

## **The Recurring Coma Epidemic in Children in India:**

### **What is it?**

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In India several epidemics of coma and fever with a high case fatality rate have largely remained mysteries(1-3). Such episodes of recurrent coma epidemic struck several states of India in epidemic form since 1997 between months of June and August. The affected states were Andhra Pradesh (1997, 2002, 2003, 2005), Maharashtra (2003) and Eastern districts of Gujarat (2004). Epidemics since 2003 were investigated in detail and results were published. The main diagnostic possibilities reported were Japanese Encephalitis, Atypical Measles Encephalitis, Chandipura encephalitis, Reye syndrome, and Epidemic Brain Attack. Heat-related encephalopathy was also mentioned as a possibility. This communication examines possible role of each of these diagnoses in causation of these epidemics.

1. Encephalopathy of Heat Hyperpyrexia(4,5): High ambient temperature (36-49°C), fever and widely scattered cases

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suggested this possibility (5,6,7). However, most epidemics occurred not at the time of high temperature but within 48 hours of heavy rains after a hot summer resulting in sudden drop in temperature and rise in humidity in the three epidemics of 1997, 2002 and 2003 (6) making this possibility less likely. Middle cerebral artery territory infarcts on neuroimaging excluded this diagnosis (6).

2. Reye Syndrome. Reye syndrome is defined as an illness that meets all of the following criteria: (a) acute noninflammatory encephalopathy documented by the clinical picture of alteration in the level of consciousness and, if available, a record of cerebrospinal fluid containing 8 leukocytes or less per mm<sup>3</sup>, or histologic sections of the brain demonstrating cerebral edema without perivascular or meningeal inflammation, (b) fatty metamorphosis of the liver diagnosed by either biopsy or autopsy or a threefold or greater rise in the levels of either the SGOT, SGPT, or serum ammonia, and (c) no known more reasonable explanation for the cerebral or hepatic abnormalities(8). Same epidemics were reported as Reye's syndrome based on gross brain oedema, case fatality rate of >50%, increased intracranial tension, improvement with antiedema measures like mannitol, absence of pleocytosis & normal protein in the CSF, rapid deterioration and death(9). However lack of liver dysfunction, presence of fever, focal signs and neuroimaging evidence of restriction of edema to arterial territories in many instances negate the diagnosis of Reye syndrome(6).

3. **Viral Encephalitis:** It is usually caused by a direct viral infection or a hypersensitivity reaction to a virus or foreign protein. The spinal fluid shows a cellular reaction and the protein is slightly elevated.

Several viruses were implicated as causes of these epidemics.

#### **A. Japanese Encephalitis (JE)**

There were major clinical and epidemiological differences between the current illness and JE(6). Occurrence within 2 days of heavy rain after a hot summer, shorter prodrome, reaching peak illness within 2 days, presence of abdominal colic, presence of diarrhea, absence of meningeal irritation in all cases, good response within 4 hours to IV mannitol, easily controllable seizures with one dose of diazepam and phenytoin, rapid progression to death within one day if IV mannitol was not given, normal CSF except for increased tension in all cases, Middle cerebral artery territory infarcts on neuroimaging, absence of sequelae in survivors and absence of extrapyramidal disorders in survivors clearly excluded JE(6).

#### **B. Chandipura Encephalitis**

The epidemics were reported as Chandipura Encephalitis by some with evidence from virus isolation, identification by electron microscopy, immunofluorescence, PCR(7,10). Young mice, infected with Chandipura virus intra-peritoneally, developed CNS lesions, with necrosis particularly affecting neurons and ependymal cells(11) proving that CHPV causes encephalitis in mice. Lack of pleocytosis and normal protein in most CSF samples in these epidemics(5,6,7,9,10) excludes significant necrosis of ependyma in humans suggesting the cause to be an acute catastrophic event (stroke) in the brain(6,12) rather than

encephalitis. Similar sentiments have been earlier expressed by other clinicians.

#### **C. Measles encephalitis**

Two outbreaks of coma in children in Warangal district of Andhra Pradesh and Vadodara district of Gujarat were attributed to measles virus by National Institute of Virology, India(13). However if there is no inflammation in the CNS, but only brain edema, the detection of virus in CSF must be viewed with some respectful skepticism(14). Some experts believe that the isolation of measles virus in these epidemics was a result of laboratory contamination with measles vaccine virus(14).

#### **D. Epidemic Brain Attack**

This epidemic coma was reported as Epidemic Brain Attack (EBA) of childhood by some based on clinical features, normal CSF in all cases, infarcts on neuroimaging and response to treatment(5,6,12,15). Brain Attack (Stroke) should be diagnosed when there are "Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin"(16). When it occurs in epidemics, it is called Epidemic Brain Attack or Epidemic Stroke(6,12).

The clinical, laboratory and neuroimaging features of most patients during these epidemics were consistent with ischemic damage suggesting the diagnosis of EBA.

The possible explanation of EBA occurring in epidemic form could be that a virus is the cause of vasculitis presenting this way but it is unlikely to be encephalitis. The possibility of laboratory contamination is also to be considered. Raised intracranial tension is a common feature of Reye syndrome and Epidemic Brain Attack. If all major cerebral

### Key Messages

- Selection as well as timing of an investigation are crucial to make a diagnosis in mystery diseases.
- Laboratory contamination or errors must be considered whenever unexpected results are obtained.
- Fever, alteration of sensorium without rash or meningeal signs of irritation, normal CSF, epidemic within 2 days of heavy rain after a hot summer and neuroimaging features of infarction should suggest the diagnosis of EBA.

arteries are involved, Epidemic Brain Attack can mimic Reye syndrome. Presence of fever and focal signs differentiate EBA from Reye syndrome.

Reasons for acute onset with sudden death in EBA is severe brain edema due to ischemia of large areas of brain caused by transient vasospasm of Middle Cerebral Artery(6), resulting in herniation and compression of the brainstem.

Fever, alteration of sensorium without rash or meningeal signs of irritation, normal CSF, epidemic within 2 days of heavy rain after a hot summer and neuroimaging features of infarction are main features suggesting diagnosis of EBA.

The exact etiology of the sequence of events in these attacks is unclear. Whether this multi-region outbreak was caused by a large batch of contaminated food being distributed to the different regions by a transport chain or by an unusual organism, spread by an environmental vector or immigrant strains distributed by people returning from holiday requires further epidemiological studies.

*Conclusion:* The episodes of acute coma in children being reported from various parts of India in recent years do not appear to be viral encephalitis. EBA seems to be the most likely pathological diagnosis the cause of which is largely unclear. Role of Chandipura Virus as

an evolving human pathogen requires further confirmation(12).

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### REFERENCES

1. Khan N. Jamshedpur fever. Indian J Med Sci 1954; 8: 597-608.
2. Rodrigues FM, Patankar MR, Banerjee K, Bhatt PN, Goverdhan MK, Pavri KM *et al.* Etiology of the 1965 epidemic of febrile illness in Nagpur city, Maharashtra state, India. Bull World Health Organ 1972; 46: 173-179.
3. Potharaju NR. Viral encephalitis-Indian scenario. Indian J Pediatr Neurol 2002; 1: 67-77.
4. Sriramachari S. Heat hyperpyrexia: time to act. Indian J Med Res 2004; 119: vii-x.
5. John TJ. Chandipura virus, encephalitis, and epidemic brain attack in India. Lancet. 2004; 364: 2175-2177.
6. 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; 131-143.
7. Rao BL, Basu A, Wairagkar NS, Gore MM,

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- 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: 869-874.
8. CDC case definitions print page. Reye Syndrome. 1990 Case Definition. Clinical case definition. Available from URL: [http://www.cdc.gov/epo/dphsi/print/reye\\_syndrome\\_current.htm](http://www.cdc.gov/epo/dphsi/print/reye_syndrome_current.htm). Accessed June 20, 2006.
  9. John TJ. Outbreak of killer brain disease in children: mystery or missed diagnosis? *Indian Pediatr* 2003; 40: 863-869.
  10. Chadha MS, Arankalle VA, Jadhav 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;73:566-570.
  11. Jortner BS, Bhatt PN, Sollitare GB. Experimental Chandipura virus infection in mice, I: virus assay and light microscopic studies with emphasis on neuropathologic observations. *Acta Neuropathol* 1973; 23: 320-325.
  12. Potharaju NR and Potharaju AK. Is Chandipura virus an emerging human pathogen? *Arc Dis Child* 2006; 91: 279-280.
  13. 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* 2001;50: 1198.
  14. John TJ. Encephalopathy without rash, caused by measles virus? More evidence is needed. *Indian Pediatr* 2003; 40: 589-593.
  15. Hussain IHM. Viruses and Epidemic "Brain Attacks": New Agents, New Challenges. *J Pediatr Neurol* 2004;2:117-119.
  16. Tunstall-Pedoe H. World Health Organization MONICA Project Monitoring Trends and Determinants in Cardiovascular Disease: A major international collaboration. *J Clin Epidemiol* 1988; 41: 105-114.
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