Investigating the Muzaffarpur Outbreaks in the Backdrop of Western Uttar Pradesh Experience: The Way Forward

The death of more than 130 children in Muzaffarpur, Bihar during the summer months of 2019 due to Acute encephalitis syndrome (AES) has raised an intense debate on the probable etiology of the killer disease. The recurrent outbreaks of the disease are reported since 1995, and several attempts have already been made by the different teams to clinch the exact etiology [1,2]. The key recent investigations were performed by three sets of expert-groups – John, *et al*. [3], the Natioal Center for Disease Control (NCDC), India, and Centre for Disease Control (CDC), United State (US) group [4], and by the pediatrician in-charge of Shri Krishna Medical College Hospital (SKMCH), Muzaffarpur [5]. While the first two groups identified litchi toxins, namely methylene cyclopropylglycine (MCPG) and methylene cyclopropylalanine (MCPA or hypoglycin A), responsible for the development of an acute hypoglycemic encephalopathy (AHE) amongst malnourished, poor, rural children [3,4], the latter suggested extremely high environmental temperature and humidity in the region resulting in 'heat stroke' that led to encephalopathy [5]. Due to the lack of documented hyperpyrexia in all the cases, and early morning onset of symptoms, there were few takers for the heat stroke theory. The litchi-toxins theory was more acceptable and the Bihar State Health Ministry started following the preventive measures as suggested by the groups who put forward this theory. The number of cases and deaths declined sharply in the following four years, 2015 to 2018 only to resurface in a much significant number in 2019.

A previous similar recurrent epidemic in many districts of Western Uttar Pradesh (UP), the so-called 'Saharanpur encephalitis' [6], was investigated by an independent group of investigators and the etiology was identified as toxicity due to oral ingestion of a local weed [7]. There are many similarities between the western UP and Muzaffarpur outbreaks; yet the approach, investigations and the outcomes are quite different (***Table* I**).

In the Western UP outbreak, step-wise investigation approach was adopted and as a first step a proper 'case definition' with exclusion and inclusion criteria was formed. Based on its strict application, the disease was initially identified as an encephalopathy [6]. The next step was the histopathological examination of few target organs, which hinted toward toxin-mediated necrosis of liver and muscles (thus the term (acute hepato-myoencephalopathy (HME) syndrome) [6,7]. The differences in approaches in the two outbreak investigations are presented in (***Table* I**).

With the re-emergence of the outbreak in Muzaffarpur this year, the debate on the exact etiology has reignited. While the role of any microbiological agent as the main trigger has been abandoned by most investigators, the focus is now on the litchi toxins and heat stroke as probable theories. Despite many 'missing links' like inconsistent findings of hypoglycemia and hyperthermia, lack of profuse vomiting (a hallmark of MCPA toxicity), 'mismatched' seasonality (paucity of unripe fruits at the peak of the outbreaks when the entire crop is matured), no clarity on toxic levels (LD50) of toxins that cause dose-dependent toxicity, occurrence in children too young to eat the fruit, lack of hepatic dysfunctions despite mitochondrial involvement, flawed selection of controls in case-control study, lack of study of toxins in the body fluids of healthy siblings and peers living in the same household or village, the doubtful role of rapid correction of hypoglycemia on prevention of deaths, the litchi toxin theory was considered as the most plausible one.

A detailed case-control study in western UP helped in identifying the putative toxin which turned out to be anthraquinone derivatives contained in the beans of the weed, *Cassia occidentalis* [7]. Previous published literature confirmed the biological plausibility of causation in vertebrates. The cause-effect relationship of the *Cassia occidentalis* with acute HME syndrome in Wistar rats was subsequently demonstrated [8]. These detailed studies also helped in further outbreaks like the one in Sylhet, Bangladesh (2007-08) [9] and another in Malkangiri, Orissa (2016).

Currently, the outbreak investigations in India are at the crossroads**.** The need is to conduct investigations which are detailed and comprehensive, and performed in a coordinated and step-wise manner without any fixed notion.

TABLE I COMPARATIVE ANALYSIS OF INVESTIGATIONS OF WESTERN UP AKA 'SAHARANPUR' AND 'MUZAFFARPUR' OUTBREAKS

Parameters	*'Saharanpur outbreaks' [8,9]*	*'Muzaffarpur outbreaks' [4]*
Affected regions/districts	Many districts of western UP, Uttarakhand and Haryana	Few districts of Bihar (mainly Muzaffarpur and adjoining districts like Vaishali, East Champaran, etc)
Epicentre of the outbreak	Saharanpur	Muzaffarpur
Years of onset	Late 1990s to 2010	From 1995 onwards
Seasonality	Early winter months, October and November mainly	Peak summer months, May and June
Age groups of cases	2-10 years (73% from 2-4 years)	1-15 years (72% from 1-5 years)
Median age	3.92 year	4 years
Mean age	3.78 ± 1.23 year	NA
Habitat	Rural, semi-rural and peri-urban	Rural mainly
Socioeconomic status	Low	Very low
Sex	60% females	55% males
Malnutrition	No	Yes (16% wasted; 65% stunted)
Siblings	Affected	No
Clustering	1-2 cases per village	No
Clinical presentation		
Fever	87.2% (before presentation)	39% (during hospital stay)
Vomiting	98.1%	18%
Seizures	29.1%	94%
Altered sensorium	76.4%	95%
Bleeding	16.4%	NA
Shock	7.3%	NA
Pica	Yes	NA
Laboratory investigations		
Raised hepatic aminotransferases	96.4%	NA
Hypoglycemia	47.3% (S. Glucose< 50 mg/100mL)	62 % (S. Glucose < 70 mg/100mL)
Hypoglycorrhachia (CSF glucose <45 mg%)	42.3% cases	21%
Serum CPK and LDH	Raised	NA
Blood ammonia	Raised (in 60% samples)	NA
Microbiological studies (including viral studies)	Negative	Negative
Other investigations		
Neuroimaging	Normal	50% had cerebral edema on MRI
EEG	Not done	73% abnormal
Histopathology	Done (liver, brain & muscles biopsies)	Not done
Epidemiological studies	Yes	Yes
Animal studies	Yes*	Not done
Toxicology studies	Done**	Done
Toxin involved	Anthraquinones, mainly Rhein	MCPG and MCPA
Mortality	76.4%	32%
Final diagnosis		
Clinical entity	Toxin mediated encephalopathy (Acute Hepatomyoencephalopathy syndrome)	Toxin mediated encephalopathy (Acute Hypoglycemic Encephalopathy?)
Etiology	Consumption of *Cassia occidentalis* beans	Consumption of unripe litchi by malnourished children

NA=Not available; MCPG= methylene cyclopropylglycine; MCPA= methylene cyclopropylalanine; CPK: Creatine phosphokinase; LDH: Lactase dehydrogenase.

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Intravenous Ondansetron to Reduce Intravenous Rehydration – Will it be Successful?

We read with interest the research article by Rang, *et al.* [1] published recently in *Indian Pediatrics*. Though the article is very informative, we have some concerns:

It is clearly established that ondansetron is an effective antiemetic [2]; hence, comparing the efficacy of intravenous (IV) ondansetron with a placebo in reducing vomiting episodes and the need for IV rehydration is unfair. The results reflected are expected (*e.g.*, comparing vomiting episodes at 4, 8 and 24 hours between the ondansetron group and placebo groups). To put this into perspective, it is like comparing reduction in fever in two groups; to one group after giving paracetamol and the other after administering a placebo, and saying that there was a significant decrease in fever in the subjects in the paracetamol group. Instead, it would have been more informative and useful, if the authors had compared two different routes of administration of ondansetron.

The process of double blinding is not clear as a statement in the article mentions that "the study physician opened the envelope to determine which treatment the subject would receive." It is desirable to describe the process of blinding by explaining who was blinded rather than use terms like double blind or triple blind.

The Oral rehydration solution (ORS) administration must also have been a challenge for the caregivers/ hospital staff who were providing ORS at 0.5 mL/kg every 2 minutes. The question that comes to our mind is as to how it was adhered to, especially in these young children? Rehydration has been mentioned as 'adequate' when the child consumed ≥40 mL/kg of ORS solution, but the time over which it was consumed has not been elucidated. Furthermore, there has been no mention on the day from the start of symptoms that the patients were recruited into the study. This information is important, as those included later may have responded differently from those presenting earlier. Similarly, the work-up for etiology of diarrhea was either not done or was not provided, and the definition of 'persistent vomiting' that prompted the physician to advise IV rehydration has also not been mentioned.

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