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2013-2014 Investigation Findings of Unexplained Acute Neurologic Illness Outbreak, Muzaffarpur, Bihar – Brief Note

Outbreaks of an acute neurologic illness commonly described as AES (acute encephalitis syndrome) have been reported in Muzaffarpur, Bihar since 1995; there have been several subsequent outbreaks. In most outbreaks, it was found that the illness primarily affected previously healthy young children (mostly in age-group 2-5 years), and was typically characterized by acute onset seizures and altered mental status in early morning hours, quickly deteriorating to coma and associated with high mortality. Outbreaks have occurred in the dry, hot months of May and June, and coincide with Muzaffarpur's litchi harvesting season.

In the years 2013 and 2014, National Centre for Disease Control (NCDC) and partner institutions, US Centers for Disease Control and Prevention (CDC), National Vector Borne Disease Control Programme and Indian Council of Medical Research (ICMR), conducted systematic investigations of this outbreak illness with the use of four key methods: examining clinical parameters, conducting descriptive and analytic epidemiologic field studies, performing detailed laboratory testing of human biologic specimens, as well as collection and laboratory analysis of environmental specimens.

EVALUATION OF INFECTIOUS ETIOLOGIES

Clinical parameters indicated that the majority of patients presented without prodrome or fever on admission, that cerebrospinal fluid (CSF) cytology and biochemistry were unremarkable, and that the magnetic resonance imaging (MRI) brain showed no evidence of inflammation; together these findings suggested that an infectious etiology was unlikely. Pathogen-based testing of human biologic specimens at NCDC using enzyme-linked immunosorbent assay for antibodies, polymerase chain reaction (PCR) and virus isolation techniques were negative for Japanese encephalitis virus, West Nile virus, Chandipura, enteroviruses and 11 viruses tested with a multiplex PCR platform (Herpes simplex viruses 1 and 2, human herpes viruses 6 and 7, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, parechovirus, adenovirus, enteroviruses and parvovirus B19). In previous years, National Institute of Virology, ICMR based Nipah testing (PCR) had also been negative. Further, human biologic specimens sent to the US CDC Pathogen Discovery Laboratory were evaluated for any novel bacterial or viral etiologies using 16s ribosomal testing, pan viral PCR, and next generation metagenomic sequencing; results indicated no evidence of an infectious etiology. Additionally, entomology studies by NCDC and previously by the Centre for Research in Medical Entomology, ICMR did not suggest either adequate density of specific vectors nor presence of antigens in them to suggest any vector-borne infectious etiology. Thus, the illness diagnosis was finally concluded to be an acute encephalopathy, and not infectious encephalitis.

The next steps in the investigation involved evaluating noninfectious etiologies of pesticide toxicity and heavy metals. Clinical and epidemiologic parameters were not consistent with pesticide or heavy metal toxicity. The National Institute of Occupational Health (NIOH), ICMR analyzed and compared acetylcholinesterase and butyrylcholinesterase levels between biologic specimens of case-patients (affected children) and controls (well children) and found no evidence to suggest organophosphate pesticide toxicity. Specimens submitted to the US CDC National Center for Environmental Health laboratories were additionally analyzed for the presence of other metabolites of herbicides (atrazine) and organophosphates (dialkylphosphate), which yielded negative results for all tests. The NIOH also tested for evidence of pesticide residues in food grains, water, local vegetation and fruits (litchi) specimens taken from case patient homes, which again tested negative. Additionally, the US CDC laboratories tested for a battery of over 25 heavy metals and found no evidence to support heavy metal toxicity in human specimens.

The clinical study findings also revealed severe levels of hypoglycemia in the majority of case-patients, suggesting that this was an outbreak of acute hypoglycemic encephalopathy, likely due to a

noninfectious agent. Timely glucose assessment and correction, which was recommended after the 2013 investigation, demonstrated encouraging response and may have, in part, explained a significant reduction in mortality observed in 2014 compared to 2013. Further, the characteristic finding of an early morning illness onset in a previously healthy child and the seasonal nature of this outbreak suggested the possibility of a seasonally available exogenous toxin which somehow acted on the child's glucose metabolism, and to which a child might be particularly vulnerable in the early morning fasting hypoglycemia state. Clinical and epidemiologic analysis indicated that the case-patients were found more likely to be malnourished than controls (well children in the same area), which again suggested that the toxin may have an increased effect on those with depleted glycogen stores.

Similar outbreaks of hypoglycemic encephalopathy have been documented in West Africa and West Indies Islands, where the illness was found to be associated with ackee fruit ingestion, due to the presence in the ackee fruit of a naturally occurring compound called hypoglycin, which causes disruptions in glucose metabolism which result in abnormal fatty acid accumulation and severe hypoglycemia. Given that litchi belongs to the same botanical family (Sapindaceae) as the ackee fruit, and also has a natural compound called methylenecyclopropylglycine (MCPG) that is a homologue of hypoglycin, which is also known to cause a similar disruption of fatty acid/glucose metabolism as the ackee fruit in experimental animal studies, it was decided to proceed with testing for association between the Muzaffarpur outbreak illness and these naturally occurring toxins (MCPG and hypoglycin) along four lines of investigation: 1) Evaluation of an epidemiologic association between exposure to MCPG/hypoglycin-containing fruits (litchi) and illness; 2) Assessment for the presence of hypoglycin or MCPG metabolites (MCPA or MCPF) in urine specimens of affected children; 3) Assessment of biomarkers of abnormal accumulation of fatty acids (organic urinary acids and acylcarnitines) in biologic specimens of cases and 4) Assessment for the presence of hypoglycin or MCPG in litchi specimens from the affected areas.

The epidemiologic case-control studies conducted in both years 2013 and 2014 show significant associations between visit to fruit orchard in the previous 24 hours and having illness.

Furthermore, with more detailed questioning, the 2014 case-control study further shows a significant association between consuming litchi in previous 24 hours and having illness.

The US CDC National Center for Environmental Health laboratories evaluated and confirmed the presence of both MCPG and hypoglycin metabolites in urine specimens of case-patients and also the disruption of fatty acid metabolic function by identifying biomarkers of the same (organic acids, including· dicarboxylic acid, in urine and medium and long-chain acylcarnitines in blood) in human specimens. These abnormal findings (MCPG, hypoglycin or abnormal elevations in fatty acids) were not observed on evaluation of any specimens of controls (well children). These laboratories also detected both hypoglycin and MCPG in the aril (fruit) and seeds of litchi fruits collected from Muzaffarpur in the year 2014.

It is also noted that even in some Asian countries - Vietnam and Bangladesh - outbreaks of similar unexplained illness in litchi growing regions have been reported and an ecological association of illness and litchi plantation surface proportion was established in Vietnam outbreak investigations. Also, similar outbreaks are now reported from Malda district of West Bengal, another litchi growing region. Characteristically, these outbreaks from Vietnam, Bangladesh, Malda and West Africa/West Indies present as similar acute neurological illness in very young age children described as acute onset seizures and altered mental status, usually in early morning hours, quickly deteriorating to coma and with high mortality. These outbreaks have also similarly been reported to coincide with litchi/ackee fruits harvesting season.

NCDC/CDC AND PARTNER AGENCIES: COLLABORATIVE INVESTIGATIONS OF MUZAFFARPUR OUTBREAKS, 2013-2014

In 2013 and 2014, NCDC/CDC conducted hospital-based surveillance, a field-based epidemiologic study and coordinated laboratory and environmental testing in Muzaffarpur to:

- Examine clinical features, clinical course, management and outcomes of hospitalized cases in the selected hospitals
- Determine the etiology of the outbreak illness
- Identify risk factors for illness.

The participating tertiary care hospitals in Muzaffarpur were Shri Krishna Medical College Hospital (SKMCH) and Krishnadevi Deviprasad Kejriwal Maternity Hospital (KDKMH). The case definition utilized to

identify affected/ill children with the suspected outbreak illness was:

A child ≤15 years admitted to a participating hospital during surveillance period of late May to mid-July with–

- Altered mental status in the last 7 days
- New onset seizures in the last 7 days (excluding simple febrile seizures).

Real time data were collected for all patients admitted at SKMCH or KDKMH who met the case definition. This included clinical history, exam, neurologic evaluation, anthropometric measures, outcome, as well as routine hospital laboratory tests, and, in a selected number of patients, electroencephalograms (EEGs) and MRIs. Specimens were collected from all patients and submitted to specialized referral laboratories, including NCDC-based virology laboratory testing, CDC-based pathogen discovery, NIOH laboratory-based pesticide exposure testing and CDC National Center for Environmental Health-based toxicological testing.

Epidemiologic and environmental investigations included field entomologic survey, as well as an epidemiologic case-control study, which included detailed examination and comparison of exposures to food, water, insects, animals, agriculture, chemicals between ill children (cases) and well children (controls).

In the case-control study, for each case enrolled in surveillance, TWO AGE-MATCHED well children (CONTROLS) were enrolled: one HOSPITAL control, who was admitted to a participating hospital without any CNS symptoms, and one COMMUNITY control, who was residing in same (year 2013) or neighboring village (year 2014), without any CNS symptoms. Home visits and collection of standardized data on epidemiologic and environmental exposures (cases and controls) were conducted.

2013 INVESTIGATION

During May 17 to July 22, 2013, a total of 133 children were admitted to the two main referral hospitals in Muzaffarpur with illnesses that met the investigation case definition. Of these, 94 (71%) patients were from Muzaffarpur; other patients were from six neighboring districts. Among the 133 patients, 71% were aged 1-5 years, 94% had generalized seizures and 93% had altered mental status.

Clinical Findings, 2013

Most (61%) patients were afebrile at admission; the case fatality rate was 44%. Among 56 patients with CSF examined, 31 (55%) had normal cytology (white blood cell [WBC] count ≤5 mm^3); 48 of 59 (81%) had normal CSF protein (<45 mg/dL), and 46 of 61 (75%) had normal CSF glucose (>45 mg/dL) levels. At admission, 20 (21%) of 94 patients had hypoglycemia (blood glucose 70 mg/dL).

Laboratory: Infectious Pathogen Testing, 2013

CSF samples were tested at NCDC for selected infectious pathogens known to cause encephalitis in the region. Of 60 CSF specimens tested for Japanese encephalitis virus by immunoglobulin M (lgM) capture enzyme-linked immunosorbent assay, 33 by PCR, and 33 by virus isolation, all were negative. Sixteen convalescent serum specimens, collected 14 days after illness onset, also were negative for Japanese encephalitis virus by lgM assay. Thirty CSF specimens examined by reverse transcription-PCR for flaviviruses and 13 examined more specifically for West Nile virus also were negative, as were 23 evaluated for Chandipura virus. Fourteen CSF specimens evaluated by PCR and virus isolation for enteroviruses did not demonstrate evidence of infection.

Subsequent infectious disease testing of approximately 40 patient specimens in the US CDC Pathogen Discovery Laboratory did not reveal any evidence of an infectious etiology on evaluation by 16s ribosomal testing for bacterial pathogens, as well as pan-viral family PCR and next generation metagenomic sequencing for viral pathogens.

Laboratory: Pesticide Testing, 2013

Evaluation of case and control blood specimens at NIOH for acetylcholinesterase and butyrylcholinesterase levels to assess for the possibility of organophosphate poisoning did not indicate any evidence of poisoning by this agent. Additionally, NIOH scientists evaluated food, grains and water specimens collected from the homes of over 10 case patients for pesticide residues of over 29 agents; these test results were also negative.

Epidemiologic Findings, 2013

Analysis of risk factors for death among 94 affected children showed that low blood glucose at admission was more common among those who died (odds ratio [OR] = 2.6; 95% confidence interval [CI] = 1.0-7.2). A case-control study enrolled 101 case-patients and 202 age-matched controls, 101 from the hospital and 101 from the community. Ill children had spent a greater amount of time in agricultural fields or orchards (matched OR = 2.6; CI = 1.2-5.2) than controls. Anthropometric

data on 24 patients suggested that younger patients (those aged <5 years) were more likely to have wasting (>2 standard deviations below the median weight for height of the reference population) than controls in the same age group (p = 0.03).

2014 INVESTIGATION

Building on the 2013 findings, NCDC and CDC again investigated the outbreak in 2014, using: 1) facility-based clinical surveillance; 2) epidemiologic case-control and environmental studies to examine risk factors for illness, including toxin exposures and nutritional indices and 3) comprehensive laboratory evaluation of patient specimens and environmental samples to search for infectious pathogens as well as selected pesticides, heavy metals and naturally occurring plant or fruit toxins. Suspected patients were promptly tested for hypoglycemia on arrival at the hospital, before being given any treatment. Patients admitted with the suspected outbreak illness were recommended to receive immediate intravenous dextrose therapy.

Clinical Investigation Findings: 2014

During May 26 to July 17, 2014, a total of 390 patients admitted to the two referral hospitals in Muzaffarpur with illnesses that met the same case definition used in 2013 were evaluated by the NCDC/CDC investigation team. Among the patients, 213 (55%) were male, the median age was 4 years (range = 6 months-14 years) and 280 (72%) were aged 1-5 years. Most patients were from Muzaffarpur district (70%), although patients also were reported from six surrounding districts. As in previous years, clustering of cases was not observed; the illness of each affected child appeared to be an isolated case in various villages (approximate population per village = 1,000). The outbreak peaked in mid-June, with 147 cases reported during June 8-14, 2014. The number of cases declined significantly after the onset of monsoon rains on June 21, 2014 (Fig. 1).

Caregivers reported that affected children were previously healthy and experienced an acute onset of convulsions, often between 4:00 am and 8:00 am, frequently followed by a decreased level of consciousness. Of 345 patients with recorded data, 324 (94%) had seizures on admission and 267 (77%) had altered mental status. Of 357 patients with body temperature measured on admission, 219 (61%) were afebrile (≤99.5°F [≤37.5°C]). The case-fatality rate was 31%.

Of 62 patients with CSF collected for analysis, 52 (84%) had normal WBC counts, 58 (94%) had normal protein and 49 (79%) had normal glucose levels. Of 327 patients with blood glucose measurement on admission, the median blood glucose level was 48 mg/dL and

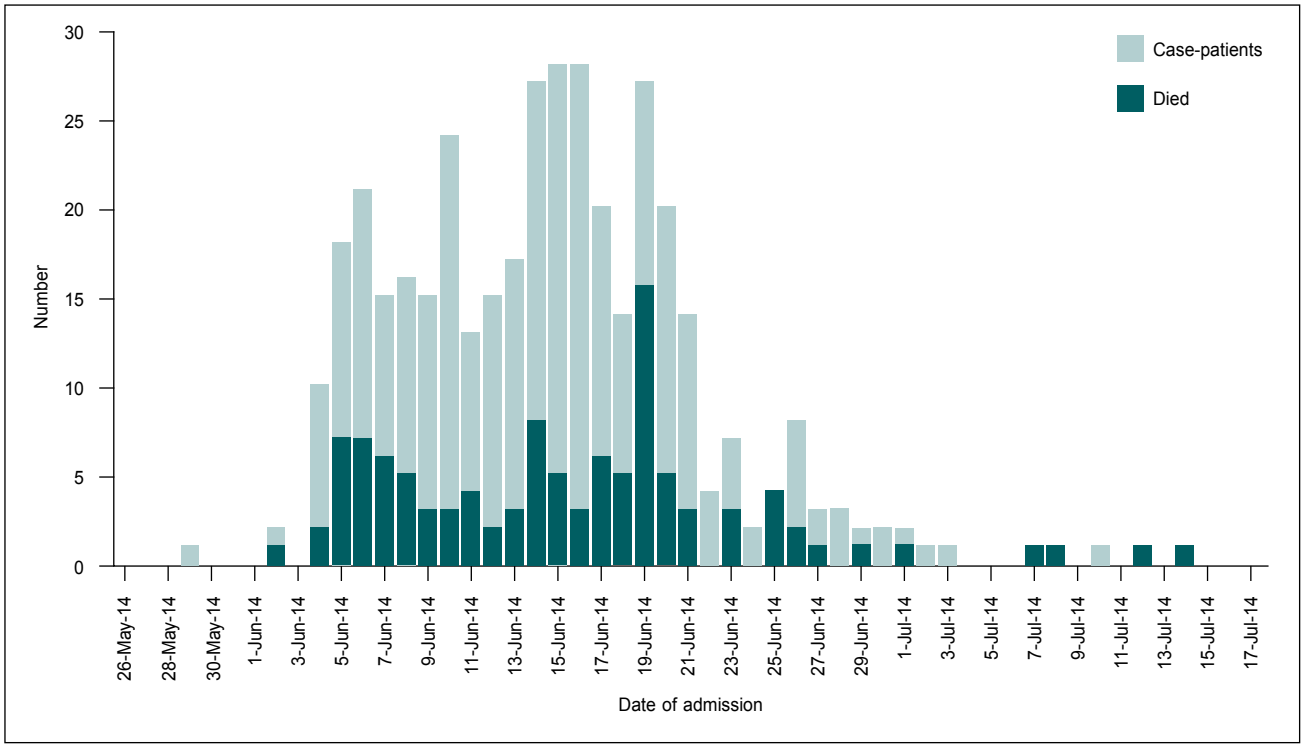

Figure 1. Epidemic curve of patients with acute neurologic illness, Muzaffarpur (2014).

Epidemiologic Findings, 2014

Key risk factors	Cases (N = 104)	Controls (N = 208)	mOR (95% CI)
Ate litchi*	67/103 (65%)	98/204 (48%)	2.1 (1.2-3.5)
Ate litchi from ground*	30/90 (33%)	31/136 (23%)	1.7 (0.9-3.4)
Ate rotten litchi*	23/88 (26%)	19/130 (15%)	2.4 (1.0-5.5)
Visited fruit orchard*	52/100 (52%)	62/195 (32%)	2.9 (1.6-5.1)
Parent visited fruit orchard*	29/95 (31%)	39/198 (20%)	1.8 (1.0-3.1)

171 (52%) and 204 (62%) patients had glucose levels of ≤50 mg/dL and ≤70 mg/dL, respectively. Brain MRI of 16 patients selected at random revealed no focal abnormalities or changes suggestive of inflammation. EEG in 30 cases demonstrated findings consistent with generalized encephalopathy.

Exposures that were examined, but not associated with illness

- Peel litchi with mouth, bite litchi seed†, eat litchi seed†, chew litchi seed†, eat unripe litchi†, eat litchi peel†
- Mother or father work in litchi orchard
- Other seasonal fruits, vegetables, nuts, herbs
- Drinking water source (pump, surface, piped)
- Exposure to insecticides† or chemicals† sprayed in and around house or nearby fields/orchards (each asked separately)
- Exposure to medications†, aspirin†, traditional medicines.†

† < 5% cases or controls reported exposure.

Laboratory: Infectious Pathogen Testing, 2014

Laboratory diagnostic testing at NCDC of 17 CSF specimens for Japanese encephalitis virus and West Nile virus by PCR was negative. Additionally, evaluation of 12 CSF specimens with a multiplex PCR platform assay with the capacity to detect 11 viruses* also was negative.

Laboratory: Pesticide, Herbicide, Heavy Metal Testing, 2014

Specimens submitted to NIOH indicated no significant difference detected in RBC acetyl and butyryl cholinesterase levels between cases and controls. Additionally, case specimens submitted to CDC National Center for Environmental Health for atrazine (herbicide) and dialkylphosphate (organophosphate) metabolites were also negative. Evaluation for food, grains, water, litchi specimens collected from the homes of case patients for pesticide residues again tested negative. Additionally, specimens of 80 patients tested at CDC did not reveal any evidence of elevated levels of >25 metals in blood and urine of 80 cases, including lead, mercury, arsenic, tin and iodine.

Urinary Organic Acids and Acylcarnitines (to Assess for Abnormal Accumulation of Fatty Acids), 2014

Emory University USA analysis of plasma from 80 cases and urine from 75 cases showed approximately 90% had abnormal profiles of urine organic acids and approximately 90% had abnormal profiles of plasma acyl carnitines. These findings indicate abnormal disruption of metabolic function and fatty acid metabolism that match well with expectations from the proposed mechanisms of hypoglycin A and MCPG. Analysis of 19 of control urine samples (2013) have been analyzed for urine organic acids with 17 being normal or essentially normal and 2 showing trace amounts of acylglycines - not elevated to the magnitude found in cases.

Laboratory: CDC Lab Analysis of Urine for Toxins (Metabolites of Hypoglycin and MCPG), 2014

The urine metabolites of hypoglycin A and MCPG were measured by isotope-dilution followed by liquid chromatographic separation and mass spectrometric detection. The assay's analytical range was linearly proportional (R > 0.99) from the lower limit of detection (LOO) of 0.1-20 μg/mL. A set of 96 individual human urine samples were commercially obtained from Tennessee Blood Services (Memphis, TN, USA) and found to be below the assay's LOO when analyzed.

Metabolites of both hypoglycin A and MCPG were identified in urine samples from cases. Of the 72 case samples from 2014 that had adequate volume for analysis, 65% had detectable levels of either metabolite of hypoglycin A (MCPA) or metabolite of MCPG (MCPF). Specifically, 65% had detectable levels of the metabolite of hypoglycin A (MCPA) and 46% had detectable levels of the metabolite of MCPG (MCPF). All but one of the samples with detectable levels of the metabolite of MCPG also had detectable levels of the metabolite of hypoglycin A. All 35 control urine samples from 2013 had no detectable levels of metabolites of hypoglycin A or MCPG.

Laboratory Testing: CDC Lab Analysis of Litchi Fruit

Litchi fruits were collected from orchards in four blocks of Muzaffarpur, Musahari, Motipur, Bochahan and Minapur. Both Shahi and Chinese variety fruits were collected, and in each fruit variety, samples of unripe, ripe, fallen and rotten fruits were collected. Thus far, at the CDC National Center for Environmental Health laboratory, unripe litchis and ripe litchis collected from three blocks of Muzaffarpur district (Musahari, Motipur and Bochahan) have been tested.

In each instance, homogenized extracts of litchi fruits were analyzed by liquid chromatographic separation and high-resolution mass spectrometric detection. A readily available hypoglycin A standard was provided by colleagues at United States Department of Agriculture (USDA) and used to analyze the high-resolution data obtained from the fruit. Precursor and product accurate mass spectra were obtained within 1 ppm and 10 ppm error, respectively, on a Thermo QExactive mass spectrometer.

Using high resolution mass spectrometry, the labs analyzed unripe and ripe fruit samples from the following blocks: Bochahan, Musahari and Motipur. For hypoglycin A, in both ripe and unripe fruit, mass spectrometry analysis was consistent with the presence of hypoglycin A in seed and aril portions of fruit from each of the blocks. For MCPG, in both ripe and unripe fruit, the current mass spectrometry analysis (without isotopically labeled standards) was not sufficiently informative to detect or rule out the presence of MCPG in seed or aril portions of fruit. When isotopically labeled standards are available, labs will be able to complete these analyses and quantify the amounts of toxin(s) present. Similar qualitative work conducted on these litchis at the USDA laboratory has also identified hypoglycin A as well as suspected MCPG in the aril of the litchi fruit (unripe and ripe specimens, of both Shahi and Chinese varieties).

Recommendations

A. Reduce Mortality

Recommendations

1 Rapid assessment and correction of hypoglycemia

- Through Information Education and Communication (IEC) and sensitization workshops - Increase awareness among community, field level health workers (ASHAs, Balwadi/Anganwadi workers, Auxiliary Nurse Midwives, Multipurpose workers, School health staff, etc.) and health staff at Primary Health Centers (PHCs)/Commercial Health Centers (CHCs) referral treatment centers on - symptoms of this illness for early detection, - about availability of free ambulatory services for early transportation, - about availability of facilities for rapid assessment and correction of glucose at nearest government health facility as well as - about availability of specialized treatment facilities at identified referral centers for early lifesaving interventions.
- Provision of adequate numbers of glucometers to all PHCs/CHCs/referral treatment centers for timely detection of low blood glucose.
- Train PHCs/CHCs/referral treatment centers staff on assessment of glucose using glucometer in children presenting with history of seizures and/or altered sensorium.
- Provide and train staff of PHCs/CHCs/referral treatment centers on protocol for correction of hypoglycemia in children with suspected outbreak illness/altered sensorium.

2. Strengthen diagnostic and critical care capacity at all levels of health care

- As characteristically most cases report sickness in early morning hours, availability of a trained medical doctor during night in the outbreak season months of May to July at all PHCs/CHCs in the district is essential for early detection and management of cases.
- Provide and train staff of PHCs and CHCs on protocol for first-line of lifesaving health care.
- Strengthen diagnostic facilities at all identified referral treatment centers for timely and appropriate diagnosis
  - Strengthen laboratory facilities for electrolytes, liver function tests, CSF cytology/biochemistry and bacteriology tests
  - Post adequate number of trained pathologists/laboratory technicians for round the clock specimen collection, testing and reporting
  - Provide adequate numbers of pulse oximeters
  - Provide facilities of EEG and post EEG trained technicians

- Provide facilities of CT scans and MRI brain and post trained Radiologists/Technicians
- Encourage collecting biopsy specimens and histopathology testing to confirm a tissue diagnosis of encephalopathy.

- Strengthen specialized manpower for assessment and treatment of cases
  - Post adequate number of pediatricians at each of the identified referral treatment centers to handle increased case load during outbreak season
  - Short-term deputation of a neurologist and a critical care specialist during outbreak season
  - Provide treatment guidelines and train pediatricians of the identified referral treatment centres on this treatment protocol
  - Provide training in critical care to pediatricians of the identified referral treatment centers

Purpose: Reduce Illness	
Recommendations	
3	**Through IEC:** Increase awareness among community on providing at night-time a full meal of home-made complex and low glycemic index carbohydrate (whole intact grains - such as barley and oats); this would help maintain a stable postprandial blood glucose and possibly minimize risk of early morning fasting hypoglycemia.
4	Improve general nutritional status: Undertake projects to reduce malnutrition among young children, especially the rural children of low socioeconomic status.
5.	Considering the finding of detection of hypoglycin and MCPG (natural hypoglycemic compounds known to be present in fruits of litchi family) metabolites in urine specimens of a large proportion of case-patients, it would be advisable to make efforts by IEC to minimize consumption of litchi fruits among young children in rural areas of affected district, pending further investigations in this regards.

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FDA Approves New Formulation of Tiopronin for Cystinuria

The US FDA has approved an enteric-coated delayed-release formulation of tiopronin for treatment of cystinuria, a rare inherited disorder that causes an increase in cystine levels in the urine, leading to recurring cystine kidney stones. Tiopronin tablets can be taken with or without food, "an advancement over the original formulation, which has limiting food restrictions, and also provides the potential to reduce the number of tablets necessary to manage cystinuria," Eric Dube, PhD, Chief Executive Officer of Retrophin, said in a news release... (*Medscape*)

Low LDL Cholesterol and Hemorrhagic Stroke

Lower levels of low-density lipoprotein (LDL) cholesterol were tied to a higher risk of intracerebral hemorrhage (ICH), an epidemiological study in northern China reported.

People with LDL cholesterol concentrations under 70 mg/dL had a significantly higher risk of developing hemorrhagic stroke than people with LDL levels from 70 through 99 mg/dL, reported Xiang Gao, MD, PhD, of Pennsylvania State University in University Park and co-authors. The findings are published in the journal *Neurology*.

Heart Defect-Cancer Link Present Already in Youth

The association between congenital heart disease (CHD) and cancer is observed in young people too, and it's not just from radiation exposure, researchers found. People with CHD included in a Swedish registry showed more than double the risk of cancer compared with healthy controls when followed up to age 41 (1.9% vs 0.9%, HR 2.24, 95% CI 2.01-2.48), according to a report published online in *JAMA Network Open*.

"This finding suggests that particular attention should be paid to early warning signs of cancer and promotion of a healthy lifestyle," said the investigators led by Zacharias Mandalenakis, MD, PhD, of the University of Gothenburg, Sweden.

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