Acute Encephalitis Syndrome in India: Complexity of the Problem

Milind M. Gore*

Abstract

Acute encephalitis syndrome (AES) is an epidemiological term used to describe central nervous system disease due to infectious causative organism. AES is a serious condition needing critical care. High mortality rates and residual deficit in survivors also stresses the seriousness of the problem. AES occurs as a sporadic case or can be seen in the form of outbreaks. Many viral, non-viral causes have been investigated and identified in India with a sizeable number of cases still with unidentified causes. The review is aimed at compiling the reports from various laboratories in India to compare the incidence, seasonality and the complexity in diagnosis, management, and prevention.

Keywords: AES, JE, aetiology, India.

Introduction

India is a vast country with multiple weather and terrain patterns to give rise to tremendously divergent ecological presentations. This, mixed with differences in periodicity of monsoon seasons, agricultural and animal husbandry practices, and socio-economic and cultural differences gives rise to myriad mixture of situations. As children are more vulnerable, they face the brunt of all these in the form of sporadic and outbreak situations.

In order to capture a large number of cases of encephalitis, a broad definition was introduced for surveillance by WHO as Acute encephalitis syndrome (AES) on the lines of Acute flaccid paralysis (AFP). Clinically, a case of AES is defined as a person of any age, at any time of year, with acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures).

Various levels of surveillance systems exist in our country. National Vector Borne Diseases Control Program (NVBDCP), State Government laboratories, and Indian Council of Medical Research (ICMR) through its network of labs also contribute in tracking the AES. The major data compilation is carried out by NVBDCP and according to its website, number of AES cases with or without definitive diagnosis is depicted in fig 1. Large numbers of cases are reported from Assam and Uttar Pradesh.

Figure 1. Statewise mean AES incidence in India (Data from NVBDCP website)  

*Scientist G and Officer in Charge, National Institute of Virology, Gorakhpur Unit, BRD Medical College Campus, Gorakhpur- 273013. E-mail: gore.milind@gmail.com
There are a large number of causative agents that can give clinical presentation of AES. They belong to bacterial, parasitic, fungal and viral. Many of these occur as sporadic and a few of them occur in outbreak form. Defining the causal relationship between a microbe and encephalitis is complex. Granerod et al.9 gives a detailed account of etiological entities. In the Indian context, in addition to the sporadic causes of AES, many viral causes in the form of sporadic cases have been detected. Sporadic encephalitis and encephalopathies that have been associated with viral infections are caused by Herpes simplex viruses (HSV), rabies, Epstein Barr virus (EBV), measles, mumps etc. In addition, in a large outbreak of Chikungunya (CHIK) and dengue viruses, a few encephalitis and encephalopathy cases have been detected.7 Viral diseases and encephalitis can occur in the form of outbreaks also. In India, Japanese encephalitis virus (JEV) and Chandipura virus (CHPV) have been known to cause large scale outbreaks in various parts of the country. West Nile virus encephalitis that was detected as sporadic cases earlier also seems to be emerging as outbreak in Assam and Kerala. In eastern Uttar Pradesh (UP), outbreaks of Enterovirus encephalitis are also seen. This review deals with each of these dominant causative agents, its geographical spread, seasonality, morbidity and mortality. In addition, probable control measures and problems in diagnosis will also be dealt with.

Diagnosis of AES cases

Diagnosis of encephalitis has always been a challenge to clinicians and public health investigators. Of all the pathogens reported to cause encephalitis, the majority are viruses. However, despite extensive testing, the aetiology of encephalitis remains unknown in most patients.8 However, it is not necessary to know the causative agent of all the cases as most of the viral encephalitis cases can be treated and managed based on the symptoms.

Clinico-pathological diagnosis of AES is carried out based on series of clinical and routine laboratory findings. Analysis of cerebrospinal fluid (CSF) for cells, proteins and sugar level can differentiate between viral and bacterial causes of AES. A confirmatory diagnosis by bacterial culture can also be done. Many a times, based on the clinical signs and symptoms only antibacterial and anti-tubercular therapy is instituted and response to the therapy is taken as confirmation of clinical diagnosis.

In order to understand the contribution of various methods and diagnosis of encephalitis, studies have been conducted in USA and UK. In California Encephalitis Project, undertaken from 1998 through 2005, a total of 1570 patients were enrolled in ten clinical profiles. A confirmed or probable etiological agent was identified for 16% of cases of encephalitis: An additional 13% of cases had a possible aetiology identified.9 This rate dropped to 17% in encephalitis patients. Enteroviruses were causative factor in large number of cases of aseptic meningitis.10 In another multicentric study in UK, out of 203 patients with encephalitis, 86 patients (42%) had infectious causes, which included HSV, varicella zoster virus (VZV), and Mycobacterium tuberculosis (M.tb). Out of the remaining cases, seventy five had unknown causes and 42 patients had acute immune mediated encephalitis.11 In JE endemic areas of south east Asia like Thailand, Vietnam etc. confirmed that JE diagnosis is seen in about 18-20% of the cases only.

Definitive diagnosis of CNS viral infection is dependent upon either virus isolation from CSF or brain biopsy, or the demonstration of a virus specific intrathecal antibody response. Laboratory investigations such as viral culture although specific, lack sensitivity and frequently fail to provide results within a clinically useful period.12 Advent of Polymerase chain reaction (PCR) assays for detection of organism has added a new dimension to the diagnostic methods. However, the detection of the organism depends upon the duration between sample collection and onset of the disease. The virus can be detected in the first few days only.

Outbreak situation

Outbreak is occurrence of similar illness in a defined season and locality. Thus there will be pattern of similar cases occurring within a specific ecological niche. In an outbreak situation, confirmation of diagnosis in few cases followed by enumerating clinically similar cases to fix the aetiology is used. Thus diagnosis of each case is not required as a basic epidemiological rule. Occurrence of cases in a particular setting in time and space with similar signs and symptoms can be taken as a diagnosis for all the cases with similar presentation. Other factors like association with known diseases, age distribution, spreading pattern, seasonality are also taken into consideration. Thus identification of causative agent in few cases and clinically correlating them with other cases can be done. A background infection rate and data on persistence of IgM
antibody in subclinical cases also need to be understood. In case of AES, which is a tip of the epidemiological pyramid, subclinical input of fever cases, and less complicated cases in OPD set up also should be taken into consideration before fixing an aetiological causative agent. If the agent is transmitted by a vector or has an amplifying host, demonstration of their role also helps in fixing the etiological causes. Many of these factors are essential to understand, as they will be helpful in developing preventive measures. A vaccination drive, upgradation of routine immunizations, vector control, water and sanitation methods, and public education programs will depend upon the type of agent causing the outbreak.

Japanese Encephalitis Virus

JEV is a flavivirus and it falls under JE serogroup and comprises of five genotypes. Though outbreaks of encephalitis attributed to JEV were reported in Japan as early as 1871, it was not until 1924 that JEV was isolated from a clinical case in Japan. JE is a major seasonal health problem in many rural areas in India and other parts of Asia.\(^{13}\) Two epidemiological patterns of JE are recognized. In southern tropical areas, the disease is endemic with occurrence of sporadic cases throughout the year. In temperate zones and the subtropics, outbreaks have a marked seasonal pattern, usually occurring during the rainy season.\(^{14, 15}\)

JE Virion

JEV is an enveloped virus of ~ 50nm and contains structural proteins envelope (E) and membrane glycoprotein (prM/M) and has nonstructural proteins (NS1-NS5). The virus neutralizing epitopes are present on Envelope protein and thus it is the most important protein in terms of protection and vaccine development.\(^{16}\)

Earliest studies on JEV strain variance were reported by Chen et al.\(^{17}\) who based on 12% nucleotide (ntd) divergence, divided the viruses into 4 genotypes. Using 107 E gene sequences revealed five distinct genotypes of JEV however, it has only one serotype.\(^{18}\) Genotype I includes isolates from northern Thailand, Cambodia, and Korea. This has been isolated from human cases in UP and West Bengal in India.\(^{19, 20}\) Genotype II includes isolates from southern Thailand, Malaysia, Indonesia, and Northern Australia. Genotype III includes isolates from mostly temperate regions of Asia, including Japan, China, India etc and genotype IV includes isolates from Indonesia, mostly those isolated in 1980- 1981. Majority of the viruses studied to date fall into genotype III, suggesting that this genotype has spread the most widely.\(^{14}\) 3D envelope protein structure and antibody neutralization assay with vaccine sera indicated that all genotypes are neutralized and vaccine offers protection.

Transmission

JEV is transmitted by mosquitoes in an enzootic cycle involving birds, particularly wading ardeids such as herons and egrets and pigs. Many mosquito species are potential vectors, but Culex species such as Culex tritaeniorhynchus and Cx. vishnui, which breed in rice paddies and other dirty water, are especially important\(^{21- 24}\) and correlates with outbreaks.\(^{25- 28}\) Although many animals can be infected with the virus, only those which develop high viremia are important in the natural cycle.\(^{29}\) Birds may also be responsible for the spread of JEV to new geographical areas.\(^{13}\) Humans become infected when they are bitten by infected mosquitoes. Although the virus has occasionally been isolated from human peripheral blood, viremia is usually transient and titers low. Humans are therefore considered as dead end hosts from which transmission does not occur. The ratio of apparent to inapparent infections with JEV is quite low (~ 1:100- 1:300) and most human infections are asymptomatic or result in a non-specific flu- like illness.\(^{30}\)

JE in India

In India, JE was first recognized serologically in 1955 followed by isolation 1958\(^{31}\). The first major outbreak occurred in Burdwan and Bankura districts of West Bengal in 1973.\(^{32}\) In India, rise in JE incidence and outbreaks have occurred in 25 states including Odisha and Delhi NCR region.\(^{33}\) JE outbreaks in south India are mainly centred during the months of August to December,\(^{34, 35}\) and in north India during May to October.\(^{33, 41- 45}\) The state of UP has been a constant focus of JEV activity every year. The second half of 2005 saw one of the largest outbreaks of JE in three decades that has occurred in northern India in recent years.\(^{36}\) In UP, after the vaccination drives since 2006, overall incidence of JE has decreased (7.1% of AES). However in Assam, percentage of JE remains high (37.8% of AES).\(^{5}\) Figure 2 depicts average incidence of confirmed JE cases during 2008- 12. Average mortality due to JE has been estimated to be between 14- 16%. In earlier studies, it has been estimated to be about 37%.\(^{3}\)
Serosurveys for anti JE antibodies

Serological response to any virus in normal population gives the extent of circulation of infectious agent. NIV has carried out extensive serological surveys of humans and pigs from different states of India. The survey results have demonstrated a wide prevalence of antibodies to JE virus. During studies on immunogenicity of attenuated JE vaccine at Burdwan, Goa and Gorakhpur region during 2006-2010, it was noted that about 40-45% of children in the age group of 1-15 yrs have neutralizing antibodies against JE virus. Seropositivity increased as per the age group as expected due to yearly exposure to JE infection. Serological evidence of JE virus infection in various animals and birds has also been noted at varying degree. As Culex mosquitoes also bite cattle and goats, absence of viremia indicates that these animals do not have any role in spreading JE in nature and thus can be used as sentinel animals to monitor JE activity.

Clinical features and residual deficits

Detailed clinical and radiological features of various AES patients are given in another article. In endemic regions, young children who lack immunity are the most often affected, while spread of the virus to new regions where immunity is not present in population leads to a wide age range of age groups.

JE vaccines: Existing Vaccines

a) A live JE vaccine produced in primary hamster kidney cells, involving the stable neuro-attenuated SA 14-14-2 strain of JEV, has been licensed for use in China since 1988. Protective efficacy was approximated at 98% after two doses of the vaccine. The vaccine has been introduced in India since 2006 as a single dose vaccine for paediatric age group and millions of doses have been given without any neurovirulence or side effects. Since 2011, the vaccine has been introduced under routine immunization for children aged 9 months-1 year with second dose between 1.5-2 years. The vaccine has also been prequalified by WHO for human vaccine use.

b) Vero cell derived inactivated vaccine manufactured by InterCell Inc (ICS1) and marketed by Biological E in India has been approved in many countries. The vaccine is based on attenuated JE virus strain SA 14-14-2.

c) Vero cell derived inactivated vaccine (JENVAC) manufactured by Bharat Biological International Ltd based on Indian JE virus strain 821564 XY isolated by National Institute of Virology from Kolar Karnataka has been approved for all age groups in India. The virus strain has been stabilized for longer shelf life. Both inactivated vaccines have shown protective ability against all the genotypes of JE virus.
d) Live-attenuated 17D Yellow fever (YF) virus is one of the safest and most effective vaccines ever produced. ChimeriVax-JE is a chimeric vaccine in which the PrM and E genes of attenuated JEV strain SA14-14-2 were inserted into an infectious cDNA clone of the 17D YF vaccine strain. The vaccine has been licensed in many south eastern countries for human use as it shown to be safe and immunogenic.

Comments

JE will keep on posing a major threat in India. Better surveillance, prompt action, and continued vaccination are the keys to prevent human cases in future. Waning of vaccine induced immune response; introduction in newer areas will have to be constantly monitored in future. Development of single dose vaccine capable of giving long term immunity over various genotypes is also needed. In addition, improvement of piggeries, newer very low cost stable vaccines for piglets will help in reducing the burden, if not eradication of this virus. Co-circulation of flavivirus also poses a major problem for surveillance and public health monitoring. More specific diagnostic procedures to differentiate in these with ease of bedside testing need to be developed. Monitoring of mosquitoes, their infectivity, and capability of village level decision making for mosquito preventive methods also are the topics for further work in public health domain.

West Nile Virus

West Nile virus (WNV) is also a flavivirus similar to JEV in many respects. The structure, homology in envelope and other proteins, vectors and the related circulation pattern make it undistinguishable from JE in many respects. In India, serological evidence of WNV activity along with isolations from mosquitoes and humans was seen at low level since early 60s. However, WNV outbreaks as seen in USA since 1998 were not observed. In Assam, during 2007 there was a suspicion of occurrence of WNV encephalitis cases amongst the so called JE positive cases. A detailed analysis and isolation could be achieved during 2008 outbreak and has been seen on a regular basis since then.

World scenario

The natural transmission cycle involves an enzootic (sylvatic) mosquito- bird- mosquito cycle, primarily involving Culex species mosquitoes as primary vectors. In the past decade, however, epidemics/ epizootics have occurred in several countries, including Russia, Romania in Eastern Europe to North African countries including Israel. Since 1999, outbreaks of WNV encephalitis have been occurring on regular basis in Eastern USA and are spreading to Midwest also. Recently, WNV infection has also been reported from Xinjiang, China. Serological evidence of WNV infection in animals has been detected in Nepal also.

WNV is endemic in some parts of India and sporadic cases of the WN virus fever occurred in many areas. Over a span of 30 years and from varied sources, several strains of WN virus have been isolated at NIV. There are reports of WNV isolation from sources as varied as different species of mosquitoes, bats, human blood and even from the brains of children with fatal encephalitis. WNV encephalitis in the form of outbreak was first documented in North- eastern region (NER) of India during the year 2006 from four districts of the state of Assam. Since 2011, WNV encephalitis cases have regularly been reported in Kerala also.

Strain variations and pathogenicity of WN virus isolates

Full genome based phylogeny analysis classified WNV isolates into five distinct genetic lineages. Lineage 1 included all the viruses isolated in USA since 1999. Lineage 2 included some of the eastern European isolates, while lineage 3 and 4 were Rabensburg isolate and Russian isolate. Most of the Indian isolates formed a lineage 5 and were thought to be less pathogenic. However, recent isolates of WNV are from lineage 1.

Comments

Spread of West Nile virus outbreaks is just a question of time, as conditions that allow taking it's root already exist. Its pattern of inducing immunity in pigs and other animals need to be studied to understand the amplifying host. Simultaneously, development of low cost tests to diagnose and differentiate between JE and WN infection needs to be undertaken. Dominant mosquito species and their bionomics also should be studied. As there is no vaccine yet, it is necessary to start vaccine development for WNV infection.

Chandipura

CHPV is a member of the order Mononegavirales, family Rhabdoviridae, and genus Vesiculovirus. During the year 2003, a large outbreak of acute
encephalitis involving 329 children with 183 deaths (CFR 55.6%) was reported between June and August 2003 from many districts of Andhra Pradesh state which was confirmed to be due to CHPV. Simultaneously, another encephalitis outbreak was reported during June to August 2003, in 15 districts (11 in Vidarbha and 4 in Marathwada) of Maharashtra state, involving about 400 encephalitis cases with 115 deaths. Presence of anti CHP IgM antibodies in about 20% of the cases and absence of other known causes of encephalitis indicated that the CHP virus was the most important etiological agent in this outbreak. Subsequently, the CHP encephalitis was detected in Banaskantha district of eastern Gujarat. CHPV encephalitis outbreaks continue to occur on regular basis in Vidarbha and Telangana regions. The transmission of this virus has been proven through sand flies and explains the rural prevalence of the disease. The virus circulation is quite extensive and large population in affected area shows neutralizing antibody response to CHPV.

**Diagnosis**

CHPV encephalitis occurs in children below the age of 15 yrs. The clinical presentation is different from that of other viruses. The rise of fever is rapid and mortality rate is very high with seizures, diarrhea, and vomiting. Evolution of illness was very rapid with high fatality (47%). Majority of deaths occurred within the first 24 hrs of illness due to brainstem involvement. The seasonality is mainly before the rainy season during the months of May- June. Diagnosis can be carried out by demonstration of viral RNA in CSF or serum by RTPCR, as well as by presence of IgM antibodies to CHPV. An IgM diagnostic test has been developed by NIV and is supplied to Govt. labs in endemic regions.

**Comments**

Chandipura virus outbreak taught us that apparently nonpathogenic virus can take a form of fatal outbreak. As we had isolated the virus earlier, it was easy to detect the same and develop assays quickly. It is thus necessary to have long term surveillance and monitoring of viruses that are transmitted by various arthropods.

**Nipah Virus**

Nipah virus (NiV), zoonotic paramyxovirus was implicated as the cause of a highly fatal (case-fatality ratio 38%– 75%), febrile human encephalitis in Malaysia and Singapore in 1999 and in Bangladesh during the winters of 2001, 2003, and 2004. The natural reservoir of NiV is presumed to be fruit bats of the genus *Pteropus*. Evidence of NiV infection was detected in these bats in Malaysia, Bangladesh, and Cambodia. In the Malaysian outbreak, NiV was introduced into the pig population, and most of the human cases resulted from exposure to ill pigs. Human- to- human transmission of NiV was also documented during the outbreak in Faridpur, Bangladesh. The disease presented mainly as acute encephalitis with usually a short incubation period of less than two weeks, with the main symptoms of fever, headache, and giddiness followed by coma. Distinctive clinical signs include areflexia, hypotonia, hypertension, tachycardia and segmental myoclonus. Clinical manifestations of the cases in Siliguri were similar to those of NiV cases in Bangladesh, and were proven to be due to NiV. Another outbreak from India was also reported at Nadia at the Indo- Bangladesh border during 2009 (NIV Annual report). Subsequently, NiV RNA was detected in fruit bat in India also.

**Chikungunya**

Chikungunya virus (CHIKV) belongs to family *Togaviridae*, genus *Alphavirus*. The virus was first isolated from the serum of a febrile human case in Tanzania in 1953. Illness is often acute and lasts 3 to 5 days. The incubation period is usually about 2 to 4 days. The most significant symptom is arthralgia, which is present in a large number of cases. This may persist in a small proportion of cases for months or years and mimic rheumatoid arthritis. The rash if present (most commonly on the trunk) is macular or maculopapular; rarely petechiae may be present. Severe hemorrhagic symptoms have not been reported among CHIKV cases in Africa; however, they have been reported in some cases in South and Southeast Asia.

In India, the first outbreak was recorded in Kolkata, in 1963, followed by epidemics during 1964 in the east coast areas like Chennai, Pondicherry, Vellore, Vishakhapatnam and...
Dengue virus belongs to the family flaviviridae and is transmitted by Aedes mosquitoes. It is found in most tropical and subtropical areas of the world. Every two out of five individuals in the world are at risk from dengue. There are four serotypes of Dengue virus and these viruses do not give cross protection from infection with other serotypes.  

Dengue causes a spectrum of diseases in humans ranging from classical dengue fever (DF) to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). The risk of DHF is much higher during secondary DEN infections.

The current thinking is that DHF is not a different phenomenon but a more severe form of the disease. Plasma leakage has also been evidenced in dengue fever.

Co- positivity of dengue and JE in serology has been seen in many labs. However, severe cases of JE negative with Dengue positive have been reported. In many areas, large scale dengue outbreaks occur with various clinical presentations every year. Solomon reported CNS involvement of dengue virus in about 4% of encephalitis cases in Vietnam as early as 2000. Over the years, many reports have been seen in the literature. In India, serious manifestations of dengue involving CNS have also been noted. Acute neuromuscular weakness associated with dengue virus infection has also been noted.

Dengue encephalopathy/ encephalitis, still seen as a rare manifestation, has also been reported. Gupta et al. have seen association of dengue virus in ADEM cases also. Many centres are reporting higher and consistent percentage of dengue seropositivity, in some cases detection of NS-1 antigen in patients with severe CNS manifestations also been reported. Most of these cases also have other forms of clinical symptoms with hepatomegaly, pedal oedema, pleural effusion etc.

**Comment**

On the background of large number of uncomplicated cases and a few severe hemorrhagic forms of dengue infection, CNS involvement is being seen more consistently over the years. With the availability of genomic and antigenic determinations along with serology, more cases will be identified. As CNS infection is still a rare phenomenon in dengue infection, seasonality, background dengue fever cases should also be taken into account to arrive at the opinion. However, a better vigilance is urgently needed to identify the neurotropic signature sequences, if any, through isolation and characterization of CNS infections associated with dengue virus for future.

**Enterovirus Encephalitis**

Enteroviruses belong to family Picornaviridae, which are small RNA viruses. Members include viruses like polio, Coxsackie, ECHO etc. There are numerous EVs and extensive molecular biology approach has resulted in classification into various subtypes. Human EVs have been collectively called as non- Polio Enteroviruses (NPEV). EV infections are a significant cause of morbidity and mortality throughout the world. In addition to polio, encephalitis and meningitis,
EVs have been associated with many human diseases, including myocarditis, pancreatitis, and chronic inflammatory myopathy. Many non-polio human EVs are quite common, causing an estimated 10–15 million or more symptomatic infections in the US alone. The long-term consequences of EV infection of CNS are largely unknown. Also, EVs have been linked to autoimmune-like diseases, including diabetes, chronic inflammatory myopathy, and chronic myocarditis, perhaps in part due to the long-term presence of viral material.

CNS infections with Enteroviruses

Internationally, EV meningitis and encephalitis are common and can contribute to about 20-30% of CNS infections worldwide. Identification of EVs in CSF as a diagnostic tool has been a challenge and lower frequencies have been detected by other workers. It has been recommended that detection of EV in other body fluids in acute samples should also be considered and cases may be labelled as “probable” EV encephalitis cases. Many EV including EV 71 have been associated with encephalitis in south-east Asia, Spain, Austria, Brazil etc. It was also observed that signs and symptoms may not show the pattern observed in another region. This EV 71 in Austria was not associated with Hand-foot-and-mouth disease.

Encephalitis associated with Enteroviruses in India

EV mediated meningitis was recognized as a clinical entity in clinical practice and was named loosely as viral meningitis. After the advent of RTPCR facilities at many hospitals more detailed approached have emerged. During last few years, AES has been studied in Gorakhpur region by NIV and SGPGI. During 2006 outbreak of AES at Gorakhpur, NIV could isolate and demonstrate EV 76 from CSF in many cases. A few cases of Coxsackievirus B3 (CB3) were also detected. Recently, work at SGPGI on AES cases revealed that about 40% of cases from Gorakhpur region could be diagnosed as EV mediated. Thus based on the clinical diagnosis large number of the cases of AES in this region can be attributed to be caused by EV infection. Further analysis of these isolates revealed predominance of eechovirus 21 associated with an epidemic during the rainy seasons of 2010 and the circulation of eechovirus 1, CB1, EV75, EV76, CB5, and eechovirus 19. In addition to CNS, other diseases have been shown to be associated with Enteroviruses in SGPGI series. In southern India, EV 75 was also detected. In Northern India in Aligarh, EV 71 was detected in AES cases.

Comments

AES associated with EV infections is increasingly being identified all over India. Along with CNS symptoms, associated symptoms like myocarditis and multiorgan involvements are being seen. As detection of viral genome is difficult due to delayed presentation of cases, a serological test in the form of EV IgM detection should be used for diagnosis. Large number of AFP cases continue to occur all over India with substantially higher percentages in UP and Bihar. As the chances of developing a vaccine(s) for all these EVs like polio are nearly impossible, public health measures for prevention need to be undertaken on priority.

Other Infectious and Non-Infectious Causes

In addition to the above mentioned etiological causative agents, AES can have numerous other infectious or infection associated aetiologies. Among them, major cause is bacterial meningitis. Streptococcus pneumonia, Haemophilus influenzae, Neisseria meningitides are some of the dominant and usually encountered bacterial infections. AES due to Rickettsiae (including scrub typhus, Rocky Mountain spotted fever) has been documented. Meningitis due to Mycobacterium tuberculosis leading to tubercular meningitis is also encountered. In addition, Cystisarcoses, cerebral malaria, enteric fever associated with AES are also seen in most of the regions. Amongst the viruses, herpes simplex virus, cytomegalovirus, varicella zoster virus, human herpes virus 6 and 7, measles, mumps, and rabies can lead to AES. Most of these infections can be identified using combination of CSF picture, CT and MRI scans, and pathogen detection tests like bacterial culture, PCR, or serology. All these agents cause AES throughout the year and give a background load of sporadic AES in the hospitals. Among these, herpes family and bacterial infections can be treated with appropriate antibiotics and antivirals. Using high throughput platforms Human Parvovirus B4 has also been detected in CSFs of AES cases from south India. In addition, hepatic encephalopathy, renal encephalopathy and septic encephalopathy are the secondary causes of AES. These also can be diagnosed and treated. Among the viral measles virus infection can give range of CNS presentations. Acute disseminated encephalomyelitis (ADEM) after measles is an example of a post-infectious encephalitis.
ADEM is an immune-mediated inflammatory disorder of the CNS, typically transitory and self-limiting.

Among the apparently non-infectious causes that are emerging as conspicuous aetiologies are anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and ADEM. Anti-NMDAR encephalitis is increasingly recognized in children, comprising 40% of all cases. The neuropathology of NMDAR encephalitis consists of mild meningeal and perivascular parenchymal lymphocytic inflammation, usually centred on the Sommer sector of the hippocampus and amygdala.

In both these, mainly white matter is involved and can occur as secondary to previous infections. In addition, hyponatremia causing encephalitis like symptoms is also encountered. However this can be diagnosed by serum sodium levels and can be treated easily.

Unresolved Outbreaks in India

There are few unresolved outbreaks of encephalitis in India. Saharanpur in UP witnessed severe outbreaks of encephalitis during 2003-05 mainly in the winter season with mortality in the range of 60%. Attempts to isolate and identify the etiological agent failed. One of the theories that were put forward was the poisoning by *Cassia occidentalis* seed that are eaten by children in that region. Similarly, encephalitis outbreaks occur at regular intervals in Muzaffarpur District, Bihar during summer. The disease occurs mainly in children of litchi workers with mortality to the tune of 63%. In addition to sudden onset, hyponatremia in majority of the children was the unique feature. Attempts to detect and isolate agents have failed. Similar outbreaks also occur in Vietnam.

Concluding Remarks

AES in sporadic form and in outbreak form will continue to occur all over the country. Better personal hygiene and nutrition along with proper immunization will decrease the incidence of bacterial meningitis. In order to prevent JE in children, continued vaccination will have to be undertaken. However, in the absence of known vaccines against dengue, CHIKV, CHPV, EV prevention is the best key. After detection of a case, a rapid action in instituting preventive measures is necessary. This means that there is a need to develop a good reporting system that can quickly alert the health officials for preventive measures. An integrated approach of reporting and preventive is the need of the hour.

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