Seizure (2005) 14, 521–525

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

CASE REPORT

Status epilepticus induced by star fruit intoxication in patients with chronic renal disease

Meng-Han Tsai [a], Wen-Neng Chang [a], Chun-Chung Lui [b], Kun-Jung Chung [c], Kuo-Tai Hsu [d], Chi-Ren Huang [a], Cheng-Hsien Lu [a], Yao-Chung Chuang [a,*]

[a] *Department of Neurology, Chang Gung Memorial Hospital-Kaohsiung, 123 Ta Pei Road, Niao Sung Hsiang, Kaohsiung Hsien 83342, Taiwan*
[b] *Department of Diagnostic Radiology, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung, Taiwan*
[c] *Emergency Department, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung, Taiwan*
[d] *Department of Nephrology, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung, Taiwan*

Received 8 April 2005

KEYWORDS
Star fruit;
Status epilepticus;
Neurotoxicity;
Chronic renal disease

Summary Star fruit has been reported as containing neurotoxins that often cause severe neurological complications in patients with chronic renal disease. We report two patients with chronic renal failure at a pre-dialyzed stage who developed refractory status epilepticus after ingestion of star fruit. In addition, we review 51 cases in the literature. Among 53 patients, 16 patients presented with epileptic seizures (30%). The mortality rate was as high as 75% in patients with seizures. On the other hand, in patients without seizures, the mortality rate was only 0.03%. There is a poor correlation with the degree of underling renal function and mortality due to intoxication. We propose that epileptic seizure is significantly associated with poor prognosis, and that status epilepticus is an unpredictable and potentially fatal complication in star fruit intoxication. We advise consultant neurologists that star fruit intoxication must be considered when patients with chronic renal disease present with seizures or other unexplained neurological or psychiatric symptoms. Since no effective treatment has been established, star fruit consumption should be avoided in patients with chronic renal disease, especially in the elderly.

Introduction

Star fruit (*Averrhoa carambola*), which originated in Southeast Asia in prehistoric times, has been cultivated in many tropical and warm subtropical areas including Taiwan, Brazil, Thailand, Malaysia, Indonesia, India and Southern China. This fruit was introduced into the American tropics 150 years ago. Becoming increasingly popular in Western markets, Taiwanese and Brazilian star fruits are also available in many European countries and Canada. In Taiwan, this fruit is usually consumed fresh or as pickled juice. Star fruit is also recommended as a diuretic or as an expectorant and cough suppressant. However, outbreaks of star fruit intoxication have been reported in patients with chronic renal

* Corresponding author. Tel.: +886 7 7317123; fax: +886 7 7318762.
E-mail address: ycchuang@ms87.url.com.tw (Y.-C. Chuang).

1059-1311/$ – see front matter
doi:10.1016/j.seizure.2005.08.004

disease.[1–7] Characteristically, these patients present with variable neurological symptoms that have been suggestive of the neurotoxic effects of star fruit.[2,3,5,6]

The most common symptoms in star fruit intoxication include persistent and intractable hiccups, vomiting, variable degrees of disturbed consciousness, psychiatric symptoms, decreased muscle power, paresthesia, paresis, insomnia, epileptic seizures and death.[1,3,4] The mortality rate after star fruit intoxication ranges as high as 20–40%.[1,3,4] According to a large series of star fruit intoxication reported from Taiwan,[1] conscious disturbance is suggested as being associated with poor prognosis. Nevertheless, the role of epileptic seizures in star fruit intoxication is infrequently mentioned in the literature, particularly regarding neurologic issues.

Herein, we report two patients with chronic renal failure at a pre-dialyzed stage who developed refractory status epilepticus after ingestion of star fruit. In addition, we review reported cases of star fruit intoxication in the literature. This study aims to elucidate the relationship of seizures and the neurotoxicity of star fruit and to ascertain whether the high mortality rate in such patients is associated with the occurrence of seizures.

Methods

Two patients with chronic renal disease who had acute neurological complications and status epilepticus after consumption of star fruit were reported. A Medline research was conducted to identify published papers regarding star fruit intoxication between 1967 and February 2005. In addition, other relevant articles that had been published in Taiwanese journals were searched through a prominent reference database in Taiwan, ''Index to Chinese Periodical Literature''. Our attention focused on the epileptic seizures occurring during the course of star fruit intoxication.

Results

Patient 1

An 84-year-old female had been diagnosed with chronic renal insufficiency, but hemodialysis was not clinically required yet. She had nausea, incoherent speech, echolalia and bizarre behavior after consuming three fresh star fruits over three days. Thus, the patient was admitted to our hospital. On initial examination, her blood pressure was 175/103 mmHg, and her body temperature was 36.4 °C. The initial laboratory investigation revealed that glucose was 9.1 mmol/L, blood urea nitrogen (BUN) was 18.56 mmol/L, creatinine (Cr) was 671.84 μmol/L, sodium was 143 mmol/L, potassium was 5.4 mmol/L, ammonia was 36.98 μmol/L, and white blood cell count was 8.6×10^9/L. The brain computed tomography scans showed negative findings, and the cerebrospinal fluid (CSF) study revealed normal results. There was no history of alcoholic or drug addition, other systemic diseases, psychiatric disorders or use of medication.

On the secondary day of admission, she later experienced conscious disturbance, rapidly progressing into a coma. Moreover, epileptic seizures with focal motor onset developed, which evolved into status epilepticus. The seizures began from the left side and were initially clonic in nature, later becoming secondary generalized tonic–clonic seizures. She received intravenous phenytoin, phenobarbital, and valproic acid treatment, but epilepsia partialis continua over the left part of the face and shoulder still persisted for three days. The epilepsia partialis continua was finally controlled by propofol use. Although under propofol therapy, an electroencephalogram (EEG) showed bilateral periodic lateralized epileptiform discharges. Brain magnetic resonance imaging (MRI) revealed regional hyperintensities over the bilateral parietoocciptital gray matter with right-side predominance on T2-weighted images and diffusion-weighted images (Fig. 1). Despite performing hemodialysis, the patient died on day 23.

Patient 2

A 74-year-old male with chronic renal insufficiency presented with persistent hiccups and vomiting after ingestion of two fresh star fruits. On day 3,

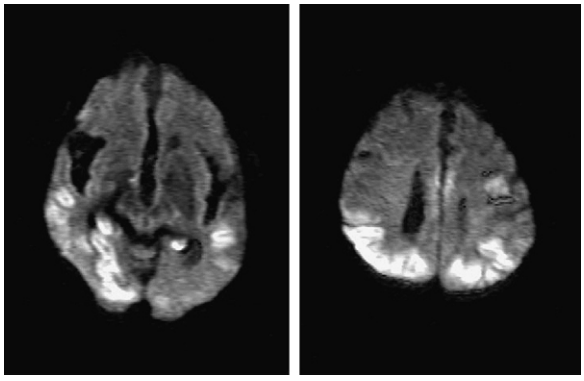

Figure 1 Axial view of diffusion weighted image (10000/112/1; b = 1000 s/mm^2) shows restrictive diffusion at the bilateral parietooccipital cortex with right-side predominance in Patient 1.

Table 1 Clinical features of 16 patients with epileptic seizures induced by star fruit intoxication.

Patient (reference)	Age/sex	Renal condition	Symptoms[a]	Amount of ingestion	Cr (μmol/L)	Therapy	Outcome
1	84/F	Pre-dialysis	1, 2, 3, 5	3 pieces in 3 days	671.84	H/D, AED, propofol	Death
2	74/M	Pre-dialysis	1, 2, 4, 5	2 pieces	415.48	H/D, AED	Death
3[3]	—	H/D	1, 2, 5	4 pieces	—	Supportive	Death
4[3]	—	H/D	1, 2, 4	300 ml of juice	—	Supportive	Death
5[3]	57/M	CAPD	1, 2, 3, 4, 5	2 pieces	539	CAPD	Death
6[3]	—	H/D	1, 2, 3, 4, 5	—	—	H/D, CVVHD	Alive
7[3]	—	IPD	1, 2, 4, 5	500 ml of juice	—	IPD, CAVHAD	Death
8[3]	—	CAPD	1, 2, 4, 5	3 pieces	—	IPD	Death
9[3]	55/F	CAPD	1, 2, 3, 4, 5	1 piece	601.12	CAPD, H/D	Death
10[8]	61/M	CAPD	1, 2, 4, 5, 7	6 pieces in 1 week	—	H/D	Death
11[7]	64/F	Pre-dialysis	1, 2, 3, 4, 5	2 pieces in 1 day	804.44	H/D, AED, plasma exchange	Death
12[9]	72/M	H/D	1, 2, 4, 5, 6	1/2 piece	627.64	H/D, AED	Alive
13[5]	71/M	Pre-dialysis	1, 2, 4	2—3 pieces in 2 weeks	450.84	H/D, AED, propofol	Death
14[5]	45/F	Pre-dialysis	1, 3, 4, 5	1—2 pieces in 5 days	866.32	H/D, AED, plasma exchange	Death
15[4]	52/F	CAPD	1, 4	—	—	Supportive	Alive
16[2]	40/M	Pre-dialysis	1, 2, 4, 5	5 pieces in 2 days	1812.2	H/D, AEDs	Alive

M: male; F: female; (—) not available; H/D: hemodialysis; CAPD: continuous ambulatory peritoneal dialysis; IPD: intermittent peritoneal dialysis; CVVHD: continuous venovenous hemodialysis; CAVHAD: continuous arteriovenous hemodialysis; AED: antiepileptic drugs.

[a] Symptoms: 1, epileptic seizure; 2, conscious disturbance; 3, agitation; 4, hiccup; 5, vomiting; 6, paresis or paresthesia; 7, headache; 8, insomnia.

he presented with mental confusion, disorientation and agitation. He was later brought into our emergency room. Initial laboratory data showed that glucose was 5.83 mmol/L, BUN was 18.2 mmol/L, Cr was 415.48 μmol/L, sodium was 133 mmol/L, potassium was 5.1 mmol/L and ammonia was 26.42 μmol/L. There was no fever or infectious signs, and the white blood cell count was slightly elevated to 12.2×10^9/L. The CSF study revealed negative results. Brain MRI revealed old left cerebellar infarction and age matched brain atrophy.

After admission, the patient's consciousness progressively deteriorated, and hiccups and vomiting persisted. Moreover, clonic seizures and facial twitching developed, evolving to status epilepticus. The status epilepticus was refractory to phenytoin and valproic acid therapy. Although emergency hemodialysis was performed, he died on day 7.

Data analysis

A total of 53 patients were included in this study. There were 16 patients who had seizures after star fruit intoxication and 37 patients without seizures occurring during intoxication. Clinical features of the 16 patients with seizures are summarized in Table 1.

The patients were aged between 39 and 84 years. All of the patients had variable degrees of chronic renal disease. In the patients with seizures, 10 patients (62%) had end-stage renal disease on regular dialysis and 6 (38%) were in a pre-dialyzed condition. On the other hand, in the patients without seizures, 27 (73%) patients had received regular dialysis and 10 (27%) were in a pre-dialyzed condition. Among the 16 patients with seizures, 15 patients[2–5,7,8] had convulsive seizures and one (Patient 12)[9] had non-convulsive status epilepticus. The overall mortality rate was 24.5%. However, the mortality rate among the 16 patients with seizures was 75%. On the other hand, in patients without seizures, only one patient died, and the mortality rate was 0.03%.

Discussion

Patients with chronic renal disease are vulnerable to developing intoxication through drugs or toxins, and star fruit is probably the only natural fruit that is

associated with neurotoxicity in such patients with renal insufficiency.[10] The first report of star fruit neurotoxicity appeared in 1980,[11] with star fruit extract injected intraperitoneally into normal mice, resulting in convulsions. Moreover, intracerebroventricular injection of the fruit extract in rats or mice induces immediate and persistent tonic–clonic convulsions.[3] It has been postulated that an excitatory neurotoxin of an unknown nature exists in star fruit, which could be responsible for the neurological complications in patients with chronic renal disease.[3]

From our observation, we found that seizures present in 30% of patients with star fruit intoxication, and most patients have convulsive[2–5,7,8] or non-convulsive[9] status epilepticus. The mortality rate of patients with seizures occurring after star fruit intoxication is significantly higher than of patients without seizures. Obviously, this result implies that epileptic seizures are a poor prognostic factor in star fruit intoxication.

There is a poor correlation with the degree of underlying renal function and the mortality of intoxication, while more severe symptoms may develop in those patients with pre-dialyzed condition as opposed to those with end-stage renal disease. In this study, we found epileptic seizures progressing to status epilepticus and death in patients with various renal function status. It is clinically important to know that status epilepticus may be a fatal neurological complication following star fruit intoxication, not only in end stage renal disease but also in patients with pre-dialyzed renal disease.

Seizure is a common neurological complication in patients with renal failure, which may be caused by uremic encephalopathy, disequilibrium dialysis syndrome, hypertensive encephalopathy, fluid and electrolyte disturbances, drug intoxication, intracranial hemorrhage, and central nervous system infections.[10] However, our patients were not in a serious uremic stage, and they had not previously undergone hemodialysis before. The status epilepticus occurred immediately after ingestion of star fruit, suggesting the convulsant effect of neurotoxin in star fruit. Based on the results of brain MRI scans, CSF studies, clinical information and biochemistry data, other medical causes for the seizure could be excluded in our patients.

Although star fruit has enriched potassium content, hyperkalemia has not been suggested as causing death in reported cases.[1,3] Our results were consistent with this notion. Our two patients also presented with no severe hyperkalemia. Furthermore, we found that the amount of ingestion was not related to the symptoms or mortality. Even a small amount of star fruit can cause severe neurological complications and death. The degree of severity of intoxication is variable. We supposed that ethnic and genetic factors might participate in the clinical presentations within the neurotoxicity of star fruit.

Some researchers suspect that there are different toxins in different star fruit subspecies, as well as a powerful neurotoxin that can accumulate in blood and cross the blood–brain barrier in patients with chronic renal disease, eventually causing refractory status epilepticus.[3,7] Single voxel proton and ^{31}phosphorous MR spectroscopic studies revealed elevation of lactate, elevation of inorganic phosphate, and reduced phosphocreatine and nucleoside triphosphates in the cerebral cortex in an intoxicated patient.[8] The metabolic changes indicated the neurotoxin could interfere with oxidative phosphorylation and cause energy deprivation. Although the exact nature of star fruit neurotoxin remains obscure, oxalate, being abundant in star fruit, has been proposed as a possible candidate for acute nephropathy and neurotoxicity.[12] More recently, a neurotoxic fraction was obtained from star fruit, which is different from oxalic acid in chemical characterization.[13] The mechanism of convulsant activity is believed to specifically act on GABAergic and glutamatergic transmission systems.[13] The definite neurotoxin responsible for star fruit intoxication has not yet been identified. Further studies are needed to elucidate the exact molecule that causes the neurotoxicity.

The unknown neurotoxin in star fruit has been suggested as dialyzable, and intensified dialysis should be tried as a means of therapy in intoxicated patients.[1,3] In our two patients, the status epilepticus was characterized by focal convulsion and myoclonus, which is refractory to intravenous administration of phenytoin, phenobarbital and valproic acid. Even though convulsions could be controlled by propofol therapy in Patient 1, EEG studies still showed epileptiform discharges, and a brain MRI showed regional hyperintensities over the gray matter on T2-weighted images and diffusion-weighted images, suggesting this patient was still in the ictal period. Consistent with other reported cases with seizures,[2,5–7] treatment with antiepileptic drugs and hemodialysis were unsuccessful. Plasma exchange has been suggested as an effective treatment of status epilepticus caused by star fruit intoxication.[7] This suggestion requires further confirmation, particularly in the timing, frequency and dosage of plasma exchange. Although status epilepticus in star fruit intoxication is associated with high mortality, further studies are necessary in the future to develop a more effective antiepileptic drug regimen and novel

neuroprotective strategies to reduce brain damage caused by neurotoxin-induced energy deprivation.

In conclusion, neurological and psychiatric symptoms are common presentations, but are often ignored in star fruit intoxication. Epileptic seizure is significantly associated with poor prognosis, and status epilepticus is an unpredictable and potentially fatal complication of intoxication. We warn consultant neurologists that star fruit intoxication must be considered when patients with chronic renal disease present with seizures or other unexplained neurological or psychiatric symptoms. Because no effective treatment has been established, star fruit consumption should be avoided in patients with chronic renal disease, especially in the elderly.

References

1. Chang JM, Hwang SJ, Kuo HT, Tsai JC, Guh JY, Chen HC, et al. Fatal outcome after ingestion of star fruit (*Averrhoa carambola*) in uremic patients. *Am J Kidney Dis* 2000;**35**:189—93.
2. Ho MP, Pai MF, Fan CD, Chang KS. Neurological manifestations induced by star fruit (*Averrhoa carambola*) intoxication in patients with chronic renal failure: two cases report. *J Taiwan Emerg Med* 2001;**3**:31—6.
3. Neto MM, da Costa JA, Garcia-Cairasco N, Netto JC, Nakagawa B, Dantas M. Intoxication by star fruit (*Averrhoa carambola*) in 32 uraemic patients: treatment and outcome. *Nephrol Dial Transplant* 2003;**18**:120—5.
4. Tse KC, Yip PS, Lam MF, Choy BY, Li FK, Lui SL, et al. Star fruit intoxication in uraemic patients: case series and review of the literature. *Intern Med J* 2003;**33**:314—6.
5. Wang JL, Cheng CH, Wu MJ, Chen CH, Shu KH. Status epilepticus in two patients with chronic renal failure after ingestion of star fruit. *Kidney Dial (Taiwan)* 2000;**12**:166—9.
6. Wu CC, Denq JC, Tsai WS, Lin SH. Star fruit-induced neurotoxicity in two patients with chronic renal failure. *J Med Sci (Taiwan)* 2002;**22**:75—8.
7. Yap HJ, Chen YC, Fang JT, Huang CC. Star fruit: a neglected but serious fruit intoxication in chronic renal failure. *Dial Transplant* 2002;**31**:564—7.
8. Chan YL, Ng HK, Leung CB, Yeung DKW. ^{31}Phosphorous and single voxel proton MR spectroscopy and diffusion-weighted imaging in a case of star fruit poisoning. *AJNR Am J Neuroradiol* 2002;**23**:1557—60.
9. Chang CH, Yeh JH. Non-convulsive status epilepticus and consciousness disturbance after star fruit (*Averrhoa carambola*) ingestion in a dialysis patient. *Nephrology (Carlton)* 2004;**9**:362—5.
10. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. *Clin Neurol Neurosurg* 2004;**107**:1—16.
11. Muir CK, Lam CK. Depressant action of averrhoa carambola. *Med J Malaysia* 1980;**34**:279—80.
12. Chen CL, Fang HC, Chou KJ, Wang JS, Chung HM. Acute oxalate nephropathy after ingestion of star fruit. *Am J Kidney Dis* 2001;**37**:418—22.
13. Carolino ROG, Beleboni RO, Pizzo AB, Vecchio FD, Garcia-Cairasco N, Moyses-Neto M, et al. Convulsant activity and neurochemical alterations induced by a fraction obtained from fruit *Averrhoa carambola* (Oxalidaceae: Geraniales). *Neurochem Int* 2005;**46**:523—31.