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AABID M. RATHER*
IRSHAD A. NAWCHOO
AIJAZ H. GANIE
AIJAZ A. WANI

Economic Botany and Reproductive Biology Laboratory,
Department of Botany,
University of Kashmir,
Srinagar 190 006, India
**For correspondence.*
e-mail: abid.bot@gmail.com

Recurrent outbreaks of hypoglycaemic encephalopathy in Muzaffarpur, Bihar

Earlier we had reported that the recurring annual seasonal outbreaks in Muzaffarpur district, Bihar, of what used to be considered viral encephalitis and called 'acute encephalitis syndrome' since no virus could be detected, is acute encephalopathy[1]. Our report was based on a limited study and retrospective analysis of case records. The outbreaks are restricted to April–July with a peak in June[2–5]. In 2014, the outbreak started in the first week of June and we conducted a prospective data cumulation effort during June, as reported here. Clearly, the disease is a form of 'hypoglycaemic encephalopathy' as described below.

One of us (A.S.) is attending pediatrician in a local private hospital that creates a special ward every year as soon as the outbreak begins and treats children with acute central nervous system (CNS) disease without any user-fee charges. We planned data collection from children who conformed to a case definition designed for simplicity and reasonable specificity and sensitivity. The case definition was any child with acute onset of severe CNS disease with loss of consciousness and seizures. All cases hospitalized under A.S. during the first two weeks of June 2014 are included for this analysis.

Children were examined and minimum essential laboratory tests were conducted. We had a treatment protocol in the case of children for whom the laboratory results excluded bacterial meningitis, cerebral malaria and encephalitis (characterized by more than 10 cells/cumm in the cerebrospinal fluid, CSF). However, during the two weeks no child with meningitis, encephalitis or malaria was hospitalized. This year we tested blood glucose level immediately after hospitalization and infused 10% dextrose (volume according to body size) irrespective of the glucose concentration.

There were 26 children conforming to the case definition in the first two weeks of June, while there was none during the preceding four weeks in May. Among them, 24 (92%) were between 2 and 10 years of age. All children had been well (according to their parents) the evening before, but were found early in the morning with seizures and loss of consciousness, with or without vomiting and/or fever. In all children CSF was under increased pressure (judged by the speed of flow), but without inflammatory cell response: all cell counts were below 5/cumm. Twenty-two (84.6%) children had hypoglycaemia (less than 70 mg/dl); 20 (77%) had moderate to severe hypoglycaemia (7 with 31–40 mg/dl and 13 below 30 mg/dl).

Acute encephalitis usually begins with a prodromal phase with fever and systemic, non-CNS-specific, symptoms lasting a few days before convulsions and/or loss of consciousness occurs. The CSF will contain more than 10 cells/cumm. In the absence of prodromal phase before onset and of any inflammatory cell response in CSF, we confirm the diagnosis of acute encephalopathy in all the cases, confirming our earlier report[1].

All case-children were given 10% dextrose infusion in addition to per-protocol anticonvulsants and supportive nursing care. The response to dextrose was encouraging. We are unable to compare it with any control children; A.S. has treated children with this disease over the past several years but has not seen such rapid response with any other treatment. Thus, 15 children (58%) recovered so fast that they could be discharged home within two days. Two more children could be sent home well after 3–4 days of hospitalization. The parents removed three children from the hospital during the course of illness. Among the remaining 23, six died, with case fatality rate of 26%. This is the lowest fatality rate in our experience of the attending pediatrician.

While most children who later recovered had been given treatment within 4 h of onset of illness, there was delay in treatment for the six who died. Three of them had more than 9 h of delay; three others had more than 4 h of delay. Although the numbers are too small to derive any definitive conclusion, infusing dextrose within 4 h of onset tended to save lives.

In every child the onset was in the morning hours, pointing to a pathogenetic process related to overnight fasting. A metabolic derangement process is obvious as hypoglycaemia was frequent. We do not have objective measurements of height, weight and mid-arm circumference to confirm chronic under-nutrition, but visually all children appeared to be slim without subcutaneous fat. We need to study if under-nutrition is a determinant (risk factor) or just background noise.

In conclusion, the disease is a form of 'hypoglycaemic encephalopathy'. The restriction of outbreak to summer months has been interpreted as indicative of heat-encephalopathy (heat exhaustion, hyperpyrexia or heat stroke)[4,5]. Although there is no pathognomonic laboratory test abnormality to confirm or exclude heat disease, the restriction of cases to children, consistent early morning onset and absence of hyperpyrexia in the majority are points precluding heat as the cause. Among our case-children 12 had normal body temperature, 11 had low-grade fever and only 3 had high fever (103–104°F) at the time of hospitalization.

Human physiology has complex mechanisms to maintain euglycaemia to protect brain cells from the ill-effects of hypoglycaemia. Apparently a pathway (fatty acid oxidation or Kreb's cycle, both mitochondrial) is deranged by some environmental noxious stimulus that is both recurrent and confined temporally to April–July and spatially to Muzaffarpur and the surrounding districts. Muzaffarpur is famous for lychee. The temporal and spatial distributions coincide with lychee harvesting, suggesting an association, as had been observed in Vietnam and Bangladesh too[6,7].

Three possible noxious stimuli have been proposed. One is high heat and humidity, but we have already ruled it out as mentioned above[5]. The second is poisoning by pesticides used for protecting lychee fruits[7]. The third is methylenecyclopropylglycine that has been shown to be present in lychee seed[1]. Further research is necessary to identify the exact cause of acute hypoglycaemic encephalopathy in children in Muzaffarpur so that specific preventive intervention can be designed. However, early infusion of 10% dextrose is a life-saving treatment.

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ARUN SHAH[1]
T. JACOB JOHN[2,*]

[1]*Kejariwal Maternity and Child Hospital,*
Muzaffarpur, India
[2]*439 Civil Supplies Godown Lane,*
Kamalakshipuram,
Vellore 632 002, India
**For correspondence.*
e-mail: tjacobjohn@yahoo.co.in