Indian J Med Res 145, May 2017, pp 584-587
DOI: 10.4103/ijmr.IJMR_409_17

Quick Response Code:

Editorial

Acute encephalitis in India: An unfolding tragedy

In spite of a major economic and epidemiological transitions being underway, infectious diseases continue to remain a major public health problem in India[1,2]. In addition to a number of endemic diseases, recent epidemics of H1N1pdm09, dengue and other infectious diseases demonstrate the ongoing vulnerability to the threat of emerging infections[3]. While existing environmental, climatic and socio-economic factors contribute to the risk, the impact can be worse with weak health systems, inadequate resources and poor preparedness and response mechanisms.

Acute encephalitis: A public health enigma

Acute encephalitis defined as the 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) is clearly a pressing public health emergency in India[4]. Recurrent epidemics of encephalitis of unknown aetiology have occurred in the country. Between 2008 and 2014, there have been more than 44,000 cases and nearly 6000 deaths from encephalitis in India, particularly in Uttar Pradesh and Bihar. In 2016, there has been a rise in encephalitis, with over 125 children reported to have died in one hospital in Gorakhpur alone[5].

Characterized by high case-fatality rate (CFR), the disease occurs in seasonal outbreaks every year, taking a heavy toll of life, especially of children below 15 yr of age. The patients often present with acute onset of fever and altered consciousness, with a rapidly deteriorating clinical course, leading to death within hours. Many of those who survive may have residual disability impacting on long-term quality of life. While Japanese encephalitis virus (JEV) is the leading diagnosed cause of acute encephalitis, other causes include enteroviruses, scrub typhus, measles and other viruses circulating in the local area. In many cases, however, no etiological agent is determined, and such cases are categorized broadly as acute encephalitis syndrome (AES).

The disease was clinically diagnosed in India for the first time in 1955 in the southern State of Madras, now Tamil Nadu[6]. At present, the disease is endemic in as many as 171 districts in 19 States[4]. During 2016, 11,651 case and 1301 deaths were reported to the National Vector Borne Diseases Control Programme (NVBDCP), with a CFR of around 11 per cent[7]. Most deaths were from Uttar Pradesh, followed by West Bengal, Assam and Bihar.

As an epidemic prone disease, outbreaks have occurred in many States, with the CFR higher than that noticed during non-epidemic months. The first major epidemic caused by JEV was reported from Burdwan and Bankura districts of West Bengal in 1973 followed by another in 1976[8]. In the 1973 outbreak, 700 cases and 300 deaths were reported.

In 1978 and thereafter, outbreaks were reported from 18 States and Union Territories. In Uttar Pradesh, the first report of an epidemic was in 1978, during October and November, when >3500 cases and 1100 (33%) deaths occurred[9]. Thereafter, extensive and recurrent outbreaks have been reported in the State, especially during 1988 and 2005. The most devastating outbreak was in Gorakhpur district in 2005 affecting 6061 cases with 1500 deaths[10]. It was followed by further outbreaks in 2006 and 2007, with 2320 cases and 528 deaths and 3024 cases and 645 deaths, respectively[11]. JEV was identified as the causative agent in some cases, while in some studies, besides scrub typhus *Enterovirus* was identified as the infective agent[12]. This led to India launching a JE vaccination programme in 2006, which in 2014 became part of the National immunization programme[13]. The programme now makes the vaccine available in 179 districts in nine States where the disease is highly prevalent.

The neighbouring State of Bihar, particularly the Muzaffarpur district, has been reporting cases of acute encephalitis among children since 1995. In 2011, there were 147 cases and 54 deaths (CFR 36.7%) in the district. In the following year, 469 cases and 178 deaths were reported from health facilities with CFR of 38.6 per cent[14]. The age of the hospitalized cases ranged from six months to 16 yr with 92 per cent below the age of 10 yr. Fifty three per cent were females.

The clinical presentation included sudden onset of convulsions with clenching of teeth and loss of consciousness, mostly in the early morning, with no prodrome or sequelae. Many of them did not have fever. Hypoglycaemia was a common feature (50% of the observed cases). The serum and cerebrospinal fluid examinations were, however, inconclusive. On an average, one case was seen per village. All cases occurred during May and June, which coincided with the litchi plucking season in the district.

To better characterize clinical and epidemiologic features of the illness, the Indian National Centre for Disease Control and US CDC carried out a detailed epidemiological investigation during 2013 and 2014[15]. As in previous years, no clustering of cases was observed; the illness of each affected child appeared to be an isolated case in various villages. As most cases did not report fever or other signs of inflammation, illness was labelled as neurological disorder. A common finding was low blood glucose (<70 mg/dl) on admission, a finding associated with a poor outcome. Rapid assessment and correction of hypoglycaemia through provision of dextrose, however, helped in reducing mortality (from 44% in 2013 to 31% in 2014)[15]. No evidence of any infectious aetiology was found, supporting the possibility that exposure to a toxin might be the cause.

A recent study has also postulated a relationship between consumption of litchi and AES[16]. This case-control study indicates that the outbreak has resulted from toxicity following consumption of litchi fruits, which contains hypoglycin A and methylene cyclopropylglycine (MCPG). The investigators further claim to have demonstrated the presence of MCPG and hypoglycin in litchi and the metabolites of these toxins in human biological specimens. The study however, did not compare litchi-associated cases with controls drawn from the affected community but with sick controls lacking neurological disease and no history of altered mental status or seizures in the previous three months and admitted to a case-surveillance hospital less than seven days from admission of the case[17]. Most outbreak investigations including this are often based on hospital data and little community-based data are available.

More recently, a large outbreak has been reported among a JE-unvaccinated population in a tribal district of Malkangiri in Odisha State, caused much concern. The outbreak which began in early September 2016 accounted for 325 AES cases from 164 villages in the district by end of November, including 91 deaths (CFR: 28%) (AC Dhariwal, personal communication). Of the 548 serum samples tested, 158 (29%) were JE positive. The cases were reported from 164 villages of the district. Most of the cases were children below 10 yr of age, mean age being three years. Common clinical presentation included fever, pain in abdomen, recurrent vomiting, lethargy, convulsions and loss of consciousness.

Programmatic issues and opportunities

Considering the urgency and the serious nature of the problem, the Government of India has set in motion a multi-pronged strategy encompassing preventive, case management and rehabilitation aspects developed through detailed inter-ministerial consultations. This comprehensive approach to AE prevention and control is being implemented by the Ministry of Health and Family Welfare, in collaboration with five other government ministries, with a budget allocation of ₹4038 crores (USD approximately 660 million) for the five-year period (2012-2013 to 2016-2017)[4]. The programme focuses on activities including public health interventions, expansion of JE vaccination, improved case management, medical and social rehabilitation, provision of drinking water and sanitation and improved nutrition.

Some of the critical issues the programme must address urgently include the following.

Most importantly, the aetiology of a significant number of AES cases which still remains incompletely understood. While it is generally believed that JEV today contributes to 10-15 per cent of encephalitis cases, cause of other cases remains largely unknown. The inability to isolate an infectious aetiological agent in a majority of AES cases presents a critical and fundamental challenge to effective prevention and management. Without adequate knowledge of aetiology and mode of transmission, strategies for its prevention and management can be neither formulated nor implemented effectively.

A number of theories have been put forward based on clinical, laboratory and ecological findings, but these are yet to be confirmed conclusively. One such theory relates to the possible link with litchi fruits in Muzaffarpur, Bihar, since the outbreaks occur in litchi fruit growing region in India, and cases tend to peak during litchi harvesting season[18]. Besides India, outbreak reports from Vietnam and Bangladesh and review of epidemiological data also suggest that litchi-associated encephalitis can occur[19-21]. However, these potential associations have neither been confirmed in most outbreaks nor are the exact mechanism of action clear. The other possibility is that AES of unknown aetiology is caused by an infectious agent or toxin which is not yet fully characterized. Therefore, systematic epidemiological studies are needed to clearly elucidate the aetiology, transmission, risk factors and environmental exposures in disease causation in affected States including Odisha.

Second, AE surveillance in India remains poor, and the actual disease burden, its distribution and trends are still not known. Intensified surveillance for AE as a part of overall vector-borne disease surveillance, especially focusing on the laboratory diagnostic component, can help better characterize the epidemiology and the disease burden so as to advocate for and guide programmatic interventions. NVBDC has developed a national 'Acute Encephalitis Syndrome (with special reference to JE) Surveillance Guidelines' for reporting AE as per the standard case definition[22]. The underlying factors that may play an important role in disease causation as well as in mortality such as malnutrition, poverty and various other socio-economic and environmental determinants must also be ascertained and addressed along with the health system performance.

Third, the clinical ambiguity is adding to the confusion on the diagnosis, as to whether the cases are of encephalitis or encephalopathy, a different neurological disorder or any combination. In this regard, it is important to carefully obtain data on the clinical presentation and thereby develop a case definition as relevant. This has not yet occurred in India. Moreover, in view of the rapid deterioration and fatal outcomes, seeking of medical care early and correction of hypoglycaemia in the beginning of illness are essential to ensure better health outcomes[23]. The management of critically ill children at the primary care level as well as the secondary and tertiary care levels and capacity building to make available trained workforce in the health system to tackle this problem is not only a clinical necessity but also ethical imperative.

Fourth, while the cause of acute encephalitis remains generally unknown in most cases, many cases are attributed to JEV, a vaccine-preventable infection transmitted through the bite of infected mosquitoes. Though both sexes are equally affected, males usually outnumber females. Subclinical or inapparent infections far outnumber the symptomatic JE cases, at a ratio of 250 or 500:1, meaning that there are often not more than 1-2 cases being reported per village[24]. Various public health measures used to prevent JE include control of mosquitoes, protection from mosquito bites using personal protection measures such as mosquito nets, protective clothing or applying mosquito repellents[25]. Keeping the pigs away from human dwellings and JE immunization are also strongly advocated.

Finally, the Ministry of Health and Family Welfare responsible for implementing the government's comprehensive and multi-sectoral strategy should invest urgently on addressing the identified issues and adopt a One Health approach with active role also of sectors other than health including veterinary and environmental sectors.

In conclusion, the frequent and often predictable outbreaks of acute encephalitis in different parts of the country constitute a huge challenge to public health in India. Besides demonstrating the vulnerability of the populations to emerging infections, the frequent occurrence of acute encephalitis outbreaks with high case fatality, calls for enhanced health system capacity and a focussed approach in responding to such threats and thereby protecting the lives of poor and socially vulnerable populations.

Jai Prakash Narain[1,*], A.C. Dhariwal[2] & C. Raina MacIntyre[1]

[1]Department of Infectious Disease Epidemiology, School of Public Health & Community Medicine, University of New South Wales, Sydney, Australia & [2]National Vector Borne Disease Control Programme, Ministry of Health & Family Welfare, Delhi 110 053, India

[*]*For correspondence*: narainjp88@gmail.com

Received March 9, 2017

References

1. Narain JP. Public health challenges in India: Seizing the opportunities. *Indian J Community Med* 2016; *41* : 85-8.
2. Narain JP, Bhatia R. The challenge of communicable diseases in the WHO South-East Asia Region. *Bull World Health Organ* 2010; *88* : 162.

3. Dikid T, Jain SK, Sharma A, Kumar A, Narain JP. Emerging & re-emerging infections in India: an overview. *Indian J Med Res* 2013; *138* : 19-31.
4. Narain JP, Lal S. Responding to the challenge of acute encephalitis syndrome/JE in India. *J Commun Dis* 2014; *46* : 1-3.
5. The Times of India. Encephalitis to be Made 'Notifiable Disease': Government (news article published on August 11, 2016); 2016. Available from: *http://www.timesofindia.indiatimes.com/city/delhi/Encephalitis-to-be-made-notifiable-disease-Govt/articleshow/53651028.cms,* accessed on August 22, 2016.
6. Webb JK, Perreira SM. Clinical diagnosis of arthropod borne type viral encephalitis in children in North Arcot district, Madras State, India. *Indian J Med Sci* 1956; *10* : 572.
7. National Vector Borne Disease Control Programme, New Delhi. Acute Encephalitis/Japanese Encephalitis cases and deaths in the country since 2010. Available from: *nvbdcp.gov.in/Doc/je-aes-cd-23july.pdf*, accessed on March 26, 2017.
8. Banerjee K, Sengupta SN, Dandawate CN, Tongaonkar SS, Gupta NP. Virological and serological investigations of an epidemic of encephalitis which occurred at Bankura district, West Bengal. *Indian J Med Res* 1976; *64* : 121-30.
9. Kumari R, Joshi PL. A review of Japanese encephalitis in Uttar Pradesh, India. *WHO South East Asia J Public Health* 2012; *1* : 374-95.
10. Indian Council of Medical Research. Japanese Encephalitis (JE) AES: Disease Specific Documents for X11 Plan; 2014. New Delhi. Available from: *www.icmr.nic.in/publications/hpc/PDF/annexure%2014.pdf*, accessed on March 6, 2017.
11. National Vector Borne Disease Control Programme (NVBDCP). Directorate General of Health Services, Ministry of Health and Family Welfare. New Delhi. April 2009. Available from: *http://nvbdcp.gov.in/je-cd.html*, accessed on March 6, 2017.
12. Sapkal GN, Bondre VP, Fulmali PV, Patil P, Gopalkrishna V, Dadhania V, *et al.* Enteroviruses in patients with acute encephalitis, Uttar Pradesh, India. *Emerg Infect Dis* 2009; *15* : 295-8.
13. National Health Mission. Routine Immunization, Government of India. Available from: *http://www.nrhm.gov.in/nrhm-components/rmnch-a/immunization/background.html*, accessed on January 20, 2017.
14. National Centre for Disease Control, India. Outbreak of Acute Encephalitis Syndrome in Bihar; 2012. Available from: *http://www.ncdc.gov.in/writereaddata/linkimages/NCDC%20Newsletter3457335027.pdf*, accessed on January 20, 2017.
15. Shrivastava A, Srikantiah P, Kumar A, Bhushan G, Goel K, Kumar S, *et al.* Outbreaks of unexplained neurologic illness – Muzaffarpur, India, 2013-2014. *MMWR Morb Mortal Wkly Rep* 2015; *64* : 49-53.
16. Shrivastava A, Kumar A, Thomas JD, Laserson KF, Bhushan G, Carter MD, *et al.* Association of acute toxic encephalopathy with litchi consumption in an outbreak in Muzaffarpur, India, 2014: A case-control study. *Lancet Glob Health* 2017; *5* : e458-66.
17. Spencer PS, Palmer VS. The enigma of litchi toxicity: An emerging health concern in Southern Asia. *Lancet Glob Health* 2017; *5* : e383-4.
18. NCDC Newsletter. Vol. 2; 2013. Available from: *http://www.nicd.nic.in/writereaddata/linkimages/Newsltr04143506613236.pdf,* accessed on December 24, 2016.
19. John TJ, Das M. Acute encephalitis syndrome in Muzaffarpur: Hypothesis of toxic origin. *Curr Sci* 2014; *106* : 1184.
20. Paireau J, Tuan NH, Lefrançois R, Buckwalter MR, Nghia ND, Hien NT, *et al.* Litchi-associated acute encephalitis in children, Northern Vietnam, 2004-2009. *Emerg Infect Dis* 2012; *18* : 1817-24.
21. Islam S. Outbreak of illness and deaths among children living near lychee orchards in Northern Bangladesh. *ICDDRB Health Sci Bull* 2012; *10* : 15-22.
22. Guidelines for Surveillance of Acute Encephalitis Syndrome (With special reference to Japanese Encephalitis). NVBDCP; 2006. Available from: *http://www.nvbdcp.gov.in/Doc/AES%20guidelines.pdf*, accessed on December 24, 2016.
23. Guidelines: Clinical Management of Acute Encephalitis Syndrome Including Japanese Encephalitis, Government of India, NVBDCP; 2009. Available from: *http://www.nvbdcp.gov.in/Doc/Revised% 20guidelines%20on%20AES_JE.pdf,* accessed on September 29, 2016.
24. World Health Organization. Japanese Encephalitis fact sheet. Available from: *http://www.who.int/mediacentre/factsheets/fs386/en/*, accessed on September 29, 2016.
25. Sen PK, Dhariwal AC. National program for prevention and control of Japanese encephalitis and acute encephalitis syndrome: A multipronged strategy with inter-ministerial convergence. *J Indian Med Assoc* 2015; *113* : 191-5.