## Editorial

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# Acute encephalitis syndrome — an unsolved mystery !

Acute encephalitis syndrome (AES) can be defined as an acute onset of fever with change in mental status (confusion, disorientation, inability to talk, coma) and/ or new onset seizures (excluding simple febrile seizures).

Japanese encephalitis virus (JEV) is the leading diagnosed cause of acute encephalitis, others being 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).

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.

The last decade has seen a rise in the incidence of unexplained illness in form of outbreaks of sudden neurological deterioration and a high mortality especially among children in the district of Muzaffarpur and adjoining areas.

The first recorded incidence of the mystery illness started in 1995. The outbreaks coincide with the harvesting season of Litchi (mid-May and early June), a seasonal fruit of this region. The affected children mostly belonged to poor socio-economic backgrounds with clinical features usually starting in the early morning period.

The data at Sri Krishna Medical College & Hospital, Muzaffarpur from the year 2012-2018 reported 814 admissions with AES of which there were 292 (35.8%) deaths. Few cases (35) of Japanese encephalitis were also discovered during the period with fatality in 8 cases.

There have been many theories of possible etiological factors including infectious encephalitis, exposure to pesticides and consumption of Litchi but none of these have been proven to be the causative factors.

In 2011, there were 147 cases and 54 deaths in the district. In the following year, 469 cases and 178 deaths were reported from health facilities with CFR of 38.6 per cent. The age of the hospitalized cases ranged from six months to 16 yr. with 92 per cent below the age of 10 year. Fifty three per cent were females.

In 2014, NCDC and CDC investigated this illness with Hospital based clinical surveillance, epidemiological case control study, comprehensive lab testing to study the role of etiological agents like naturally occurring toxins, pesticides, infectious pathogens and toxic elements.

Between May 26, and July 17, 2014, 390 patients meeting the case definition were admitted to the two referral hospitals in Muzaffarpur. Among these, 213 (55%) were boys, median age was 4 years (range 6 months-14 years), and 280 (72%) were aged 1-5 years. Most patients (273; 70%) were from Muzaffarpur district; cases were reported from all 16 blocks of Muzaffarpur district. Clustering of cases was not observed; each affected child seemed to be an isolated case in a village (approximate population per village 2500). The outbreak peaked in mid-June, with 147 cases reported during June 8-14, 2014, and declined substantially after June 21, 2014.

Caregivers reported that affected children were previously well and 366 (94%) had sudden onset of symptoms less than 24 h before admission. Further, 224 (66%) of 342 patients with recorded data reported illness onset between 300 h and 800 h. Of patients with recorded data, 326 (94%) of 348 reported one or more seizures and 345 (95%) of 362 reported altered mental status before admission; 301 (87%) of 347 patients were unconscious on presentation.

Of 357 patients with recorded admission measurements, the median temperature was 37.2°C (99°F; range 35.6–40.6), and 219 (61%) were afebrile (≤37.5°C [≤99.5°]). Among 386 patients with recorded data, 122 died (case fatality rate 32%).

On detailed clinical assessment of 52 patients, 48 (92%) showed no focal neurological deficits. Brain MRI of 16 patients showed no focal lesions, signal abnormalities, or changes suggestive of inflammation; eight patients (50%) showed mild to moderate cerebral oedema. Clinical severity did not noticeably differ between participants with and without cerebral oedema. EEG in 30 cases showed findings consistent with generalised encephalopathy in 22 (73%); seven showed epileptiform discharges. Of 62 patients with CSF collected for analysis, 52 (84%) had normal WBC counts ($<0.5\times10^6$ cells per L), 58 (94%) had normal protein (<450 mg/L), and 49 (79%) had normal glucose (>2.50 mmol/L) concentrations. Of 327 patients with blood glucose measurement on admission, the median blood glucose level was 2.66 mmol/L (range 0.44–23.98), and 100 (31%) patients had glucose concentration of 1.67 mmol/L or less, 171 (52%) patients had glucose concentration of 2.78 mmol/L or less, and 204 (62%) patients had glucose concentrations of 3.89 mmol/L or less. Of 349 patients with available information, 239 (69%) had a record of receiving dextrose therapy during hospital stay; of these, 173 (73%) survived.

Exposures that were significantly associated with illness included litchi consumption, visiting a fruit orchard, and absence of an evening meal (defined as eating the last [non-litchi] meal before 1900 h.

Among those who consumed litchis, cases were more likely to eat unripe litchis, eat rotten, report eating litchis from the ground versus from the tree and report eating partially eaten litchis.

No association was noted between illness and consumption of raw vegetables or medications, drinking water source, or exposure to insecticides or chemicals sprayed in and around the house or nearby fields or orchards .

The absence of an evening meal in the previous 24 h significantly modified the relation between litchi consumption and illness.

At NCDC, laboratory diagnostic testing of 17 CSF specimens for Japanese encephalitis virus and West Nile virus by PCR, and an additional 12 CSF specimens with an 11-virus multiplex PCR platform assay were negative. All other samples were negative for all assays tested.

Among 73 case-patient urine specimens assessed, 47 (64%) contained metabolites of hypoglycin A (MCPA-Gly), 33 (45%) contained metabolites of MCPG (MCPF-Gly), and 32 (44%) specimens contained both metabolites.

On assessment, 67 (89%) of 75 specimens showed abnormal urinary organic acid profiles and 72 (90%) of 80 specimens had abnormal plasma acylcarnitine profiles, consistent with severe disruption of fatty acid metabolism.

Of 36 litchi arils analysed from Muzaffarpur, observed concentrations ranged from 12.4 µg/g to 152.0 µg/g hypoglycin A and 44.9 µg/g to 220.0 µg/g MCPG. Within each batch tested, the unripe fruit contained higher concentrations of both MCPG and hypoglycin A than did the ripe fruit.

Children in Muzaffarpur frequently spend the day eating litchis and some skip the evening meal. Skipping evening meal, by itself results in low blood sugar levels during the night. This is particularly so in the case of young children as they have limited hepatic glycogen reserves. Hypoglycin A and methylenecyclopropylglycine (MCPG), which are naturally present in litchi fruit, make the condition worse. The toxins block enzymes involved in normal glucose metabolism and this results in an inability to synthesis glucose leading to acutely low level of blood sugar. The build-up of other metabolic by-products could also have an adverse effect (encephalopathy) on the child.

The recommendations following the investigations recommended that litchi consumption should be minimised in young children, avoid skipping evening meals and a rapid hypoglycaemia correction on presentation should be implemented.

However, some unexplained questions still remain like absence of clustering, presentation in infants who are too young to consume litchi and an absence of fever.

Over the last two years, number of cases presenting has reduced significantly. There is still a mystery over the real causative factor leading to the epidemics. There is need for further research and investigation to ascertain the real cause of the illness.