PERSPECTIVE

Infectious Causes of Acute Encephalitis Syndrome in India – Decadal Change and the Way Forward

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The diagnosis and management of encephalitis were previously largely based on clinical grounds and minimal laboratory investigations. Japanese encephalitis (JE) gets considered as the probable diagnosis in most encephalitis cases. However, reports of JE in adults and the elderly are increasing after the JE vaccine introduction among children in 2006. The Nipah virus (NiV) emerged in 2002 and continues to afflict humans in new geographic areas. Many other infections cause encephalitis, including Chandipura, chikungunya, dengue, and West Nile. Significant advances in diagnostic testing like multiplex testing panels and metagenomic approaches along with sequencing have helped in the detection of new etiologies. Recent years have witnessed an increase in climate-sensitive zoonotic diseases with encephalitis. This highlights the importance of the One Health approach in studying the impact of climate change-associated infectious diseases on human health. The government of India's efforts to develop health research infrastructure would help future responses to emerging infectious disease epidemics.

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Acute encephalitis syndrome (AES) is an illness presenting with the acute onset of fever and either change in mental status with symptoms such as confusion, disorientation, coma, or inability to talk, and/or new onset seizures excluding simple febrile seizures. Encephalitis in clinical practice is considered synonymous with herpes simplex virus (HSV) encephalitis (HSE) in sporadic cases [1]. However, Japanese encephalitis (JE) is the most common cause of AES cases in endemic areas during specific seasons, and especially during outbreaks [2]. There has been a significant decline in JE contribution to AES in the last decade [3]. However, reports of JE, though still mostly reported among children, are also being reported in adults and the elderly [4], year-round beyond known seasonality [5], and outside endemic regions, including some urban areas [6].

The Nipah virus (NiV) is a zoonotic virus, with fruit bats serving as the natural host. It is transmitted through animals, contaminated food, and human-to-human. It has a case fatality rate estimated at 40-75%, which may vary in outbreak settings. Clinical presentation ranges from asymptomatic (subclinical) infection, mild acute respiratory infection to fatal encephalitis. It has no specific treatment or vaccine available. Since its emergence [7] in 2002, it continues to affect humans in new geographic areas [8], which is a concerning development. Chandipura virus (CHPV) is an arbovirus transmitted by sandflies. It was identified as the causative agent of the explosive encephalitis outbreak in Central India in 2003-2004, with a case fatality rate as high as 75%, reported within 24 hours of symptoms commencement. CHPV encephalitis outbreaks [9] and the seasonal increase in cases in early monsoon period have been reported in central, western and eastern India [10].

Trends in AES Morbidity and Mortality

In India, the National Vector Borne Disease Control Programme (NVBDCP) reports thousands of cases of AES every year [11]. JE is an endemic disease in our country and causes more than 2,500 cases and over 500 deaths annually [12]. No specific treatment exists for JE, and cases are managed with supportive care services. Currently, vaccines are the only effective preventive measure against the disease. The JENVAC (inactivated Vero cell-derived) vaccine is an indigenously developed vaccine, is safe and neutralizes genotype I-IV of JEV, with seroconversion rates of more than 90% [13]. There has been a decline in JE cases in certain geographical areas, due to increased awareness, prevention practices and vaccination uptake. The NVBDCP reports that the mortality from AES has declined from 12.27% in the year 2015 to 3.86% in 2022.

Significant advances in diagnostic testing have happened with the availability of technologies like fully automated multiplex polymerase chain reaction (PCR) panels, where multiple pathogens can be detected simultaneously in a short duration of time. These still remain underutilized for CNS infections, although they are widely used for syndromic diagnoses like sepsis, gastrointestinal and respiratory illnesses [14]. The 'metagenomics' approach refers to the interrogation of the complete genetic material from a clinical sample [15]. It has great potential for helping clinicians in reaching a timely diagnosis. The recent advent of unbiased high-throughput sequencing (HTS) technologies to detect previously unrecognized or novel pathogens offer remarkable opportunities in undiagnosed encephalitis cases [16].

Although, there are consensus clinical guidelines provided for the diagnosis and management of encephalitis in children [17], there are new developments in the decade that require updating of the recommendations, along with the development and evaluation of diagnostic and management algorithms for different population subgroups at most risk, that could be applicable across India and also based on the regional differences [18]. An increase in climate-sensitive zoonotic diseases is getting much-needed attention recently. There is a need for prioritizing the research on climate change using the One Health approach. This article provides perspectives on infectious causes of encephalitis in India based on the changing etiological spectrum.

Before the 21st Century, the most common infectious cause of sporadic encephalitis in clinical practice among immunocompetent individuals was HSV. It was also associated with immunocompromised individuals infected with HIV-1 and AIDS in India. The testing for serodiagnosis and seroepidemiology studies were mostly done using an indirect immunofluorescence test [19]. The molecular methods of diagnosis using real-time PCR have been helpful in early and quick diagnosis along with the determination of viral load, helping clinicians in the decision on continuation or stopping of antiviral therapy.

Sporadic encephalitis cases have also been associated commonly with the pandemic influenza A (H1N1) in 2009 and rarely with Parvovirus B4, rabies, dengue and enteroviruses [20], Chikungunya [21], and West Nile [22]. Nonviral causes of encephalitis include scrub typhus [23] and leptospirosis [24], which are treatable by affordable and widely available drugs like azithromycin and doxycycline. *Neisseria meningitidis, Haemophilus influenzae*, and *Streptococcus pneumoniae* are other bacterial agents which cause AES. Also, postinfectious encephalitis in a few cases merits attention and efforts due to the additional possibility of co-infections. There are other non-infectious causes like auto-immune or antibody-mediated encephalitis along with metabolic, toxic and other encephalopathies.

The JE virus activity in India was reported first in 1952. The first human case of JE was reported from Tamil Nadu in 1955. The first epidemic of JE was reported in Bankura, West Bengal and subsequently in Uttar Pradesh in 1978. It continued to afflict human populations after the 1990s [2]. Following the epidemics in 2005 reported nationwide [25], JE vaccination was introduced as an emergency measure in 2006 as a vaccination campaign using the live-attenuated SA 14-14-2 JE vaccine among children aged 1-15 years.

Improvements in serological diagnosis and molecular assays using the RT-PCR have helped in early diagnosis. The attribution of the JE virus as the cause had been reported in 10-40% of cases of encephalitis during the largest outbreaks in Uttar Pradesh until 2005. The epidemiology of JE is changing in India following the implementation of JE vaccination in endemic districts. JE virus genotype-I was reported in India in 2011 and genotype-III recently. JE vaccination has been considered the most important tool for JE prevention and control. After the introduction of a single dose of live-attenuated SA 14-14-2 JE vaccine at 16-24 months in routine immunization schedules in 2010, an additional dose at 9-12 months was included since 2013. Many other new vaccines have been developed and introduced in India.

The changing clinical and laboratory profile of AES in Uttar Pradesh along with the association of non-JE viral and non-viral infectious agents, including enteroviruses, have highlighted the need for algorithms for clinical investigations and etiological testing. The importance of cerebrospinal fluid (CSF) for diagnostic testing has also been highlighted along with the novel developments in testing using the multiplex panels and metagenomics. This has become more important due to urban areas experiencing sporadic JE cases recently [6]. There are increasing cases and also outbreaks of JE among adults and the elderly following childhood vaccination [4]. Also, JE cases are getting reported year-round, as against peculiar seasonality in the post-monsoon period earlier, in non-endemic areas and beyond the known season [5]. However, JE may get misdiagnosed or wrongly associated with encephalitis due to issues of cross-reactivity and less specificity of serodiagnosis relying on the use of IgM ELISA assays.

Several epidemics of coma and fever in children with high case fatality rates occurred at regular intervals, in Telangana (erstwhile Andhra Pradesh) in 1997, 2002, 2003, 2005; Maharashtra and eastern districts of Gujarat in 2003, 2004 and elsewhere. These recurrent epidemics were caused by the CHPV, indicating the emergence of CHPV in the Indian subcontinent.

A recent systematic review [26] has documented that COVID-19 infection could present as encephalitis; with most frequent neurological presentations being similar to those of JE, depending upon the severity of the disease including simultaneous respiratory damage [27]. Lack of a characteristic CSF profile and a negative PCR test result may make its diagnosis less evident, though autoimmune neuropathogenesis is likely. The clinicians should consider neurological involvement in COVID-19 cases with altered mental status or behavioral changes.

There are various difficulties in pointing out the cause in most cases of encephalitis based on only clinical information. There is a need to consider clinical as well as epidemiological parameters in differential diagnosis for rationalizing testing [17]. Diagnosing encephalitis is a very costly affair. The physicians could consider rationalized testing based on clinical clues [28]. There are efforts being made recently to provide algorithms at the national level [18]. However, as studies are not reported from different geographies and endemic areas (**Table I**), there are difficulties in prescribing testing algorithms that could be applied across India [18].

Etiological Testing and Research

There are some operational issues regarding the availa-bility of appropriate and timely clinical specimens for diagnostic testing. CSF collection may not be possible in cases with clinical contraindications, lack of expertise and consent from patient relatives. Also, the non-availability of convalescent sera in the later phase of illness may be due to high mortality in the early course of illness, loss of patients to follow-up and lack of interest and motivation of patients and physicians alike**,** after recovery from an acute illness [5]. With decreasing contribution of JE in AES following JE vaccination [3], it is important to investigate other causes of encephalitis. Due to decreased burden of HIV/AIDS, and the elimination efforts for malaria and tuberculosis, it is a need to consider research on other potential causes of encephalitis.

Dengue-associated encephalitis, ranging from mild encephalopathy to severe encephalitic clinical presentation, is increasingly being recognized in tropical and subtropical countries, with a reported incidence rate varying from 0.5 to 20% [29]. A case of encephalitis or viral meningitis with normal CSF cellularity, in a dengue-endemic region, is likely to be due to dengue in 75% of the patients, followed by HSV-1 [30].

Since the year 2014, many surveillance and etiological research studies were undertaken, mostly in high-endemic regions in Uttar Pradesh, West Bengal, and Assam. The medium-endemic region in Maharashtra (Vidarbha region) and Telangana, erstwhile Andhra Pradesh (northern region) lacked such studies. These studies were undertaken for understanding the contribution of JE and other common infectious agents associated with AES. Dengue encephalopathy and rickettsial fevers were also considered for testing. Establishing enhanced hospital-based surveillance and searching for multiple infectious agents through virus research and diagnostic laboratories (VRDL) have changed the scenario in the last decade.

Clinical Management Issues

Strengthening of primary and secondary care hospitals is

Table I Infectious Causes of Acute Encephalitis Syndrome (AES) in India

Immunocompetent patients
Virus: Japanese encephalitis virus (JEV),[a] Herpes simplex virus (HSV),[b,c] Chandipura virus (CHPV),[a,b] (Telangana, Maharashtra, Gujarat, Odisha, Bihar), Nipah virus (NiV),[a,b] (West Bengal, Kerala), Enteroviruses,[b,c] Dengue,[a] Influenza A (H1N1) (H3N2),[a,c] Kyasanur forest disease (KFD), Rabies, Chikungunya,[a] West Nile (Assam, Kerala),[a] Zika
Bacteria: *Mycobacterium tuberculosis;*[b] *Orientia tsutsugamushi* (Scrub typhus);[a] Leptospira (Assam, Kerala, Others);[a] *Neisseria meningitides* (<1%)
Parasite: *Plasmodium falciparum, Naegleria fowleri*[b,c]
Immunosuppressed patients
Virus: HIV, EBV, CMV, Parvovirus B19, Human herpes virus 6
Unvaccinated children
Virus: Measles, Mumps, Rubella (clusters), Chickenpox (clusters), *Bacteria: Streptococcus pneumoniae* (~1%), *Haemophilus influenzae* (<1%)
Newer agents
Virus: SARS-CoV-2 (direct or autoimmune-mediated)[c]

[a]Outbreak potential; [b]to be considered based on clinical presentation and tested if clues or pointers are available; [c]Acute necrotizing encephalitis (ANE). Modified from: Standard Treatment Workflow (STW) for the management of Acute Encephalitis Syndrome (AES) in children, developed by the Indian Council of Medical Research (https://stw.icmr.org.in/images/pdf/Paediatrics/Paediatrics_Acute_Encephalitis_syndrome.pdf)

urgently needed along with preferential strengthening of tertiary care hospitals for decreasing the case fatality rate of AES. Decreased transport times to the nearest health-care settings and early management of raised intracranial pressure (ICP) and convulsions have brought significant improvements in survival.

Clinicians and public health authorities have started immunization against JE. However, AES is caused by many agents other than JE. Vector control, mass immunization with the JE vaccine to all below 15 years of age, and strengthening of peripheral hospitals with oxygen and mannitol, along with measures in place for decreasing transport times, could help decrease mortality and disabilities of JE, and also AES in future.

Climate Change and AES

The temperature rise, increased CO_2 levels, and changes in land use can drive extreme weather events resulting in outbreaks of JE/AES in previously naïve regions [31].Temperature is a critical factor for vector competence of JEV and mosquito survival [21]. Thus, climate change can cause the emergence of JEV in novel temperate regions. Extended warm days, and erratic rains causing flash floods and water stagnation, can contribute towards a breeding environment for the JE vector. Modelling studies have predicted that climate change can also provide opportunities for viral sharing amongst the wildlife, presently silently harboring them, and could in turn facilitate zoonotic spillover [32]. Thus, it may be postulated that novel viruses with the potential to cause AES could gain access to naïve human population in future.

Future Perspectives

Pradhan Mantri Ayushman Bharat Health Infrastructure Mission (PM-ABHIM) launched in October, 2021, is the largest Pan India scheme for public health infrastructure since 2005. It intends to fill in critical gaps in health infrastructure, surveillance and health research, spanning both urban and rural areas. It aims to make the communities *atmanirbhar* or self-reliant by establishing a strong healthcare system, which can effectively respond to epidemics across the nation, develop the core capabilities to deliver a One Health approach in the prevention of infectious diseases and build information technology (IT) enabled surveillance systems [33].

Artificial Intelligence (AI): Potential in AES Diagnosis

Machine learning (ML), the most common form of AI, is a technique of fitting models to data statistically and to 'learn' by training the models. The focus of AI, as early as the 1970s, has been on disease diagnosis and treatment [34]. 'Precision medicine' predicts what treatment and management protocols are most likely to succeed based on various patient attributes and treatment contexts. It has been applied effectively in the field of cancer [35]. AI may become an important tool in the future for the early, accurate diagnosis of AES cases, thus leading to better treatment and prognosis.

Conclusions

A significant decrease in the burden of vaccine-preventable diseases was seen after the implementation of vaccinations against measles, rubella and mumps, along with improved rabies vaccines as pre-exposure and also post-exposure prophylaxis, and with effective vaccines against Japanese encephalitis since 2006. However, many treatable causes of encephalitis such as scrub typhus, leptospirosis, malaria, tuberculosis and sepsis need guidelines for early diagnosis and proper management. The increasing endemicity and frequent outbreaks of dengue will need attention and timely efforts. The astute pediatrician will need to detect cases, seek diagnostic testing timely and engage with the health services. Awareness of possible para- and post-infectious encephalitis including SARS-CoV-2 encephalitis could help drive research for the betterment of therapies and improving the outcomes. Significant advances in diagnostic technologies have helped in the detection of novel etiological agents of infectious encephalitis. The national, state and local governments have become responsive to the health challenges. The ongoing PM-ABHIM is one such example by the Government of India. Such efforts will prove useful in the management of encephalitis to prevent mortalities and morbidities in future.

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