Recurrent annual outbreaks of a hepato-myo-encephalopathy syndrome in children in western Uttar Pradesh, India

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Background & objectives: Outbreaks of an acute encephalopathy syndrome affecting children, with high case-fatality, have been reported in western Uttar Pradesh, India for the last many years. We investigated these cases in Bijnor district and present our findings.

Methods: Fifty five children aged 2-10 yr hospitalized from 2003 to 2005 in Bijnor, Uttar Pradesh, with features of acute encephalopathy were selected by defined clinical criteria. Various laboratory investigations were performed.

Results: The disease had peak incidence in early winter months. Previously healthy, 2-4 yr old rural children (mean age-3.78 yr) of very low socio-economic background were most vulnerable. Almost all had vomiting preceding unconsciousness and a majority had mild fever and abnormal behaviour/agitation. Abnormal posture of trunk and limbs were distinctive features. Fluctuation of blood pressure was seen in three-quarter cases. Serum aminotransferases, creatine phosphokinase and lactic dehydrogenase levels were found markedly raised virtually in all cases in whom the tests were performed. Serum glucose was found low (<50 mg/dl) in 47.3 per cent cases at presentation. Cerebrospinal fluid (CSF) was under normal or low pressure and without pleocytosis in all cases. No microorganism could be isolated from serum, CSF, urine and visceral specimens. Neuroimaging performed in two cases was also normal. Liver biopsy performed in 21 cases showed acute hepatotoxic injury in all with marked hydropic change and perivenular necrosis. Tibial muscle biopsy done in 8 cases showed focal necrosis while brain biopsy taken in 2 cases had mild spongiosis with focal gliosis. Forty two children succumbed to their illness (case fatality 76.4%), most within 72 h of presentation. Survivors did not show any neurological deficit.

Interpretation & conclusion: Our findings showed that the outbreaks were due to a multi-system disease with toxic injury to liver, muscles and brain (hepato-myo-encephalopathy) and not due to viral encephalitis as believed so far. The cause remains unknown but several features suggest the possibility of phytotoxin-induced pathology.

Key words Acute encephalopathy - hepato-myo-encephalopathy syndrome
In many parts of India, children are prone to Japanese encephalitis (JE), endemically or in outbreaks.1-2 Outbreaks of other acute encephalitis-like syndromes also occur, mostly in northern and central India.3-8 Such outbreaks are often conflated with encephalitis. In some reports, encephalitis was defined simply as acute brain disease in febrile children, thus losing diagnostic specificity.8,10,12 Many outbreaks were not investigated satisfactorily.11 These have been reported as “mystery disease” in the absence of specific diagnosis.9,13-15 The strikingly common features included sharp seasonality, absence of prodrome, rapid progression to unconsciousness, cerebrospinal fluid (CSF) without pleocytosis and very high mortality. Either the child died or fully recovered in a matter of 2-4 days. Among various proposed diagnoses, the common ones were viral encephalitis due to measles or Chandipura viruses or Reye’s syndrome, especially when brain oedema was present or acute vascular ischaemic attack. The clinical features did not concur with viral encephalitis and in two instances, the very same outbreak was reported twice with mutually incompatible diagnoses.16,18 No putative diagnosis or causative agent was consistently confirmed in subsequent outbreaks. During investigations the urgency was to identify aetiology, but as the weakest component was epidemiology, distinguishing the nature of one outbreak from another has been difficult or impossible.

Outbreaks of encephalopathy occur annually in many western districts of the State of Uttar Pradesh in India.7,13-15,17,19,20 We have observed it in Bijnor district over several years.7,14 The Indian Council of Medical Research investigated it in the neighbouring Saharanpur district in 2003 and reported: “Common clinical symptoms included mild to moderate fever for short duration, vomiting, irritability, altered sensorium followed by coma and death within 24 h after hospitalization. Abnormal movements, inability to suckle (suck) and teeth grinding were observed in a few patients. Marked irritability was also observed which remained even after heavy sedation…. however, no neck rigidity was observed. The age range was 1-10 yr with no significant difference in male to female ratio…. Patients appeared malnourished and from poor socio-economic background with poor hygiene.” Of the 59 specimens (CSF, serum, throat swab, urine) collected from 34 patients (among whom 28 died) admitted to the Government District Hospital, Saharanpur, none was positive for virus or diagnostic antibody against JE, dengue, West Nile and Chandipura viruses.

The close similarity of the clinical and demographic features described above, and those of the cases investigated by us over the three consecutive years in Bijnor, is described in this paper. We present here a previously unrecognized disease entity in India.

Material & Methods

Outbreaks occurred in 2003 through 2005, in a secondary care private sector paediatric hospital at Bijnor, the headquarters town of Bijnor district, U.P. (altitude 1342 ft. above sea-level; between 29’ 2 and 29’ 58 degree north latitude and 78’ 0 and 78’ 57 degree east longitude), were investigated. Hospitalized children with the following criteria were included: acute onset and rapid progression of unconsciousness in a previously well child; CSF without pleocytosis; no malarial parasite on blood smear; no plausible clinical diagnosis to explain the disease. Detailed clinical and demographic information was entered in a pre-designed form.

Laboratory investigations (other than in inclusion criteria) were serum aminotransferases and random glucose in all cases and blood coagulation profile and peripheral blood leucocyte count in the majority. In many children additional tests included: serum creatine phosphokinase (CPK), lactic dehydrogenase (LDH), ammonia and bilirubin; presence/titres of IgM class antibodies against a number of viruses (known to be associated with acute brain disease) and Leptospira
species; blood, CSF and urine bacterial culture; viral isolation studies on serum, CSF, urine and visceral specimens. All biochemical and bacteriology tests were done in private sector diagnostic laboratories in Bijnor, Meerut or New Delhi, using standard protocols and internal quality controls. For antibody tests against measles and JE viruses commercial kits were used: (Anda by Anda Biologicals of Italy, Wellcogen from Murex Biotech of UK or from Calbiotech of USA). In 2004 selected sera (25), CSF (18), urine (4), throat swabs (7) and liver tissue (5) were submitted to the National Institute of Virology in Pune for virus isolation (JE, measles, Chandipura, other) and antibody tests.

Magnetic resonance imaging (MRI) of brain was done on two children. Postmortem brain tissue was collected in two children in 2004 and Tibial skeletal muscle biopsies (from tibialis anterior muscle) were obtained in 8 children in 2005. Liver tissue was obtained from 5 children (postmortem, wedge section) in 2004 and in 16 children by percutaneous needle aspiration biopsy in 2005. Tissue specimens were fixed in formalin and processed for paraffin sections.

Fig. 1. Distribution of cases in Bijnor district (Block map). Inset A shows district map of Uttar Pradesh, shaded area shows affected districts. Inset B shows map of India with Bijnor district within the box.
Routine hematoxylin and eosin stained sections and (when needed) sections after required special stains were examined by one of us (NCN).

**Results**

**Epidemiology and demography**: A total of 55 children satisfied inclusion criteria over the three years (Table I). They were hospitalized only during September through December each year, the vast majority (87.3%) in October and November. All were in the 2-10 yr age group, with strong predilection in younger children, with three-quarters of cases (72.7%) in the 2-4 yr age group. The mean age (years) of the cases was 3.6 ± 1.40 (2003), 4.7 ± 1.50 (2004) and 3.6 ± 0.70 (2005) and 3.78 ± 1.23 for the entire group and median age 3.92 yr. A slight female preponderance was noted (female to male ratio 1.5). Most (85.4%) of children were rural residents and the remaining were from peri-urban semi-rural communities. Almost all belonged to very low socio-economic strata of the society. More than one sibling was affected only in one family.

The children were from different parts of the district, usually 1 or 2 per village per year (Fig. 1). The western ‘damper’ (nearer to river and low lying) areas were more frequently affected, such as the villages of Kiratpur (Kiratpur block), Chandpur (Jalilpur block), Haldaur and Daranagar (Haldaur block), Rawli, Mandawar, and Nagal Soti (Chandak block), and Najibabad (Najibabad block) (Fig. 1).

**Clinical Features**: The illness started suddenly and children developed depressed sensorium progressing rapidly to unconsciousness and coma. Although fever was recorded in 87.2 per cent children, most were afebrile at the time of admission but developed fever while on treatment. Thus, fever was not found to be the first symptom of the illness. Unconsciousness was preceded by vomiting in nearly all (98.1%) children, and with abnormal behaviour and agitation in three-quarters (76.4%) of them. Extreme irritability was noted in more than half (58.2%) and one distinctive feature of the disease, present in one-third (34.6%) of children, was abnormal posturing of trunk and limbs, associated with up-rolling of eyeballs, frothing at mouth, protrusion of tongue, teeth-grinding, biting, scratching and pinching of hair, clothes or other body parts (Table II).

<table>
<thead>
<tr>
<th>Table I. Epidemiological features of cases</th>
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<tr>
<td>Parameters</td>
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<tr>
<td>n=15</td>
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<tr>
<td><strong>Month of onset:</strong></td>
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<tr>
<td>September</td>
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<td>October</td>
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<td>November</td>
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<td>December</td>
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<td><strong>Habitat:</strong></td>
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<td><strong>Sex:</strong></td>
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<td>Hindu</td>
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<tr>
<td>Muslim</td>
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<tr>
<td><strong>Age group (yr):</strong></td>
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<tr>
<td>2–4</td>
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<td>5–7</td>
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<td>8–10</td>
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Generalized convulsions in the hospital or history of seizures prior to hospitalization was present in only 29.1 per cent of children. Respiratory abnormality (hyperpnoea, jerky and irregular respiration) was noticed in 25.5 per cent cases. Dilated, poorly reacting pupils and absent Doll’s eye movements were seen in 45.5 and 49.1 per cent cases, respectively. Although signs of circulatory collapse were noted in only 4 (7.3%) cases at presentation, fluctuation of blood
pressure during treatment was noticed in 72.7 per cent cases. Majority of the cases showed variation in systemic arterial pressure – ascending gradually to plateau much beyond 95th centile followed by sudden, precipitous fall and circulatory collapse, which resulted in death in several cases.

The duration of illness before admission was 48 h or less in 58.2 per cent cases. Neither history of rash nor any overt sign of any exanthematous fever was found in any child and there was no measles or varicella in the community during September to December. History of giving aspirin was found in only one child.

**Biochemical findings:** Apart from low CSF glucose 7 (47.3%), other CSF parameters were essentially normal in all children. There was no pleocytosis, protein was not raised, and opening pressure was either normal or low as judged by speed of flow. Grossly deranged liver function tests were found in almost all children. Serum aminotransferases were raised (ALT and AST; mean values- 2711.3 IU/L and 2637.5 IU/L, normal range: 5-49 IU/L and 0-45 IU/L, respectively) in 96.4 per cent cases. Raised prothrombin time along with abnormal profile of coagulation factors was detected in 89.6 per cent cases. Serum bilirubin was only marginally raised in 8 (21.6%) cases and none had clinical jaundice at the time of presentation. Serum glucose was found to be low (<50 mg/100ml) in 26 (47.3%) cases.

Six out of 10 samples tested for serum ammonia had value of > 50 µg/dl (normal range: 17-82 µg/dl). Though history of aspirin ingestion was found in only one case, 7 of the 8 serum samples tested had traces

<table>
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<th>Table II. Clinical features of study cases</th>
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<tr>
<td>Clinical Features</td>
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<tr>
<td>H/o fever before admission</td>
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<tr>
<td>H/o vomiting preceding unconsciousness</td>
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<td>Abnormal behaviour and/or agitation</td>
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<tr>
<td>Abnormal posturing</td>
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<tr>
<td>Teeth grinding, biting, pinching and</td>
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<td>scratching body parts</td>
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<tr>
<td>Seizures at presentation or</td>
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<td>preceding unconsciousness</td>
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<tr>
<td>Diarrhoea</td>
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<td>Gastrointestinal bleeding</td>
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<td>Shock</td>
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<td>Fluctuation of blood pressure (during</td>
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<td>treatment)</td>
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<tr>
<td>Respiratory abnormality (at presentation)</td>
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<tr>
<td>Absent Doll’s eye movements</td>
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<td>Dilated, poorly reacting pupils</td>
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<td>Total duration of illness (h) before</td>
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<td>presentation:</td>
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<td>&lt; 24</td>
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<td>24–48</td>
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<td>48–96</td>
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<td>&gt; 96</td>
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Serum creatine phosphokinase (CPK) and serum lactic dehydrogenase (LDH) levels were measured only on cases in 2005. All had markedly raised CPK (tested in 10, mean value 1849.3 units/ml, normal range: 24-195 units/ml) and LDH (tested in 5, mean value 3942.4 units/ml, normal range: 240-480 units/ml). Further, 2 out of 4 positive CPK samples had raised (>25 units/ml, normal range 0.00-25 IU/L) (Ck-MB) fraction, which signify myocardial toxicity21.

Microbiological studies: All the specimens of urine, throat swab, blood, and CSF tested for bacterial and viral cultures were negative for growth of any pathogen. IgM antibodies against measles were reported in 13 sera (of 40 tested) and 3 CSF (32 tested). Other antibody tests, namely IgM against varicella zoster (8 cases), hepatitis A (6 cases), herpes simplex 1 (4 cases), JE (2 cases), influenza A and B (4 cases), and leptospirosis (3 cases) were negative except for weakly positive IgM against varicella zoster in 2 samples.

Neuroimaging: MRI brain scans performed on two children did not show any abnormality.

Histopathological studies: Of the 21 liver biopsies (including 5 postmortem tissues), 17 showed histological abnormalities. Marked hydropic change affecting almost all hepatocytes and ballooning of several, together with single cell, focal or perivenular necrosis in acinar zone 3 or zone 2 and 3 were the most striking abnormalities (Figs. 2 and 3). This pattern was present in all, with only slight variations in severity in a few. Randomly distributed mild, focal, small macrovesicular fatty change was seen in a few cases, but diffuse microvesicular fat as seen in Reye’s syndrome was not seen in any case. There was no inflammatory response, except for occasional, mild, focal, mononuclear cell infiltration in a few portal tracts. No viral inclusions were seen. There was no sinusoidal dilatation or congestion and the

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>2003 (n=15)</th>
<th>2004 (n=22)</th>
<th>2005 (n=18)</th>
<th>Total n=55 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised serum aminotransferases (AST/ALT &gt; 6 fold)</td>
<td>15/15</td>
<td>22/22</td>
<td>16/18</td>
<td>53/55 (96.4)</td>
</tr>
<tr>
<td>Low serum glucose level</td>
<td>8/15</td>
<td>12/22</td>
<td>6/18</td>
<td>26/55 (47.3)</td>
</tr>
<tr>
<td>Raised serum CPK level</td>
<td>—</td>
<td>—</td>
<td>10/10</td>
<td>10/10 (100.0)</td>
</tr>
<tr>
<td>Raised serum LDH level</td>
<td>—</td>
<td>—</td>
<td>5/5</td>
<td>5/5 (100.0)</td>
</tr>
<tr>
<td>Normal serum bilirubin level</td>
<td>3/5</td>
<td>10/16</td>
<td>16/16</td>
<td>29/37 (78.4)</td>
</tr>
<tr>
<td>Abnormal coagulation profile</td>
<td>10/10</td>
<td>20/21</td>
<td>13/17</td>
<td>43/48 (89.6)</td>
</tr>
<tr>
<td>Leucopenia (TLC &lt; 4,000/c.mm)</td>
<td>6/15</td>
<td>6/22</td>
<td>3/10</td>
<td>15/47 (31.9)</td>
</tr>
<tr>
<td>Raised serum ammonia level</td>
<td>1/1</td>
<td>3/4</td>
<td>2/5</td>
<td>6/10 (60.0)</td>
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<tr>
<td>Positive IgM measles serology:</td>
<td></td>
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<td></td>
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<tr>
<td>– Serum</td>
<td>3/9</td>
<td>7/21</td>
<td>3/10</td>
<td>13/40 (32.5)</td>
</tr>
<tr>
<td>– CSF</td>
<td>1/6</td>
<td>1/17</td>
<td>1/9</td>
<td>3/32 (9.7)</td>
</tr>
</tbody>
</table>

*Number positive/number tested

CPK, creatine phosphokinase; LDH, lactic dehydrogenase; TLC, total leucocyte count.
centrilobular and sublobular veins did not have endothelitis, thrombosis or perivascular hyalinization. In the four cases, liver had mild, focal hydropic change and mild steatosis with small but macrovesicular fat. Of these, 2 children had mildly elevated and 2 had normal serum transaminase levels; 3 children had recovered. The histological features strongly suggested a dose-related acute toxic injury.

Muscle tissues had small, focal areas of sarcoplasm degeneration, hyalinization or lysis, with mild to moderate proliferation of sarcolemmal nuclei (Fig. 4) and occasional mononuclear cell infiltration in the surroundings. There was no vasculitis or myositis. The two brain tissues had mild spongiosis with focal gliosis, but there was no inflammation and no viral inclusion bodies.

**History of drug treatment:** A detailed history of drugs taken before admission was obtained in all cases. The prescriptions and medicines held by the parents were inspected; the referring doctors and those who gave initial treatment were interviewed. It was found that aspirin was no longer used routinely as an antipyretic, and only one child was given it. Anti-emetics (metoclopramide in 61.8% cases), antibiotics (72.7%), steroids (52.7%), anti-convulsants (20%), and mannitol (45.5%) were the most commonly used drugs before referral.

**Treatment of children in the hospital:** All children were treated conservatively as for acute hepatic failure. They were given hypertonic dextrose intravenously, parenteral vitamin K, lactulose enemas and frequent bowel washes, fresh blood or fresh frozen plasma, intravenous mannitol (20%) or
frusemide, anticonvulsants when needed, ionotropes and oxygen. Any disturbance of electrolytes and acidosis were corrected. Children were nursed with heads elevated. No treatment protocol was found to consistently improve outcome. Corticosteroids were not employed and anti-brain-oedema measures were found to be ineffective.

The outcome of illness: The disease progressed rapidly and 42 of the 55 children died (most within 12-48 h of illness), with case fatality of 76.4 per cent. Those who survived recovered quite dramatically within 72 h of admission, without any neurological sequel. On those children who we had seen subsequently, no neuro-psychiatric abnormality was observed. The numbers of children who died were 13 in 2003 (case fatality 86.7%), 17 in 2004 (77.3%) and 12 in 2005 (66.7%). Totally only 13 (23.6%) recovered. The numbers of children who died were 1 of 2 in September (case fatality 50%), 13 of 17 (76.5%) in October, 24 of 31 (77.4%) in November, and 4 of 5 (80%) in December. The mean ages of the children who survived the illness and those who died were 3.96 ± 1.90 and 3.69 ± 0.97 yr, respectively. None of these differences were statistically significant (‘t’ test).

Discussion

All 55 children selected with specific criteria, seen across 3 consecutive years had closely similar clinical, epidemiological and laboratory investigational features and constituted a homogenous group. The subset examined by histopathology had characteristic pathomorphological features. Thus, one complex disease, with multi-system involvement, had occurred in all children. As the combination of the pathology of liver, muscle and brain is unlike any known infectious or non-infectious disease, the term hepato-myoo-encephalopathy seems appropriate. High levels hepato-myoo-encephalopathy of serum transaminases were seen in all but two children and significant hepatocellular involvement without features of viral infection was present in every liver biopsy examined. These changes strongly suggest an acute hepatotoxic damage. The severity of cell damage seemed to parallel the level of serum transaminases. The picture was quite different from the panlobular microvesicular steatosis of Reye’s syndrome or that of viral hepatitis or infectious diseases involving the liver, such as melioidosis, typhoid fever or malaria. The normal opening CSF pressure as judged by speed of flow, lack of brain oedema in MRI scans, and lack of response to anti-brain-oedema treatment are in contrast to Reye’s syndrome.

The pathology of striated muscle was focal fibre injury without myositis, vasculitis or fat accumulation. Serum CPK and LDH were high in all cases in whom these were measured and the myocardium-related Ck-MB fraction was raised in 2 of the 4 cases tested. Fluctuating blood pressure and circulatory collapse noted in three-fourth of cases were possibly due to myocardial damage. The brain tissues had only mild spongiosis with focal gliosis, and no inflammation characteristic of encephalitis. The absence of CSF pleocytosis along with lack of signs of inflammation on brain biopsy reflect the pathology other than that of infectious encephalitis.

The disease affected young children during a particular time period in each of the three years, as in the previous years. Annual outbreaks of disease having similar clinico-epidemiological characteristics and high mortality, variously called ‘acute encephalitis’, ‘encephalopathy’ or ‘mystery disease’ have been observed in Bijnor and eight other nearby districts of western Uttar Pradesh and one adjoining district of the State of Uttarakhand since 1998. The earlier investigators did not define discriminatory clinical criteria, but with seasonality, fever and the striking brain involvement, presumed and pursued viral infection as the cause of illness. The case description of the ICMR study has many common features with our description, the most obvious ones being the narrow age range and clear seasonality,
preferential prevalence in poorer families, rapid onset
and short duration of illness, vomiting preceding loss
of consciousness, marked degree of irritability,
abnormal movements, and very high case-fatality20.
We suggest that the cases in that study had the same
hepato-myo-encephalopathy, rather than acute
encephalitis. But for the biochemical and morpholo-
gical abnormalities detected in our study, the multi-
system involvement and the possibility of a non
infectious, possibly toxic, aetiology of the disease
would not have been apparent.

Reye’s (or Reye-like) syndrome has been
reported many times in several previous outbreaks
of an acute encephalopathy disease in Nagpur and
Haryana/western UP5,6,17. However, we have found
several features that are different from those of
Reye’s syndrome in this study. Although there was
encephalopathy, intracranial pressure was not raised,
unlike in Reye’s syndrome6,9,22. In several other
‘encephalitis-like’ outbreaks, increased CSF opening
pressure, absence of CSF pleocytosis, brain oedema
on neuroimaging, correlation of recovery with anti-
oedema treatment, lack of neurological deficits on
recovery and on limited occasions the finding of
microvesicular liver steatosis constituted a strong case
in favour of Reye’s syndrome5,6,9. Reye’s syndrome
itself is not necessarily one disease with one aetiology,
but a clinico-pathological presentation of a systemic
disease process, particularly involving the
mitochondrial metabolic pathway23. We speculate that
a toxic injury may be involved in such outbreaks in
northern India, since usually the syndrome occurs only
sporadically.

Anti-measles IgM antibodies were detected in a
small proportion of cases. However, this finding
cannot be relied upon, as the tests used commercially
available diagnostic kits without local validation. The
laboratories were not participating in any external
quality assurance scheme. For these reasons, and as
there was no measles virus activity in the community
during or prior to the outbreaks, we believe there is
no causal association with measles virus. We are
aware of the diagnosis of measles virus brain disease
in a few similar outbreaks in the past, by other
investigators, but such results are neither plausible
nor confirmed12,16. Measles virus was reportedly
cultured from the CSF, a finding that has been
questioned for reliability16,24.

Our findings suggest the possibility of toxin-
induced organ/tissue damage. Since young children
are exclusively involved, some environmental toxin,
rather than a chemical toxin related either to agriculture
or to malaria control, is more likely. In India, an
outbreak of liver disease caused by senecio alkaloid
was reported from Rajasthan State in 197725, but both
adults and children were affected in that episode.
There are reports of environmental toxin-mediated
outbreaks in children in other countries, with clinical
similarities to Indian outbreaks26-29. The hepatotoxic
agents like pyrrolizidine alkaloids and plants producing
these, aflatoxins and amatoxin of Amantia phalloides
have been associated with acute onset hepatopathy30.
Our case description has similarities to the out
break of encephalopathy in Burkino Faso, due to
cosumption of unripe ackee fruit28. For these
circumstantial reasoning, we suggest that the western
UP outbreaks exemplified by the Saharanpur and
Bijnor outbreaks in recent years may be due to some
environmental toxin, possibly from local plant flora.
The seasonal restriction to September to December
could be due to the post-monsoon growth spur/flowering/seed formation in such plants. We are
currently conducting a case-control study in order to
search for potential candidate plant agents.

In conclusion, we have identified the clinico-
pathological nature of annual seasonal outbreaks of
acute severe illness with unconsciousness and high
case-fatality in young children in Bijnor district in
western UP as hepato-myo-encephalopathy of
unknown aetiology. The pathology does not support
an infectious cause, but a toxic injury, possibly due to a phytotoxin, may be involved.

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