Indian Academy of Pediatrics (IAP)

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Newer Research and recommendations In Child Health

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Dear fellow IAPans,

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Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc.

Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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An algorithmic approach to identifying the aetiology of acute encephalitis syndrome in India: results of a 4-year enhanced surveillance study . www.thelancet.com/lancetgh Vol 10 May 2022

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BASED ON ARTICLE

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ABSTRACT

Background: Acute encephalitis syndrome (AES) poses a major health burden in India and is known to cause outbreaks from time to time. Although Japanese encephalitis virus (JEV) accounts for around 15% of reported cases, the etiology of most cases remains unknown. The present study is aimed to establish an enhanced surveillance network and to use a standardized diagnostic algorithm in India to establish etiology of AES.

Methods: In this large-scale, systematic surveillance study in India, patients presenting with acute encephalitis syndrome (i.e., acute onset of fever with altered mental status, seizure, or both) to any of the 18 participating hospitals across Uttar Pradesh, West Bengal, and Assam were evaluated for JEV (serum and cerebrospinal fluid [CSF] IgM ELISA) as per standard of care. Between 2014 and 2016, specimens that were negative for JEV IgM antibodies at enhanced surveillance sites were transported to the designated referral laboratory within 48–72 h for additional testing. Serological assays tested for IgM antibodies, in the following order of priority, to O tsutsugamushi (Scrub Typhus Detect IgM ELISA; InBios, Seattle, WA, USA), dengue virus (Dengue IgM Capture ELISA; National Institute of Virology, Pune, India), and West Nile virus (West Nile Detect IgM Capture ELISA; InBios, Seattle, WA, USA). CSF specimens were tested by real-time PCR in the following order of priority for Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, herpes simplex virus type 1, and enteroviruses. Based on the surveillance results from 2014 to 2016, the algorithm was revised in January, 2017, to include simultaneous testing of serum for IgM antibodies to dengue virus and scrub typhus by ELISA at the district hospital laboratories, in addition to testing serum and CSF samples for JEV IgM antibodies. At referral laboratories, testing for dengue NS1 antigen (Dengue NS1 Ag Test Kit; J Mitra, New Delhi, India), chikungunya (Chikungunya-IgM capture ELISA kit; National Institute of Virology, Pune, India), and Leptospira (Panbio Leptospira IgM ELISA; PanBio, Brisbane, QLD, Australia) in serum, and for Zika virus RNA in serum and CSF (Trioplex real-time RT-PCR assay;15 CDC, Atlanta, GA, USA) was initiated as well as the pathogens that were assessed in 2014–16. This testing included confirmatory testing for scrub typhus and dengue virus. In accordance

with WHO and NVBDCP guidelines, detection of JEV IgM antibodies in CSF, serum, or both, was considered to be evidence of JEV. In each of the other serum assays, detection of IgM antibodies to a specific pathogen (ie, dengue virus, scrub typhus, West Nile virus, chikungunya, or Leptospira), in the setting of negative results to all other pathogens, was considered to be evidence of infection. Detection of nucleic acids to any one of the pathogens tested in CSF, in the setting of negative results to all other pathogens, was evidence of confirmed infection.

Findings: Between Jan 1, 2014, and Dec 31, 2017, 11295 patients with acute encephalitis syndrome were admitted to the 18 participating sentinel sites. Of these participants, 10107 (89·5%) patients were enrolled in enhanced surveillance as 1188 (10·5%) patients were excluded because of death within the first 6 h of admission or discharge against medical advice before enrolment. Of the 5786 patients who were enrolled in surveillance between 2014 and 2016 and provided samples of CSF, serum, or both, JEV was detected in 1023 (17·7%) samples. Among patients with available serum specimens who tested negative for JEV, scrub typhus was detected in 645 (18·5%) of 3489 individuals tested, dengue virus in 161 (5·2%) of 3124, and West Nile virus in 22 (0·7%) of 3136. Evaluation of CSF specimens from patients testing negative for JEV detected S pneumoniae in 37 (1·3%) of 2847 individuals and herpes simplex virus in 18 (0·6%) of 2896. Other pathogens, including H influenzae, enterovirus, and N meningitidis, were uncommonly detected.

In 2017, with the implementation of a modified testing algorithm that included testing for JEV, scrub typhus, and dengue virus at the district hospital, 4321 patients who provided samples of CSF, serum, or both; JEV was detected in 618 (14·3%) individuals tested, scrub typhus in 511 (14·3%) of 3579, and dengue virus in 198 (5·3%) of 3768. Additional evaluation of serum specimens at referral laboratories identified chikungunya in 67 (4·8%) of 1402 individuals, Leptospira in 39 (2·4%) of 1599, and West Nile virus in seven (0·3%) of 2523. Compared with chikungunya and Leptospira, scrub typhus was more commonly detected in patients younger than 15 years (scrub typhus 16·0% vs chikungunya 3·0% vs Leptospira 0·5%). Evaluation of CSF specimens at the referral hospital showed evidence of S pneumoniae infection in 37 (1·6%) of 2311 individuals, and low detection of other pathogens. Zika virus was not detected in any patient. Among patients evaluated in 2017, the prevalence of detected pathogens differed across Assam, Uttar Pradesh, and West Bengal. The proportion of evaluated patients detected to have dengue virus was similar across the three geographical regions under surveillance. The prevalence of JEV varied from 7·9% in Uttar Pradesh to 19·9% in Assam, while that of scrub typhus ranged from 3·7% in Assam to almost 25·0% in Uttar Pradesh and West Bengal. Chikungunya was more commonly detected among evaluated patients in Assam than in Uttar Pradesh and West Bengal and Leptospira was detected more commonly in West Bengal and Assam than in Uttar Pradesh.

Overall, with the implementation of the diagnostic testing algorithm between 2014 and 2016, an aetiology was identified in 1921 (33·2%) of 5786 patients with acute encephalitis syndrome who provided a sample of either CSF or serum and in 1446 (38·3%) of 3774 who provided both serum and CSF specimens. Compared with existing standard of care, this finding represented a 2·1-times increase in the number of patients with acute encephalitis syndrome of identified aetiology (p <,0.0001). The addition of testing just for scrub typhus (567 [20·6%] of 2758 patients) and dengue virus (127 [5·3%] of 2411) to standard of care (ie, JEV evaluation) would have yielded almost the same increase in the number of patients with acute encephalitis syndrome of identified aetiology (1364 [36·1%]).

In 2017, with the implementation of the updated diagnostic testing algorithm, an aetiology was identified in 1484 (34·3%) of 4321 patients with acute encephalitis syndrome who provided a sample of either CSF or serum and in 936 (40·3%) of 2324 who provided both serum and CSF specimens.This finding represented a 3·1-times increase in the number of patients with acute encephalitis syndrome of identified aetiology, compared with existing standard of care (299 [12·9%]; p<0·0001). Expanding testing from evaluation of JEV IgM antibodies to include scrub typhus, dengue virus, chikungunya, and Leptospira only would have yielded nearly the same increase in the number of patients with acute encephalitis syndrome of identified aetiology (888 [38·2%]).

Interpretation: Causative organisms for AES in India is not just restricted to JEV. Laboratory surveillance led to a finding of other non-JE AES etiologies such as , scrub typhus, dengue virus, and other viral, bacterial, and Rickettsial aetiologies. Implementation of a systematic diagnostic algorithm in an enhanced surveillance platform resulted in a 3·1-times increase in identification of the aetiology of acute encephalitis syndrome, besides JEV alone, and highlighted the importance of scrub typhus and dengue virus as important infectious etiologies in India. These findings have prompted revision of the national testing guidelines for this syndrome across India.

COMMENTARY

In 2008, term AES was coined by World Health Organization (WHO) for surveillance and proper reporting of suspected encephalitis cases in India 1 .WHO defined an AES case as "a person of any age, at any time of the year with an 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 seizure)"1. The AES patients usually have unwanted outcome with rapidly worsening clinical condition leading to death within hours. Those 30–40% who survive have had residual neurological sequelae leading to poor quality of life 2. The history of AES in India has paralleled with that of the Japanese encephalitis virus (JEV) since the first report in 1955 from Vellore, Tamil Nadu.3. AES is now endemic in 171 districts of 19 states of India.2

Following a large outbreak in 2005, the Government of India introduced vaccination for Japanese encephalitis virus (JEV) in highly affected regions., and in 2006, a national level AES surveillance guideline was developed by National Vector-Borne Disease Control Programme (NVBDCP) for reporting of AES cases and suspected or confirmed JE cases as per standard case definition (NVBDCP 2006) 1. NVBDCP's sentinel surveillance is primarily focused on JEV testing among patients with suspected acute encephalitis syndrome. Systematic testing for pathogens other than JEV is not routinely performed.4-6. Among reported cases of acute encephalitis syndrome, only 14–18% are associated with JEV infection and the aetiology of most cases in India remain unknown. 7. Laboratory surveillance led to a finding of other non-JE AES etiologies such as enterovirus, scrub typhus, dengue virus, and other viral, bacterial, and Rickettsial aetiologies 8. Evaluations from single centers in Uttar Pradesh and Bihar have reported frequent detection of dengue virus and scrub typhus in patients with acute encephalitis syndrome. 9-11.

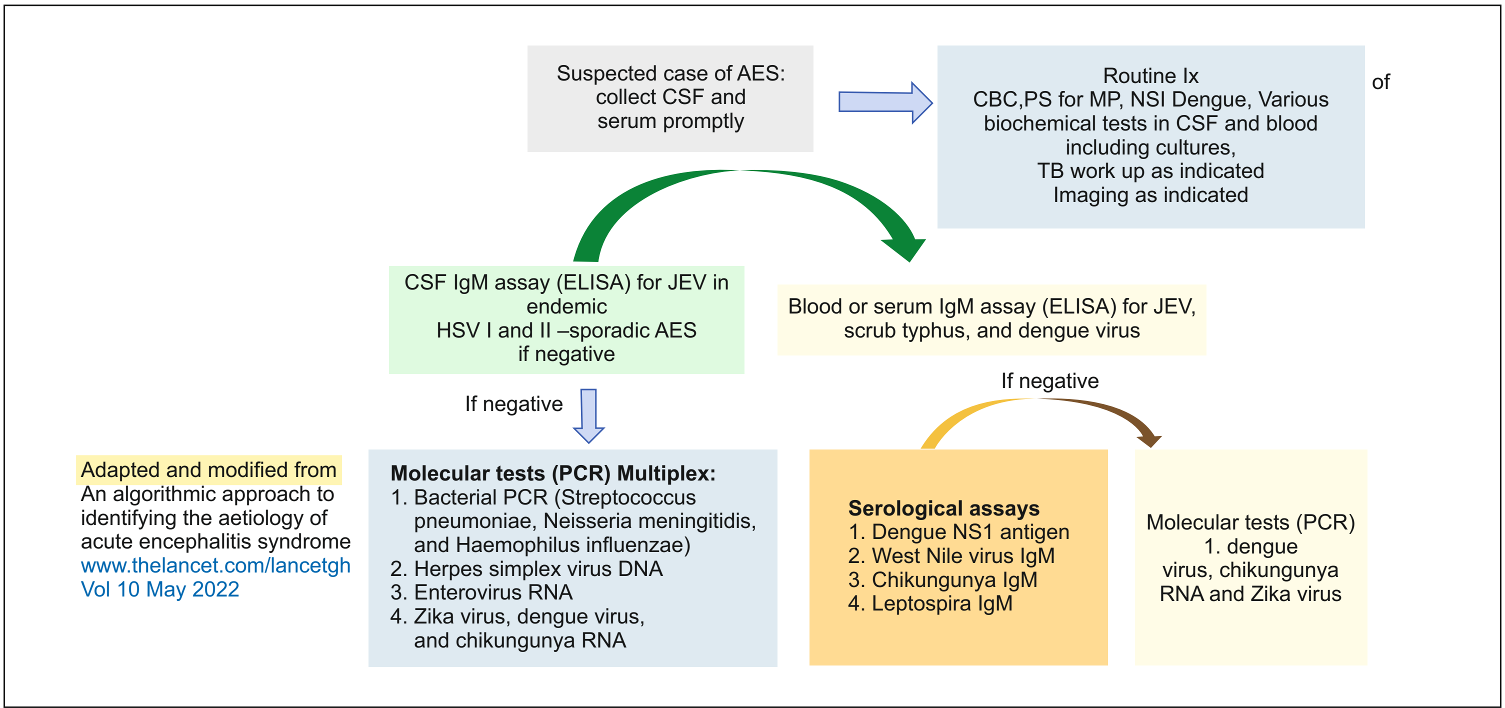
Therefore an enhanced surveillance network was established at sites in the three states of India(Uttar Pradesh, Assam, and West Bengal) with the highest burden of acute encephalitis syndrome. Together, these 3 states accounted for 63–73% of acute encephalitis syndrome cases reported to the NVBDCP between 2014 and 2017.This study included almost 25% of all cases of acute encephalitis syndrome reported in India between 2014 and 2017, and it represents the largest systematic effort to evaluate non-JEV aetiologies of acute encephalitis syndrome in India 4. Between 2014 and 2016, use of a uniform laboratory algorithm that incorporated testing for not only JEV but also eight other pathogens (scrub typhus, dengue virus, and West Nile virus by serum IgM ELISA, and for Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, dengue virus, herpes simplex virus, and enterovirus by CSF PCR) resulted in a 2·1-times increase in the number of patients with acute encephalitis syndrome of identified aetiology, compared with existing standard of care (ie, JEV testing alone). The addition of testing for three more pathogens(chikungunya and Leptospira serum IgM by ELISA and Zika virus serum and CSF by PCR) to this algorithm and the incorporation of expanded testing at the district level in 2017 resulted in a 3·1-times increase in the number of patients with acute encephalitis syndrome of identified aetiology. Both these observations were statistically significant.

Importance of the study: This is the largest pan-India enhanced surveillance study carried out over a period of 4 years. The most commonly identified pathogens were JEV , and non-JEV pathogens include scrub typhus, and dengue virus, which together accounted 90% of cases of acute encephalitis syndrome with an identified aetiology. This large-scale surveillance highlights importance of evaluating patients for other pathogens as well. On the results of this platform, the national programme in India revised the national guidelines to include an algorithm-based diagnostic approach to evaluating acute encephalitis syndrome. 12-13.

Various control programmes and therapeutic modalities can be implemented by state and central government as per the causative organism identified for AES. For JE ; vector control , piggeries management by its segregation from human habitat and JE immunization are very crucial. Similarly, the findings of other non-JE etiologies of AES shifted the control strategies in other sectors 8.The detection of pathogens that are treatable with antimicrobials, such as scrub typhus and Leptospira,malaria, etc. further underscores the importance of systematic testing to guide prompt and appropriate clinical management of these patients with intact outcome.. Detection of pathogens like dengue, chickengunya etc. will help regulatory authorities to implement preventive measures and vaccination against dengue viruses. The finding of enterovirus in AES samples calls for better hygiene and safe drinking water. Detection of Orientia tsutsugamushi (scrub typhus) in AES samples led the use of empirical doxycycline or azithromycin drugs for the treatment of febrile illnesses.8.

A way forward: Despite the significant increase in the proportion of patients with acute encephalitis syndrome with an aetiology identified by enhanced testing algorithm, the aetiology was not detected in more than half of patients. In country like us CNS TB and the AES caused by other Rickettsia species are also to be kept in mind. Hence additional evaluation for these and other pathogens with multiplexed molecular methods, next generation sequencing approaches are of paramount importance.

At IAP it is now time to rewrite our diagnostic algorithm for establishing etiology of AES. Empiric use of doxycycline for scrub typhus is also justifiable in all cases of AES in areas endemic for scrub typhus. Introduction of pneumococcal conjugate vaccine in NIP is a welcome step for the prevention of pneumococcal meningitis;one of the most common cause of bacterial meningitis. With the recent nightmare of unprecedented pandemic of COVID 19, we need to keep a close watch on emerging and reemerging CNS infections and para/post-infectious immune mediated insults to CNS.



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