



Recent Trends and Changing Aetiology of Acute Encephalitis Syndrome in India

Amresh K. Singh^{1*}, Ankur Kumar¹ and T. N. Dhole²

¹*Department of Microbiology, BRD Medical College Gorakhpur, Uttar Pradesh, India.*

²*Department of Microbiology, Hind Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.*

Authors' contributions

This work was carried out in collaboration among all authors. Author AKS designed and conceptualized this review, edited the first draft and corrected the final manuscript. Author AK co-edited, searched and analyzed the online resource material. Author TND reviewed, corrected and analyzed. All authors read and approved the final manuscript.

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ABSTRACT

Acute Encephalitis Syndrome (AES) poses a great public health problem in India, occurring both in epidemics and sporadically. Although bacteria, viruses and protozoan parasites may cause encephalitis, among these; the viruses are the most common and important cause of encephalitis Japanese Encephalitis virus has been considered as leading cause of AES in India mostly occurs among children. 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. Recently, increased incidence of scrub typhus is being reported from Northern India especially eastern part of Uttar Pradesh and western part of Bihar, as reported 25% infectious aetiology in one third of the AES cases and emergence of *O. tsutsugamushi* infection an important causative agent of AES in India. A recent outbreak of "AES" in June 2019 was found in Muzaffarpur, Bihar India. As reported the Muzaffarpur district has initiated an investigation into the case of 672 children who were admitted with "AES" and more than 150 children have died. Case fatality rate among children due to JE was found very low now because changing aetiology of AES across various districts of Bihar.

*Corresponding author: E-mail: amresh.sgpgi@gmail.com;

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1. INTRODUCTION

Acute Encephalitis Syndrome (AES) poses a great public health problem in India, occurring both in epidemics and sporadically. The magnitude of problem has been estimated to be approx. 50,000 cases and 10,000 deaths due to the AES annually leads to morbidity and mortality [1].

The World Health Organization (WHO) in 2006 has defined the Acute Encephalitis Syndrome (AES) as “Clinically any person of any age at any time of year presenting with acute onset of fever and a 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)”. Some other clinical features in AES might be included; increase in irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness [1,2]. Japanese Encephalitis (JE) virus has been considered as leading cause of AES in India mostly occurs among children. AES is a group of clinically similar neurologic manifestation caused by several different viruses, bacteria, fungus, parasites, spirochetes, chemical/ toxins etc. There is seasonal and geographical variation in the causative organisms among AES cases [3].

JE is a common mosquito borne flaviviruses causing encephalitis and one of the leading causes of viral encephalitis worldwide, mostly prevalent in eastern and southern Asia, covering a region with a population of over three billion[3]. Most infections of JE are asymptomatic, but if clinical illness develops, it causes significant morbidity and mortality [4,5].

The term AES is now being used for surveillance in all encephalitis endemic zones irrespective of the aetiology. An accurate identification of microbial agents is essential for surveillance & patient management including reduction of disease burden. It is well documented that some of these aetiologies are preventable or treatable hence, the common viral aetiological agents of AES and epidemiology is the need of hour to be study at a large scale in the vicinity of India especially among children [6]. Although such literature is very important tool of knowledge enhanced the understanding of AES, we have limited this review to population-based studies that was focused on outbreak investigations,

surveillance, aetiology and epidemiology of AES [6].

The complexity of AES aetiology is very difficult to rule out on the basis of clinical features but unknown aetiology therefore the clinicians are facing the challenge of understanding wide range of causes and high rate of neurological impairment due to pathogenesis of AES and differential diagnosis and treatment option of disease therefore we have focused on the changing aetiology and outbreak investigations illustrating how the perspective of AES has also been changed in India over period [4,6,7].

Although these studies have enhanced the understanding of AES, we have limited this review to population-based studies that have focused on outbreak investigations, surveillance and epidemiology of AES [6].

2. AIMS OF THIS STUDY

The aims of this study are to understand the recent trends and changing aetiology of AES and its management in India.

3. METHODOLOGY

3.1 Study Material for Analysis

This review study is based on the present scenario and data of AES in India by using good quality of research articles, WHO guidelines on Encephalitis, Guidelines clinical of AES Syndrome management including JE. Government of India, Directorate-National vector borne disease control programme (NVBDCP) and Ministry of Health and Family welfare (MOH&FW) Government of India, encephalitis data, Integrated Disease Surveillance Program (IDSP), and centre for disease control (CDC) newsletters.

3.2 Selection Criteria

We used medical subject heading key words encephalitis, acute encephalitis syndrome, epidemiology and aetiology of AES and its management in India for the primarily search, study field keywords and selection criteria to identify the most relevant articles. We also screened reference lists of original articles, review articles, reviews and book chapters on encephalitis to know the epidemiology and

changes in the etiological agents over a time in different geographical area of India.

3.3 Types of Source Material

The source material was prepared by studying relevant documents such as original research articles, reviews, journals and book chapters on encephalitis studies were obtained and data was abstracted classify as aetiology, epidemiology, prevalence, incidence or outbreak of AES studies.

4. EPIDEMIOLOGY OF AES

The epidemiology of AES and JE cases from 2014 to 2018 in last five years have been changed with huge variation AES and JE positive cases over the years. AES cases are increasing day by day and JE cases are limiting in recent trends of encephalitis in India as seen in Fig. 1.

4.1 Spectrum of Disease

The total number of AES positive cases was 11,388, while the number of JE positive cases reported in India in 2018 was 1,678. This indicates a shift in the perception of the spectrum of aetiology of AES in India. It is observed that most AES cases in India are contributing to non-JE aetiology in the country.

Therefore, the disease spectrum of AES seems to be very wide and may be caused by a variety of viruses, bacteria, protozoa, fungi, or infections in aetiology; however, most AES are considered viral aetiology. AES surveillance is parallel to JE

surveillance for practical purposes because of its over-impact on JE. In 2014, the total number of AES cases and deaths reported from India were 10,853 and 1,717, and cases for JE were 1,657 (~ 15%) and 293 (~ 17%), respectively. This indicates that there is also an undetectable or neglected aetiology of AES, which accounts for 85% and it should also be shown in Fig. 2 [2,3,4].

For decades, JE has been considered the leading cause of 50,000 cases of AES in Asia and 10,000 deaths each year. The history of AES in India parallels that of JE, the virus was first reported in 1955 from South India (Vellore, Tamil Nadu). Various follow-up studies have concluded that most AES in India is due to JE, which is previously considered to be the main cause of AES in India [6]. However, several recent studies have reported that novel viruses, such as Enterovirus (ENV) Chandipura virus (CHPV) and Nipah virus (NV), can cause AES in the region's endemic for JE. This change may reflect either a true epidemiological impact or the use of improved diagnostic tests for the current aetiologies of AES in India [4,6].

In recent years after 2012, AES cases in India have shifted towards JE Aetiology. Based on the reports Uttar Pradesh (UP), Bihar, Assam, West Bengal and Tamil Nadu have been identified as JE endemic Zones in India. In 2013, 2,205 people were infected with JE solely from the monsoon to the end of November, and the number of deaths due to JE increased to 590 (Indian Express, November 26, 2013). In 2014 trends of AES & JE cases, UP (3,329 cases, 627

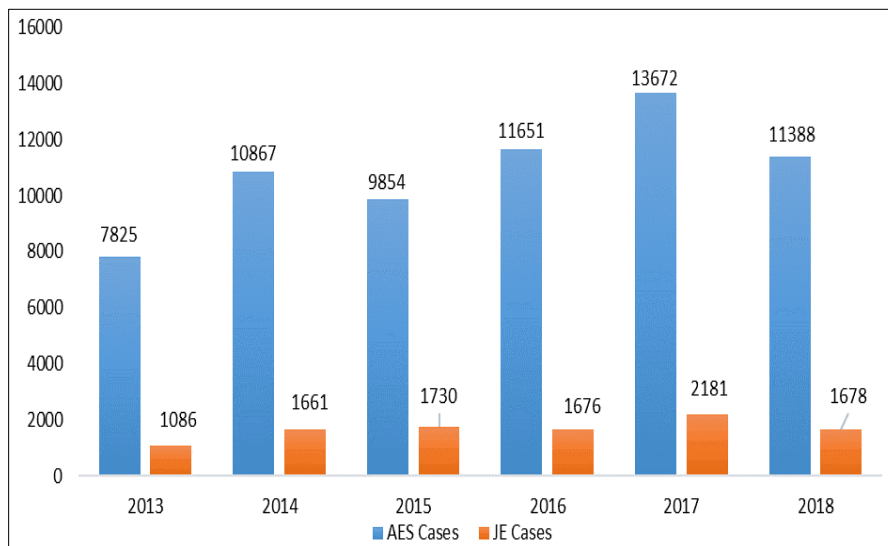


Fig. 1. AES/JE cases reported from 2013 to 2018 in India

deaths), Assam (2,194 cases, 360 deaths), West Bengal (2,381 cases, 169 deaths), and Bihar (1,385 cases, 355 deaths) (A38) were reported and scattered cases of AES were also found non endemic zones such as Eastern Gujarat, Andhra Pradesh, Rajasthan and Kerala. According to a report of Indian Express, September 22, 2015; JE was the leading cause of death during that period, and virologists identified another cause of the toxin-mediated illness [4].

In 2016 the total AES cases were 11,651 and case fatality rate (CFR) was 11.2% and it's parallel to JE cases were 1,676 and CFR was 17.5% which was high as compared to AES CFR same trends continue in 2017 and 2018 found in India. Sen et al also analysed similar observation in their review study claimed that the CFR due to AES has been below 20% in recent years, which was around 30-40% during the previous decades. However, there is a wide variation in CFR as reported by different states and also in different districts of affected AES area. Analysis to distinguish variation in CFR in relation to geographic location, accessibility of health care facility and performance of health facility would be useful for designing more effective disease control strategies as shown in Figs. 2 and 3 [4].

In 2016, the total AES excluding JE cases were 11,651 and the case fatality rate (CFR) was 11.2% and this was just higher to total JE cases reported 1,676 and CFR 17.5%, respectively, which was found in India in 2017 and 2018 compared to the AES CFR. Sen et al. and others found similar observation in their review study, stating that CFR was less than 20% due to AES in recent years and of 30-40% of previous decades as seen in Figs. 2 and 3. However, there is wide variation in CFR as reported in different states and different districts of the affected AES region. Analysis to distinguish variation in CFR in relation to geographic location, accessibility of health care facility and performance of health facility would be useful for designing more effective disease control strategies [4].

5. AETIOLOGY OF AES

The aetiology of AES is known to occur worldwide in two forms, either as outbreaks of encephalitis or as sporadic encephalitis. The causative agents of outbreaks of encephalitis depend largely on the geographic distribution of the aetiological agents besides the seasonal, environmental, viral and host factors [7].

Although bacteria, viruses and protozoan parasites may cause encephalitis, among these the viruses are the most common and important cause of encephalitis [8]. For instance, St. Louis encephalitis, West-Nile virus, Western Equine Encephalitis, Eastern Equine Encephalitis and Venezuelan Equine Encephalitis viruses are common causes of outbreaks of encephalitis in the Americas, while Murray Valley Encephalitis virus is commonly encountered in Australia and Japanese encephalitis virus (JEV) is highly prevalent in South East Asian countries [9]. In contrast, sporadic encephalitis is commonly caused by viruses belonging to the Herpesviridae family [Herpes Simplex Virus 1 and 2 (HSV), Varicella Zoster Virus (VZV), Human Herpes Virus-6 (HHV6)] and Enteroviruses. In the immune-compromised individuals *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Cryptococcus neoformans* and JC virus are frequently encountered as aetiological agents of AES. The aetiological agents that are known to cause AES in India including bacteria, fungus, viruses and protozoan parasites may cause encephalitis [10-13].

The aetiology of AES in India can be classified on the basis of viral, bacterial, fungal and parasitological microorganisms and their correlation with clinical findings as shown in Fig. 4.

5.1 Viral Aetiology of AES

Viruses are the most common and important cause of encephalitis. Cases of AES have been reported from many states of India, but the aetiological agent has been identified in only 20%–30% cases [9,10]. Among all, viral encephalitis that is encountered in India, JE appears to be of greater significance during outbreaks as well as in sporadic cases [9-11].

5.1.1 Japanese encephalitis

Japanese encephalitis (JE) is a major cause of viral neurologic disease related to public health. The Japanese encephalitis virus (JEV) belongs to the Flaviviridae family and genus Flavivirus, which is transmitted by mosquitoes to vertebrates *Culex tritaeniorhynchus*, *Culex vishnui* and *Culex pseudovishnui*. It is one of the most prominent forms of viral encephalitis worldwide, most prevalent in East and South Asia, with a population of more than three billion people living in countries where the JE virus is endemic [12]. The traditional estimate is that

between 50,000 and 1,75,000 cases occur annually, with an estimated 10,000 to 15,000 deaths [13]. According to the WHO, JE is native to Asia and the Pacific, especially in South Asia and the Western Pacific. According to WHO statistics, 3,187 JE cases were reported from around the world in 2013; Of these, 42% are from the Southeast Asian region, 80% of whom are from India. As shown in Fig. 2 [12,14], 30% – 50% of South and East Asia is attributed to CFR among JE cases.

In 1973, a death rate of 42.6% occurred in Bankura, West Bengal. Subsequently, the disease spread to other states and spread to different parts of the country. In 1978, cases were reported from 21 states and union territories. In Uttar Pradesh, the first major JE epidemic occurred in Gorakhpur in 1978, with 1,002 cases and 297 deaths. From 1978 to 2005,

the encephalitis claimed more than 10,000 deaths in the state. In the year 2005, Uttar Pradesh experienced a devastating outbreak of JE, mostly in Gorakhpur with 6,061 cases and 1,500 deaths; Another outbreak occurred in 2006, with 2,320 cases and 528 deaths as shown in Fig. 5 [12,13,15].

5.1.2 Dengue virus

Dengue is a widespread arboviral disease in tropical and subtropical regions of the world. Dengue fever is an arthropod borne viral disease of public health significance and one of the rapidly emerging global threat [7]. Dengue is caused by a virus of the Flaviviridae family and there are 4 distinct, but closely related, serotypes of the virus that causes dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Recently, a fifth serotype (DEN-5) was discovered in 2013 from Bangkok.

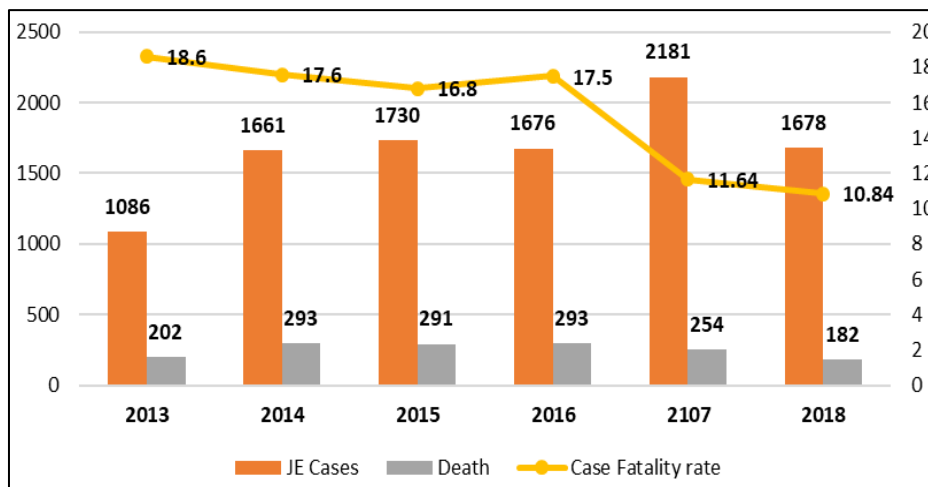


Fig. 2. Biostatistical analysis of JE cases reported from 2013 to 2018 in India

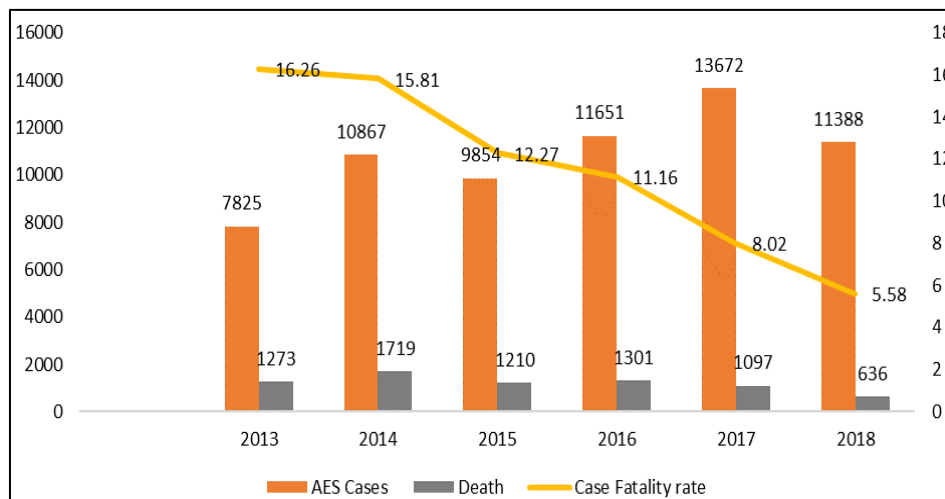


Fig. 3. Biostatistical analysis of AES cases reported from 2013 to 2018 in India

Viral	Bacterial	Fungal	Parasitological
<ul style="list-style-type: none"> • Japanese B Encephalitis Virus (JE) • Herpes simplex virus (HSV) • Enterovirus 71 & ECHO virus • Dengue virus • Chikungunya virus • West Nile virus (WNV) virus • Herpes viruses (HHV6, EBV, VZV) • Cytomegalovirus • Measles virus • Rubella virus • Mumps virus • Rabies virus • Zika virus • Poliovirus • Nipah virus • -Kyasanur forest disease virus 	<ul style="list-style-type: none"> • <i>Streptococcus pneumoniae</i> • <i>Haemophilus influenzae</i> • <i>M.tuberculosis</i> • <i>Neisseria meningitidis</i> • Group B <i>Streptococci</i> • <i>Orientia tsutsugamushi</i> • <i>Rickettsia typhi</i> • <i>Treponema pallidum</i> • <i>Leptospira</i> • <i>Listeria monocytogenes</i> • <i>Mycoplasma pneumoniae</i> • <i>Actinomyces</i> • <i>Staphylococcus aureus</i> • <i>E.coli</i> • <i>Klebsiella pneumoniae</i> • <i>Pseudomonas aeruginosa</i> 	<ul style="list-style-type: none"> • <i>Cryptococcus neoformans</i> • <i>Candida spp</i> • <i>Blastomyces dermatitidis</i> • <i>Histoplasma capsulatum</i> (not common in India) 	<ul style="list-style-type: none"> • <i>Plasmodium falciparum</i> • <i>Cysticercus cellulosae</i> • <i>Naegleria fowleri</i> • <i>Acanthamoeba</i> • <i>Schistosoma japonicum</i> • <i>Toxoplasma gondii</i>

Fig. 4. Aetiology of AES in India

Dengue, an arboviral infection, as per WHO estimates, this has shown a 30-fold increase globally over the past five decades. It accounts for about 50 to 100 million people infected and leads to approximately 5,00,000 hospitalizations annually. Several reports in India, especially from Uttar Pradesh, have identified dengue virus as an aetiological agent in AES [16,17,18].

5.1.3 Chikungunya virus

The chikungunya virus spreads to the public through infected mosquito bites. Mosquitoes become infected when feeding on an already infected person. Chikungunya virus is most commonly transmitted to people by the *Aedes aegypti* and the *Aedes albopictus* mosquito.

Fever and arthritis are the most common symptoms. Other symptoms may include headaches, muscle pain, joint swelling or rash. The fever is usually biphasic after 1-6 days of remission. Infection can also progress to cause infection to Central nervous system considered as emerged as one of the newer causative agents of AES in India. Outbreaks have occurred in different countries like Africa, Asia, Europe, Indian and Pacific oceans. The first notified outbreak of chikungunya was happened in Kolkata in 1963. This was followed by epidemics in Tamil Nadu, Andhra Pradesh and Maharashtra in 1964–65 and 2006. More than 15,00,000 cases of chikungunya were reported with *A. aegypti* implicated as the vector in Indian outbreak [19,20].

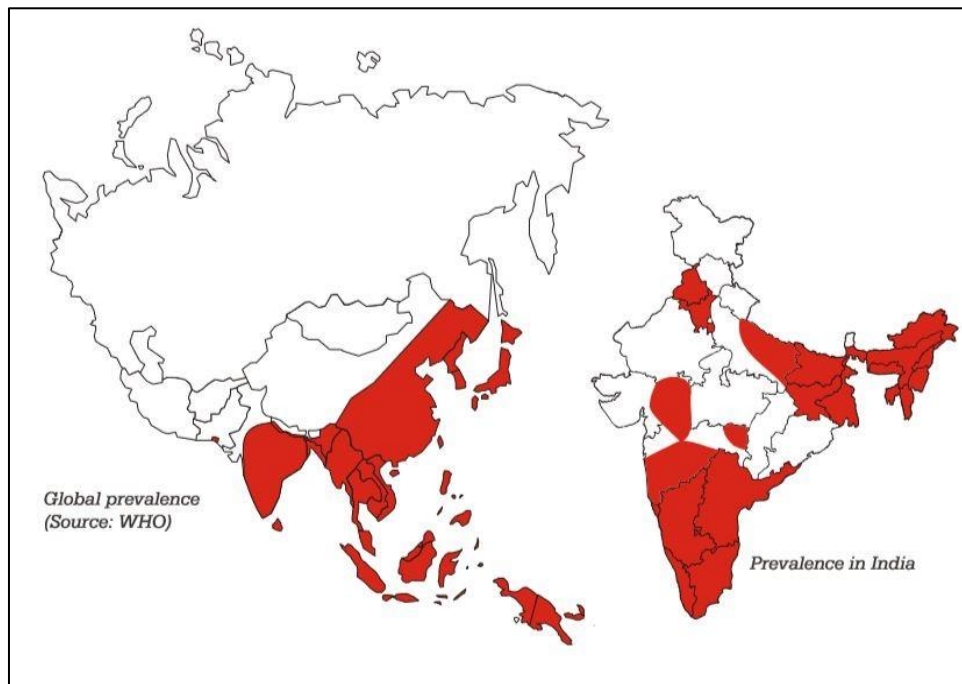


Fig. 5. Epidemiology of Japanese encephalitis (Image courtesy by NIV Pune, India)

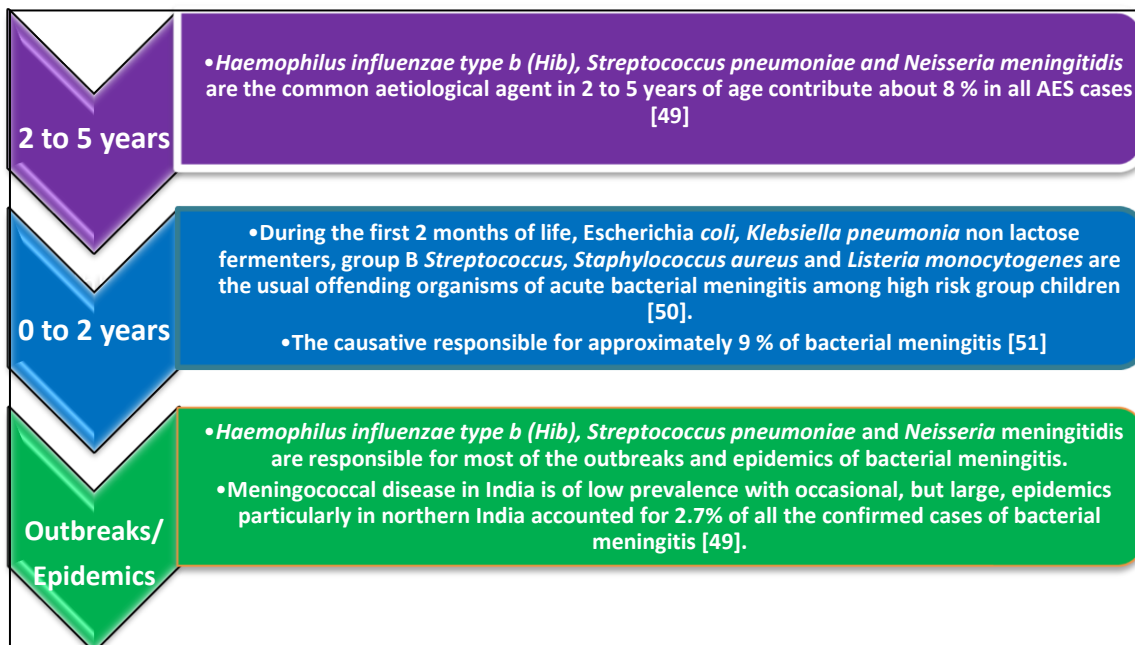


Fig. 6. Overview of bacterial meningitis epidemiology

5.1.4 West Nile Virus (WNV)

West Nile Virus (WNV) is now common in India and is known to cause acute encephalitis. However, its geographic prevalence and quantitative contribution to acute encephalitis in India have not been systematically studied

[21,22]. The cases of acute febrile sickness and encephalitis were reported in 3 districts of Maharashtra and Udaipur, Rajasthan. WNV neutralizing antibodies have been detected in human sera collected from Tamil Nadu, Karnataka, Andhra Pradesh, Maharashtra, Gujarat, Madhya Pradesh, Orissa, and

Rajasthan. Serologically confirmed cases have also been reported from Vellore and Kolar districts. The separation of WNV from fatal cases of encephalitis has been reported from Mysore and Kolar districts of Karnataka. Recently, WNV has been reported from Assam, which belongs to the endemic zone of JEV. The outbreak of WNV was also reported in 2011 from Kerala where 208 AES cases were reported with 4 deaths [7,8,21].

5.1.5 Enteroviruses

Enteroviruses have been identified as causes of acute encephalitis in India. In recent years, enterovirus infection has been detected by reverse transcription PCR in CSF samples of 66 out of 306 (21.5%) AES cases in all 8 districts of Eastern Uttar Pradesh. Sequencing and phylogenetic analyses of PCR products from 66 (89.3%) samples showed similarity with EV-89 and EV-76 sequences. EV-75 was identified as an aetiological agent in 5 out of 106 (4.7%) children with AES between 2005 and 2007 in Bellary, Karnataka. Another study reported EV-71 as the most common aetiological agent, accounting for 42.1% of hospitalized children with suspected viral encephalitis in western Uttar Pradesh. EV-71 infection caused significant deaths (50%) and illness in children. EV-71 has emerged as an important cause of AES, although it is rarely associated with disease in India. Enterovirus 71 and ECHO (enteric cytopathogenic human orphan viruses) are the most common viruses that cause severe encephalitis in India [7].

5.1.6 Herpes viruses

Herpes simplex encephalitis (HSE) is the most common clinical manifestation of other causes of encephalitis in the Herpesviridae family, with HSV-1 occurring in more than 90% of childhood and adult cases of HSE. In contrast, HSE-2 is the cause of HSE-2 neonatal and occasional adult cases. Unlike HSV-1, HSV-2 is the most common cause of aseptic meningitis (usually in patients with primary genital herpes), and both HSV-1 and HSV-2 have been implicated in recurrent meningitis (*Mollaret meningitis*) [23]. Neonatal HSE results from spread of HSV-2 infection in new-borns obtained in the genital tract during childbirth. HSE occurs at any time of year and affects gender, children and adults. Pathologically, herpesvirus causes severe necrotizing encephalitis, and the clinical course is rapidly progressing over several days. Acute anaemia and recent memory loss occur in one

fifth cases [24]. Sudden onset of headache, confusion and consciousness change, meningism, aphasia or mutism (46%), focal neurological deficits such as hemiparesis and aphasia develop when HSE is not treated, and coma and seizures occur during illness [25].

The herpes group of viruses is one of the most common causes of AES in India. The herpes group in India ranges from 13% to 59.10% in Karnataka [26], Eastern India [27] and UP [28,29] and other states and 7.19% to 55% in other Asian countries [7,8,30]. The herpes group is the most common cause of acute sporadic encephalitis in the developed world and in India [7]. All these viruses have specific antiviral therapy available (acyclovir), and real-time PCR for early detection of RNA virus detection alerts the clinician to initiate specific treatment and prevent excessive deaths and illnesses and prevent the high mortality and morbidity [7].

5.1.7 Cytomegalovirus (CMV)

Cytomegalovirus encephalitis is rare in general population but is common in immunodeficiency and neonates. In the autopsy study, 12% of all HIV-infected patients and 2% of transplant recipients had cytomegalovirus encephalitis [20]. In an immunodeficient host, cytomegalovirus encephalitis is usually clinically appeared as febrile episode and meningoencephalitis (headache, confusion, rarely convulsions, dysphasia and coma). Cerebrospinal fluid shows pleocytosis, mildly elevated protein, and normal glucose [22]. Cases of coexistence of HSV and cytomegalovirus encephalitis have been reported in immunocompetent and immunocompromised hosts [23,24]. Neuro-pathology is characterized by ventriculo-encephalitis and over half of these patients have HIV encephalopathy, toxoplasma encephalitis or primary central nervous system lymphoma. CMV, measles virus (MV), mumps virus (MPV) and rubella virus (RV) are also present in a considerable number of sporadic and outbreak cases in India. Ganciclovir is the treatment of choice for CMV encephalitis.

5.1.8 Nipah virus

Nipah virus encephalitis was detected in pig farmers in Malaysia between 1998 and 1999 and subsequently recorded among abattoir workers in Singapore. Nipah virus encephalitis is a wide-ranging epizootic encephalitis with direct transmission from animal to human, unlike other epizootic encephalitis (JE, WNV encephalitis,

EQV encephalitis), where vector transmission is the rule. More than 200 people have been affected in Malaysia alone and the cluster outbreak has severely damaged the pig farming industries [25].

Nipah virus is an infectious disease that is spread by the secretions of infected bats. It is transmitted to humans through contaminated fruits, infected animals, or in close contact with infected human [31].

Specific clinical signs include segmental myoclonus, arflexia, hypotonia and dysautonomia (hypertension and tachycardia). Early findings in cerebrospinal fluid was abnormal in 75% of cases, EEG showed slow waves that extended with focal abnormalities over the temporal regions (75%) and magnetic resonance imaging (MRI) of the brain during the acute phase of the illness showed extensive focal lesions in the subcortical and deep white matter., may be a reason of very high CFR [25].

In India, the Nipah virus (NiV) encephalitis outbreak occurred in 2001 from Siliguri, West Bengal. Sixty-six cases of encephalitis were identified, and CFR was 74%. Subsequently, in April 2007, 30 fevers with severe respiratory distress and/or neurological symptoms caused 5 deaths from Nadia in West Bengal [9]. Recently in May 19, 2018, first NiV outbreak was reported from Kozhikode, Kerala, India. There have been

17 deaths and 18 confirmed cases till 1st June 2018 [31].

5.1.9 Chandipura virus

Prevalence of acute encephalitis of unknown origin was investigated by Rao et al. from Andhra Pradesh in 2003 [31,32]. The outbreak, which has a high mortality rate of 55.6% in children, is caused by the Chandipura virus, which is a family member of the Rhabdoviridae and the genus of vasiculovirus. First identified in 1965, from the blood of two adult patients with febrile illness from Chandipura (Nagpur) in Maharashtra, the Chandipura virus, as a human pathogen, has been addressed only when the virus is linked to this virus [32,33]. Subsequently, the Chandipura virus was identified as an aetiological agent in the outbreak from Gujarat in 2004 [34] and in hospital-based surveillance of acute encephalitis in children from Maharashtra [35,36], Telangana, Andhra Pradesh reported cases of this virus [37].

5.1.10 Other viral agent causing AES

There was a study in Rajasthan for monitoring AES, and they were reported Enterovirus (EV) (4.50%), Dengue Virus (DV) (3.94%), Human Metapneumovirus (MPV) (3.80%), Mumps Virus (MV) (2.67%) and Rubella Virus (RV) (0.84%). EV-71 virus is an important agent developing encephalitis most often as sporadic cases as shown in Fig. 1 [7].

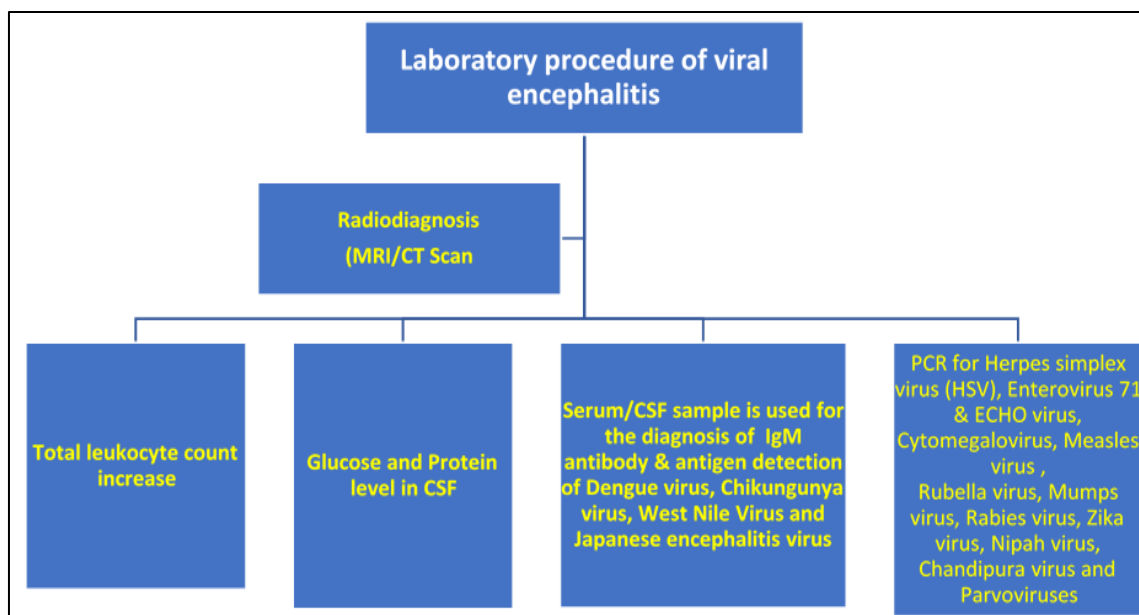


Fig. 7. Laboratory procedure of virus causing encephalitis

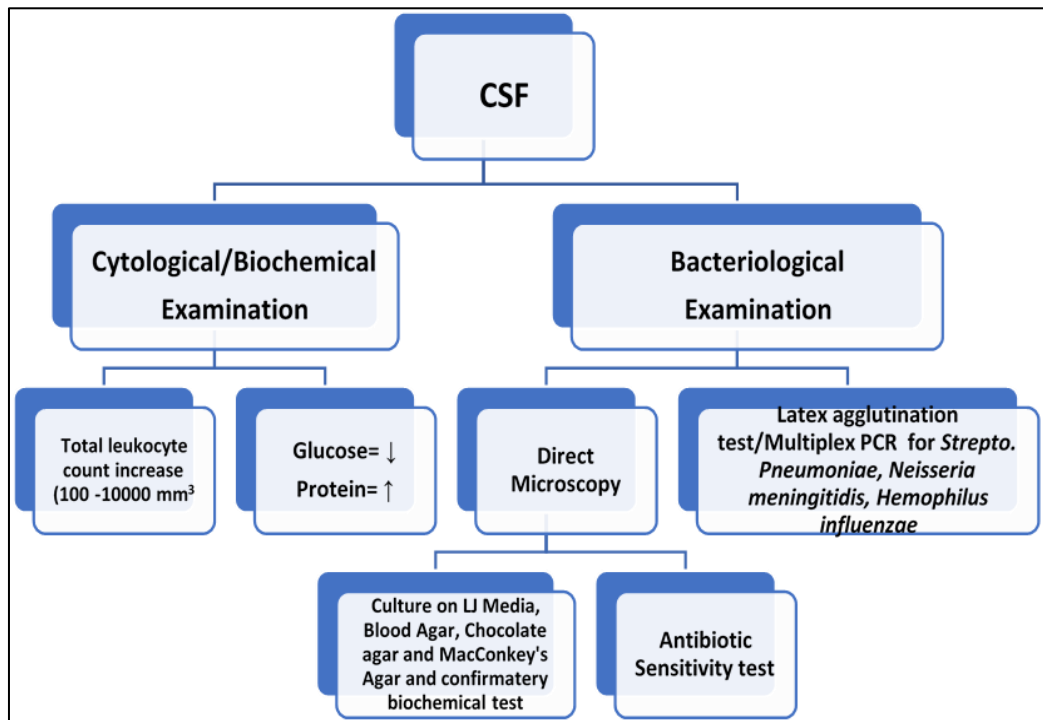


Fig. 8. Schematic algorithm for laboratory diagnosis of suspected bacterial meningitis cases

A study was conducted in Rajasthan for the surveillance of AES, and they reported enterovirus (EV) (4.50%), dengue virus (DV) (3.94%), human metapneumovirus (MPV) (3.80%), mumps virus (MV) (2.67%) and rubella virus (RV) (0.84%). EV-71 is an important emerging encephalitogenic virus [8]. In similar study, low positivity was observed to these viruses from 0.19% to 2.6% from Eastern India, but higher positivity to all these viruses from one study from Western UP (EV-71 in 42.1%, MV in 21.1% and MPV in 10.5%) [8,28-30,39]. Whereas, EV was not reported in another study from UP [8,28-30]. On the other hand, very high positivity was reported for EV 71 (35.1%) from New Delhi [8,39-41].

Before the start of nationwide, measles, mumps and rubella (MMR) vaccination programs, mumps and measles encephalitis are the most common causes of suspected children in early 19th century in developed countries, these viruses have almost disappeared; However, they continue to be the most common causes of AES in developing countries, probably due to suboptimal immunization rates, between 2000-2010, an unexpected change in the AES scenario, and non-JE prevalence is constantly increasing most likely to be caused by other viruses such as enteroviruses [8,27-29,38-41].

5.2 Bacterial Aetiology of AES

Bacterial aetiology is the cause of meningitis and meningoencephalitis infections in children and adult populations worldwide. Acute bacterial meningitis (ABM) is the leading cause of death worldwide and chronic neurological sequelae [42,43]. Bacterial meningitis is an inflammation of the meninges, particularly arachnoid and pia mater, associated with the invasion of bacteria into the subarachnoid space [42,43].

5.3 Magnitude of Bacterial AES

According to the World Health Report (WHO) among cases of the bacterial meningitis, rates of morbidity and mortality are high. Apart from infections, an estimated 1.2 million cases of bacterial meningitis are diagnosed each year, of which 1,35,000 are fatal [44-46]. ABM remains a common life-threatening condition in children. In a multicentric survey in India, ABM accounted for 1.5% of admissions in paediatric wards and an average case mortality rate of 16% [45,46].

ABM is essentially a childhood disease, mainly due to the poor immune response in this age group. About 95% of cases occur between 1 month and 5 years. Poor socio-economic status, congestion, recent colonization with pathogenic bacteria, close contact with patients, splenic

dysfunction, and communication across the cerebrospinal fluid (CSF) mucocutaneous barrier (congenital or acquired) increased risk of meningitis[47].

ABM is a medical emergency, so providing early diagnosis and treatment can save lives and reduce illness. Besides infections, it is estimated that at least 1.2 million cases of bacterial meningitis occur each year; Of these, 135,000 were fatal [47]. The world health report by WHO states that, there were 20,000 deaths in Africa, 18,000 in the US and 73,000 in Southeast Asia reported high mortality due to the bacterial meningitis as shown in Fig. 6 [45,47-51].

5.4 Bacterial Agents Causing AES

Aetiology of acute bacterial meningitis is associated to the age of the patient with the background of several host factors. During the first 2 months of life, *Escherichia coli*, *Klebsiella pneumoniae* and other Gram-negative bacilli, group B *Streptococcus*, *Staphylococcus aureus* and *Listeria monocytogenes* are the usual offending organisms. In children between 2 months to 12 years, bacterial meningitis is primarily due to *H. influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis* [45-47].

In children with severe malnutrition, compromised immunity or anatomical defects, infection can occur by other microbes like *Staphylococcus*, *Salmonella*, *Pseudomonas*, *Rickettsia typhi*, *Leptospira*, *Nocardia*, *E. coli*, *Klebsiella pneumoniae*, *Legionella*, *Acinetobacter* spp., *Burkholderia cepacia* complex [44-47].

5.4.1 Scrub typhus

Scrub typhus is a severe febrile illness reported from many parts of India, caused by rickettsial pathogens *Orientia tsutsugamushi*, and is characterized by an eschar, lymphadenopathy, multisystem involvement and a rapid response to doxycycline. CNS involvement in scrub typhus in the form of meningitis/ meningoencephalitis has been recently reported from India and it has emerged as a new aetiological agent causing AES [7]. Recently, scrub typhus has been reported from North India, particularly from Uttar Pradesh and Bihar, Among 25% AES cases as an infectious aetiology in one third of the AES cases in India [29,48].

5.4.2 *Mycobacterium tuberculosis*

Mycobacterium tuberculosis is a causative agent of tuberculous meningitis (TBM) and is the most

common form of central nervous system (CNS) tuberculosis. TBM is responsible for high frequency of neurologic sequelae and mortality if not treated timely. TBM is associated with the multifactorial risk including diabetes mellitus, alcoholism, dystrophia, cell mediated immune mechanism defects, commonly exist in the patients with human immunodeficiency virus (HIV) infection or other immunosuppressive disease, and in even in immunocompetent individuals [48]. The risk factors of the TBM, including dystrophia, alcoholism, diabetes mellitus and cell-mediated immune mechanism defects, commonly exist in the patients with human immunodeficiency virus (HIV) disease, immunosuppressive diseases, and even in immunocompetent individuals [52,53].

5.5 Fungal Aetiology of AES

The most common form of fungal meningitis is *Cryptococcus neoformans* (mainly found in dirt and bird droppings). Cryptococcal meningitis most often occurs in people who are immunocompromised and suffering with AIDS, but also in healthy people. Although treatable, fungal meningitis often recurs in half of affected individuals [48]. Fungal meningitis is treated with high-dose antifungal agents, usually given in hospital IV, and the use of new azoles in such kind of fungi infections [54,55].

5.6 Parasitological Aetiology of AES

Parasitic causes include cysticercosis (tapeworm infection in the brain), which is common in Southeast Asia, including India, Cerebral malaria caused by *Plasmodium falciparum* is an important agent of AES in India. There are rare cases of amoebic meningitis, sometimes related to freshwater swimming, which can be rapidly fatal in AES cases [7].

5.7 Non-infectious Aetiology of AES

In addition, many of non-infectious conditions can contribute to cause encephalopathic syndromes. These include neoplastic diseases, intracranial malignancy and cysts, drugs, toxins, acute disseminated encephalomyelitis, cortical-venous thrombosis, neuroleptic malignancy syndrome, collagen vascular disorders and other systemic metabolic disorders [7]. Therefore, such conditions should be addressed timely to prevent AES neurological sequelae.

5.7.1 Current status of AES in Bihar

A recent outbreak of AES in June 2019 was found in Muzaffarpur and the adjoining districts of

Bihar state in India reported the Muzaffarpur district administration has initiated an investigation into the case of 672 children who were admitted with AES. More than 150 children have died because of AES across various districts of Bihar. AES has affected 222 blocks in 12 districts of Bihar. AES, incidentally, is an umbrella medical condition named by WHO where children are admitted with neurological manifestations which include mental confusion, disorientation, convulsion, delirium or coma [56].

Common risk factors linking the outbreaks are the hot and humid months of May and June. Also, all the children suspected (with AES) were from rural area and low-income families and are severely malnourished. In their study, John and colleagues had also identified a fruit toxin in unripe litchis as responsible for triggering low sugar levels (hypoglycaemia) and subsequently AES among children already suffering from malnutrition [57]. "The toxin methylene-cyclopropyl-glycine (MCPG) in unripe litchi is merely a trigger and important predisposing factor for malnutrition in Bihar. Most of the deaths have been attributed to low blood sugar level (hypoglycaemia). Another study in 2017 by researchers from India's National Centre for Disease Control (NCDC) and the CDC, Atlanta USA corroborated the litchi toxin link. The study linked these seasonal deaths of children to consumption of litchi fruits laden with two naturally occurring toxins hypoglycin A and MCPG [58].

6. LABORATORY ALGORITHM OF AES

Early diagnosis and proper management of JE & AES cases aimed to reduce case fatality through, strengthening of diagnostic and clinical management of JE cases, at primary health care facility (PHCs/CHCs) and district hospitals [3].

In order to avoid AES and JE related morbidity, mortality and complications in endemic areas, estimation of the actual disease burden and development of appropriate control measures need to be intensified in JE and AES endemic areas. AES burden can be estimated satisfactorily if the facilities for the diagnosis of AES are made available at district level hospitals in India.

Diagnosis of cerebral malaria requires demonstration of asexual form of *P. falciparum* in peripheral blood smear, in thick and thin blood smear films stained by Giemsa stain and antigen detection by rapid card test and polymerase chain reaction (PCR).

The diagnosis of cysticercosis including radiodiagnosis—computed tomography scan (CT) and magnetic resonance imaging (MRI) and antigen or antibody detection by enzyme linked immunosorbent assay technique (ELISA) [3,50] as shown in Figs. 7 and 8.

7. CONCLUSION

Today, world is more concerned about the non-communicable diseases, but still some part of world is battling with these kinds of infections especially in northeast part of India, therefore it is important to identified accurate aetiology of AES for the management. In a resource limited country like India, testing all the AES samples for all the possible pathogens is a remote possible. Therefore, an algorithmic approach for the diagnosis of encephalitis is advocated which may serve many purposes, including patient management, research, and facilitating public health disease surveillance.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric

- Allergy immunology and Infection Group National Guidelines. *J Infect.* 2012;64:449-77.
2. World Health Organization. Acute encephalitis syndrome. Japanese encephalitis surveillance standards. January 2006. From WHO-recommended standards for surveillance of selected vaccine preventable diseases. WHO/V&B/03.01. Available:<http://www.WHO.int/vaccinesdocuments/DocsPDF06/843> (Accessed on 8 August, 2012)
 3. Guidelines clinical management of Acute Encephalitis Syndrome including Japanese Encephalitis. Government of India. Directorate of National Vector Borne Disease Control Programme 22, Shamnath Marg, Delhi-110054 Directorate General of Health Services, Ministry of Health & Family Welfare.
 4. Ghosh D, Basu A. Japanese encephalitis-a pathological and clinical perspective. *PLoS Negl Trop Dis.* 2009;3:e437.
 5. Tsai TF. Factors in the changing epidemiology of Japanese encephalitis and West Nile fever. In: Saluzzo JF, editor. *Factors in the Emergence of Arboviral Diseases.* Amsterdam: Elsevier; 1997; 179–89.
 6. Joshi R, Kalantri SP, Reingold A, Colford JM Jr. Changing landscape of acute encephalitis syndrome in India: A systematic review. *Natl Med J India.* 2012; 25(4):212-20.
 7. Ravi V, Mani R, Govekar S, Desai A, Lakshman L, et al. Aetiology and Laboratory Diagnosis of Acute Encephalitis Syndrome with Special Reference to India. *J Commun Dis.* 2014;46:12-23.
 8. Tiwari JK, Malhotra B, Chauhan A, Malhotra H, Sharma P, Deeba F, et al. Aetiological study of viruses causing acute encephalitis syndrome in North West India. *Indian J Med Microbiol.* 2017;35: 529-34.
 9. Cassady KA, Whitley RJ. Pathogenesis and pathophysiology of viral infections of the central nervous system. In: Scheld WM, Whitley RJ, Durack DT (eds). *Infections of the nervous system.* Lippincott-Raven, Philadelphia. 1997; 722.
 10. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al. The management of encephalitis: Clinical practice guidelines by the infectious diseases society of America. *Clin Infect Dis.* 2008;47:303-27.
 11. Yong YK, Chong HT, Wong KT, Tan CT, Devi S. Aetiology of viral central nervous system infection, a Malaysian study. *Neurol Asia.* 2008;13:65-71.
 12. Tiwari S, Singh RK, Tiwari R, Dhole TN. Japanese encephalitis: A review of the Indian perspective. *Braz J Infect Dis.* 2012; 16:564–73
 13. Sen PK, Dhariwal AC, Jaiswal RK, Lal S, Raina VK, Rastogi A. Epidemiology of acute encephalitis syndrome in India: Changing Paradigm and Implication for Control. *J. Commun. Dis.* 2014;46(1):4-11. [ISSN: 0019-5138]
 14. World Health Statistics 2015. Geneva: World Health Organization; 2015. Available:https://www.who.int/gho/publications/world_health_statistics/2015/en/
 15. Japanese encephalitis. National Institute of Virology. New Delhi: Indian Council of Medical Research. Available:www.icmr.nic.in/pinstitute/niv/JAPANESE%20ENCEPHALITIS.pdf (Accessed on 15 Jul 2017)
 16. Mishra G, Jain A, Prakash O, Prakash S, Kumar R, Garg RK, Pandey N, Singh M. Molecular characterization of dengue viruses circulating during 2009-2012 in Uttar Pradesh, India. *J Med Virol.* 2015 Jan;87(1):68-75. DOI: 10.1002/jmv.23981
 17. Kumar R, Tripathi S, Tambe JJ, Arora V, Srivatsava A, Nag VL. Dengue encephalopathy in children in Northern India: clinical features and comparison with non-dengue. *J Neurol Sci.* 2008;269(1-2): 41-48.
 18. Koshy JM, Joseph DM, John M, Mani A, Malhotra N, Abraham GM, et al. Spectrum of neurological manifestations in dengue virus infection in Northwest India. *Trop Doct.* 2012;42(4):191-4.
 19. Chikungunya. World health Organization. Available:https://www.who.int/denguecontrol/arbo-viral/other_arboviral_chikungunya/en/
 20. Chikungunya Virus Home. Geographic Distribution Centre for disease control and prevention, Atlanta USA. Available:<https://www.cdc.gov/chikungunya/transmission/index.html>
 21. George S, Gourie-Devi M, Rao JA, Prasad SR, Pavri KM. Isolation of West Nile virus from the brains of children who had died of

- encephalitis. Bull World Health Organ. 1984;62:879-82.
22. John TJ, Verghese VP, Arunkumar G, Gupta N, Swaminathan S. The syndrome of acute encephalitis in children in India: Need for new thinking. Indian J Med Res. 2017;146(2):158–161.
 23. DeBasi RL, Tyler KL. Recurrent aseptic meningitis. In: Davis LE, Kennedy PGE, eds. Infectious diseases of the nervous system. Oxford: Butterworth-Heinemann. 2000;445–80.
 24. Davis LE. Diagnosis and treatment of acute encephalitis. The Neurologist. 2000; 6:145–59.
 25. Chaudhuri A, Kennedy PGE. Diagnosis and treatment of viral encephalitis Postgrad Med J. 2002;78:575–583.
 26. Ramamurthy M, Alexander M, Aaron S, Kannangai R, Ravi V, Sridharan G, et al. Comparison of a conventional polymerase chain reaction with real-time polymerase chain reaction for the detection of neurotropic viruses in cerebrospinal fluid samples. Indian J Med Microbiol. 2011; 29:102-9.
 27. Rathore SK, Dwibedi B, Kar SK, Dixit S, Sabat J, Panda M, et al. Viral aetiology and clinico-epidemiological features of acute encephalitis syndrome in eastern India. Epidemiol Infect. 2014;142:2514-21.
 28. Beig FK, Malik A, Rizvi M, Acharya D, Khare S. Etiology and clinico-epidemiological profile of acute viral encephalitis in children of Western Uttar Pradesh, India. Int J Infect Dis 2010;14: e141-6.
 29. Jain P, Jain A, Kumar A, Prakash S, Khan DN, Singh KP, et al. Epidemiology and etiology of acute encephalitis syndrome in North India. Jpn J Infect Dis. 2014;67:197-203.
 30. Granerod J, Crowcroft NS. The epidemiology of acute encephalitis. Neuropsychol Rehabil. 2007;17:406-28.
 31. Surveillance and outbreak alert. Nipah Virus. Outbreak of Nipah virus encephalitis in Kerala state of India WHO in South-East Asia. Available:http://www.searo.who.int/entity/merging_diseases/links/nipah_virus/en/
 32. Rao BL, Basu A, Wairagkar NS, Gore MM, Arankalle VA, Thakare JP, et al. A large outbreak of acute encephalitis with high fatality rate in children in Andhra Pradesh, India, in 2003, associated with Chandipura virus. Lancet. 2004;364:869–874.
 33. Bhatt PN, Rodrigues FM. A new arbovirus isolated in India from patients with febrile illness. Chandipura. Indian J Med Res 1967;55:1295–1305.
 34. Chadha MS, Arankalle VA, Jadi RS, Joshi MV, Thakare JP, Mahadev PV, et al. An outbreak of *Chandipura virus* encephalitis in the eastern districts of Gujarat state, India. Am J Trop Med Hyg. 2005;73:566-570.
 35. Investigation of outbreak of encephalitis in Nanded district and some districts of Vidarbha region of Maharashtra, Annual Report 2003–2004. National Institute of Virology (NIV), Pune. 2004;3–4.
 36. Encephalitis in Bhandara and Nagpur, Maharashtra, Annual Report 2005–2006. National Institute of Virology (NIV), Pune. 2006;8(25).
 37. Tandale BV, Tikute SS, Arankalle VA, Sathe PS, Joshi MV, Ranadive SN, et al. Chandipura virus: A major cause of acute encephalitis in children in North Telangana, Andhra Pradesh, India. J Med Virol. 2008;80:118–24.
 38. Narain JP, Dhariwal AC, MacIntyre CR. Acute encephalitis in India: An unfolding tragedy. Indian J Med Res. 2017;145(5): 584–587.
 39. Ghosh S, Basu A. Acute Encephalitis Syndrome in India: The Changing Scenario. Ann Neurosci. 2016;23(3):131–133.
 40. Kumar P, Pisudde PM, Sarthi PP, Sharma MP, Keshri VR. Status and trend of acute encephalitis syndrome and Japanese encephalitis in Bihar, India. Natl Med J India. 2017;30:317-20. Available:<http://www.nmji.in/text.asp?2017/30/6/317/239070>
 41. Karmarkar SA, Aneja S, Khare S, Saini A, Seth A, Chauhan BK, et al. A study of acute febrile encephalopathy with special reference to viral etiology. Indian J Pediatr. 2008;75:801-5.
 42. Flexner S. Experimental cerebrospinal meningitis in monkeys. J Exp Med. 1907;9 (2):142–167. DOI:10.1084/jem.9.2.142.
 43. Hoffman O, Weber RJ. Pathophysiology and treatment of bacterial meningitis. Ther Adv Neurol Disord. 2009;2(6):1–7.
 44. Mani R, Pradhan S, Nagarathna S, Wasiulla R, Chandramuki A. Bacteriological profile of community acquired acute bacterial meningitis a ten-year retrospective study in a tertiary

- neurocare centre in south India. Indian Journal of Medical Microbiology. 2007;25 (2):108-114.
45. Aneja S, Aggarwal A. Acute Bacterial Meningitis. Indian Paediatrics. 1997;(34): 1097-1109
46. WHO Expert Committee and WHO Statistics. Statistics about Meningitis. Prevalence and incidence statistics for meningococcal Meningitis Global health observatory data; 2011. Available:http://www.who.int/gho/epidemic_diseases/meningitis/en/.
47. Kabra SK, Kumar P, Verma IC, Mukherjee D, Chowdhary BH, Sengupta S, et al. Bacterial meningitis in India-an IJP survey. Indian J Pediatr. 1991;58:505-511.
48. Das P. Infectious disease surveillance update. Lancet Infect Dis. 2005;5: 475–6.
49. Jayaraman Y, Veeraraghavan B, Chethrapilly Purushothaman GK, et al. Burden of bacterial meningitis in India: Preliminary data from a hospital-based sentinel surveillance network. PLoS One. 2018;13(5):e0197198.
50. Sastry AS, Bhat SK. Essentials of medical microbiology. IInd ed. Jaypee Brothers medical Publishers. 2019; 504-06.
51. Singh AK, Kumar A, Gaur V, Jasuja K, Pandey J, Mishra R. Bacteriological profile of acute bacterial meningitis at a tertiary care hospital of North India. Int J Res Med Sci. 2016;4:4387-93.
52. Grace E. Marx and Edward D. Chan, Tuberculous meningitis: Diagnosis and treatment overview. Tuberculosis Research and Treatment. 2011;9. [Article ID 798764] Available:<https://doi.org/10.1155/2011/798764>
53. Luo M, Wang W, Zeng Q, Luo Y, Yang H, Yang X. Tuberculous meningitis diagnosis and treatment in adults: A series of 189 suspected cases. Exp Ther Med. 2018;16 (3):2770–2776.
54. Meningitis and encephalitis fact sheet. National Institute of Neurological Disorders and Stroke. National Institutes of Health Bethesda MD. 2018;1-14. Available:<https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Meningitis-and-Encephalitis-Fact-Sheet>
55. Meningitis. Paediatr Child Health. 2001; 6(3):126–127. DOI:10.1093/pch/6.3.126 Available:<https://doi.org/10.1093/pch/6.3.126>
56. Srivastava A. Bihar encephalitis outbreak: Litchi alone not responsible for spread of AES among children. India Today; 2019. Available:<https://www.indiatoday.in/india/story/bihar-encephalitis-outbreak-litchi-alone-not-responsible-for-spread-of-aes-among-children-1559237-2019-06-30>
57. John TJ, Das M. Acute encephalitis syndrome in children in Muzaffarpur: Hypothesis of toxic origin. Curr. Sci. 2014; 106:1184–1185.
58. Srivastava V. Bihar's annual AES outbreaks continue to mystify. Nature India. DOI:10.1038/nindia.2019.82 Available:<https://www.natureasia.com/en/inindia/article/10.1038/nindia.2019.82>

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