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India's crises-acute encephalitis syndrome: A review

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Abstract
Encephalitis refers to acute inflammatory process affecting the brain. AES may present as encephalitis, meningoencephalitis or meningitis and may be caused by viruses, bacteria, mycobacteria, rickettsia and rarely by toxoplasma. Encephalitis is an inflammation of the brain tissue. The most common cause is viral infections. In rare cases, it can be caused by bacteria or even fungi. Viral infections are most common and important cause of encephalitis. JE and Dengue are more prevalent in South East Asia1.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, this is a systematic review of published studies to understand the altering backdrop of AES in India.

Keywords: encephalitis, acute encephalitis syndrome, Japanese encephalitis syndrome, aetiological agents

Introduction
Encephalitis is an inflammation of the brain tissue. The most common cause is viral infections. In rare cases, it can be caused by bacteria or even fungi. There are two main types of encephalitis: primary and secondary. Primary encephalitis occurs when a virus directly infects the brain and spinal cord. Secondary encephalitis occurs when an infection begins in another part of the body and then spreads to your brain. Encephalitis is a rare but serious, life- threatening disease [1].

Symptoms of encephalitis
The symptoms of encephalitis can range from mild to severe.

Mild symptoms include
- Fever
- Headache
- Vomiting
- Stiff neck
- Lethargy (exhaustion)

Severe symptoms include:
- Fever of 103°F (39.4°C) or higher
- Confusion
- Drowsiness
- Hallucinations
- Slower movements
- Coma
- Seizures
- Sensitivity to light
- Unconsciousness

Infants and young children show different symptoms.
- Vomiting
- Bulging fontanel (soft spot in the scalp)
- Constant crying
- Body stiffness
- Poor appetite

In a tragic story, about fifty children lost their lives in Bihar after consuming toxic lychees. According to several reports, the fruit was infested with viruses and the patients had symptoms similar to those of acute encephalitis syndrome (AES), a deadly brain disease. All children experienced similar symptoms, with a sudden drop in blood sugar that led to their premature death [2].

What is acute encephalitis syndrome (AES)?
AES affects the central nervous system, mainly in children and young adults. Start with a high fever, then alter neurological functions causing mental disorientation, seizures, confusion, delirium and coma. The epidemic is usually reported during the monsoons (June-October). However, the incidence is also reported in April-June in Bihar. Acute encephalitis syndrome (AES), which has claimed the lives of more than 100 people in the Muzaffarpur region of Bihar, is a serious neurological disease that causes inflammation of the brain.
The symptoms of AES, commonly known as "chamki bukhar", may include headache, fever, confusion, stiff neck and vomiting. The disease most often affects children and young adults and can lead to mortality.
According to the National Health Portal (NHP), viruses are the main causative agents of AES cases, although other sources such as bacteria, fungi, parasites, chemicals, toxins and non-infectious agents. They have also been questioned [3].
Encephalitis refers to an acute inflammatory process that affects the brain. AES can be in the form of encephalitis, meningoencephalitis or meningitis and can be caused by viruses, bacteria, mycobacteria, rickettsia and rarely by toxoplasma. Viral infections are the most common and most important cause of encephalitis. JE and dengue are more common in Southeast Asia [4]. As part of the efforts to control JE, the World Health Organization (WHO) provides a set of standards for JE surveillance, which require the identification of patients with AES [5, 6]. According to the WHO clinical case definition, the

AES is defined as an acute onset of fever and a change in mental status, including symptoms such as confusion, disorientation or inability to speak and / or a new onset of seizures, excluding Febrile seizures in a person of any age at any time of the year [7].

What is Japanese Encephalitis?

Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia [8]. It is a mosquito-borne disease caused by a flavivirus that circulates between birds, pigs and humans [9]. JE is caused by a zoonotic flavivirus which is one of the common causes of AES. EJ is difficult to eradicate because it is transmitted from natural reservoirs such as pigs, birds which are important amplifying hosts and humans are implicated as accidental hosts. JE has been effectively controlled by vaccination programs in several Asian countries such as Japan, Korea, China and Thailand [10]. Culex tritaeniorhyncus is the main vector for JE in Nepal.

Pathophysiology and pathogens

Encephalitis is an inflammation of the brain tissue. Once the virus enters the blood, it begins to migrate to the brain tissue and multiplies in number. As soon as the signal reaches our immune system, it generates a response in the form of an inflamed brain or we can say an inflamed brain. When this self-generated response and this infection combine, it leads to viral encephalitis and mainly affects the spinal cord and our central nervous system causing damage to brain cells by blood vessels infected with the virus [11].

Acute encephalitis syndrome (AES) is a serious public health problem in India. It is characterized by an acute onset of fever and a change in mental state (mental confusion, disorientation, delirium or coma) and / or a new onset of convulsions in a person of any age at any time of the year. The disease most often affects children and young adults and can cause considerable morbidity and mortality [12].

Viruses are the main causative agents of cases of AES, although other sources such as bacteria, fungi, parasites, spirochetes, chemicals, toxins and non-infectious agents have also been reported in the past few years. Past decades [13].

The Japanese encephalitis virus (JEV) is the main cause of SEA in India (between 5% and 35%). Herpes simplex virus, influenza a virus, West Nile virus, Chandipura virus, mumps, measles, dengue, parvovirus B4, enterovirus, Epstein-Barr virus and typhus brush, S. pneumoniae are the other causes. AES sporadically and epidemics in India. The Nipah virus, the Zika virus are also found as causative agents of AES. The etiology in a large number of SEA cases has not yet been identified [14].

This syndrome is very complex. It can be caused by viruses, bacteria, fungi and various agents. The Japanese encephalitis virus (JE) is the most common cause of SEA in India, and it is estimated that the union health ministry accounts for between 5 and 35% of cases due to JE. But the syndrome is also caused by typhus, dengue, mumps, measles and even the Nipah or Zika virus [15].

The AES associated with the pathogen can be distinguished from other etiologies of encephalopathy by considering its essential characteristics: sudden onset of fever; cerebrospinal fluid including inflammatory cells or confirmation based on MRI and the presence of pathogenic antibodies or specific antibodies [16, 17].

The causative agents of AES associated with pathogens can be classified into six main independent categories: viral, bacterial, parasitic, spirochetes, fungi and their toxins. The Japanese encephalitis virus (JEV) is the main cause of viral AES in Southeast Asia [18]. Other predominant viral agents that are not JEVs are HSV, enterovirus, Coxsackie virus, dengue virus, Nipah virus (NiV) and HIV. Bacterial AES can be caused by Leptospira, Mycobacterium tuberculosis, Brucella, Orientia tsutsugamushi (Scrub typhus) and Ehrlichia chaffeensis [19]. It is also known that certain parasites cause AES, such as Trypanosomes cruzi, Schistosoma mansoni, Toxoplasma gondii and Plasmodium falciparum [20].

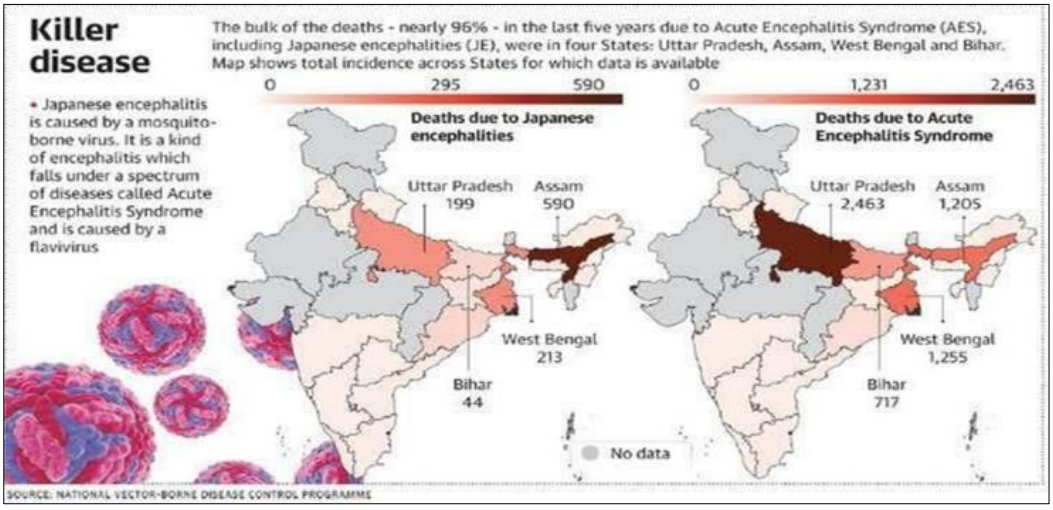

Fig 1

Why are children more at risk here?

It has been determined that infant mortality rates are the highest among all those affected.

The reason for this is the lack of nutrition, which leads to an inadequate blood sugar level and also compromises your immunity.

Relationship between hypoglycemia, children and AES

Bihar government officials say that BSE is a syndrome, not a disease, and it has been discovered that the cause of death in these children was prolonged hypoglycemia which resulted in delayed treatment. In 2014, the research work entitled “Epidemiology of acute encephalitis syndrome in India: paradigm shift and implication for control”, co- author of six researchers, established a parallel between Muzaffarpur and the Vietnamese province of Bac Giang, where the children Malnutrition suffered from SAE and hypoglycemia which coincided with the lychee orchards in the neighborhood. "The possible association with a toxin in lychee or in the environment must be documented. Methylenecyclopropylglycine (MCPG), which is known to contain lychee fruit, has been shown to cause hypoglycemia in laboratory animals, "said the study. The study found that several children in Muzaffarpur who suffered from SEA before 2014 have a history of visits to lychee orchards. The impact is worse in malnourished children who remain hungry for several hours [3].

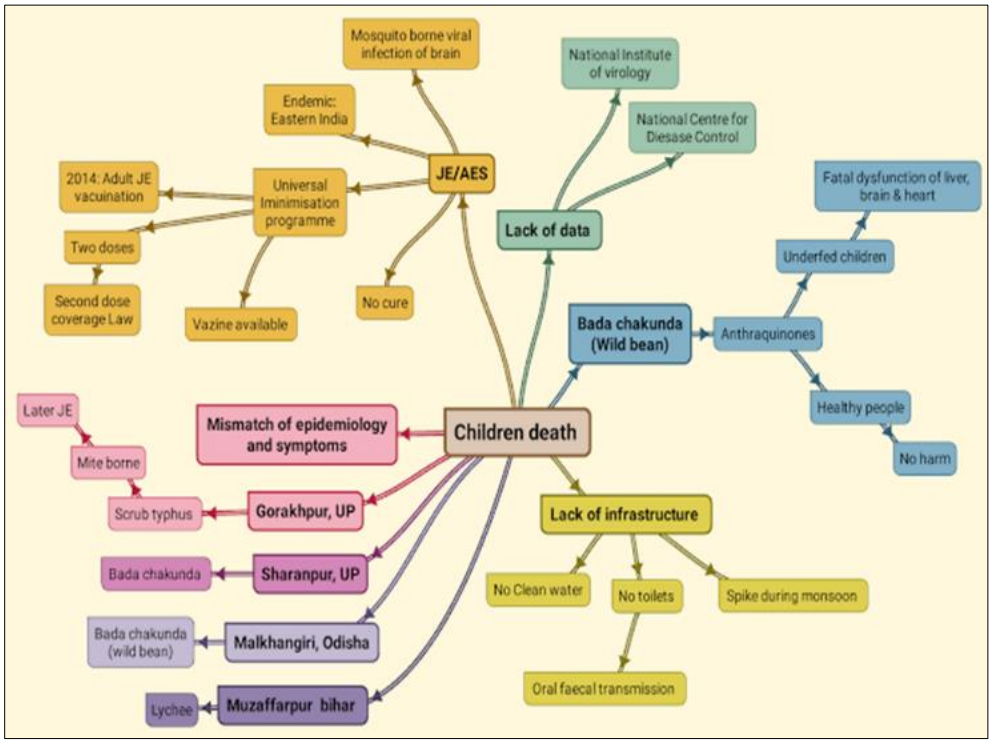

Fig 2: Some parameters related to death from acute encephalitis syndrome and Japanese encephalitis syndrome

Malnourishment a key

"The association of lychees and deaths from the presence of infectious organisms is well documented, but we cannot attribute this factor solely as a cause of death. There are many factors,” says Dr. Om Srivastava, an infectious disease expert. He added that hypoglycemia itself is not sufficient reason to explain the death unless the condition continues and cannot be corrected. “There are other contributing factors that increase the risk of death. Malnutrition is one,” he said. Dr. Arun Shah, former president of Bihar of the Association of the Indian Academy of Pediatrics, said: "A center for disease control, the Atlanta team and the virologist CMC Vellore, the findings of Dr. Jacob John in the past has been reduced to malnutrition, heat, humidsity and poor hygiene as reasons for SEA.” The onset of AES is mainly reported in the morning, especially when a child is missing food the night before and the blood sugar is going down again. "A malnourished child has no liver sugar reserves," says Shah. He says that even if eating lychee or its seeds has nothing to do with AES, it is possible that malnourished children who eat unripe or rotten lychee may experience an aggravated AES due to toxins (MCPG). Present in lychee [3].

Management

The management of acute encephalitis can be guided by a practical approach involving 3 “Es”: emergent issues, epilepsy, and etiology. An overview of acute management of patients is provided in the figure, and typical doses of therapeutic agents are listed in table 3.

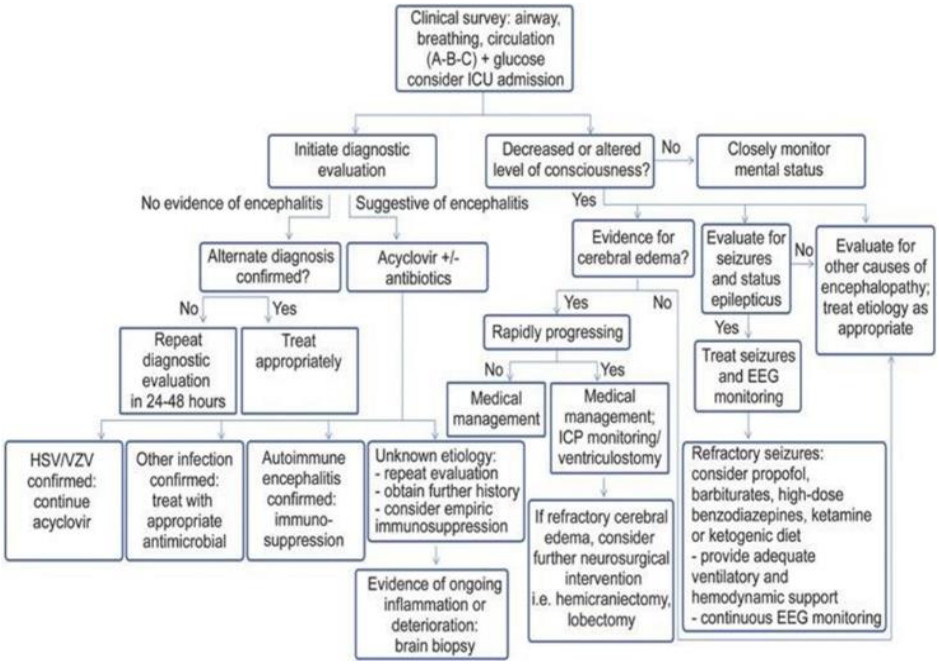

Fig 3: Approach to management of patients with suspected encephalitis

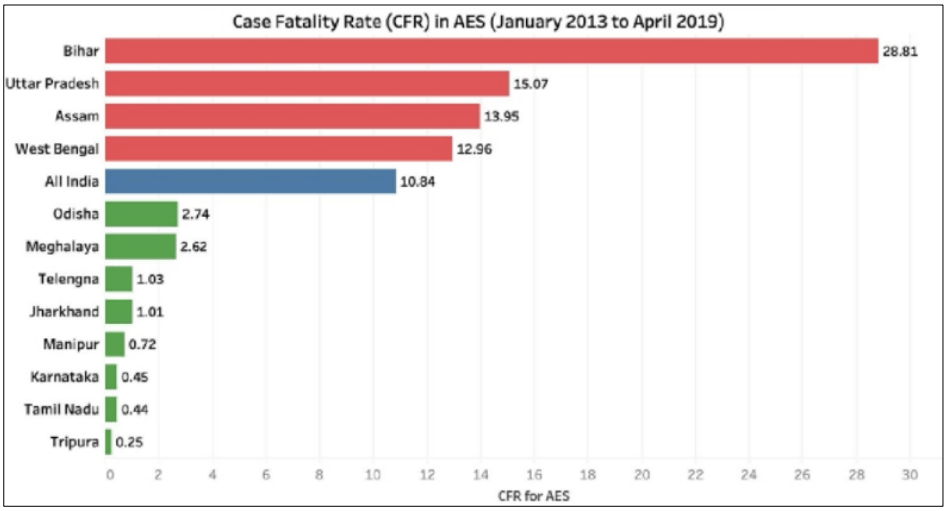

Fig 4: case fatality rate in AES (January 2013 to April)

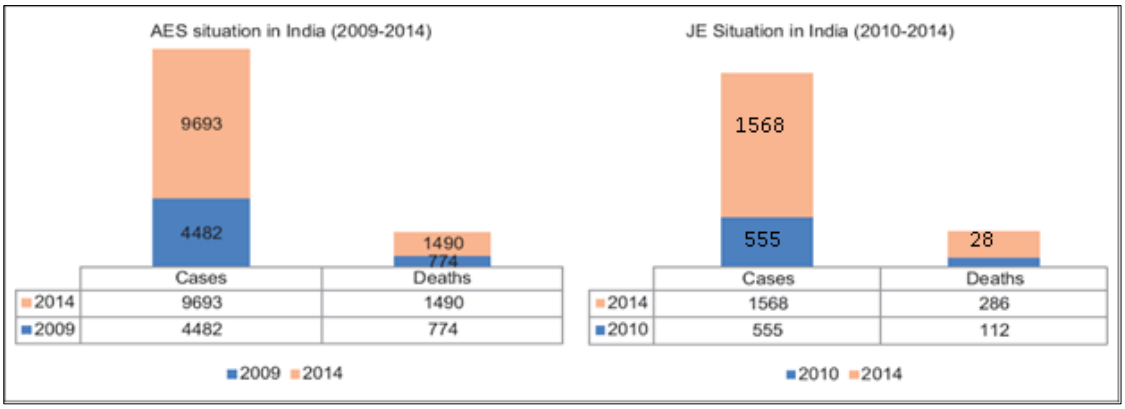

Fig 5: cases and deaths of AES and JE situations in India (2019-2014)

Treatment

Table 3: Therapeutics agents commonly used in encephalitis

Indication	Typical dosing/administration[a]
Cerebral edema[e8]	Mannitol 0.25 to 1 g/kg bolus every 4–6 hours
	Hypertonic saline
	Active brain herniation, 23% saline (30 mL bolus via central venous access)
	Maintenance, 2%–3% saline (250–500 mL boluses or continuous venous infusion; 3% saline via central venous access)
Seizures and status epilepticus[e12]	
First line, initial dosing	Lorazepam 0.1 mg/kg IV up to 4 mg per dose
	Midazolam 0.25 mg/kg IM up to 10 mg maximum
	Diazepam 0.15 mg/kg IV up to 10 mg per dose
Second line, initial dosing	Fosphenytoin 20 mg PE/kg IV
	Levetiracetam 1,000–3,000 mg IV
	Valproate sodium, 20–40 mg/kg IV
Third line, loading dose	Propofol 1–2 mg/kg
	Phenobarbital 20 mg/kg IV
	Pentobarbital 5–15 mg/kg IV
Herpes simplex encephalitis[17]	Acyclovir, 10 mg/kg IV q 8 hrs × 14–21 days
Autoimmune encephalitis, acute[e16,e17]	
First line	Methylprednisolone 1,000 mg IV q day × 5 days
	IV immunoglobulin, 0.4 g/kg IV q day × 5 days
	Plasma exchange, 5–7 exchanges administered every other day
Second line	Cyclophosphamide, body surface area × 800 mg IV
	Rituximab, 1,000 mg IV × 1, followed by second dose in 2 weeks

[a]Drugs and dosing recommendations are provided only as guide; clinical conditions and drug effects must be carefully considered prior to drug administration.

Discussion

Our investigation includes the different areas which are affecting by Japanese encephalitis syndrome and acute encephalitis syndrome. These are deadly syndrome among the all over India. It has been reported that every year the cases of this disease spread very fast there has been a rise in cases between 2008 and 2014, with nearly 44, 000 cases and 6000 deaths reported from India alone, particularly in Bihar, where children have repeatedly fallen prey to this disease. Japanese encephalitis (JE) is the most common and most important viral mosquito-transmitted encephalitis in humans, with approximately 30,000 to 50,000 cases and 15,000 deaths per year. About 20% to 30% of cases of JE are fatal and 30 to 50% cause permanent neuropsychiatric sequelae [21, 22]. Children remain the main victims of the disease [23, 24]. In India, almost all states have reported cases of JE, with the exception of Jammu and Kashmir, Himachal Pradesh and Uttaranchal [25]. The northeast region (NE region) of India, particularly the upper part of Assam State, has experienced recurrent episodes of JE of varying magnitudes from July to October each year [23].

In India, it has been reported that AES and JE from 171 districts in 19 states. In India, the JE virus has been isolated from more than 15 mosquito species belonging to the genera Culex, Aedes and Anopheles; Culex tritaeniorhynchus and Culex vishnui are considered the main vectors [29]. A major JE outbreak was reported in eastern Uttar Pradesh

(UP) in 2005 with more than 6,000 cases and 1,500 deaths. This led to the introduction of the JE vaccine in endemic areas. The causative agents of AES associated with pathogens can be classified into six main independent categories: viral, bacterial, parasitic, spirochetes, fungi and their toxins. The Japanese encephalitis virus (JEV) is the main cause of viral AES in Southeast Asia [18]. Other predominant viral agents that are not JEVs are HSV, enterovirus, Coxsackie virus, dengue virus, Nipah virus (NiV) and HIV. Bacterial AES can be caused by Leptospira, Mycobacterium tuberculosis, Brucella, Orientia tsutsugamushi (Scrub typhus) and Ehrlichia chaffeensis [19]. It is also known that certain parasites cause AES, such as Trypanosomes cruzi, Schistosoma mansoni, Toxoplasma gondii and Plasmodium falciparum [20] According to the National Health Portal (NHP), viruses are the main causative agents of AES cases, although other sources such as bacteria, fungi, parasites, chemicals, toxins and non-infectious agents.

Conclusion

This review article conclude the different factors and cases of death also it conclude the different causative agents of acute encephalitis and Japanese encephalitis syndrome. The symptoms of AES, commonly known as "chamki bukhar", may include headache, fever, confusion, stiff neck and vomiting. The disease most often affects children and young adults and can lead to mortality.

It has been determined that infant mortality rates are the highest among all those affected. The reason for this is the lack of nutrition, which leads to an inadequate blood sugar level and also compromises our immunity.

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