989 ⁴¹	Rourkela, Orissa	254 (40.1)	65.8	Serum (4)	HI for JEV	Two JEV-positive
Sharma, 1990 ⁴⁰	Haryana	294 (69.7)	na	Serum (10)	HI for JEV	80% JEV-positive
Neogi, 1995 ²⁸	Manipur	na	na	Serum (16)	JEV IgM ELISA	75% JEV-positive
Thakre, 1997 ³⁰	Sangli, Maharashtra	52 (3.8)	na	Serum (52)	JEV IgM ELISA	9.6% JEV-positive
Wairagkar, 1997 ³²	Chandigarh	51 (52.9)	100†	Serum (11), CSF (17)	JEV, dengue, WNV IgM ELISA, measles IgM ELISA, cell line isolation, RT-PCR for measles	Two isolates confirmed to have measles RNA. Another 4 isolates showed CPE suggestive of measles, on cell line inoculation, IgM anti-measles antibody 17/28 (60%)
Rao, 1999 ³⁸	Anantapur, Andhra Pradesh	212 (18.8)	100*	Serum (31)	JEV IgM ELISA	94% JEV-positive
Victor, 1999 ³¹	Dharmapuri, Tamil Nadu	3 (na)	100*	None	na	na
Kaur, 2000 ⁴⁴	Assam	152 (42.1)	50.6*	Serum (44)	JEV IgM ELISA	90.9% JEV-positive
Chadha, 2001 ¹⁴	Siliguri, West Bengal	66 (74)	All adults¶	Serum (17), urine (6)	Nipah and measles IgM/IgG, Nipah RT-PCR	Nipah antibody 9/17 (52.9), Nipah RNA 5/6 (83.3)

First author, year	District, State	Number of AES (CFP)	Per cent children	Human samples evaluated (number)	Diagnostics performed	Aetiological agents detected
Rao, 2003 ¹¹	Warangal, Andhra Pradesh	329 (55.6)	100*	Serum (54), CSF (10), brain aspirates (55), brain tissue (1), throat swab (22)	Serology/PCR for JEV, WNV, dengue, paramyxoviruses, rabies, enteroviruses, influenza, coronaviruses and mycoplasma, Chandipura serology/PCR/cultures (cell lines), intracerebral mice inoculation	Chandipura virus isolated from 3/22 throat swabs, one brain aspirate, two blood clots; Chandipura virus RNA detected in 4/21 throat swabs, 5 serum samples, one brain aspirate; 15/46 patients IgM/IgG-positive for Chandipura virus antibodies
Gupta, 2004 ⁴⁵	Gorakhpur, Uttar Pradesh	115 (22)	90.4*	None	na	na
Chadha, 2004 ⁴⁶	Vadodara, Gujarat	26 (78.3)	100	Serum (20), CSF (8), throat swab (14), urine (10)	JEV, WNV, dengue IgM ELISA; Chandipura IgM ELISA; RT-PCR for flaviviruses (serum), paramyxoviruses (urine), enteroviruses (serum) and Chandipura (serum and CSF); mouse brain/cell line inoculation (Chandipura PCR positive)	Chandipura virus isolated in one serum sample; 9/20 (45%) samples positive for Chandipura RNA on PCR; 2/20 (10%) serum samples positive for enterovirus RNA (echovirus 1 and poliovirus 1); 3/20 sera Chandipura IgM-positive
Gupta, 2004 ⁴⁷	Bellary, Karnataka	73 (1.4)	84†	None	na	na
Kumar, 2005 ⁴⁸	Lucknow, Uttar Pradesh	278 (37.7)	100	Serum/CSF (223)	JEV IgM ELISA (Xcyton)	JEV IgM-positive 77/223 (34%)
Parida, 2005 ⁴⁹	Gorakhpur, Uttar Pradesh	326 (23)	na	Serum (185), CSF (141)	JEV IgM ELISA RT-PCR for JEV Viral isolation in cell lines	JEV isolation 7/326 (2.1%); JEV RNA on PCR 12/326 3.6%; JEV IgM-positive (50% serum, 30% CSF samples)
Sapkal, 2006 ⁹	Gorakhpur, Uttar Pradesh	1912 (21.5)	100*	CSF (306), blood (304), throat swab (120), rectal swab (120)	Viral isolation in cell lines Enteroviral RT-PCR	Enteroviral RNA 66/306 (21.5%) CSF samples. Also in 6% rectal swabs, 4% throat swabs, 6% serum samples
Gurav, 2007 ¹³	Nagpur, Maharashtra	78 (43.6)	100*	CSF (18), serum (71)	JEV and Chandipur IgM ELISA, PCR for Chandipur virus	Chandipur RNA in 2/18 (11%) CSF and 22/71 (31%) serum samples; anti-Chandipur antibodies in 2/18 (11%) CSF and 8/71 (11%) serum samples; 39/78 (50%) diagnosed as Chandipur encephalitis

CFP case-fatality proportion Gp B Group B chik chikungunya JEV Japanese encephalitis virus CSF cerebrospinal fluid HI haemagglutination inhibition WNV West Nile virus DEN2 dengue serotype 2 virus na not available CPE cytopathologic effect Cut-off age used to define paediatric age group ‡ 10 years † 12 years; * 15 years, || 18 years ¶ This was likely to be a point source epidemic, from a single hospitalized case¹⁵

from the pre-1975 period, and viral diagnosis was based on CSF, stool and serum samples that were inoculated on cell lines or mouse brain. Five studies⁵⁰⁻⁵⁴ from northern and southern India suggested enterovirus (i.e. Coxsackie A6, A9, B2, B5, Echovirus 7) as the key aetiology; one study⁵⁵ from southern India suggested that JEV was an important aetiology; and another⁵⁶ from central India was negative for all viruses tested.

JEV epidemics were reported in different parts of India between 1975 and 1999. Six surveillance studies⁵⁷⁻⁶² were reported from this time-period, four of which included viral diagnostic testing. These studies were planned to determine the proportion of AES cases due to JEV infection in those regions where previous epidemics had occurred. These studies performed either viral isolation or demonstrated the presence of anti-JEV IgM antibodies. The proportion of cases due to JEV in these studies ranged from 11% to 60%.

We found nine surveillance studies^{10,12,63-69} performed between 2000 and 2010; five^{63,64,67-69} of them found JEV to be the key aetiological agent. These studies, conducted in regions previously known to be endemic for JEV, focused on testing samples for

arboviruses. Other studies had variable results with one study suggesting a non-viral metabolic aetiology for most cases, for all patients tested negative for all viruses.⁶⁶ Two studies^{10,65} from Delhi and adjacent areas found multiple aetiologies for AES cases: about a third of all patients with AES had enterovirus-71 infection and the remaining had either measles, mumps, JEV, dengue, herpes or varicella infections. In another surveillance study from the region with a previous Chandipura virus epidemic, Chandipura virus was found in 45% of the patients tested.¹²

DISCUSSION

This review presents the clinical, aetiological and historical profile of AES in India. Most studies were done in children, and have had a high case-fatality proportion (median 37%, IQR 24%–54%). While most studies done between 1975 and 1999 looked for and identified JEV as a key aetiological agent, enteroviruses and Chandipura virus replaced JEV as the major cause of AES in most studies published after 2000. More recent studies have investigated a wider spectrum of potential viral aetiologies and have used more advanced diagnostic techniques.

AES outbreaks often have a high mortality and hence are a major public health concern in India. Since the first major reported outbreak of AES from eastern India (Bankura, West Bengal) in 1973,^{70,71} parts of the country have been devastated by numerous outbreaks with striking regularity. The surveillance for sporadic cases of AES has been limited.⁵ Subsequent to early studies from Lucknow (1957–58)⁵⁰ and Vellore (1960–61),⁷² the Indian Council of Medical Research initiated JEV surveillance in many parts of the country, focusing on mosquito-borne viruses. In these studies, investigators conducted serological tests and isolated viruses, collecting zoonotic and entomological evidence with an eye towards finding JEV as the aetiological agent. Surveillance studies conducted in the same regions that had experienced prior AES outbreaks reported about one-quarter to one-half of all cases to be seropositive for IgM antibodies against JEV.^{61,62,69} As a result, most outbreaks are presumptively attributed to JEV, before any investigations are initiated.

In recent years, investigations into large outbreaks of AES have been negative for JEV (or a flavivirus). Instead outbreaks were found to be due to a rhabdovirus (Chandipura virus),^{11,48} or water-borne enteroviruses.⁹ These outbreaks have also occurred in hot and humid seasons, have predominantly affected children, and have had a high case-fatality. Surveillance studies conducted in inter-epidemic period have also found other aetiologies. It needs to be emphasized that in the absence of a definite viral diagnosis, other predictors of aetiology such as clinical features, seasonality and prognosis may not be able to distinguish between aetiologies. While viral diagnosis is tedious and expensive, and may not be possible for individual patients, it must be done periodically at population levels to record epidemiological shifts.

Several factors might account for enteroviruses replacing JEV as the major cause of AES. First, JE vaccination campaigns, launched in endemic districts, may have brought about this shift. According to a recent systematic review of AES surveillance studies globally,² JE vaccination programmes in developing countries reduce the incidence of JE and bridge the gap between the incidence of AES in developed and developing countries. This observation is supported by epidemiological data which show that the introduction of JE vaccination in endemic regions reduced the overall incidence of AES.⁷³ Second, it is likely that once the incidence of JE falls either due to vaccination or due to periodic fluctuations in the circulation of JEV or its vector, AES caused by other neuropathogenic aetiological agents are ‘unmasked’, although at a much lower incidence. Advances in molecular diagnostics, viral culture and isolation, as well as use of an extended panel of tests for potential aetiological agents could be other factors leading to increased frequency of identification of alternative aetiologies.

The emergence of non-JEV aetiologies in outbreaks and surveillance studies directly impacts preventive measures for AES. While vector control programmes and JEV vaccination remain important strategies, the presence of other agents calls for designing and implementing novel preventive strategies that would focus on containment of water-borne enteroviruses and vectors for Chandipura virus. This will need a multisector approach involving health, water resources, sanitation and rural development departments. Recently the thought process on such an approach has been initiated.⁷⁴ In addition, we also need to move from JE surveillance to surveillance for the entire spectrum of AES, so that evidence-based public health actions can be planned and carried out.

While this review is based on a thorough search of the literature, it has certain limitations. Publication bias is a major limitation

because studies with negative or uncertain aetiological outcome might not have been published in biomedical journals. Such technical reports and unpublished documents from national and regional disease control organizations often do not find their way to scientific journals. Second, earlier researchers seldom used a battery of tests that would include all possible viruses causing AES. Not only did the studies lack consistency, they also differed from one another in respect to the viral diagnostic methods employed, and the range of aetiologies for which diagnostic tests were included. For example, researchers investigating outbreaks of AES were more likely to look for JEV if this virus was also reported from the same region in the past. Third, big outbreaks are more likely to be investigated and reported, and surveillance studies are more likely to be conducted, because they are more likely to impact public health. Lastly, in the recent past India has seen epidemics of Chikungunya and dengue, which mostly present as fever-arthralgia and fever-rash, respectively. There are isolated case reports of these aetiologies presenting as AES, and hence these are not extensively included in this review. Despite these limitations, we believe that this review would help to improve our understanding of AES in India, especially with regard to key aetiologies, and also would help to focus an agenda for future research.

AUTHOR CONTRIBUTIONS

RJ, SP, AR and JC conceived the study and helped in design of the study protocol. RJ performed the data collection and analysis, and wrote the first draft. All authors reviewed the manuscript, provided critical inputs and agreed with the final contents.

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TABLE II. Surveillance studies of acute encephalitis syndrome (AES) reported in India

First author, year, study type	District, State	Number of AES cases (CFP)	Per cent children	Human samples evaluated (number)	Diagnostic tests performed	Aetiological agents detected
Paul, 1957–58 ⁵⁰	Lucknow, Uttar Pradesh	27 (na)	na	CSF (4), stool (42)	Intracerebral mouse inoculation; cell line inoculation	One cytopathogenic agent (Coxsackie B5) from CSF, and 13 from stool samples
Carey, 1960–61 ⁵⁵	Vellore, Tamil Nadu	61 (na)	na	CSF and serum samples	HI for JEV	JEV isolated in 3 cases; presumptive/compatible JEV diagnosis in another 51/61 cases
Nair, 1961–67 ⁵²	Delhi	254 (na)	100*	CSF and stool (254 each)	Intracerebral mouse inoculation	One CSF sample positive for Coxsackie A9; 15 (6%) stool samples positive for an enterovirus; rest not tested for other pathogens
John, 1967–68 ⁵⁴	Nagpur, Maharashtra	255 (na)	100†	Serum (146), CSF (172), rectal swab (215), throat swab (217), urine (120), others (189)	Cell line inoculation	Enteroviruses (Echovirus 7, Coxsackie B2, and untypable) isolated from 8 CSF samples; overall in 20 children enterovirus was isolated from one of the samples
Madhavan, 1967–68 ⁵¹	Pondicherry	26 (na)	na	Serum (5), CSF (15), rectal swab (1), stool (1)	Cell line inoculation	Enteroviruses (Echovirus 7) isolated from CSF samples of 8 cases
Benkappa, 1973–74 ⁵³	Bangalore, Karnataka	64 (89.8)	100†	Serum (23), CSF (33), brain tissue (26), throat swab (40), rectal swab (55)	Intracerebral mice inoculation; cell line inoculation	Coxsackie A6 in one CSF sample; 8 other enteroviruses in other non-brain/CSF samples
Hardas, 1974–75 ⁵⁶	Nagpur, Maharashtra	90 (na)	100†	CSF (68), stool (16), throat swab (41), rectal swab (31)	Cell line inoculation	No agent isolated from CSF, only three cytopathogenic effects seen; 8 enteroviruses isolated from non-CSF samples
Kumar, 1985–88 ⁶²	Lucknow, Uttar Pradesh	740‡ (37)	100†	CSF (394), brain tissue/serum	Intracerebral mice inoculation; HI/CFT WNV, dengue, JEV, Chikungunya	JEV-positive 92/394 (23.3%); samples of 14 patients were positive for other viruses.
Chaudhuri, 1985–89 ⁵⁹	Burdwan, West Bengal	762 (25–35)	100†	None	na	na
Chattopadhyaya, 1986–95 ⁵⁸	Arunachal Pradesh	162 (62.3)	47.5¶	None	na	na
Devi, 1992–93 ⁶⁰	Cuttack, Orissa	35 (14)	100†	CSF (35)	JEV IgM ELISA	JEV IgM-positive 4/35 (11.4%)
Chatterjee, 1996–99 ⁵⁷	Burdwan, West Bengal	204 (na)	na	Serum (204)	HI for JEV/dengue/WNV	45/204 (22%) positive for JEV
Kabilan, 1998–99 ⁶¹	Madurai, Tamil Nadu	37	100†	Serum (37), CSF (37)	HI and cell IFA for JEV	JEV in 22/37 (59.5%) cases
Kabilan, 2002–03 ⁶⁸	Cuddalore, Tamil Nadu	58 (na)	100¶	Serum (48), CSF (47)	JEV IgM serum/CSF; JEV cellular antigen (IFA); JEV RT-PCR	JEV cellular Ag in CSF/toxo-IFA in 14/47 (32%); JEV-RNA 11/17 (65%) cases; JEV IgM CSF in 6/47 (13%); JEV IgM serum in 3/38 (8%)
Kumar, 2003–05 ⁶⁴	Lucknow, Uttar Pradesh	265 (30.1)	100¶	Seum (238)	IgM ELISA dengue; HI for JEV/dengue; dengue PCR	Dengue IgM in 52/238 (22%); Dengue RNA in 21 cases; JEV HI-positive 9/44 (20.4%)
Vashishtha, 2003–05 ⁶⁶	Bijnor, Uttar Pradesh	55 (76.4)	100¶	Serum/CSF, Brain/liver tissues	Measles and JEV antibody tests (IgM-ELISA)	All samples negative for viral aetiology; liver biopsy suggested hepatic necrosis
Potula, 2003 ⁶⁹	Pondicherry	300 (35.8)	100**	Serum/CSF (212)	JEV cellular antigen (IFA); CSF JEV IgM antibodies;	184/212 (86.7%) JEV Ag-positive; 91/212 (42.9%) JEV IgM-positive

First author, year, study type	District, State	Number of AES cases (CFP)	Per cent Children	Human samples evaluated (number)	Diagnostic tests performed	Aetiological agents detected
Tandale, 2005–06 ¹²	Warangal, Andhra Pradesh	90 (54.4)	100¶	Serum (52)	CSF micro-neutralization test IgM ELISA for JEV, Chandipura, WNV; Chandipura RT-PCR	Chandipura RNA in 20/44 (45.4%); Chandipura IgM in 3/44 (6.8%)
Karmarkar, 2004–05 ⁶⁵	Delhi	157†† (na)	100¶	CSF (57)	CSF IgM antibodies against herpes, measles, mumps, rubella, varicella, JEV, dengue. Microneutralization for EV71 antibodies, cell line inoculation	EV71 20/57 (35.1%); measles/ mumps 10/57 (17.5%); JEV/ dengue 6/57 (10.5%); herpes/VZV 2/57 (3.6%); others 3/57 (5.4%); unknown 16/57 (28%)
Roy, 2005 ⁶⁷	Lucknow, Uttar Pradesh	57 (na)	61.4	Paired serum (13)	HI test for JEV	JEV-positive 7/13 (53.8%)
Saxena, 2005, ⁶³ unknown	Gorakhpur, Uttar Pradesh	38 (na)	100	Paired CSF and serum (38)	IgM-ELISA for JEV	JEV-positive 21/38 (55.2%)
Beig, 2004–06 ¹⁰	Aligarh, Uttar Pradesh	87 (50)	100	CSF (87)	Viral isolation, micro- neutralization for EV71, ELISA for measles, mumps, herpes, varicella, JEV	Enterovirus 71 (42%), measles (21%), varicella (15%), mumps (10%), JEV (0%)

All studies were prospective, hospital-based except where mentioned. CFP case-fatality proportion CSF cerebrospinal fluid HI haemagglutination inhibition WNV West Nile virus DEN2 dengue serotype 2 virus JEV Japanese encephalitis virus na not available IFA immunofluorescence agglutination CFT complement fixation test VZV varicella zoster virus Cut-off age used to define paediatric age group * 10 years † 12 years ¶ 15 years ** 18 years ‡ Of these 740 cases, in 240 a non-viral diagnosis was established. In another 38 encephalopathy was considered to be related to measles. Of the remaining 462 patients, 394 underwent virology investigations || The other viruses included adenoviruses (5), parainfluenza and influenza (4), polio, coxackie, echovirus (1 each) and untypable (2) †† Of these 157 cases, 94 were of non-viral aetiology and remaining 57 were viral encephalitis suspects. Although CSF samples of all 151 patients were collected, only 57 samples were subsequently evaluated for virology studies.

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Erratum

In the ‘Correspondence’ section of Volume 25, Number 3, in the letter titled ‘Is vasovagal syncope really a diagnostic problem?’ (*Natl Med J India* 2012;**25**:186–7), the correct name of the third author is Lucia Krí•ová. We regret the error.

—Editor