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LITCHI TOXICITY – THE MYSTERY DISEASE

Neurology

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KEYWORDS

INTRODUCTION

In India, seasonal outbreaks of an acute unexplained neurological illness have been reported since 1995 from Muzaffarpur, Bihar, the largest litchi (lychee) fruit cultivation region in the country.[1] These recurring outbreaks begin in mid-May and peak in June, coinciding with the month-long litchi harvesting season. Children from poor socioeconomic backgrounds in rural Muzaffarpur comprise most of those affected. Illness is characterised by acute seizures and changed mental status, frequently with onset in the early morning,[2] and is associated with high mortality. A wide spectrum of causes has been proposed for this illness, including infectious encephalitis, exposure to pesticides, and a potential association with litchi fruit consumption.[3–6] Despite numerous investigations, neither a cause nor risk factors for illness have been confirmed among affected individuals.

Review of Litchi Toxicity -

Published reports of a toxic hypoglycaemic syndrome in the West Indies 7-9 that was due to the effects of hypoglycin A, a toxin found in the ackee, which is a fruit in the same botanical family as litchi, raised the prospect of a litchi-associated toxin. Of specific interest was the potential role of methylenecyclopropylglycine (MCPG), a homologue of hypoglycin A, and a substance naturally found in the litchi seed and fruit known to cause hypoglycaemia in animal studies by inhibiting β-oxidation of fatty acids and gluconeogenesis.[10,11,12,13]

One among three long-standing mystery diseases listed in Wikipedia is acute encephalitis syndrome (AES) in Muzaffarpur, Bihar[14]. This disease has remained for over two decades without determining a cause for it; hence it is called mystery disease.

How is it possible that lychee, a deliciously sweet tropical fruit, could induce a fatal hypoglycemic encephalopathy in children? The answer is straightforward: the edible fruit (aril) of lychee or litchi (Litchi sinensis or Litchi chinensis), and other members of the Soapberry family (Sapindaceae), contains unusual amino acids that disrupt gluconeogenesis and β-oxidation of fatty acids. This is well established in relation to both litchi fruit and, more particularly, fruit of its cousin, the ackee plant (Blighia sapida), a member of the Sapindaceae originating in west Africa and transplanted in the 18th century to the Caribbean.

In The Lancet Global Health, Aakash Shrivastava and colleagues [15] study of Indian children with litchi-associated encephalopathy unequivocally pins the blame on the litchi fruit itself, as predicted by previous Indian investigators[16] and by Spencer PS et al.[17] Like most, if not all, neurotoxic factors, the separation between chemicalinduced health and illness depends on dosage and individual susceptibility, which in this case translates to the number of litchi fruit consumed and the concentration of hypoglycaemic amino acids, as well as the children's age and state of nourishment. Shrivastava and colleagues[15] report that, akin to ackee, the unripe fruit of litchi has a higher concentration of hypoglycin A and its lower homologue, -(methylenecyclopropyl) glycine; the reported absence of a significant difference between the two probably arises from the small number of fruit samples tested (n=6 per batch of ripe and unripe fruit). Unfortunately, the study did not compare litchi-associated cases with controls drawn from the community and, strangely, cases were compared with sick controls lacking neurological disease and no history in the previous 3 months of altered mental status or seizures, and admitted to a case-surveillance hospital less than 7 days from admission of the case.

Why is seasonal litchi encephalopathy a relatively recent event in India, Bangladesh, and Vietnam? The most plausible explanation is the rapid expansion of commercial litchi production across Asia and beyond.[18,19] Indian production is second only to China's, from where Litchi sinensis originates and its potential toxic effects are noted in ancient literature.

Clinical features in patients are stereotype – 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[20]. Children are quite well until evening, but early next morning they are found seriously ill with brain function derangement and seizures. Undernutrition (short and underweight for age) has been observed as a consistent associated factor.

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[21]. The clinical features of ackee poisoning and Muzaffarpur AES have many close similarities, including early morning onset, encephalopathy, hypoglycaemia and high case fatality.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first comprehensive confirmation that this recurring outbreak of acute encephalopathy is associated with both hypoglycin A and MCPG toxicity from litchi consumption. This illness is also associated with absence of an evening meal. To prevent illness and save lives in Muzaffarpur, it is recommended[22] minimising litchi consumption among young children, ensuring children in the area receive an evening meal throughout the outbreak season, and implementing rapid glucose correction for children with suspected illness. Application of a similar comprehensive and systematic approach to the assessment of both infectious and non-infectious causes of unexplained illness outbreaks in other parts of the world can contribute greatly toward identifying interventions that can reduce morbidity and mortality.

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