



## Perspective

### The syndrome of acute encephalitis in children in India: Need for new thinking

#### Definition, clinical description and differential diagnoses

Acute encephalitis is the clinical diagnosis of children with acute onset of symptoms and signs of inflammatory lesions in the brain. Changes in sensorium, seizures and upper motor neuron type of altered muscle tone point to cerebral dysfunction. Brain tissue would show the pathology, but at the bedside, inflammation is surmised from pleocytosis of the cerebrospinal fluid (CSF) to predominantly lymphocytes, since the aetiology is mostly non-pyogenic infection<sup>1</sup>. The clinical picture usually consists of a prodromal phase (one to three days) with fever, malaise and headache and an encephalitic phase with continued fever, decreasing level of consciousness, seizures, abnormal movements or paralysis. Signs of meningeal inflammation are absent or minimal. Many children may succumb, but others recover through a post-encephalitic phase, the fortunate ones more or less completely, but others with sequelae of cognitive deficiencies, muscle paralysis, abnormal movements, *etc.*

Acute encephalopathy and acute meningitis - pyogenic, tubercular, fungal or viral - are other examples of acute central nervous system (CNS) diseases due to infectious or non-infectious aetiologies that can and must be differentiated from acute encephalitis. In acute encephalopathy, brain pathology is non-inflammatory, often biochemical; hence, CSF shows no pleocytosis. Onset is often without prodromal phase and tends to be in the morning hours, the child having been well the previous evening. Changes in sensorium, seizures and upper motor neuron-type muscle tone abnormalities and abnormal movements point to cerebral dysfunction. Encephalopathy occurring in clusters is often conflated with acute encephalitis outbreak<sup>2-4</sup>. Acute meningitis is diagnosed when the clinical presentation points to meningeal inflammation - with fever, headache, neck

rigidity, positive Kernig and Brudzinski signs and high pleocytosis in CSF. In pyogenic meningitis, CSF cells are predominantly polymorphonuclear leucocytes, while in most others, these are predominantly lymphocytes. While viral meningitis is often self-limited, bacterial and fungal meningitis will progress to severe brain dysfunction and death, if left untreated. When features of encephalitis and meningitis co-exist, the disease is called meningoencephalitis<sup>1</sup>.

Some systemic infectious diseases with their own distinct clinical features may occasionally present with brain function derangement. Some are due to invasion of the pathogens into CNS, as with dengue fever<sup>5</sup>, chikungunya<sup>6</sup>, scrub typhus<sup>7</sup> and leptospirosis<sup>8</sup>, but even in such instances, these should be labelled as a complication of the primary disease, instead of acute encephalitis.

Cerebral malaria, a mimicker of encephalitis, is a complication of *Plasmodium falciparum* malaria. Some CNS complications of diseases are of unclear pathogenesis, such as encephalopathy of typhoid fever, shigellosis, influenza and varicella. Children given acetyl salicylic acid for such illnesses have increased risk of encephalopathy (Reye syndrome), for which reason the drug is prohibited in children below 12 years<sup>2</sup>. In some, pathogenesis is immune-mediated inflammation, as in post-measles and post-varicella encephalitis, also called acute demyelinating encephalomyelitis (ADEM)<sup>9</sup>.

Intracranial abscess (brain/subdural) and subarachnoid haemorrhage are relatively uncommon, but for the affected child, accurate diagnosis offers the possibility of life-saving treatments. Septicaemia of various aetiologies may present with cerebral dysfunction, which, unless picked up and treated early, may be life-threatening.

In summary, all that presents with fever and cerebral dysfunction are not acute encephalitis.

No single syndrome will accommodate all these disparate clinical conditions. Each clinical entity must be diagnosed and managed according to the modern medical recommendations both for individual healthcare and community control. Many of the above are medical emergencies and must be diagnosed promptly for saving life and preserving brain functions. Misclassification or delay can entail risk to the patient.

### **Causative infections of acute encephalitis**

We confine our attention to children with normal immune functions; children with immunodeficiency may have opportunistic agents that are by and large non-pathogenic to others. Acute encephalitis is mostly caused by any of the many 'neurotrophic' viruses, many of which are vector-transmitted (arthropod-borne) arboviruses. In India, Japanese encephalitis (JE) virus is the predominant aetiology<sup>10</sup>. Due to its ecological features, namely, the requirement of 'amplifying hosts' (pigs, herons and egrets) and vectors (*Culex* species mosquitoes), there are geographic restriction to some parts of the country, mostly rice paddy growing areas, and seasonal restriction determined by vector density, mostly post-monsoon.

West Nile (WN) virus is common in India and is known to cause acute encephalitis<sup>11</sup>. However, its geographic prevalence and quantitative contribution to acute encephalitis in India have not been systematically studied, because of considerable antigenic cross-reactivity between JE and WN viruses as well as between them and dengue viruses that are even more widely prevalent.

Anthroponotic viruses such as herpes simplex virus<sup>12</sup> and mumps virus<sup>13,14</sup>, a few enteroviruses<sup>15</sup> and Epstein-Barr virus<sup>16</sup> are other causes of sporadic cases of acute encephalitis. Rarely, measles and rubella may develop a complication by way of encephalitis, but the primary disease would be concurrently evident.

Nipah virus encephalitis had occurred once in Siliguri in West Bengal but was at first misdiagnosed as measles encephalitis<sup>17,18</sup>. Chandipura virus is widely prevalent in India, transmitted by sand flies and mosquitoes, and a few reports of outbreaks of what was called acute encephalitis caused by it have been published<sup>19,20</sup>. Similar outbreaks caused by measles virus, but without clinical measles, also have been reported earlier<sup>21,22</sup>. However, how such widely prevalent viruses cause only rare outbreaks has not been explained. The clinical features of both Chandipura and measles 'encephalitis' were very similar to each

other but very dissimilar to arbovirus encephalitis. In neither was there a prodromal phase; onset was abrupt and CSF was without pleocytosis as in encephalopathy. However, because a virus was detected in brain tissue or CSF, one has to accept the diagnosis of CNS infection, in spite of the fact that the clinical picture was that of acute encephalopathy without inflammatory pathology in the brain. We recommend caution in concluding that these two viruses are the actual cause of acute encephalopathy until re-confirmed by other investigators.

In the case of the first report on Chandipura virus encephalitis, an alternate pathogenesis has been described, namely, acute vascular pathology or 'epidemic brain attack'<sup>23</sup>. Such an explanation may clarify why the clinical picture was that of acute encephalopathy; what is not clear is if the virus infection actually caused cerebral arterial thrombosis<sup>23</sup>. Among non-viral causes of acute encephalitis, Naegleria is well-recognized to cause 'primary amebic meningoencephalitis', affecting people who swim in freshwater ponds or lakes<sup>24</sup>.

Thus, acute encephalitis is a clinical syndrome with several common features but caused by various infectious agents, mostly but not exclusively viruses. It should be differentiated from all other diseases mentioned above, clinically always and aetiologically when possible. In clinical context, the addition of the word syndrome is superfluous; acute encephalitis is specific and clear enough as is the conventional practice in paediatrics.

### **Acute encephalitis syndrome (AES), an ambiguous diagnostic term**

In recent years, a diagnosis of 'acute encephalitis syndrome' (AES) has crept into medical literature in India, with a definition at variance from that of acute encephalitis in paediatric textbooks<sup>10,14,25,26</sup>. For example, AES was defined in one study as 'clinical neurologic manifestations caused by wide range of viruses, bacteria, fungus, parasites, spirochetes, chemicals and toxins'<sup>26</sup>. Obviously, the clinical pictures of such various diseases cannot fit into one clinical diagnosis of acute encephalitis, either as a disease or as a syndrome.

The clinical classification into acute encephalitis, encephalopathy, meningitis, ADEM or as complications of any disease that may cause brain dysfunction is an ethical and scientific imperative; correct management will depend on the correct diagnosis. Many of the

diseases clubbed into the ‘basket of AES’ are eminently treatable with specific therapies. Antiviral drug is available for herpes simplex encephalitis. Other cases of viral encephalitis can only be treated with supportive care. The risk to the patient in whom AES is diagnosed is that the disease may be presumed to be acute encephalitis, hence viral in origin; further investigations, even spinal tap for CSF examination, may be avoided believing that every so-called AES is viral in origin and without specific therapeutic possibilities.

### Conclusion

All acute-onset CNS diseases of children do not constitute one syndrome, but several - not only encephalitis, encephalopathy and meningitis but also CNS complications of systemic diseases, brain abscess, subarachnoid haemorrhage, *etc.* Each of these diseases must be differentiated from every other since treatment will depend on the specific diagnosis. The tendency to club them together as if they belonged to one syndrome, ‘AES’, must be avoided.

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### References

- Prober CG, Srinivas NS, Mathew R. Central nervous system infections. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, editors. *Nelson textbook of pediatrics*. 20<sup>th</sup> ed. New Delhi: Reed Elsevier India Pvt. Ltd.; 2016. p. 2936-48.
- Benakappa DG, Das S, Shankar SK, Rao BS, Prakash, George S, *et al.* Reye's syndrome in Bangalore. *Indian J Pediatr* 1991; 58 : 805-10.
- Vashishtha VM, Nayak NC, John TJ, Kumar A. Recurrent annual outbreaks of a hepato-myo-encephalopathy syndrome in children in Western Uttar Pradesh, India. *Indian J Med Res* 2007; 125 : 523-33.
- Shah A, John TJ. Recurrent outbreaks of hypoglycaemic encephalopathy in Muzaffarpur, Bihar. *Curr Sci* 2014; 107 : 570-1.
- Kumar R, Tripathi S, Tambe JJ, Arora V, Srivastava A, Nag VL. Dengue encephalopathy in children in Northern India: clinical features and comparison with non dengue. *J Neurol Sci* 2008; 269 : 41-8.
- Chandak NH, Kashyap RS, Kabra D, Karandikar P, Saha SS, Morey SH, *et al.* Neurological complications of Chikungunya virus infection. *Neurol India* 2009; 57 : 177-80.
- Varghese GM, Trowbridge P, Janardhanan J, Thomas K, Peter JV, Mathews P, *et al.* Clinical profile and improving mortality trend of scrub typhus in South India. *Int J Infect Dis* 2014; 23 : 39-43.
- Khan SA, Dutta P, Borah J, Chowdhury P, Topno R, Baishya M, *et al.* Leptospirosis presenting as acute encephalitis syndrome (AES) in Assam, India. *Asian Pac J Trop Dis* 2012; 2 : 151-3.
- Steiner I, Kennedy PG. Acute disseminated encephalomyelitis: Current knowledge and open questions. *J Neurovirol* 2015; 21 : 473-9.
- Joshi R, Kalantri SP, Reingold A, Colford JM Jr. Changing landscape of acute encephalitis syndrome in India: A systematic review. *Natl Med J India* 2012; 25 : 212-20.
- George S, Gourie-Devi M, Rao JA, Prasad SR, Pavri KM. Isolation of West Nile virus from the brains of children who had died of encephalitis. *Bull World Health Organ* 1984; 62 : 879-82.
- Panagariya A, Jain RS, Gupta S, Garg A, Sureka RK, Mathur V. Herpes simplex encephalitis in North West India. *Neurol India* 2001; 49 : 360-5.
- John TJ, Maiya PP, Jadhav M, Christopher S, Mukundan P. Mumps virus meningitis and encephalitis without parotitis. *Indian J Med Res* 1978; 68 : 883-6.
- Jain P, Jain A, Kumar A, Prakash S, Khan DN, Singh KP, *et al.* Epidemiology and etiology of acute encephalitis syndrome in North India. *Jpn J Infect Dis* 2014; 67 : 197-203.
- 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.
- Kalita J, Maurya PK, Kumar B, Misra UK. Epstein Barr virus encephalitis: Clinical diversity and radiological similarity. *Neurol India* 2011; 59 : 605-7.
- Mudur G. Indian scientists warn of “mutant measles” virus. *BMJ* 2001; 322 : 693.
- Harit AK, Ichhpujani RL, Gupta S, Gill KS, Lal S, Ganguly NK, *et al.* Nipah/Hendra virus outbreak in Siliguri, West Bengal, India in 2001. *Indian J Med Res* 2006; 123 : 553-60.
- Rao BL, Basu A, Wairagkar NS, Gore MM, Arankalle VA, Thakare JP, *et al.* A large outbreak of acute encephalitis with high fatality rate in children in Andhra Pradesh, India, in 2003, associated with Chandipura virus. *Lancet* 2004; 364 : 869-74.

20. Chadha MS, Arankalle VA, Jadi RS, Joshi MV, Thakare JP, Mahadev PV, *et al*. An outbreak of Chandipura virus encephalitis in the eastern districts of Gujarat state, India. *Am J Trop Med Hyg* 2005; 73 : 566-70.
21. Wairagkar NS, Shaikh NJ, Ratho RK, Ghosh D, Mahajan RC, Singhi S, *et al*. Isolation of measles virus from cerebrospinal fluid of children with acute encephalopathy without rash. *Indian Pediatr* 2001; 38 : 589-95.
22. Shaikh NJ, Wairagkar NS, Reddy SV, Thakare JP, Gadkari DA. Acute encephalitis without rash in Warangal, Andhra Pradesh and Vadodara, Gujarat associated with measles virus. *J Assoc Physicians India* 2002; 50 : 1198.
23. Rao PN, Kumar PA, Rao TA, Prasad YA, Rao CJ, Rajyam PL, *et al*. Role of Chandipura virus in an "epidemic brain attack" in Andhra Pradesh, India. *J Pediatr Neurol* 2004; 2 : 131-43.
24. Visvesvara GS. Free-living amebae as opportunistic agents of human disease. *J Neuroparasitol* 2010; 1 : 1-13.
25. Kakkar M, Rogawski ET, Abbas SS, Chaturvedi S, Dhole TN, Hossain SS, *et al*. Acute encephalitis syndrome surveillance, Kushinagar district, Uttar Pradesh, India, 2011-2012. *Emerg Infect Dis* 2013; 19 : 1361-7.
26. Saminathan M, Karuppanasamy K, Paulraj S, Gopalakrishnan A, Raj RB. Acute encephalitis syndrome - A complex zoonotic disease. *Int J Livestock Res* 2013; 3 : 174-7.