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Ciguatera pois g: a global issue with common management p ems

J.Y.S. TING[1]* and A.F.T. BROWN[2]

Department of Emergency Medicine, [1]Princess Alexandra Hospital, Woolloongabba 4102, Brisbane, and [2]Royal Brisbane Hospital, Herston 4006, Brisbane, Queensland, Australia

Ciguatera poisoning, a toxinological syndrome comprising an enigmatic mixture of gastrointestinal, neurocutaneous and constitutional symptoms, is a common food-borne illness related to contaminated fish consumption. As many as 50 000 cases worldwide are reported annually, and the condition is endemic in tropical and subtropical regions of the Pacific Basin, Indian Ocean and Caribbean. Isolated outbreaks occur sporadically but with increasing frequency in temperate areas such as Europe and North America. Increase in travel between temperate countries and endemic areas and importation of susceptible fish has led to its encroachment into regions of the world where ciguatera has previously been rarely encountered. In the developed world, ciguatera poses a public health threat due to delayed or missed diagnosis. Ciguatera is frequently encountered in Australia. Sporadic cases are often misdiagnosed or not medically attended to, leading to persistent or recurrent debilitating symptoms lasting months to years. Without treatment, distinctive neurologic symptoms persist, occasionally being mistaken for multiple sclerosis. Constitutional symptoms may be misdiagnosed as chronic fatigue syndrome. A common source outbreak is easier to recognize and therefore notify to public health organizations. We present a case series of four adult tourists who developed ciguatera poisoning after consuming contaminated fish in Vanuatu. All responded well to intravenous mannitol. This is in contrast to a fifth patient who developed symptoms suggestive of ciguatoxicity in the same week as the index cases but actually had staphylococcal endocarditis with bacteraemia. In addition to a lack of response to mannitol, clinical and laboratory indices of sepsis were present in this patient. Apart from ciguatera, acute gastroenteritis followed by neurological symptoms may be due to paralytic or neurotoxic shellfish poisoning, scombroid and pufferfish toxicity, botulism, enterovirus 71, toxidromes and bacteraemia. Clinical aspects of ciguatera toxicity, its pathophysiology, diagnostic difficulties and epidemiology are discussed.

Keywords: ciguatera poisoning; toxinological; food-borne illness; public health; common source outbreak

INTRODUCTION

Ciguatera poisoning, a fish-borne toxinological syndrome comprising a mixture of gastrointestinal, neurocutaneous and constitutional symptoms, is encountered frequently in the tropics and increasingly in temperate regions of the world.[1–6] The global distribution and risk stratification for ciguatera poisoning is seen in Fig. 1. It is a major obstacle to the safe consumption of local and imported fish[1] and is a significant public health issue.[7] Although many cases have been recorded in Australia,[8] scant public health data exist regarding this condition due to under-detection of sporadic cases and non-mandatory notification.[1] Even amongst the medical community, ciguatera remains under-recognized.[9] This lack of awareness leads to a delay in the diagnosis, notification and treatment of ciguatera poisoning.[10] Common source outbreaks are easier to recognize, with four cases of ciguatera poisoning presenting to our emergency department in 1996. All had become symptomatic within 12 hours of eating contaminated coral trout caught off Efate Island at a resort in Vanuatu. A fifth subject with staphyloccocal bacteraemia was misdiagnosed with ciguatoxicity in the same week. Although ciguatoxicity has characteristic features, being alert to the possibility of other diagnoses even in the presence of a prior history of ciguatera poisoning is emphasized.

CLINICAL RECORD

Case 1

A 33-year-old man presented with peripheral para-

*To whom correspondence should be addressed

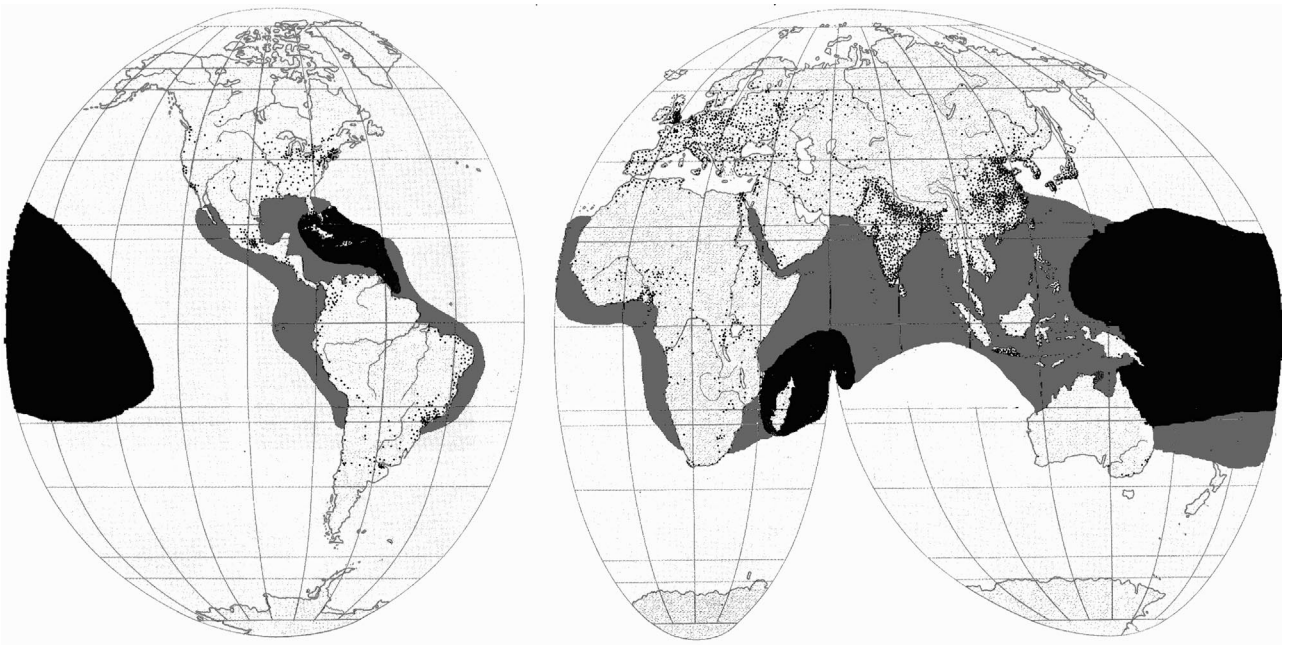

Fig. 1. Global distribution of ciguatera, with areas of high-to-moderate risk (heavy shading) and low or uncertain risk (lighter shading) identified. Reprinted from Lehane, L. and Lewis, R.J. (2000) Ciguatera: recent advances but the risk remains. *Int. J. Food Micro.,* **61**, 91–125, with permission from Elsevier Science.

doxical burning cold temperature sensitivity, circumoral and limb dysaesthesiae, myalgia, arthralgia, lethargy and pruritus. The first symptom where cutaneous temperature perception is reversed is peculiar to ciguatera poisoning. Four days previously he had eaten freshly caught coral trout during a resort holiday in Vanuatu. Within hours, he developed nausea, vomiting and diarrhoea followed by lower abdominal, testicular and penile pain. He described excruciating discomfort during penile erection and after ejaculation. He was fit and well apart from severe visual impairment due to hereditary retinitis pigmentosa.

The subject looked well and was apyrexial with normal vital observations and mental state. Mild lower abdominal and genital discomfort was found on palpation without peritonism. Neurological examination was normal apart from a left afferent pupillary defect and bilateral retinal pigmentation of retinitis pigmentosa.

All laboratory investigations were normal. A clinical diagnosis of ciguatera poisoning was made and two intravenous doses of 20% mannitol 0.5 g/kg (2.5 ml/kg) were infused over 30 minutes each, leading to the rapid resolution of symptoms. We were told that the patient's previously well female partner, who had not recently eaten any fish, experienced nausea, circumoral dysaesthesia, arthralgia, lethargy and pruritus within 24 hours of having unprotected vaginal intercourse with him. She made an uneventful recovery within a week without treatment.

Cases 2, 3 and 4

Three males aged 40, 43 and 48 years had similar symptoms to those of the index case within 12 hours of eating the same fish. In addition, one subject had intense penile pain following defecation and another penile pain including on erection. All had been previously fit and were well hydrated and without abnormal physical or laboratory findings. Cases 2 and 4 responded well to two doses of 0.5 g/kg of 20% mannitol after presenting 6 and 8 days respectively after exposure. Eight days after exposure, Case 3 experienced symptomatic improvement with a single dose of mannitol although symptoms recurred a week later. No subject had symptoms at 1-month follow-up.

Case 5

A 63-year-old man presented independently in the same week as the previous cases, declaring that his ciguatera poisoning was back. He had eaten frozen fish bought at a supermarket in Brisbane. He then developed myalgias, abdominal pain, nausea, vomiting, diarrhoea, paraesthesiae, headache and fevers. He believed these symptoms to be identical to those experienced on two separate occasions, 6 and 20 years previously, when he had been diagnosed with ciguatera poisoning.

He looked unwell with a temperature of 38°C, had moderate dehydration with poor skin turgor, pulse 100/minute, blood pressure 100/60 mmHg supine with a small postural drop on sitting up. No clinical

features of respiratory, genitourinary, gastrointestinal, cardiac, joint, skin or ENT infection were present. The patient was orientated to time, place and person and demonstrated no meningism or rash. An upgoing left Babinski reflex was elicited with an otherwise normal neurological examination.

On presentation, his white cell count was 6.83×10^9/l ($2.0-7.5 \times 10^9$) with moderate left shift and neutrophil vacuolation. Platelet count was 72×10^9/l ($140-400 \times 10^9$) with a haemoglobin of 13.1 g/dl (13.5–18.0). Abnormal serum electrolytes and liver function tests included creatinine 0.15 mmol/l (0.06–0.14), total bilirubin 14 μmol/l (0–20), alkaline phosphatase 36 u/l (35–140), gamma glutamyltransferase 40 u/l (0–50), alanine aminotransferase 147 u/l (0–35), aspartate transaminase 181 u/l (0–35) and creatine kinase 850 u/l (30–210). Microscopy of mid-stream urine revealed leukocytes 10×10^6/l ($< 10 \times 10^6$), erythrocytes 40×10^6/l ($< 10 \times 10^6$) and epithelial cells $< 10 \times 10^6$/l ($< 10 \times 10^6$). Culture was not performed due to the absence of bacteria on microscopy.

The patient and his wife were convinced of the diagnosis of ciguatera. Mannitol had been used with success 6 years previously, and following intravenous rehydration with 1 litre of Hartmann's solution, 0.5 g/kg of 20% mannitol was administered without symptomatic improvement.

Persistent fever and headache, a rising white cell count with worsening thrombocytopenia and liver function tests alerted us to the possibility of sepsis. A chest X-ray was normal. Three sets of blood cultures were obtained. A computed tomography (CT) head scan showed a right parietal lobe hypodense lesion without mass effect suggestive of an intracranial collection. Cerebrospinal fluid (CSF) analysis showed 200×10^6/l leukocytes ($< 5 \times 10^6$) with 96% neutrophils, 5×10^6/l erythrocytes ($< 5 \times 10^6$), no bacteria on Gram stain, glucose 4.7 mmol/l (2.5–5.0) and protein 870 mg/l (150–600). Further testing for encapsulated yeast-like cells, cryptococcal antigen and acid-fast bacilli was negative. There was no growth on CSF culture after 14 days.

Intravenous ceftriaxone and flucloxacillin was commenced. Blood cultures grew a pure growth of *Staphylococcus aureus* within 24 hours, and a final diagnosis of staphylococcal bacterial endocarditis of the mitral valve (vegetations seen on transoesophageal echocardiography) with septic embolic infarction of the brain was made. The patient eventually made a full recovery.

DISCUSSION

Even though symptoms of ciguatera poisoning were described by European explorers to the New World as early as the 16th century,[6] the term ciguatera is credited to F. Poey, an ichthyologist who observed the similarity between symptoms of ciguatera poisoning and an illness caused by a land mollusc or 'cigua' in 1866.[3] Captain James Cook and his crew suffered ciguatoxicity in the New Hebrides in 1776 after eating red bass.[4]

Queensland, where most ciguatera cases in Australia occur, released clinical details of 617 cases from 225 outbreaks over 23 years in 1988.[11] Major outbreaks tend to be sporadic and localized,[1,10] occurring in travellers returning from ciguatera-endemic areas or with the consumption of contaminated imported fish.[6,12,13] Although more than 400 fish species are potential vectors,[1,6] fish caught along the tropical coast of Australia such as narrow-barred mackerel (*Scomberomorus commersoni*), barracuda (*Sphyraena jello*) and coral trout (*Plectropomus* spp.) are most often implicated.[8] Large reef fish of more than 3 kilograms from 'at risk' areas are more susceptible due to the concentration of toxin up the food chain.[5,6,14] It is advisable to avoid eating such fish altogether to minimize exposure to ciguatera, or for 6 months after ciguatera poisoning to prevent a relapse.[1,5,6,14] Furthermore, sale and human consumption of the moray eel, chinaman, red bass and paddletail fishes, well recognized to be ciguatera prone, are discouraged in Australia.[7]

Ciguatoxin is a lipid-soluble, heat stable polyether toxin without colour, taste or smell produced by the dinoflagellate *Gambierdiscus toxicus* found on macroalgae in coral reefs. It is the most important of 20 toxins implicated in ciguatera poisoning.[1,15] *G. toxicus* is consumed by small herbivorous fish that are eaten by larger fish that are consumed by humans. These toxins are progressively concentrated up the food chain, being harmless to the fish host themselves.[1,6,15]

Typical features of ciguatera poisoning include acute gastroenteritis (nausea, vomiting, diarrhoea and abdominal pain) within 6–12 hours of contaminated fish ingestion. This is followed within 12–72 hours by characteristic neurocutaneous symptoms comprising circumoral and limb paraesthesia, dysaesthesia and pathognomonic paradoxical apparent temperature sensation reversal. During this stage, musculoskeletal features such as myalgia, arthralgia, cramps and weakness as well as pruritus, sweating and dental pain may be present.[1,6] Although the acute illness

lasts a mean of 8 days, neurological symptoms can last for months and even years.[5]

Symptom severity is dose-dependent, with the ingestion of the fish's head, liver or viscera causing more severe poisoning as toxins are concentrated in these tissues. Rarely, vasomotor dysregulation leading to haemodynamic instability may precede paralysis and coma. When recognized and treated early, death from circulatory or respiratory failure occurs in less than 1% of cases.[1,6,15] Symptoms worsen with alcohol consumption, and can recur with future fish exposure, even to non-ciguatoxic fish. The latter occurs at subthreshold toxin doses suggesting immunologically mediated sensitization to ciguatoxin following an initial exposure.[1,6,16]

Although intravenous mannitol is considered the most effective treatment for ciguatera poisoning, it has not been directly compared with other agents in controlled clinical trials.[15–23] Its therapeutic effect was discovered fortuitously in 1988, when two men who became unconscious from severe ciguatera poisoning responded within minutes after mannitol was administered for presumed cerebral oedema. A further 22 ciguatoxic patients had rapid relief of symptoms, including one with circulatory failure.[18] Since then, case reports and treatment series from around the world have reported success with the use of mannitol in ciguatera poisoning, particularly when given early. Five of 12 ciguatoxic adults in one series improved with a 1.0 g/kg infusion of mannitol.[17] Neurological symptoms responded well to mannitol in 14 of 16 patients in another series.[20] Because mannitol is inexpensive, widely available and relatively easy to administer, it is a suitable choice for the treatment of ciguatera poisoning in isolated areas of the world where ciguatera is endemic.[16]

An intravenous dose of 1 g/kg of 20% mannitol (5 ml/kg) given over 30 minutes is recommended.[17,18,21–23] This dosing regimen is more effective than 0.5 g/kg given over a longer period, with smaller doses or slower infusion rates implicated in treatment failures.[17,19] Mannitol administered within 48 hours completely relieved symptoms in 35 ciguatoxic patients.[21] Although mannitol is more effective when given early,[15,16,18] a response has been seen in patients who have been symptomatic for up to 8 weeks.[21] Our case series reaffirms the efficacy of intravenous mannitol in the treatment of ciguatera poisoning, even as late as 7 days after fish ingestion (in Case 4).

Repeating mannitol treatment to reduce persistent or recurrent symptoms if there is an initial favourable response has some merit.[8,15–17,19] A second 0.5 g/kg dose of mannitol was administered to three of four subjects in our series with sustained benefit, with the third subject unable to stay for a second treatment. He relapsed without an apparent precipitant such as alcohol use or further fish consumption. This observation supports the use of repeated doses of mannitol to reduce the risk of ongoing ciguatoxic symptoms.[15]

It is unclear exactly how mannitol improves symptoms of ciguatera poisoning,[15] although there are several postulates. Mannitol may inhibit the ciguatoxin-induced opening of neurone membrane sodium channels,[8,15,20] thereby reducing cellular excitability and repetitive action potential generation.[1] It neutralizes ciguatoxin[17] and establishes osmotic gradients that reduce ciguatoxin-induced perineural oedema.[16,19] Mannitol increases the dissociation of ciguatoxin from its cell membrane binding site[24] and inhibits ciguatera cytotoxicity in cell bioassays *in vitro*.[25]

Mannitol is safe to use in ciguatera poisoning, with few side-effects reported.[1,18] Correction of dehydration from vomiting and diarrhoea prior to its administration will ameliorate fluid losses from an osmotic diuresis.[17] One patient had brief postural presyncope after treatment. However, the most common complaint was discomfort at the infusion site. Due to its hyperosmolarity, 20% mannitol causes venous irritation resulting in infusion site pain and thrombophlebitis. Dilution of mannitol and intravenous lignocaine boluses does not satisfactorily relieve this pain.

Extract from leaves of *Argusia argent*, a traditional New Caledonian remedy, have been shown to be effective *in vitro*.[26] Certain local anaesthetic agents may have the ability to inhibit sodium channels that have been modified by ciguatoxin. Orally administered tocainide safely alleviated ciguatoxic symptoms in three adult males in a small open-label trial.[27] Local anaesthetic agents prevent binding of ciguatoxin molecules to their neuronal receptors but also non-selectively block normal sodium channels *in vitro* (personal communication Professor R. Lewis). Although promising, these agents have no proven efficacy in humans.[16] Non-proven therapies also include calcium gluconate, nifedipine, amitriptyline,[6,15,28] and vitamin B_{12}.[8] Symptomatic treatment includes analgesics for musculoskeletal symptoms, antihistamines for pruritus[3,15] as well as antiemetics and antidiarrhoeals.[29] Gastrointestinal charcoal decontamination remains speculative, with its use recommended in other non-infective fish and shellfish poisonings.[6]

Our cases were unusual in that three of four subjects had severe penile pain including on erection and ejaculation. This has rarely been reported. Case 1

supports the premise that ciguatoxin may be transmitted in semen during sexual intercourse, with dyspareunia in an unaffected woman following intercourse with her affected male partner having previously been reported.[30] Geller[31] *et al.* encountered an unaffected man in whom penile pain occurred after intercourse with his symptomatic female partner.

Case 5 cautions against making the diagnosis of ciguatera poisoning based on symptoms that imitate previous episodes, in the presence of markers for sepsis such as persistent fever, rising neutrophil leukocytosis and other suggestive clinical and laboratory indices. The lack of a therapeutic response to mannitol should also alert the clinician to a possible alternative diagnosis. Apart from ciguatera, acute gastroenteritis followed by neurologic symptoms may be due to paralytic or neurotoxic shellfish poisoning, scombroid and pufferfish toxicity, botulism, enterovirus 7, toxidromes and in our case bacteraemia.[6,15,32]

Ciguatera poisoning remains under-recognized despite being frequently encountered in Australia,[1,8,14,17] leading to treatment delay or omission. Symptoms may then become persistent and occasionally debilitating.[16,33] Delayed or incorrect diagnosis is partly attributable to the lack of confirmatory tests for ciguatera poisoning in humans.[1] As there is no validated diagnostic test for ciguatera poisoning in humans (personal communication Professor R. Lewis), it remains a clinical diagnosis based on the presence of early gastroenteritis after suspect fish ingestion followed by neurocutaneous and musculoskeletal symptoms. Clusters of humans affected in common source outbreaks are easier to recognize.[6,7,10,12]

The effects of intraperitoneal injection of suspect fish samples into mice was the first bioassay for ciguatoxin[34] and remains the most widely accepted measure of ciguatoxin bioactivity.[25,35] The response of domestic cats to being fed suspect fish preceded the use of the mongoose for this purpose in endemic areas.[15,34] Animal testing takes days to complete and is not useful in clinical management.

Immunologically based detection methods avoid animal welfare concerns inherent in animal testing.[25] A sheep anti-ciguatoxin IgG enzyme-linked immunoassay and more recently a monoclonal antibody membrane immunobead assay to detect contaminated fish may be used to monitor the fishing industry but has no diagnostic application in humans.[1,4,6] Furthermore, these tests demonstrate immunological cross-reactivity with other fish polyethers, giving rise to false positive results.[36]

The use of a cell bioassay that responds rapidly to the sodium channel activating action of ciguatoxin in a dose-dependent manner has been shown to correlate well with mouse bioassays.[25] Liquid chromatography and mass spectrometry was used to detect Pacific ciguatoxin-1 in the flesh of a large coral cod consumed by 20 patients who subsequently developed ciguatoxicity.[37]

Despite these advances, there is currently no marine toxinological detection facility for public health surveillance in Australia.[1,14] An Australian National Biotoxin Strategy is under development to better coordinate public health surveillance and response to ciguatera and other marine toxins (personal communication Professor R. Lewis). The adverse impact of ciguatera poisoning extends beyond health care into the fishing industry. Fisheries are of great economic importance in the Pacific Islands. Following ciguatera outbreaks, damage occurs to the fishing industry, trade and tourism. Human health suffers due to reluctance to consume fish, a primary source of dietary protein in this region. It is ironic that in some Pacific locations, 90% of fish eaten is imported and comes out of a can.[28]

CONCLUSION

Ciguatera poisoning remains a global toxinological threat for fish eaters.[1–6] Large numbers of inhabitants are afflicted seasonally with consumption of local ciguatera prone fish in endemic areas.[28] Isolated and small group common source outbreaks are frequently encountered in Australia[1,8,14,17] but less often in Europe[2] and North America.[4,5] With imported contaminated fish becoming increasingly available to consumers in non-endemic areas,[1] ciguatera poisoning will become a greater public health issue.[7] Travellers to endemic areas may develop symptoms on returning to their homes.[13] Clinicians in non-endemic areas will therefore encounter this condition more frequently. Without a test to detect the presence of ciguatoxin in humans,[1] diagnosis is made clinically by recognizing a characteristic constellation of symptoms and signs following consumption of suspect fish. These include pathognomonic neurocutaneous symptoms following acute gastroenteritis.[1,6] When correctly identified, ciguatera poisoning can be effectively treated with intravenous mannitol.[15–23] The greater likelihood that sustained symptomatic relief will occur with early treatment emphasizes the importance of making the correct diagnosis early.[15,16,18] There may be a therapeutic role for local anaesthetics[16,27] and traditional remedies such as leaves of *Argusia argent*.[26]

Apart from ciguatera, acute gastroenteritis followed by neurologic symptoms may be due to paralytic or

neurotoxic shellfish poisoning, scombroid and pufferfish toxicity, botulism, enterovirus 71, toxidromes and in our case bacteraemia.[6,15,32] Fever and other markers for sepsis, muscle weakness and features of histamine toxicity are not seen with ciguatera poisoning. As there are no confirmatory tests for ciguatera, the diagnosis is made by recognition of a characteristic mixture of gastrointestinal, neurocutaneous and constitutional symptoms after the exclusion of alternative diagnoses.

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