INVITED COMMENTARY

The Changing Landscape of Brain Infections in India

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Acute onset of fever with alteration in consciousness with or without seizures is an important cause of hospital admissions among children in large parts of India. Such a presentation is mainly caused by invasion of the brain by an infectious agent – virus, bacteria, protozoa, rickettsiae, mycoplasma etc., but also by a host of non-infectious brain inflammations, infectious encephalopathies and other functional (such as toxic or metabolic encephalopathy) and structural brain disorders if associated with fever due to another cause [1]. In 2006, the World Health Organization (WHO) coined the term 'acute encephalitis syndrome' (AES) for the purpose of surveillance of Japanese encephalitis (JE) which was an important cause [2]. AES is a symptom complex, the etiology of which varies with region.

The most important cause of AES in India over almost 4-5 decades (1970s to 2024) has been JE. Since the first large epidemic reported from Bankura in West Bengal in 1973 [3], there have been repeated annual epidemics and outbreaks in monsoon and post-monsoon season in southern and eastern states, extending upto Gorakhpur division in eastern Uttar Pradesh (UP). It may be mentioned here that JE is a severe viral encephalitis with a fulminant clinical course, high risk of mortality and permanent neurological sequelae, and unfortunately, with no specific antiviral treatment available so far. The year 2005 saw a severe epidemic in UP, after which the Government of India imported the Chinese live attenuated vaccine (SA-14-14-2 strain) and administered it in campaign mode to children aged 1-15 years in affected districts [4]. JE vaccine was later included in the National Immunization Schedule in 181 JE endemic districts of India in 2011. In fact, after poliomyelitis, JE control took centre stage as an international priority for preventing death and disability in affected regions. International agencies and governments rolled out evidence-based public health measures to control JE. Since around 2015, the prevalence of JE as a cause of AES in UP did come down to less than 10% [4].

Since the early 2000's an illness with fever, encephalopathy, rash, low platelets, bleeding manifestations, mildly raised liver enzymes and a peculiar non pitting edema is being seen and reported from various parts of the country - dengue with encephalopathy (DE) [5]. Dengue infection has also been proven to invade the brain as an infectious encephalitis [6]. It was proposed that a neurotropic strain of the virus was in circulation.

In UP, although JE incidence as a cause of AES came down but AES itself did not decrease. This was baffling for some years, until it was realised that scrub typhus meningoencephalitis (STM) had replaced JE as the dominant cause in the eastern districts [7]. There were increasing reports of scrub typhus (ST) from various parts of the country – both North and South. The ecological conditions for spread of ST exist over large parts of our country. For some reason, STM is a common manifestation of ST infection in India. Fortunately, STM is a milder illness than JE and responds well to antimicrobials – tetracyclines and azithromycin. State governments issued directives to treat acutely febrile children in Gorakhpur division with empirical doxycycline at primary health centres [8]. Minocycline has the added advantage of having neuroprotective properties and achieving much higher levels in the brain [9].

India has also witnessed localized outbreaks of acute encephalopathy in Saharanpur [10] and later in Muzaffarpur, Bihar [11] which upon investigation were held to be toxic in origin. West Nile virus and Chandipura virus are both prevalent in India but their contribution to AES is not clear. The latter was implicated as the cause of 'Epidemic brain attack' reported from Andhra Pradesh in 2003. India remains endemic for rabies. Primary amebic meningoencephalitis due to Naegleria infection acquired by swimming in freshwater ponds occurs sporadically. Nipah virus is another agent associated with outbreaks of severe encephalitis in Kerela and West Bengal [12].

Misra and Kalita have differentiated two clinical syndromes of encephalitis prevalent in northern India – pure neurological illness (exemplified by Herpes simplex encephalitis, rabies and JE) and others with systemic manifestations also – rash, thrombocytopenia, bleeding,

liver function derangement (dengue, STM, cerebral malaria, leptospirosis etc) [13]. This approach may prove useful in the initial work up and treatment in other parts of the country as well.

Establishing an etiological diagnosis of AES is a difficult task even in affluent settings. This is illustrated by the California Encephalitis Project conducted in USA around the turn of the century, in which confirmed diagnosis was possible in only 16% [14]. Virological investigations are complex, expensive and require a sophisticated infrastructure. Many non-infectious illnesses can mimic brain infections. Timing of sample collection is important. These difficulties can be precluded to some extent by using the multiplex polymerase chain reaction (PCR) technology wherein several pathogens can be tested in a single test. PCR for a panel of agents relevant to the region can be designed. Another strategy applicable to resource constrained settings is to develop 'clinical prediction rules' for important pathogens.

The article by Rebecca et al in the current issue of *Indian Pediatrics* reports a 5-year (2015-19) retrospective data review from a tertiary hospital in Tamil Nadu [15]. Clinical, laboratory and radiological profiles were related to outcome. Many non-infectious disorders including poisoning, toxin or drug related, tumours and vascular causes of AES were excluded. Etiological diagnosis was established by a comprehensive array of tests – blood and CSF cultures for bacteria, serology, PCR, latex agglutination, viral isolation etc. Definitive etiological diagnosis was established in as high as 56.4% children, with a wide variety of agents involved. The study also reveals the AES patterns in southern India from where recent comprehensive data is scarce. STM (11.2%) and DE (9%) were the most common etiologies. Apparently, not a single patient over this 5-year period received a diagnosis of JE, although it is not clear as to how many were tested for JE and what test was used. Another study from South India found JE in 4% [16]. A large-scale, systematic surveillance study in 3 northern/eastern states (UP, Bihar and Assam) was conducted over 4 years (2014-17) in patients presenting with AES, using an algorithmic approach. The overall yield increased 3.1 times to 33.2%; the most commonly identified etiologies being STM (18.5%), JE (17.7%) and DE (5.2%) [17]. Comparison of these northern versus southern data suggests that JE is declining faster in southern states than the north and east. In conclusion, AES remains a challenge to physicians in India. Infectious and non-infectious etiologies have to be considered and the pattern of infection may change with region and time.

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