Acute encephalitis syndrome in children in Muzaffarpur: hypothesis of toxic origin

One among three long-standing mystery diseases listed in Wikipedia is acute encephalitis syndrome (AES) in Muzaffarpur, Bihar. This disease has remained for over two decades without determining a cause for it; hence it is called mystery disease. It occurs as annual seasonal outbreaks during the months of April–July, affecting hundreds of children with 40–60% mortality, according to local physicians. It was thought that Muzaffarpur AES is Japanese encephalitis (JE), which is widely prevalent in India; however, JE was ruled out in a recent study by Samuel et al. Another study explored several possibilities of causation of the disease and again excluded JE. These studies documented that cases coincided spatially and temporally with lychee cultivation. The investigators noted colonies of fruit-eating bats and the tendency of children eating fruits fallen to the ground and suggested the possibility of a bat virus (through saliva contamination on fruits) as a cause of the disease. Other studies concluded that the disease was not due to infection, but was due to heat stroke.

One of us (T.J.J.) visited Muzaffarpur in the 2013 season, examined children with AES and held extensive conversations with healthcare personnel, parents, family members and neighbours of the affected children. Thereafter, we searched the literature and after mutual discussions developed a hypothesis about the cause of the disease, which is presented below.

Clinical features in patients are stereotypic–sudden onset without prodromal phase, inconsistent presence of fever, brain oedema, absence of inflammatory cell response in cerebrospinal fluid (CSF) and hypoglycaemia. These clinical features and preliminary epidemiological findings of tightly restricted seasonality and geographic distribution as well as sparing of children below 2 years support the diagnosis of acute non-infectious encephalopathy as against viral encephalitis. Children are quite well until evening, but early next morning they are found seriously ill with brain function derangement and seizures. Under-nutrition (short and underweight for age) has been observed as a consistent associated factor.

Association of AES with lychee is important, interesting and challenging. In Vietnam and Bangladesh, outbreaks of AES have been reported in lychee cultivation areas and during lychee harvesting season. Investigators in Vietnam believed that the disease was caused by some unknown virus, while in Bangladesh the disease was not thought to be infectious but was attributed to pesticides used in the orchards. Curiously, both these studies and the one from Muzaffarpur showed positive correlation between number of cases and amount of lychee harvest.

Lychee (Litchi sinensis) belongs to the family Sapindaceae (soapberry). Another soapberry member, ackee (Blighia sapida), commonly cultivated in Jamaica, is the cause of a childhood (under 15 years) acute encephalopathy disease called Jamaican vomiting sickness (JVS), also referred to as toxic hypoglycaemic syndrome. The clinical features of ackee poisoning and Muzaffarpur AES have many close similarities, including early morning onset, encephalopathy, hypoglycaemia and high case fatality. A toxic substance methylenecyclopropylalanine (MCPA), also called hypoglycin A, is present in ackee unripe fruits. Ripe ackee has a small concentration (0.1 ppm), which is less by a factor of 10,000 compared to unripe fruit.

Studies related to

Figure 1. Conversion of MCPG and hypoglycine into active metabolites and their sites of inhibition of β-oxidation.
hypoglycin A toxicity revealed that the actual causative agent of JVS is a metabo-
lite of hypoglycin A called methylenecyclopropane-acetyl CoA (MCPA-CoA)\(^2\).
MCPA-CoA exerts its effect by inhibiting several coenzyme-A dehydrogenases, which are essential for gluconeogene-
sis\(^1\). Depletion of glucose reserves (the result of under-nutrition) and the inab-
ility of cells to regenerate glucose through neoglucogenesis lead to hypoglycaemia.
However, hypoglycaemia alone may not be able to explain encephalopathy, which usu-
ally persists in spite of infusion of glucose. The toxin affects mitochondrial
functions in the liver. Since brain cells require constant supply of glucose, hypo-
glycaemia triggers mitochondrial \(\beta\)-oxi-
dation of fatty acids. The putative toxin blocks this reaction with accumula-
tion of fatty acids. The putative toxin

In animal experiments, MCPA and MCPG have been shown to induce
everal genes including glucose 6-phosphate dehydrogenase (G6PD) and the
Muzaffarpur AES is caused by MCPG in
lychee. However, we do not know if it is
present only in the seed or also in the
edible fruit flesh (in ackee and lychee, the
aril is transformed as the edible part) and
if unripe lychee has more MCPG than ripe
fruits.

The similarities and differences be-
 tween hypoglycin A and MCPG in under-
nourished population or animals are
given in Table 1, which indicates the
possibility of association of Muzaffarpur
AES with lychee fruit. This hypothesis
ties up several observed features of
Muzaffarpur AES. Early morning onset
is after several hours of fasting and
points to a metabolic disease; hypogly-
caeemia points to inhibited gluconeogene-
sis and malnutrition is associated with
delepted glycogen/glucose store in the
liver. Well-nourished children are not
affected since their glycogen/glucose
store in the liver is sufficient to maintain
normal glucose levels and presumably
gluconeogenesis is not triggered.

This hypothesis is testable and we
have proposed to the Ministry of
Health in Bihar precisely to do that in
the 2014 season. Moreover, knowing that
fatty acid metabolism is deranged, treat-
ment modalities are possible to save
lives. Ensuring adequate nutritional
status in young children will prevent
this disease. If and when the lychee
connection is confirmed, children’s
behaviour modification can further help
prevention.

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Table 1. Similarities and differences between hypoglycin A and MCPG in undernourished
population or animals

<table>
<thead>
<tr>
<th>Ackee fruit (undernourished population/animals)</th>
<th>Litchi (undernourished rats)</th>
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<tbody>
<tr>
<td>Sapindaceae family</td>
<td>Sapindaceae family</td>
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<tr>
<td>Hypoglycaemia</td>
<td>Hypoglycaemia</td>
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<td>Inhibition of (\beta)-oxidation of fatty acid</td>
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<tr>
<td>Methylenecyclopropyl-alanine</td>
<td>Methylenecyclopropyl-glycine</td>
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<tr>
<td>Methylenecyclopropyl-acetyl CoA is a</td>
<td>Methylenecyclopropyl-formyl CoA</td>
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<tr>
<td>toxic metabolite</td>
<td>is a toxic metabolite</td>
</tr>
<tr>
<td>Glucose ((^\uparrow)), lactate ((^\uparrow)), non-esterified fatty acid ((^\uparrow))</td>
<td>Glucose ((^\downarrow)), lactate ((^\uparrow)), non-esterified fatty acid ((^\uparrow))</td>
</tr>
<tr>
<td>Dicarboxylic acidura ((^\uparrow))</td>
<td>Not known</td>
</tr>
<tr>
<td>Hyperketonemia (ketone bodies (^\uparrow))</td>
<td>Hypoketonemia (mechanism not known)</td>
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