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Epidemics of Acute Encephalitis in Young Children: Lychee the Sweet Hypoglycemic or a Silent Killer

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Abstract

Epidemics of acute encephalitis In young children: Lychee the sweet hypoglycemic or a silent killer a review of literature. There have been reports of children presenting with acute neurological illness from Bihar India dating back to 1995 , with recent ones being reported from China and Vietnam in 2012 and the latest ones being reported from Muzaffar India in 2014. The fact that is common to all these reports has been the association with lychee (lichi chinensis) a juicy sweet fruit grown in the summer months from May till June. Not surprisingly the cases coincide with the harvesting season of the fruit.The presentation is with varied neurological symptoms ranging from acute onset of behavioral disturbance to seizures accompanied by marked hypoglycemia with radiological evidence of cerebral edema and features suggestive of inflammation. Epidemiological and laboratory evaluations has postulated a spectrum of causes for this illness, including infectious encephalitis, exposure to pesticides and Methylenecyclopropylglycine (MCPG) a compound found in litchi seeds known to cause hypoglycemia in animal studies. Current approach to the illness is focused on reducing the mortality by prompting the affected families to seek immediate medical attention and to ensure rapid correction of hypoglycemia. The varied presentation, absence of conclusive evidence to suggest a causative pathological agent warrant need for greater research to identify the culprit pathogen. Till such time lychee continues to be a sweet hypoglycemic, a silent killer. US researchers commented that a mysterious and sometimes fatal brain disease that has afflicted children in northeastern India for years could be linked to a toxic substance in litchi fruits, -Published in Leading Newspaper. The US Centers for Disease Control and Prevention have said that more research is needed to uncover the cause of the illness, which leads to seizures, altered mental state and death in more than a third of cases. In the meantime, doctors who encounter sick children should takes steps to rapidly correct low blood sugar, which can make the disease more likely to be fatal, said the report. The outbreaks have coincided with the month-long litchi harvesting season in and around the Muzaffarpur district of Bihar state since 1995, -Published in CDC's Morbidity and Mortality Weekly Report. In 2013, some 133 children were admitted to local hospitals in Bihar with seizures and neurological symptoms. Most were aged one to five, and nearly half (44 percent) of them died. Those who died were more than twice as likely as other patients to have been admitted to the hospital with low blood sugar.

Keywords: Lychee; Hypoglycemia; Epidemics.

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There have been reports of children presenting with acute neurological illness from Bihar India dating back to 1995 , with recent ones being reported from China and Vietnam in 2012 and the latest ones being reported from Muzaffar India in 2014. The fact that is common to all these reports has been the association with lychee (lichi chinensis) a juicy sweet fruit grown in the summer months from May till June. Not

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Tests on the spinal fluid of patients came back negative for infectious agents like Japanese encephalitis virus, West Nile virus and other known pathogens in the area.A study that compared ill children to a control group in the area found that those who got sick were more than twice as likely to have spent time in orchards or agricultural fields.These findings "raised concern for the possibility of a toxin-mediated illness," commented by CDC.

More reports in 2014 from the end of May until mid-July 2015, 390 children were admitted to the two referral hospitals in Muzaffarpur with illnesses that met the same case definition used in 2013. "As in previous years, clustering of cases was not observed; the illness of each affected child appeared to be an isolated case in various villages," said the CDC, noting that about 1,000 people lived in each village.The number of cases declined significantly after the onset of monsoon rains on June 21, 2014. Parents and caregivers said the children seemed healthy until they suddenly began experiencing convulsions, usually between 4:00 am and 8:00 am, followed by an altered mental state. Most did not have a fever on admission to the hospital and were found to be hypoglycemic in many instances 31% of the children died. A report by CDC said that the 2013 and 2014 Muzaffarpur investigations indicate that this outbreak illness is an acute non inflammatory encephalopathy. MCPG (Methylenecyclopropylglycine) found in Lichi seeds may cause severe hypoglycemia and illness much the same way as a similar toxin, hypoglycin A, which has caused "acute encephalopathy in the West Indies and West Africa after consumption of unripe ackee, a fruit which belongs to the same botanical family as litchi. Outbreaks of neurological illness have also been observed in litchi-growing regions of Bangladesh and Vietnam. An investigation into the Bangladesh cases focused on pesticides used in litchi orchards, but no specific cause was found. In Vietnam investigations were carried out to find a relation between possible infectious agents that might be present seasonally near litchi fruit plantations, but it was also inconclusive. Lychee may be the culprit causing acute encephalitis syndrome (AES), affecting children in north India between April and July. The chemicals and substances that the fruit carry are similar to those found in Jamacian fruit, ackee, which is the cause of a childhood (under 15) acute encephalopathy disease called Jamaican vomiting sickness (JVS). Though there have been theories linking the disease with lychee, a new scientific study insists on the link. Researchers have said that there is an overwhelming evidence to establish the link and the government should start treatment modalities accordingly. The paper, published in May 10 issue of Current Science, states that clinical features of ackee poisoning and Muzaffarpur AES are similar. This includes early morning onset, encephalopathy, hypoglycemia and high case fatality. A toxic substance methylenecyclopropyl- alanine (MCPA), also called hypoglycin A, is present in unripe ackee, whose consumption leads to depletion of glucose levels in the child's body. Since brain cells require constant

supply of glucose, this depletion triggers abnormalities in brain too. A variant of hypoglycin A, namely methylenecyclopropyl-glycine (MCPG), is found in lychee and its consumption reduces glucose levels in the body. Muzaffarpur district of Bihar, where the disease spreads in epidemic proportions, is one of the leading districts producing lychee, which is grown from April to June.

Another study, recently published in *the journal Epidemiology and Infection*, shows that in some cases of AES in Jharkhand and Odisha, the viral agents were that of dengue and measles. Researchers from *Regional Medical Research Centre (RMRC) and School of Biotechnology of Kalinga Institute if Industrial Technology, Bhubaneshwar*, carried out the study in four tertiary-care hospitals in Bhubaneshwar and Cuttack, both in Odisha. Over 16 per cent cases were found to be caused by viral agents identified to be herpes simplex virus (HSV) while another 2.6 per cent cases were by measles. Similarly, Japanese encephalitis virus caused 1.5 per cent cases followed by 0.57 per cent by dengue virus.

Bhaswati Bandyopadhyay, Indrani Bhattacharyya, Srima Adhikary, Saiantani Mondal, Jayashree Konar, Nidhi Dawar, Asit Biswas, and Nemai Bhattacharya did a study on Incidence of Japanese Encephalitis among Acute Encephalitis Syndrome Cases in West Bengal, India.

- This study was aimed at seeing the present scenario of JE among acute encephalitis syndrome (AES) cases in West Bengal. Blood and/or CSF samples were referred from suspected AES cases to the referral virology laboratory of the Calcutta School of Tropical Medicine from different hospitals of Kolkata. IgM antibody capture ELISA was performed on the CSF and serum samples by JE virus . The present study reveals that 22.76% and 5% of the AES cases were positive for JE IgM in 2011 and 2012, respectively. JE is mainly prevalent in children and adolescents below 20 years of age. Although the percentages of JE positive cases were high in 2011, it sharply decreased thereafter possibly due to better awareness programs, due to mass vaccination, or simply due to herd immunity. However, there was a remarkable change in the percentages of JE positive cases in the years 2011 and 2012 . In males, the percentage of JE positive cases dropped from 23.84% to only 4.8% similarly in females it dropped from 21.05% to 5.2%. Surprisingly a larger number of cases were reported from Murshidabad, Bardhaman, and Howrah districts of West Bengal in 2012. But this study could not find a correlation between Litchi fruit as a cause of AES in children.

Yueming Jiang , Xuewu Duan, Daryl Joyce, Zhaoqi Zhang and Jianrong Li did a study on Advances in understanding of enzymatic browning in harvested litchi fruit(Volume18, No 11, Nov 2012) – They found that harvested litchi fruit rapidly lose their bright red skin colour. Peel browning of harvested litchi fruit is due to rapid degradation of red anthocyanin pigments. This process is associated with enzymatic oxidation of phenolics by polyphenol oxidase (PPO) and/or peroxidase (POD). PPO and POD from litchi pericarp cannot directly oxidize anthocyanins. Moreover, PPO substrates in the pericarp are not well characterised. A such the roles of PPO and POD in litchi browning needs further research. Recently, an anthocyanase catalysing the hydrolysis of sugar moieties from anthocyanin to anthocyanidin has been identified in litchi peel for the first time. Thus, litchi enzymatic browning may involve an anthocyanase–anthocyanin–phenolic–PPO reaction. Recent research focus is on characterising the properties of the anthocyanase involved in anthocyanin degradation. Associated emphasis is on maintenance of membrane functions in relation to loss of compartmentation between litchi peel oxidase enzymes and their substrates. But this has not been found to be associated with AES in human.

Juliette Paireau, Nguyen Hai Tuan, Rémi Lefrançois, Matthew R. Buckwalter, Ngu Duy Nghia, Nguyen Tran Hien, Olivier Lortholary, Sylvain Poirée, Jean-Claude Manuguerra, Antoine Gessain, Matthew L. Albert, Paul T. Brey, Phan Thi Nga, and Arnaud Fontanet Published a paper on "Litchi–associated Acute Encephalitis in Children, Northern Vietnam, 2004–2009"— Since the end of the 1990s, unexplained outbreaks of acute encephalitis in children coinciding with litchi harvesting (May–July) have been documented in the Bac Giang Province in northern Vietnam. This study revealed an independent association between litchi plantation surface proportion and acute encephalitis incidence: Incidence rate ratios were 1.52 (95% CI 0.90–2.57), 2.94 (95% CI 1.88–4.60), and 2.76 (95% CI 1.76–4.32) for second, third, and fourth quartiles, respectively, compared with the lowest quartile. This ecologic study confirmed the suspected association between incidence of acute encephalitis and litchi plantations and should be followed by other studies to identify the causative agent for this syndromeThe final outcome of the study resulted in 3 factors independently associated with AME. A positive association between disease incidence and litchi surface proportion was found: the IRRs were 1.52 (95% CI 0.90–2.57), 2.94 (95% CI 1.88–4.60), and 2.76 (95% CI 1.76–4.32) for second, third, and fourth quartiles, respectively, compared with the lowest quartile. A reduced risk was associated with density

of poultry: the IRRs were 0.62 (95% CI 0.43–0.91), 0.61 (95% CI 0.42–0.89), and 0.25 (0.15–0.43) for second, third, and fourth quartiles, respectively, compared with the lowest quartile. Relative humidity was negatively associated with disease incidence.The study found evidence of association between the outbreaks of unknown encephalitis in Bac Giang Province and litchi cultivation. The ecologic regression analysis demonstrated that the annual risk for AME in a commune increased with the proportion of litchi-cultivated surface and that the epidemics occurred earlier in the districts that harvested litchis during May–June than in those that harvested litchis during June–July. The association between litchis and acute encephalitis remains unclear. As with other emerging viruses, we face a multifactorial problem that seems to have litchi fruit production and harvest as its focal point. One possible scenario is that fruit-bearing litchi trees can attract bats, which might be the reservoir for the putative pathogen. Mosquitoes could feed on the infected bats and transmit the virus to humans who have insufficient protection against mosquito bites. Several species of bats were identified in the province, such as the frugivorous bats *Rousettus leschenaultii*, which can feed on litchi. These bats' highly gregarious, cave dwelling, and migratory characteristics facilitate their role in virus carrying and circulation. The bat population density is high during April–September (which includes the time of litchi harvest) before migration during October–March. In addition, several mosquito species were identified in Bac Giang Province: *Anopheles vagus, Armigeres subalbatus, Culex tritaeniorhynchus, Cx. vishnui*, *Cx. gelidus, Cx. fuscocephalus, Cx. quinquefasciatus,* and *Cx. bitaeniorhynchus*. Although the peak incidence of May–July correlates with the rice paddy breeding and development of *Culex* spp. mosquitoes, the paddy fields area was negatively associated with the risk for disease in univariate analysis. No data were collected on vector densities in Bac Giang. Other modes of transmission, e.g., direct contact with litchis contaminated by bat saliva, urine, or guano or with other vectors, such as insects found in litchi trees or phlebotomine sand flies, as in the case of Chandipura virus, cannot be excluded. Deforestation in Bac Giang to develop the growing of litchi trees because of their high economic value also might have disrupted the ecologic equilibrium of the province, leading to the emergence of a new vector-borne disease. The virus also might be exclusively human; use of human feces as fertilizers to enhance litchi growth in these plantations might have contaminated the soil with enteroviruses, which are known to cause fatal encephalitis in deprived children Litchi growing also depends on climate; ideal conditions include a brief dry, cool, and frost-free winter to lead to flowering, followed by warmer temperatures and moderate rainfall and humidity during fruit development and harvest . Still, climatic variations alone could not explain the spatial differences in disease risk between communes of the same province. Moreover, even if the association is not proved to be causal, the persistence of both variables (litchi surface and mean humidity) in the final model suggested that both factors are independently correlated with the patterns of the disease. Definitive identification of the infectious agent will help clarify these factors associated with AME incidence.This elaborative study did a significant analysis of outbreaks of acute encephalitis of unknown origin during the litchi harvest period in Bac Giang Province and it further strengthens the hypothesis that litchis might play a role in these outbreaks by showing that litchi cultivation was spatially and temporally associated with AME.

D.S. Dinesh, K. Pandey, V.N.R. Das, R.K.Topno, S.Kesari, V. Kumar, A. Ranjan et al published a paper on" Possible factors causing Acute Encephalitis Syndrome outbreak in Bihar, India in Int.J.Curr.Microbiol.App.Sci (2013) 2(12): 531-538—* They collected data on AES patinents from Shri Krishna Medical College andHospital, Muzaffarpur and Krishnadevi Deviprasad Kejariwal Maternity under

KDK Matri Sadan Trust at Muzaffarpur. It was found that the disease appeared in pediatric age group (median 5 years between 3 months to 10 years) coinciding with the litchi (*Litchi chinensis*) fruit season. A total of 85 cases appeared in Muzaffarpur and a few in two districts namely Sitamarhi, Sheohar and East Champaran with 31%death from June-July, 2011. The first AES outbreak investigation was conducted in Eastern India in1973(Chatterjee, 1974; Chatterjee and Banerjee, 1975). However, the first epidemic of AES appeared in 2011 in North Bihar. Only one or two cases were found in each affected village. A total of85 cases were reported The disease was presumed asa viral out break / AES due to shortduration of severe illness and altered sensorium resulting in death. There was record of 26 deaths (31%). The median age of the patients was found to be 5 years ranging between 3 months to 10 years, belonging to weaker socioeconomic section of the society. However in the outbreak at Gorakhpur, India 93.69%cases were below age group of 15 years. The sex ratio was found to be 1.2:1 male to female. Itwas 1.45:1 in Gorakhpur of Uttar Pradesh15 and 1.2:1 in Vietnam. The CSF wasnormal and the serological tests did notconfirm

Japanese B Encephalitis. This incidence coincides with large scale production of litchi, a very famous seasonal fruit grown in part of the state with a high demand of export worldwide.The incident cases with that of quantum of production of litchi is depicting a strong relationship (R2 = 0.7376, r (correlation coefficient) = 0.86) coinciding with season.The high quantum of production of litchi fruit might not be directly acting as a causative factor, but some other ecological, environmental and behavioral factors might have some indirect effect that could be acting as causative factors for high incidence of disease among th populations residing by the orchard. Outbreak of acute encephalitis in children coinciding with litchi harvesting (May-July) reported in Bac Giang Province in north Vietnam from late 1090 s. Bats were found in large number resting on trees.Most of these fruits might have been rotten due to some kind of infection through saliva of birds, bats orlizards or decaying due to bacteria. It was reported by the parents of affected patients in course of investigation that some children had eaten fallen fruits in the orchard few days before illness. Thus the possibility of transmission of pathogen through this route cannot be ignored.

Thus the direct co-relation of Litchi with AES could not be proved substantially. However it still remains a mystery and the sweet litchi fruit may continue to be a silent killer. It is now only in the disposal of the people at large and the scientific population to lead the path and show a way and do further research to establish this.

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