

## The enigma of litchi toxicity: an emerging health concern in southern Asia



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  $\beta$ -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. Ingestion of immature ackee fruit has been known for decades in Jamaica to cause a toxic hypoglycaemic encephalopathy (Jamaican vomiting sickness) in children.<sup>1,2</sup> This knowledge has been slow to reach certain parts of Asia where the so-called mysterious litchi disease has been attributed to various causes (fruit colouring, heat stroke) in Bihar, India,<sup>3</sup> to an unidentified pesticide in northwest Bangladesh<sup>4</sup> and, after an exhaustive negative virological search, to a yet-to-be-discovered neurotropic virus in northeast Vietnam.<sup>5</sup> However, the illness evolves far too quickly to be a viral disorder, with a median time of 20 h from health to death in Bangladeshi children.<sup>4</sup>

In *The Lancet Global Health*, Aakash Shrivastava and colleagues<sup>6</sup> study of Indian children with litchi-associated encephalopathy unequivocally pins the blame on the litchi fruit itself, as predicted by previous Indian investigators<sup>7</sup> and by us.<sup>8</sup> Like most, if not all, neurotoxic factors, the separation between chemical-induced 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<sup>6</sup> report that, akin to ackee, the unripe fruit of litchi has a higher concentration of hypoglycin A and its lower homologue,  $\alpha$ -(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.

That well-established data for Sapindaceae toxicity have long existed from clinical experience in Africa and the Caribbean is an important lesson for global health and neurotoxicology. A worldwide understanding of the adverse effects on the nervous system of both naturally occurring as well as synthetic chemicals will speed diagnosis and treatment of other mysterious epidemics of environmental brain disease. The Indian subcontinent is no stranger to the neurological effects of toxins in plants—eg, food dependency on the grass pea or cassava resulting in the spastic parapareses of lathyrism and cassavism, respectively.<sup>9,10</sup> Unlike these untreatable self-limiting neurological diseases, litchi and ackee encephalopathy can be arrested by restoring serum glucose concentrations. However, some children reportedly are left with cognitive deficits, muscle weakness, or movement disorder; the causes of which require investigation.

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.<sup>11,12</sup> Indian production is second only to China's, from where *Litchi sinensis* originates and its potential toxic effects are noted in ancient literature. Today, several Asian countries export litchi and other Sapindaceae, including rambutan (*Nephelium lappaceum*) and longan (*Dimocarpus longan*) for consumption abroad. In the USA for instance, unlike the regulated importation of canned ackee fruit, which must be screened for hypoglycin content, there are no restrictions on other members of the Soapberry family, including litchi. Fortunately, the high cost of these imported fruits and the likelihood that would be eaten in small quantities by well-nourished consumers, suggests there is little reason for concern in the USA.

There is, however, cause for major concern that litchi-induced seasonal toxic hypoglycaemic

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encephalopathy will not only continue to be mistaken for a viral disorder, specifically Japanese B encephalitis, but also affect other regions of Asia where commercial litchi production is increasing and poorly nourished children have access to dropped, damaged, or immature fruit that cannot be sold. Areas of concern include northwestern Bangladesh, southern China, northern India, the Terai of Nepal's Central and Eastern Development regions, the Cordillera Autonomous Region of the Philippines, northern Thailand, and northeastern Vietnam.<sup>11,12</sup> Litchi cultivation is also increasing in southern Africa, Australia, and the Americas.<sup>12</sup> Going forward, researchers need to work with the litchi industry to determine how levels of hypoglycaemic acids vary across cultivars, soil, climate, and harvest conditions. Guidance should be developed for the consumer, especially children but also adults who have a susceptible metabolic profile or who eat fruit after fasting. While resistance can be anticipated to the notion that litchi has potential toxicity, this might disappear when industry is informed of ongoing research to address the possible beneficial effects of litchi-derived glucose-lowering agents in the fight against metabolic syndrome and associated chronic health disorders. For good reason, perhaps, a song from Jamaica, where *Blighia sapida* is held as the national fruit and regularly eaten with saltfish, contains the words: "an ackee a day keeps the doctor away"!

\*Peter S Spencer, Valerie S Palmer

Department of Neurology, School of Medicine, Oregon Health & Science University, Portland, OR 97201, USA  
 spencer@ohsu.edu

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