*Indian Journal of Agricultural Sciences* **86** (3): 283–90, March 2016/Review Article
https://doi.org/10.56093/ijas.v86i3.56827

**Research Review Article**

# Acute Encephalitis Syndrome and its alleged litchi (*Litchi chinensis*) connection—A review and status

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Received: 8 October 2015; Accepted: 7 January 2016

ABSTRACT

In recent times, Acute Encephalitis Syndrome (AES), an unexplained mysterious disease is affecting people, especially young children below the age of 15 years in few Asian countries. Several hypothesis and causal factors are being suspected and studied by the researchers.Despite the stringent efforts, the causal agent of AES has not been identified till date and researchers all over the world are striving to find out the cause and remedy of this fatal disease. The concurrence of the AES, in temporal dimensions in most of the places and spatial dimension in few cases with the seasonal maturity of litchi (*Litchi chinensis* Sonn.) fruits has occasioned in the fruit being associated and judged as a possible causal agent of AES. However, the delicious litchi fruit has been consumed since centuries and thus the alleged association wants critical examination and investigation. The symptoms of the AES disease point towards a viral etiology, and several of the enteroviruses are known to cause encephalitis. This review article is an attempt to present the various supposed causal factors of AES, the critical gaps that question the association between the litchi fruits and AES and some of the serious misgivings to refute the suspected association between the consumption of litchi fruits and AES.

**Key words**: Acute Encephalitis Syndrome (AES), Blood sugar, Litchi, α-methylenecyclopropylglycine (MCPG), Virus

Litchi (*Litchi chinensis* Sonn.) is a subtropical fruit belonging to the family Sapindaceae, having its origin in Kwangtung and Fukien regions of South China. It is a non-climacteric fruit which attains maximum edible quality only after complete ripening.The fruit possesses high commercial value due to its pleasantly flavoured juicy aril, delicate taste, high nutritional value and attractive exterior pericarp (Table 1). It is proclaimed as the "queen of fruits" due to its unique delectable taste and striking appearance. The major litchi growing countries in the world are China, India, Brazil, Malaysia, Thailand, Vietnam, Myanmar, Mauritius, South Africa, Australia, New Zealand, Madagascar and Taiwan (Singh *et al*. 2012). Among them, China and India together account for about 91% of the world's total litchi production which is primarily marketed in the nearby regions due to its highly perishable nature and postharvest pericarp browning (Singh *et al*. 2012).

In recent years, the acute encephalitis syndrome (AES) has acquired major public health importance due to its epidemic nature and high mortality rate (Dinesh *et al*. 2013, Laserson 2013, Shrivastava *et al*. 2015). The symptoms include acute onset of fever with change in mental status that may lead to disorientation, coma, or inability to talk and seizures (Dinesh *et al*. 2013, Bandyopadhyay *et al*. 2015). This may happen to a person of any age at any time of the year however, the children are particularly vulnerable. It primarily affects young children of age below 15 years (mostly in age group 2-5 years), largely belonging to rural and poor socio-economic background. It has been reported that onset of AES occurs primarily during early morning hours after several hours of fasting, which points to a metabolic disease. Further, hypoglycaemia in the early morning hours indicates inhibited gluconeogenesis and malnutrition, which is associated with depleted glycogen/ glucose store in the liver (John and Das 2014). Well-nourished children are not affected since their glycogen/ glucose store in the liver is sufficient to maintain normal glucose levels and presumably gluconeogenesis is not triggered (John and Das 2014). The first AES outbreak investigation was conducted in Eastern India in 1973. However, the first epidemic of AES appeared in 2011 in North Bihar (Dinesh *et al*. 2013). It has been reported from Vietnam and Bangladesh as well (John and Das 2014).

In general, AES occurs as annual seasonal outbreaks

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Table 1 Nutritional composition of litchi and percent recommended daily intake met by the fruit

| Nutritional composition | Content (per 100 g litchi pulp) | Percent Recommended Daily Intake (RDI) supplied by 100 g litchi pulp | |
|---|---|---|---|
| | | For a healthy man (body weight 60 kg) doing moderate work | For a healthy woman (body weight 55 kg) doing moderate work |
| Energy | 66 kcal | 2.4 | 2.95 |
| Protein | 0.83 g | 1.4 | 1.5 |
| Fat | 0.44 g | 1.5 | 1.8 |
| Carbohydrate | 16.53 g | 12.7 | 12.7 |
| Fiber | 1.30 g | 3.4 | 5.2 |
| Thiamin | 0.011 mg | 0.8 | 1.0 |
| Riboflavin | 0.065 mg | 4.1 | 5.0 |
| Niacin | 0.603 mg | 3.4 | 4.3 |
| Vitamin $B_6$ | 0.10 mg | 5.0 | 5.0 |
| Vitamin C | 71.5 mg | 178.8 | 178.8 |
| Vitamin E | 0.07 mg | 0.5 | 0.5 |
| Vitamin K | 0.40 µg | 0.5 | 0.5 |
| Folate | 14.00 µg | 7.0 | 7.0 |
| Calcium | 5.00 mg | 0.8 | 0.8 |
| Iron | 0.31 mg | 1.8 | 1.5 |
| Magnesium | 10.00 mg | 2.9 | 3.2 |
| Phosphorus | 31.00 mg | 4.4 | 4.4 |
| Potassium | 171.00 mg | 3.6 | 3.6 |
| Zinc | 0.07 mg | 0.6 | 0.7 |
| Sodium | 1.00 mg | 0.04 | 0.04 |

*Source:* USDA National Nutrient Database for Standard Reference Release 27 Basic Report 09164, Litchis, raw; Dietary guidelines, National Institute of nutrition, Hyderabad; Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005) and Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate (2005) [www.nap.edu.].

during the months of April-July, affecting hundreds of children with 40-60% mortality (John and Das 2014). Several studies explored different possibilities of its causal agents. In the earlier studies by different teams, Japanese encephalitis, a bat virus, mosquitoes or bed bug bite, unhygienic conditions, virus, litchi fruit, heavy metals, pesticide residues, high temperature and/or sunstroke have been linked and reported as the possible causal factors of AES (Joshi *et al*. 2012, Dinesh *et al*. 2013, Paireau *et al*. 2012, John and Das 2014, Bandyopadhyay *et al*. 2015). Among these factors, high temperature resulting in heat stroke,virus, pesticidesor a bat virus transmitted by mosquito bites and prevailing unhygienic conditions were mostly emphasized as possible causes of AES. However, Bandyopadhyay *et al*.(2015) reported for the first time that the symptoms of AES indicate a viral etiology, which has remained unidentified till now. There may be various other ways of transmission of AES like direct contact with litchis contaminated by the saliva, urine, or guano of bats. In addition, other vectors such as insects or sand flies may be spreading the AES (Paireau *et al*. 2012, Wacharapluesadee *et al*. 2005, Geevarghese *et al*. 2005). Walsh *et al*. (1993) suggested that the disturbance caused due to deforestation in the BacGiang province in Vietnam may have disrupted the ecology balance of the region which might have resulted in a new vector-borne disease. It is possible that the alleged AES virus is solely originated from human faeces as several enteroviruses are known to cause fatal encephalitis in children (Sapkal *et al*. 2009). It was speculated that a poisonous weed, *Cassia occidentalis* may be causing encephalopathy (Vashishtha *et al*. 2007).It has been put forward by Dinesh *et al*.(2013) and Bandyopadhyay *et al*. (2015) that the litchi fruit might not be a direct reason of AES but may be linked due to various other ecological, environmental or behavioral factors resulting in high incidence of AES in litchi growing areas. However, few of the above mentioned causes were ruled out or showed inconclusive evidence. Few studies concluded that it is due to heat stroke or pesticides or virus but there is no mutual consent till date among the academicians about the causes.

The unfortunate overlapping of the AES, temporally and spatially with the seasonal maturity of litchi fruits and the presence of α-MCPG in its seed has resulted in the fruit being judged as a possible causal agent of AES (John and Das 2014). In some studies, it has been mentioned that the outbreaks of AES corresponded with litchi cultivation in space and time in Vietnam and Bangladesh, where its outbreaks were reported during the harvesting season in areas having litchi orchards (Paireau *et al*. 2012, John and Das 2014). Moreover, the litchi seeds are known to contain a lower analogue of hypoglycin A, α-methylenecyclopropylglycine (MCPG) (Gray and Fowden 1962). α-MCPG has not been analysed in the ripe or unripe litchi fruit, but has been reported to cause hypoglycaemia and derangement of fatty acid β-oxidation in liver cell mitochondria in experimental animals (John and Das 2014, Li *et al*. 1999). It is worth mentioning that litchi seeds are not edible and the fractionated data of α-MCPG in seed, pulp or peel is not available. The mechanism of toxicity of α-MCPG is related to the formation of MCP-formyl-CoA, which in turn inhibits several dehydrogenases responsible for gluconeogenesis, causing depletion of glucose reserves in the body (Melde *et al*. 1989, Melde *et al*. 1991, Ghisla *et al*. 1990, John and Das 2014). However, the association of AES has still not been confirmed with respect to litchi.

The connection between the consumption of litchi fruit and the occurrence of AES needs to be critically examined and investigated in detail. Several critical gaps and unanswered queries question the association between the litchi fruits and fatal disease AES. The authors have tried to present some of their acute reservations to avert the linking between the intake of litchi fruits and this fatal disease.

The litchi fruit has been in great demand by the consumers and is being consumed from as early as 2000 BC in China and approximately from the last 200 years in India (Singh *et al*. 2012). It was the favourite fruit of many of the Chinese emperors. The fruit aril is a rich source of several

nutritional and health promoting functional compounds (Wang *et al*. 2010, Wang *et al*. 2011, Zhang *et al*. 2013,Su *et al*. 2014). Litchi pulp contains sugars in the form of sucrose, fructose and glucose which vary in magnitudes among the cultivars. The 100 g of fresh litchi pulp contain approximately 70 mg of vitamin C which is more than the recommended daily intake for a healthy person (Table 1). It is an abundant source of the mineral nutrients which are crucial for the maintenance of health (Wall 2006). It contains very low amount of fat and sodium. Litchi fruit exhibits functional activities such as antioxidant, anti-viral and anti-cancer properties due to presence of flavonoids and other phenolic compounds. The fruit pulp is a storehouse of several antioxidant compounds such as vitamin C, vitamin E, polyphenols, flavonoids and polysaccharides (Table 1) (Wall 2006, Su *et al*. 2014). Moreover, litchi fruit is instrumental in alleviating the symptoms of anaemia. It has been documented by many workers that the fruit is helpful in improving the digestion and blood circulation (Chi *et al*. 2005, Wang *et al*. 2010, Kitadate *et al*. 2014). The thin pericarp of the litchi fruit is a treasure trove of several functional compounds like anthocyanins, flavan-3-ol derivatives including (-)-epicatechin and proanthocyanidins A1, A2, B2 and B4 (Liu *et al*. 2007, Jiang *et al*. 2013). These compounds have antioxidant, cardioprotective and anticarcinogenic activities (Prior and Gu 2005, Jiang *et al*. 2013). The high insoluble fiber content and other antioxidant components present in fruit pericarp render it anti-cancer property. The anti-cancer activity of the litchi pericarp is well documented and has been found to significantly inhibit the growth of human hepatoma cells *in vitro* as well as *in vivo* (Wang *et al*. 2006a). The litchi fruit displays anti-virus, cardio-protective and anti-diabetes properties due to presence of flavan-3-ol derivatives in the pericarp, aril and seeds but the mechanisms of these actions await complete understanding (Wang *et al*. 2006a, b, Prior and Gu 2005). The litchi pulp is a rich source of phenolics and the cultivars with high (-)-epicatechin or procyanidin content may act as possible hypoglycaemic food (Lv *et al*. 2014). Litchi fruit is a good sources of minerals, dietary fibre and phytochemicals. It has been employed in traditional Chinese medicine for its benefits on heart, spleen and liver (Mahattanatawee *et al*. 2006, Zhang *et al*. 2013). The seeds of the fruit are inedible but have proven to have numerous health benefits (Prasad *et al*. 2009).Litchi fruit has traditionally been used for relief in cough, flatulence, stomach ulcers, diabetes, obesity and testicular swelling (Ibrahim and Mohamed 2015). Considering the nutritional properties of the queen of fruits, it can be safely asserted as a gem among the fruit basket.

The traditional Chinese as well as Indian medicine system have recorded several advantages of consuming litchi fruits like improving the digestive, circulatory, excretory and reproductive systems (Zhang *et al*. 2013, Wang *et al*. 2010). The contemporary research has also revealed many important functional qualities of litchi fruit like anti-adiposity, antioxidant, anticancer, hepato-protective, antibacterial, anti-hyperlipidemic, antiplatelet, anti-hyperglycaemia, anti-mutagenic, anti-pyretic, anti-inflammatory and antiviral properties (Devalaraja *et al*. 2011, Ibrahim and Mohamed 2015). The protective ability of the fruit against the cardiovascular diseases was hailed in a study published in the journal "Molecular Medicine Reports" because of its high content of anthocyanins, polyphenolics and other bioactive compounds which acted as antiplatelet, anticoagulant, antioxidant and thrombolytic agents (Kong *et al*. 2010). The hepato-protective activity of litchi fruit pulp extract was studied on albino rats in which hepatotoxicity was induced by carbon tetrachloride by Souza *et al*. (2006) which exemplified the hepato-protective activitiy of the fruit (Bhoopat *et al*. 2011). Litchi fruit pericarp contains significant amounts of polyphenolic compounds which exhibit powerful antioxidant capacity. In addition, the anticancer activity of fruit pericarp extract has been studied and demonstrated by Wang *et al*. (2006a,b) against hepatocellular carcinoma *in vitro* and *in vivo* by the suggested mechanism of proliferating the inhibition and apoptosis induction of the cancer cells. Further, the anticancer properties of litchi fruit pericarp extract against human breast cancer *in vitro* and *in vivo* were illustrated (Wang *et al*. 2006a,b). They suggested that it would be useful for discovering a new anticancer drug. The leaves of litchi show anti-inflammatory, analgesic, antipyretic and anticancer activity without toxicity (Besra *et al*. 1996, Wen *et al*. 2014). Even, the flowers of litchi are shown to be high in antioxidant capacity with the ability to decrease levels of lipid, reduce and prevent liver damage and reduce inflammation (Liu *et al*. 2009). Litchi acts as a therapeutic fruit for diabetes, obesity and other metabolic syndromes such as diabetes induced blindness and retinopathy, as proven by several *in vitro* and *in vivo* studies (Sakurai *et al*. 2008, Lee *et al*. 2009, Kong *et al*. 2010, Obrosova *et al*. 2010, Devalaraja *et al*. 2011, Ogasawara *et al*. 2011, John and Das 2014).Litchi is a highly nutritious fruit being consumed since several centuries and there is absolute lack of any indigenous knowledge regarding its association as a causal agent with any kind of disease particularly encephalopathy. Thus, it is a vital matter demanding thorough investigation to determine whether there is any possibility of litchi being associated with AES.

Bandyopadhyay *et al*. (2015) recently reported the epidemiological investigation of the AES outbreak in Malda District of West Bengal, India. A high fatality rate of 34 deaths among the 72 admitted AES patients was recorded in that district. They have conveyed for the first time that the evidence collected indicate a viral etiology. In addition, Paireau *et al*. (2012) have reported that the presence of fever and meningeal symptoms along with the absence of high elevation of liver enzyme, suggesting a viral etiology. It has been reported that the causative virus is unidentified as of now (Bandyopadhyay *et al*. 2015). Further advanced studies using sequencing technology and resequencing micro-arrays has been recommended which may help in identification and characterization of the AES causal virus (Cheval *et al*. 2011, Bandyopadhyay *et al*. 2015). This virus

may be the cause of unexplained acute encephalitis occurring in different parts of the world. Bandyopadhyay *et al*. (2015) concluded that the virus can be a previously unrecognized virus, as a causative agent for AES. It may be an entirely new pathogen emerging due to globalization, climate change or environmental encroachment (Bandyopadhyay *et al*. 2015). The team has conveyed that the litchi fruit consumption and the resulting hypoglycaemia might have enhanced the encephalitis (AES) instead of actually being the sole or major causal factor.This study obviates the claim that AES might have been occurring only due to consuming litchi fruits.

It is worth mentioning that in some of the studies, among the affected AES children some were in the age group of below 1 year who cannot eat litchi fruits (Dinesh *et al*. 2013). It is indeed mind-boggling that if AES is occurring due to consumption of litchi, then how it is affecting children below the age of 1 year for whom eating litchi is unthinkable (Fig 1). This cannot be overlooked and plausible reason need to be found out by the researchers for this phenomenon. In addition, the findings till date do not explain as to why only some children or only one in the family are affected and not others. If it is indeed caused by a hypoglycin compound present in litchi seeds, it must result in AES in children of similar nutritional status and belonging to the same age group every time on consuming litchi fruit. The AES primarily affects children below the age of 12 years, which warrants investigation (Fig 1).These observations point towards a completely different causal agent. It may be very much possible that the focus is on the litchi fruit mainly due to temporal concurrence while the real causal agent is being missed out.

It is both interesting and shocking at the same time that the illness due to AES has not been reported from several other litchi growing areas of the world. The major litchi growing countries are China, India, Thailand, Vietnam, Bangladesh, Nepal, Phillipines, Indonesia, Mauritius, Australia, Israel, Madagascar, Central and South America, Brazil, South Africa, New Zealand, Taiwan (Table 2). However, the AES has been reported mainly from India,

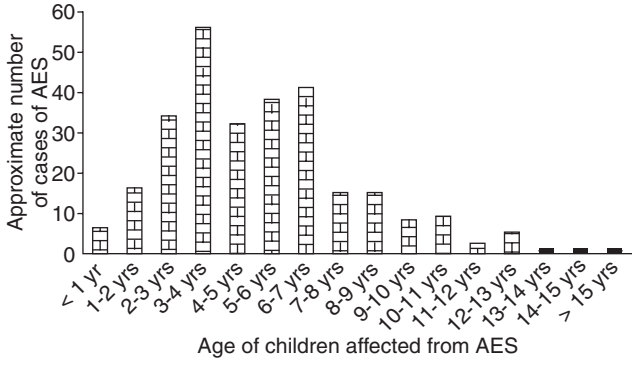


Fig 1 Representation of the age of children affected from AES *vis-a-vis* the approximate number of cases in that age group in different years. Source:Various reports from health departments and Integrated Disease Surveillance Programme, NCDC and Dinesh *et al*. 2013.

Table 2 List of countries in which litchi is grown and from where occurrence of AES has been reported

| Countries | Litchi orchards | AES occurrence |
|---|---|---|
| China | ✓ | - |
| India | ✓ | + |
| Thailand | ✓ | - |
| Vietnam | ✓ | + |
| Bangladesh | ✓ | + |
| Nepal | ✓ | - |
| Philippines | ✓ | - |
| Indonesia | ✓ | - |
| Australia | ✓ | - |
| Mauritius | ✓ | - |
| USA | ✓ | - |
| Israel | ✓ | - |
| Madagascar | ✓ | - |

*Source:* Compiled from various sources like Singh *et al*. (2012); The litchi crop in Asia and the Pacific, Regional Office for Asia and the Pacific, RAP publication 2002/16 (http:www.fao.org/docrep/), John and Das (2014).

Vietnam and Bangladesh (John and Das 2014,Paireau *et al*. 2012). This raises a doubt that why the AES is not occurring in the other litchi growing countries, if it is the cause of AES (Table 2). The AES linked to litchi fruit consumption has not been reported from China, the original habitat of the litchi. Moreover, the researchers there have not linked any kind of AES with the consumption of this nutritious fruit, which has been used traditionally for various medicinal purposes (Ibrahim and Mohamed 2015).

Furthermore, Bihar state contributes approximately 40.6% of the total litchi production in India, followed by West Bengal (16%) (Indian Horticulture Database 2014).The other major litchi producing areas in India include Jharkhand, Asom, Chhatisgarh, Uttarakhand, Punjab, Odisha, Tripura, Himachal Pradesh, Jammu and Kashmir, Jharkhand, Madhya Pradesh, Manipur, Meghalaya, Nagaland, Sikkim, Tamil Nadu, Uttar Pradesh and Karnataka (Table 3 and 4). It is highly surprising that why the cases of AES have erupted only from Bihar and one district of West Bengal, i.e. Malda

Table 3 The area and production of litchi fruit in different states of India in the year 2013-14

| State | Area ('000 HA) | Production ('000 MT) |
|---|---|---|
| Bihar | 31.48 | 234.20 |
| West Bengal | 9.30 | 93.90 |
| Jharkhand | 5.27 | 58.24 |
| Asom | 5.38 | 48.08 |
| Chhatisgarh | 5.36 | 37.63 |
| Uttarakhand | 9.44 | 30.71 |
| Punjab | 1.85 | 28.00 |
| Odisha | 4.47 | 20.32 |
| Tripura | 3.88 | 20.18 |
| Others | 7.74 | 14.04 |

*Source:* Indian Horticulture Database 2014

if it is indeed occurring due to litchi consumption (John and Das 2014, Bandyopadhyay *et al*. 2015). The areas like West Tripura in Asom, Gorakhpur and Basti in Uttar Pradesh, Gumla and Lohardaga in Jharkhand, Sarguja in Chhatisgarh and Kangra valley in Himachal Pradesh and several other places in India having litchi orchards have not reported any occurrence of AES (Table 4). One may argue that this may happen due to rampant malnutrition in the states of occurrence. However, the theory still fails since many of the other areas where litchi is being grown suffer from malnutrition in children and poverty. This state of affairs recommends a thorough investigation of the possible factors that may cause the AES and eliminate the possibility of association of AES with litchi fruit.

To delve further, we analysed the major districts in Bihar where litchi is being cultivated and consumed as a major fruit crop. The areas in Bihar where litchi is grown as a principal fruit crop are concentrated in Muzaffarpur, Vaishali, Sitamarhi, West Champaran, East Champaran, Katihar, Samastipur, Purnea and Bhagalpur (Naugachia). Litchi is also grown in Siwan, Gopalganj, Saran, Sheohar, Darbhanga, Madhubani, Begusarai, Saharsa, Araria, Kishanganj, Khagariya, Munger, Jamui, Madhepur, Supaul, Sheikhpura, Lakhisarai, Banka and Motihari districts of Bihar (Table 5). However, to our utter surprise, it was found that the AES cases were reported mainly from Muzaffarpur, Sitamarhi, Sheohar, East Champaran,Vaishali and West Champaran while the other districts of Bihar like Bhagalpur, Samastipur, Darbhanga, Begusarai, Katihar and Purnea remained unaffected (Table 5, unpublished sources, newspaper clippings). Moreover, the AES cases have been reported from Gaya district as well where the litchi is not cultivated. It was stressed upon by All India Institute of Medical Sciences, Patna and United Nations Children Fund that the AES is occurring due to enterovirus while investigating the AES cases (source: newspaper clipping). They observed that the enterovirus is spreading due to faecal and oral contamination. This situation warrants a serious thought as if AES is occurring due to litchi then why all the regions with concentrated litchi pockets are not affected.

The status of AES occurrence in relation to the temperature and rainfall on the specific days on which the AES cases were reported in hospitals of Muzaffarpur, Bihar

Table 4 Major litchi fruit producing areas in India

| | |
|---|---|
| Asom | Dibrugarh, Goalpara, Sonitpur, Lakhimpur, Jorhat, Golaghat, Kamrup, Nalbari, Barpeta, Bongaigaon, Nagaon |
| Bihar | Muzaffarpur, Vaishali, East Champaran, West Champaran, Sitamarhi, Sheohar, Samastipur, Bhagalpur |
| Chhatisgarh | Korba, Raigarh, Surguja, Jashpur, Surajpur, Balrampur, koriya, Narayanpur |
| Himachal Pradesh | Kangra (Palampur, Panchrukhi, dharmshala), Sirmour (Paonta Sahib, Dhaulakuan) |
| Jammu and Kashmir | Jammu, Samba, Kathua, Udhampur, Reasi |
| Jharkhand | Ramgarh, Ranchi, Hazaribagh, Gumla |
| Madhya Pradesh | Shahdol, Sidhi, Madla, Dindori |
| Manipur | Imphal west, Bishnupur, Imphaleast, Thoubal, Churachandpur, Chandel |
| Meghalaya | East Khasi hills, Ri-bhoi, Garo Hills |
| Nagaland | Kohima, Wokha, Mokokchung, Tuensang, Zunheboto, Phek, Kiphire, Longleng, Mon, Dimapur, Peren |
| Odisha | Sambalpur, Debagarh, Sundergarh, Rayagada, Koraput |
| Punjab | Gurdaspur, Hoshiarpur, Ropar |
| Sikkim | North Sikkim(Phidang), East Sikkim (Majhitar, Bhasmey, Rorathang, Makha, Ralep, Mulukey), South Sikkim (Kitam, Pakzor, Chalamthamthamg, Kichudumra), West Sikkim, (Sagbari, Kamling) |
| Tamil Nadu | Tiruvarur, Vellore, Vilupuram |
| Uttar Pradesh | Saharanpur, Muzaffarnagar, Kushinagar |
| Uttarakhand | Nainital, Udham Singh Nagar, Haridwar, Dehradun, Almora |
| West Bengal | Malda, Murshidabad, 24 Paraganas (North and South), Uttar Dinajpore, Cooch Behar |

*Source:* Indian Horticulture Database 2014

Table 5 Representation of the different districts of Bihar where the litchi fruit is grownand places from where AES occurrence has been reported

| Districts of Bihar | Presence of litchi orchards | AES occurrence |
|---|---|---|
| Muzaffarpur | ✓ | + |
| Vaishali | ✓ | + |
| Sitamarhi | ✓ | + |
| West Champaran | ✓ | + |
| East Champaran | ✓ | + |
| Katihar | ✓ | - |
| Samastipur | ✓ | - |
| Purnea | ✓ | - |
| Siwan | ✓ | - |
| Gopalganj | ✓ | - |
| Saran | ✓ | - |
| Sheohar | ✓ | + |
| Darbhanga | ✓ | - |
| Madhubani | ✓ | - |
| Bhagalpur (Naugachia) | ✓ | - |
| Begusarai | ✓ | - |
| Saharsa | ✓ | - |
| Araria | ✓ | - |
| Kishanganj | ✓ | - |
| Khagariya | ✓ | - |
| Munger | ✓ | - |
| Jamui | ✓ | - |
| Madhepur | ✓ | - |
| Supaul | ✓ | - |
| Sheikhpura | ✓ | - |
| Lakhisarai | ✓ | - |
| Banka | ✓ | - |
| Motihari | ✓ | - |

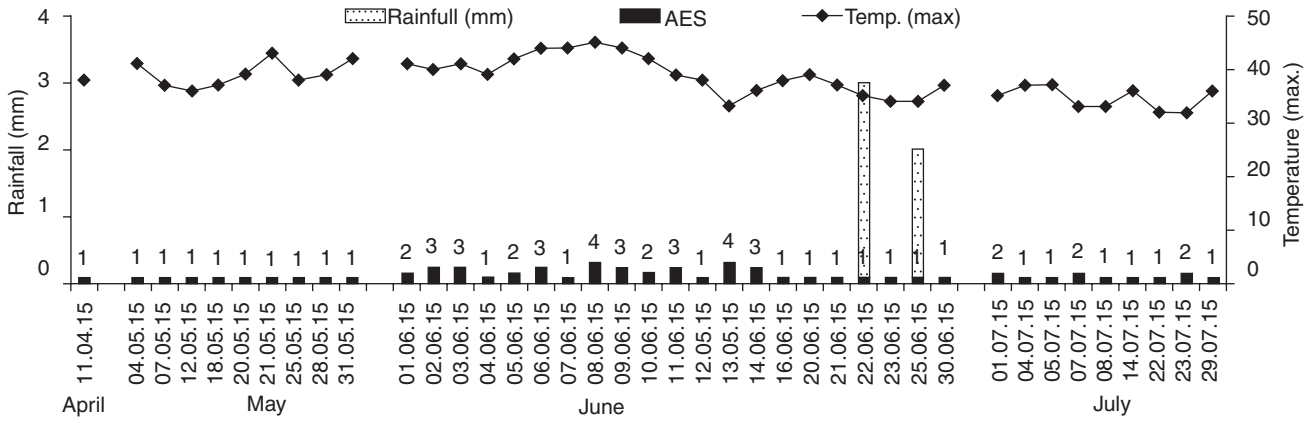


Fig 2 The status of AES occurrence in Muzaffarpur district of Bihar (India) in relation to the temperature (maximum in °C), rainfall (mm) on the particular dates of the year 2015 on which the AES cases were reported in hospitals. Source: Integrated Disease Surveillance Programme, NCDC, DGHS, MoHFW, GoI report and weather data from (http://www.accuweather.com/en/in/muzaffarpur/187232/june-weather/187232?monyr=6/1/2015&view=table)

in 2015 is presented in Fig 2. It is clearly revealed from the Fig 2 that the AES cases in Muzaffarpur were mostly reported during the hot season of May, June and July, with the exception of only two days experiencing rainfall. It has been reported earlier that the disease declines with the onset of rains and the consequent lowering of temperature. A single AES case was reported in April at Muzaffarpur during 2015.In addition, the cases of AES were reported even up till the end of July in 2015 when the fruits were no longer available (Integrated Disease Surveillance Programme, NCDC, DGHS, MoHFW, GoI report). Litchi harvesting is customarily completed by the end of June. The litchi fruits are available only for a small window of time during May and June and the occurrence of AES till July end points towards different causal agent or factors.

Interestingly, a report in a leading Hindi daily newspaper *PrabhatKhabar* referred to an abnormal increase in blood glucose levels among the children affected with AES in Muzaffarpur in 2015. This is a very vital lead and it directly counters the basic concept put forward that AES is occurring due to hypoglycaemia, caused by the α-methyl enecyclopropylglycine present in seeds of litchi fruits. The reduction in glucose levels and the inability of cells to regenerate glucose through neoglucogenesis results in hypoglycaemia (John and Das 2014). If AES is indeed occurring due to hypoglycaemia caused by litchis, no explanation is conceivable for the abnormally high blood sugar levels in the patients observed in this year. On the other hand, it has also been noted that the hypoglycaemia alone may not be able to explain encephalopathy, which usually persists in spite of infusion of glucose (John and Das 2014). It is now imperative that a fresh start should be made to look for the causes of AES by the medical fraternity.

The α-methylenecyclopropylglycine (α-MCPG) content in litchi fruit has not been analysed in the different parts of fruit such as peel, pulp, seed or at different positions of aril so far. The systematic quantitative assessment of hypoglycin in litchis at different stages of maturity, from different orchards, different states and fruits being sold in market has not been done. Thus, till the detailed profile of α-MCPG in fruit is obtained and its conformity as a causal agent of AES by its metabolites in patients is established, litchi fruit should not be singled out as a cause of AES.

The confirmation of association concerning the litchi fruit and AES can be demonstrated only if an epidemiological association between exposure to the α-MCPG containing fruit and illness is proved. The biomarkers of abnormal accumulation of fatty acids can endorse the relation. Further, α-MCPG metabolites must be obtained in the urine samples of the patients in addition to the presence of hypoglycin or α-MCPG in the litchi fruits in the affected areas. These are some serious concerns which must be addressed before validating the relation between litchi fruit consumption and AES.

Nonetheless, the precautions which can be taken presently for reducing the fatalities due to AES include many factors. It should be ensured that adequate nutritional status is maintained in young children so as to maintain normal level of glucose. Only completely ripened fruits of litchi should be consumed. The seeds of litchi fruit are inedible and are known to contain α-MCPG and thus, the children must be prevented from sucking or tasting the seeds. Fruits showing damage and rotting should be avoided for consumption. The consumption of litchi fruits should be minimized among young children in rural areas of vulnerable districts, especially by malnourished children till further investigation. Since most of the cases were reported in early morning hours, it is suggested that the public health centres of the state authorities should ensure availability of trained medical professional at night during the months of May to July in the district to ensure early detection and management of cases. The diagnostic and critical care capacity should be reinforced and strengthened at all levels of health care in the affected districts so as to ensure timely diagnosis and management of these acute encephalopathy cases. The access to rapid glucose assessment and correction by trained staff at first point of contact with health care must be provided.

The critical gaps remain unrequited till date and there are contradictory reports about AES from different sources. There is no indigenous knowledge regarding the association of AES with litchi. This fruit has been relished and hailed highly for its medicinal properties since several centuries in India, China and many other countries. It seems that unfortunately the queen of fruits has been held guilty due to the temporal and spatial occurrence of AES coincident with harvesting season of litchi. Besides, recent reports are attributing AES to an unidentified virus. This gives a strong reason to believe that AES is in all possibility not related to the consumption of litchi fruit. Therefore, in depth research are required to know and understand the real cause of AES and its remedy. The concentration of α-MCPG in different parts of litchi fruit, at different stages of growth and development in various cultivars, its possible beneficial uses and magnitude of doses with hypoglycaemic activity needs to be investigated. It is absolutely necessary to absolve this highly nutritious fruit from this accusation by conducting systematic research work, if it is being linked just for the overlapping of harvesting season. The litchi farmers, traders and consumers are all suffering huge losses due to this linking and any such association should not find place without acute evidence.

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