Review Article

Characteristic Features and Contributory Factors in Fatal Ciguatera Fish Poisoning—Implications for Prevention and Public Education

Thomas Y. K. Chan*

Division of Clinical Pharmacology and Drug and Poisons Information Bureau, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; Centre for Food and Drug Safety, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

Abstract. In this review, the main objective was to describe the characteristic features of fatal ciguatera fish poisoning and identify contributory factors, with a view to promote prevention and public education. Ciguatera-related deaths, although rare, have been reported from the Pacific, Caribbean, and Indian Ocean regions. The clinical features were generally dominated by convulsions and coma, with various focal neurological signs. Several contributory factors could be identified, including consumption of ciguatoxin (CTX)-rich fish parts (viscera and head) in larger amounts, the most ciguatoxic fish species (e.g., *Gymnothorax flavimarginatus*) and reef fish collected after storms and individuals' susceptibility. Mass ciguatera fish poisoning with mortalities also occurred when *G. flavimarginatus* and other ciguatoxic fish species were shared in gatherings and parties. The characteristic features of fatal ciguatera fish poisoning must be recognized early. The public should be repeatedly reminded to avoid eating the most ciguatoxic fish species and the CTX-rich parts of reef fish. To prevent mass poisoning in gatherings and parties, the most ciguatoxic fish species and potentially toxic fish species must be avoided. Particularly after hits by disastrous storms, it is important to monitor the toxicity of reef fish and the incidence rates of ciguatera.

INTRODUCTION

Ciguatera is caused by eating reef fish whose flesh and viscera become contaminated with ciguatoxins (CTXs).^{1,2} Toxic dinoflagellates, principally in the genus *Gambierdiscus*, produce precursor CTX, which undergo biotransformation as they pass up the food chain.³ Therefore, large predatory reef fish (e.g., moray eels, snappers, groupers, Spanish mackerels, barracudas, and humphead wrasse) are more likely to be toxic, with greater levels of the most potent forms of CTX.^{1–6} CTXs are lipid soluble and heat stable and are concentrated in the fish head, liver, intestines, roe, and other viscera.^{7,8} Large outbreaks of ciguatera and ciguatoxic fishes are mainly found in the tropical and subtropical regions of the Pacific Ocean, Indian Ocean, and Caribbean Sea, between the latitudes 35°N and 35°S.^{1,2} With increasing reef fish trade, booming international tourism, and coral reefs disruption⁸ and climate changes⁹ favoring the growth of the *Gambierdiscus* species,¹⁰ the global incidence and distribution of ciguatera are expected to increase.^{1,2} However, the public health impact of ciguatera is underestimated due to underreporting and underdiagnosis of the disease.^{8,11}

Regional variations in the incidence and manifestations of ciguatera are described in detail elsewhere.^{1,2,11} Recent reports on ciguatera incidence per 100,000 population are summarized in Table 1.^{8,12–20} In the South Pacific and Caribbean Islands, ciguatera is endemic^{14–19} and has become more common than decades ago.^{16,19} The manifestations of ciguatera can be variable depending on the types and quantities of CTX present, individuals' susceptibility, and other factors.^{1,2,5,11} Typically, gastrointestinal (e.g., nausea, vomiting, abdominal pain, and diarrhea) and cardiovascular (e.g., bradycardia and hypo-

tension) features appear within hours of toxic fish ingestion and can last for several days. Neurological features (e.g., perioral/generalized paresthesia, muscle/joint aches, fatigue, pruritus, and hot/cold temperature sensation reversal) can last for days, weeks, or months. In the Indo-Pacific Ocean regions, neurological features predominate in the acute phase, whereas in the Caribbean, gastrointestinal features are more pronounced.¹¹ In the Indian Ocean region, additional features of hallucinatory poisoning may be seen.²¹ In the most severe cases of ciguatera, life-threatening complications (e.g., severe bradycardia/hypotension, coma, respiratory failure, and convulsions) can occur.^{1,2,5,22} Deaths should be uncommon in ciguatera since reef fish (apart from moray eels) rarely accumulate sufficient quantities of CTX to be lethal in a single meal.²³ Some fatalities in the past might be avoidable if there had been access to better clinical management practices.^{1,2,23}

In this review, the main objective was to describe the characteristic features of fatal ciguatera fish poisoning and identify contributory factors, with a view to promote prevention and public education.

LITERATURE SEARCH

To identify journal articles and other relevant publications, a search of Medline (1946 to November 30, 2015), Embase (1947 to November 30, 2015), China Journal Jet (1994 to November 2015), and Google Scholar was performed, using ciguatera and ciguatoxins as the keywords. Additional reports were identified from the literature database of Center for Food and Drug Safety.^{4–6,12} All relevant reports were reviewed and the characteristic features and contributory factors in ciguatera-related deaths were determined.

REPORTS OF CIGUATERA-RELATED DEATHS

All published reports of ciguatera-related deaths identified in the literature search (1946 to November 30, 2015) are

*Address correspondence to Thomas Y. K. Chan, Division of Clinical Pharmacology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong-Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China. E-mail: tykchan@cuhk.edu.hk.

TABLE 1
Recent reports of ciguatera incidence*

Country	Years	Incidence per 100,000 people
Hong Kong	1989–2008 ¹²	1.6
Japan (Okinawa)	1997–2006 ^{8,13}	0.77
Cook Islands (Rarotonga)	1993–2006 ¹⁴	1,760
French Polynesia (Raivavae Island)	2007–2008 ¹⁵	1,400
South Pacific Islands†	1998–2008 ¹⁶	194.6 (104.3 in 1973–1983)
Montserrat	1996–2006 ¹⁷	586
U.S. Virgins Islands	2007–2011 ¹⁸	1,200
Caribbean Islands (18 countries)‡	2000–2010 ¹⁹	45.2 (34.2 in 1980–1990)
United States (Florida)	2000–2011 ²⁰	5.6

*Papers reporting prevalence figures and incidence rates expressed as person-years were excluded as direct comparison with countries listed here was not possible.

†Including Cook Islands, French Polynesia, and 15 other Pacific Island countries and territories.

‡Including Montserrat and 17 other Caribbean Epidemiology Center countries.

summarized in Table 2, according to their regions of origins, i.e., Pacific Ocean,^{24–36} Pacific/Caribbean,³⁷ Caribbean,^{38–42} and Indian Ocean.⁴³ Two other reports of deaths thought to be related to the ingestion of a shark (*Carcharhinus amboinensis*) in Madagascar^{44,45} and a fresh fish in India⁴⁶ were excluded because the clinical features^{44,46} and autopsy findings⁴⁴ were not typical of ciguatera. Moreover, the toxins responsible for the mass poisoning in Madagascar were carchatoxin-A and carchatoxin-B, not CTX.⁴⁵

In Australia, the only two fatal cases of ciguatera occurred in Queensland, after the consumption of a narrow-barred Spanish mackerel (flesh)²⁴ or sawtooth barracuda (head and viscera).²⁵ In 1965, a 25-year-old healthy female developed convulsions and coma after fish ingestion and died 10.3 hours later.²⁴ In 2001, a 87-year-old healthy male died of a heart attack and multiorgan failure 6 days after fish consumption.²⁵ If equal amounts had been eaten by him and his two family members, a combination of ~3.5 mg of P-CTX-1, ~5 mg P-CTX-2, and ~1 mg of P-CTX-3 was apparently lethal to this elderly man.²⁵

In Fuji, one person was said to have died of ciguatera after several days of hospitalization during 1975–1983.²⁶

In French Polynesia and other South Pacific island groups, three fatal cases of ciguatera occurred during 1964–1997, after the ingestion of a triggerfish (liver), snapper, or reef fish.^{27,28} A 54-year-old man developed coma and died 5 days after fish ingestion. A 42-year-old man developed coma and died 6 days after fish ingestion. A 11-year-old girl developed convulsions and coma after fish ingestion; she died of a chest infection after being in coma for 20 days. In French Polynesia, one fatal case caused by eating a snapper occurred during 1999–2005.²⁹ A 70-year-old man was admitted to intensive care unit (ICU) because of consciousness trouble and died 3 days later of myocardial infarction with rhythm troubles and chest infection.

In Hawaii, two deaths attributed to ciguatera occurred in 1964.³⁰ Two men died around 21 and 31 hours after eating reef fish, including parrotfish, *Naso unicornis*, *Acanthurus dussumieri*, and *Acanthurus xanthopterus* (or *Acanthurus mata*).

In Marshall Islands, three deaths attributed to ciguatera occurred after ingestion of a moray eel cooked by boiling.^{31,32} In 1949, there were two deaths out of 57 affected subjects

who had eaten half of an eel (183 cm × 30 cm) and the head.³¹ One person with coma died after 20 days of hospitalization. A 24-year-old man with coma and convulsions died after 14 days of hospitalization. In 1953, one person with coma and convulsions died 25 days after eel ingestion.³²

In Micronesia, one adult died of ciguatera in 1983 after eating a grouper.³³

In Papua New Guinea, there was a fatal case of ciguatera during 1935–1968, after the consumption of a goldenstriped soapfish.³⁴

In Taiwan, over 10 ciguatera outbreaks have occurred since 1991.^{35,36} Three people died in 1998, 2004, and 2011, after the ingestion of a red grouper, “doctor fish” or sardine.

In Mexico, ciguatera outbreaks were documented since 1984. In the last outbreak in 1997, there were two deaths.³⁷

In Cuba, a fatal case of ciguatera occurred in 2001.³⁸ A 47-year-old man developed coma and respiratory failure after eating a barracuda. He died 15 days after fish ingestion. Autopsy showed bronchopneumonia and cerebral edema.

In Dominica, after the passage of Hurricane David in 1979, two people died of ciguatera in 1980 after eating a triggerfish.³⁹ A 70-year-old man died one day after eating the fish head and liver. A 35-year-old woman was restless and confused before she died. The history from the husband indicated that she last ate the fish liver 2.5 weeks earlier. Her symptoms were otherwise similar to the elderly man, including a swollen finger reaction while skinning.

In Puerto Rico, after the passage of Hurricane Allen in 1980, there were outbreaks of ciguatera affecting at least 125 subjects with three deaths,⁴⁰ including a restaurant owner who died after eating a barracuda.⁴¹ The outbreaks also resulted in a government ban on the sale of barracuda and a few other possibly toxic fishes.

In Venezuela (based on a personal communication), a large outbreak affecting over 200 cases was caused by eating 30 snappers caught in Isla Los Roques, resulting in several deaths.⁴²

In Pakistan, a 39-year-old woman died of respiratory failure after eating the liver of some marine fish.⁴³

On the basis of the information available (Table 2), deaths in eight subjects occurred from 10.3 hours to 25 days (mean 6.8 days) after fish ingestion.^{24,25,27,28,30,32,38} In four other subjects, the latent period between fish consumption and deaths varied from > 3 days²⁹ to > 14–20 days.^{28,31}

Where there were sufficient details about the presenting features and clinical course (Table 2), fatal ciguatera illness was characterized by predominantly neurological (neuropsychiatric) features in all nine subjects,^{24,27,28,31,32,38} including convulsions and coma (see Discussion). In three other subjects, the brief clinical details did suggest the importance of neurological system involvement.^{25,29,43} In the Pakistan case,⁴³ respiratory failure was due to paralysis of the respiratory muscles.² In the Australian case,²⁵ multiorgan failure could include severe brain dysfunction and coma. In the French Polynesia case,²⁹ consciousness trouble requiring ICU admission might refer to semicoma or even postictal state.

DISCUSSION

It has been estimated that less than 20% of ciguatera illnesses are reported, with the extent of underreporting likely to vary between countries.^{1,8,11} In Hawaii, the actual incidence

TABLE 2
Fish species involved and clinical manifestations in ciguatera related deaths

Country (year)	Details
Australia (1965) ²⁴	F/25, ate several fried narrow-barred Spanish mackerel (<i>Scomberomorus commerson</i>) fillets; coldness, numbness, sweating, vomiting, and inability to move her limbs 4 hours later, then convulsions, semicoma, incontinence of feces; coma and convulsions after hospital admission; death occurred 10.3 hours after fish ingestion; autopsy did not reveal any significant pathology
Australia (2001) ²⁵	Her husband ate several fillets and drank a lot of beer, vomited 4 hours later; he recovered M/87 (88 kg, 164 cm), his wife and their son-in-law ate the head (~860 g) and viscera (~140 g) of a sawtooth barracuda (<i>Sphyaena putnamae</i>) in a meal of soup; the couple was admitted to hospital 2 days later with nausea, vomiting, and stomach pains; he died of a heart attack and multiorgan failure 6 days after fish ingestion; autopsy showed the death was due to myocardial infarction consequent to ciguatera; fish flesh contained P-CTX-1 (5.6 µg/kg), P-CTX-2 (7.9 µg/kg), and P-CTX-3 (1.4 µg/kg) His wife and son-in-law were recovered
Fiji (1975–1983) ²⁶	One person was reported to have died of ciguatera after several days of hospitalization
French Polynesia (1968) ^{27,28}	M/54, ate the liver of a triggerfish (<i>Balistoides viridescens</i>) cooked over a wood fire; burning sensation in mouth, nausea, vomiting, diarrhea, then unusual excitation, aimless gestures, incoherent outbursts, collapsed with dizziness, paraparesis, and lethargy progression to a coma; admitted to Tahiti hospital 2 days later; coma, dilated nonreactive pupils, restlessness, BP 180/100 mmHg, breathing 32 breaths/minute, cyanosis in the extremities, areflexia; pulmonary congestion; died 5 days after fish ingestion; autopsy was unremarkable apart from eosinophilic necrotic lesions in the liver
French Polynesia or other South Pacific island groups (1964–1997) ²⁸	F/62 and M/37 ate the flesh with little or no liver recovered M/42, ate a snapper (<i>Lethrinus miniatus</i>); nausea, vomiting, diarrhea, mild paresthesia; ~40 hours later, ataxia, dysmetria, vertigo, nystagmus (horizontal and vertical), weakness, intense pruritus, delirium, prostration, slight fever (37.8°C), bradycardia, dyspnea, agitation; 4 days after hospital admission, ophthalmoplegia, profound coma, hyperthermia (41.0–42.0°C), spastic upper limbs, left hemiparesis, conjugate deviation of the eyes, spastic contraction of right masseter, bilateral Babinski signs; died 6 days after fish ingestion His wife, who ate the same fish, was recovered
French Polynesia (1964–1997) ²⁸	F/11, ate a reef fish; ~12 hours later, paresthesia of the extremities, pruritus, diarrhea; 94 hours post-meal, right facial nerve palsy, right-sided convulsions, then obtundation, spastic four limbs; admitted to Tahiti hospital; decorticate rigidity with hyperreflexia, bilateral Babinski signs, hyperthermia (40°C) on day 4 of coma; coma and hypertonía for 20 days; death occurred after the development of a respiratory infection Three other family members, who ate the same fish, were recovered
French Polynesia (1999–2005) ²⁹	M/70 with hypertension and noninsulin-dependent diabetes mellitus (NIDDM), ate a snapper (<i>Lutjanus bohar</i>); gastroenteritis symptoms, acute asthenia; admitted to ICU because of consciousness trouble; died 3 days later because of myocardial infarction with rhythm troubles and chest infection
Hawaii (1964) ³⁰	Six of his family members, sharing the same fish, were recovered Two men died ~21 hours and ~31 hours after eating unviscerated reef fishes that were broiled, including parrotfish, <i>Naso unicornis</i> , <i>Acanthurus dussumieri</i> , and <i>Acanthurus xanthopterus</i> (or <i>Acanthurus mata</i>)
Marshall Islands (1949) ³¹	Eight other subjects who ate the same fishes were hospitalized; six were clinically ill; all eight subjects were recovered All 57 people who ate half of a yellow-edge moray eel (<i>Gymnothorax flavimarginatus</i>) and its head were poisoned; tingling/numbness of mouth, hands and feet in all and unable to talk in 50; 17 hospitalized, with coma on admission ($N = 11$) or a few hours after admission ($N = 3$), decreased function of respiratory chest muscles, convulsions, increased bronchial secretion; two deaths (see below), with autopsy showing bilateral bronchopneumonia One died after 20 days in hospital without regaining consciousness M/24 died after 14 days in hospital, being conscious for 2 days; clinical features included coma, restlessness, hysterical-like reaction, generalized tonic and clonic convulsions, conjugate deviation of the eyes to the right, areflexia, trismus, fever, profuse diaphoresis, tachypnea, Cheyne–Stokes breathing, tachycardia, and hypertension; intubated
Marshall Islands (1953) ³²	All six people who ate a cooked eel (likely <i>G. flavimarginatus</i>) had marked neurological features, including dizziness, anxiety, panic, malaise, marked difficulty in voluntary movements of facial muscles and the extremities, generalized numbness, hyporeflexia, carpopedal spasm, Chvostek's sign, Romberg's sign, severe ataxia; some had severe retching with vomiting One patient was particularly ill, with the additional features of grand mal seizures, deep coma and subsequent developments of areflexia, absent corneal reflex, no responses to painful stimuli, spastic upper limbs but generalized hypotonicity of all other muscles, fever and Cheyne–Stokes breathing, ventilated; coma for 24 days, died 25 days after eel ingestion
Micronesia (1983) ³³	One adult died after eating a grouper (<i>Cephalopholis argus</i>)
Papua New Guinea (1953) ³⁴	Two people were ill after eating a goldenstriped soapfish (<i>Grammistes sexlineatus</i>) and one died
Taiwan (1998) ³⁵	There was one death caused by eating a red grouper (probably <i>L. bohar</i>)
Taiwan (2004) ³⁵	There was one death caused by eating a “doctor fish”
Taiwan (2011) ³⁶	Two people became ill after eating an unknown fish species and one died; the causative fish was identified as sardine and palytoxin initially found in residue fish; toxicity not found in sardine from the same fish market
Mexico* (1997) ³⁷	The last reported outbreak caused two deaths
Cuba (2001) ³⁸	Eleven people became ill after eating a barracuda (<i>Sphyaena barracuda</i>); details about a fatal case and eight other subjects were analyzed M/47, weight loss of 25 kg after eating almost exclusively fish and crabs for 6 months; ate ~500 g of the fish; symptoms 40 minutes later; profuse diarrhea, dehydration, muscle cramps, arthralgia, paresthesia, progressive agitation, diplopia, ataxia, dysarthria, tremors, bradycardia, coma, respiratory difficulty, cyanosis, abundant bronchial secretions, ventilated; died 15 days after fish ingestion; autopsy showed bilateral bronchopneumonia and cerebral edema; individual susceptibility, due to nutritional deficiency and previous lipophilic toxins (seafood) exposure, was suspected 6F and 2M (aged 4–72 years, mean 39.4 years) who ate 15–375 g of fish recovered

(continued)

TABLE 2
Continued

Country (year)	Details
Dominica (1980) ³⁹	Increase in the toxicity of triggerfish (<i>Canthidermis maculatus</i>) after the passage of Hurricane David in 1979 was noted; two people died in 1980 after eating a triggerfish, and both developed finger swelling after being pricked while skinning the fish M/70, ate the cooked fish liver and head; repeated vomiting, abdominal pain, pain over the body and limbs, cramps in hands and feet, BP 200/100 mmHg, joint stiffness; died in hospital the next day F/35 with hypertension and diabetes, ate the cooked fish liver; "fuming" in the throat on swallowing; abrupt onset of symptoms 2.5 weeks later, with severe pain over the body, limbs and abdomen, repeated vomiting, cramps in hands and lower legs, and burning sensation in lower limbs; restlessness and confusion 1 day after onset of symptoms and died in hospital; her husband and children who only ate the flesh were asymptomatic
Puerto Rico (1981) ^{40,41}	Increase in the toxicity of reef fish after the passage of Hurricane Allen in 1980 was noted At least 125 subjects were affected in 1981 with three deaths (including a man who had eaten a barracuda)
Venezuela ⁴²	Over 200 subjects were poisoned after eating 30 snappers caught in Isla Los Roques, resulting in several deaths
Pakistan ⁴³	A three-member family ate the cooked liver of an unknown marine fish The wife (aged 39 years) complained of severe muscle pain over the body and electric shock like feelings from the neck to all extremities, followed by dyspnea and cyanosis; died of respiratory failure before arrival in hospital Her husband (aged 44 years) and their son (aged 5 years), with generalized muscle weakness, myalgia, elevated muscle enzyme levels, and other neurological symptoms were recovered

BP = blood pressure; ICU = intensive care unit; Caribbean Sea = Cuba, Dominica, Puerto Rico, Venezuela; Indian Ocean = Pakistan; Pacific Ocean = Australia, Fiji, French Polynesia, Hawaii, Marshall Islands, Micronesia, Papua New Guinea, Taiwan.

*It was not specified whether the ciguatera outbreak occurred in the Pacific and Caribbean coasts of Mexico.

could be 10–20 times higher than reported.⁴⁷ Underreporting may reflect a general reticence to report the illnesses and/or a lack of recognition of milder cases by the public or even health professionals.¹¹ On the other hand, large outbreaks and fatal cases,^{5,41} which are often widely publicized, can result in an increased awareness of the disease as well as a negative impact on fish consumption and fisheries developments.⁴⁸ Ciguatera affects the health and confidence of the consumers.⁴⁹ The systematic collection and analysis of epidemiological data on ciguatera should facilitate better assessment, management, and communication of its risk,⁶ especially with respect to life-threatening complications and fatalities.^{1,22}

Ciguatera is rarely fatal unless life-threatening cardiovascular, respiratory, or neurological complications occur without immediate access to emergency care. The overall mortality rate from ciguatera in the South Pacific during 1965–1977 was 0.1%.²⁸ The actual death rate could vary if the data are derived from severe hospitalized cases or mild unreported cases have been omitted. In Queensland, Australia, there were up to 2,627 cases during 1965–1984, with one death (0.04%).^{24,50} In the United States, after adjustments for underreporting and underdiagnosis, it was estimated that there were 15,910 cases annually, leading to 343 hospitalizations and three deaths (0.02%).⁵¹ These estimates were derived from the outbreak data (2000–2007) and the poison control center call data (2005–2009) using a statistical model, although there were no reported deaths. In Hong Kong, there were three to 117 outbreaks (median 19), affecting 19–425 individuals (median 68) each year during 1989–2008, and there were no deaths.¹² In Gilbert Islands (Kiribati), the Gilbertese did not usually clean or gut carnivorous or small fish before cooking.⁵² The only remembered deaths involved the very old people and individuals already debilitated by disease. In ciguatera, consumption of CTX-rich fish parts, increasing age, and repeated CTX exposures are generally associated with more severe illness.^{6,28,53,54}

Other than the mortality rates and isolated case studies,²⁸ relatively little was known about the characteristic features and contributory factors in ciguatera-related deaths. Despite

fairly extensive literature search, only several reports of fatal cases from the Pacific, Caribbean, and Indian Ocean regions could be identified (Table 2). The reports from Fiji (1975–1983),²⁶ Micronesia (1983),³³ Papua New Guinea (1953),³⁴ Taiwan (1998, 2004, and 2011),^{35,36} and Mexico (1997)³⁷ were too brief, although the fish species responsible was stated in four.^{33–36} The report from Venezuela²⁹ well demonstrated the potential of ciguatoxic fish to cause large outbreaks,⁵ with mortalities. The reports from Australia (1965, 2001),^{24,25} French Polynesia, and other South Pacific island groups (1968, 1964–1997, and 1999–2005),^{27–29} Marshall Islands (1949, 1953),^{31,32} Cuba (2001),³⁸ Dominica (1980),³⁹ Puerto Rico (1981),^{40,41} and Pakistan⁴³ were analyzed further to reveal characteristic features and contributory factors in fatal cases.

In individuals who died of ciguatera fish poisoning, the clinical features were generally dominated by convulsions^{24,28,31} and coma,^{24,27,28,31,32,38} with a variety of focal neurological deficits including ataxia,^{28,32,38} vertigo,²⁸ dysarthria,³⁸ nystagmus,²⁸ conjugate eye deviation,^{28,31} ophthalmoplegia,^{28,38} paraparesis,^{27,28} and hemiparesis²⁸ (Table 2). Other evidence of severe brain damage (e.g., Cheyne–Stokes breathing,^{31,32} dilated pupils,^{27,28} absent corneal reflex,³² decorticate posture,²⁸ bilateral Babinski signs,²⁸ and absent response to pain stimuli³²) and brain dysfunction (e.g., excitation,^{27,28} agitation,^{28,38} incoherent outbursts,^{27,28} delirium,²⁸ restlessness,^{27,28,31,39} hysteria,³¹ and panic³²) could be present. Hyperthermia²⁸ and respiratory failure^{38,43} could also occur. Convulsions, coma, severe brain damage, and focal neurological deficits (except ataxia and vertigo) are generally very rare in ciguatera,^{2,12} unless a huge CTX dose is involved.^{31,32}

Several deaths were related to the consumption of CTX-rich fish parts (viscera^{25,27,28,30,39,43} and head^{25,31,39}), whereas subjects who only ate the flesh were recovered.^{27,28,39} Subjects who survived appeared to have eaten much less.³⁸ Individuals' susceptibility must also be important, since many subjects who shared the same fish had milder symptoms and recovered.^{24,25,28–30,43} Two elderly males, with²⁹ or without²⁵ cardiovascular risk factors, died of myocardial infarction

consequent to ciguatera. Increasing age^{25,29} and weight²⁵ (with greater probability of previous subclinical exposures and accumulation of CTX) are known to be correlated with the severity and duration of ciguatera illness among the survivors.⁵³ Perhaps, individuals' susceptibility,²⁸ severe prolonged hypotension (common in severe cases),²² and underlying cardiovascular risk factors all contributed to the development of this fatal complication.

Of all the fish species responsible for ciguatera outbreaks with mortalities shown in Table 2, the yellow-edge moray eel (*Gymnothorax flavimarginatus*) (maximum 240 cm total length) should be specially mentioned. It has long been known to be the most toxic eel species.¹⁸ In the 1949 outbreak in Marshall Islands,³¹ the eel involved was about 183-cm long and 30-cm thick. Each slice was enough for four men. Half of the eel, head and the broth could cause severe poisoning in 57 people, including 14 with coma and two deaths. Eel soups are also highly poisonous.³¹ It should be remembered that the toxicity in flesh and liver (up to 15-fold more toxic than flesh) of the *Gymnothorax* species shows a strong positive relationship with the eel size.⁵⁵ In Kiribati, the P-CTX-1 equivalent toxicity in liver of a 14-kg moray eel was 539 µg/kg, 50,000 times higher than the safety level of 0.01 µg/kg.⁵⁵ Because moray eels can accumulate such high CTX levels, the public must be warned that ingestion of an average portion of the flesh (and particularly the liver) can be lethal.^{31,55}

The public should be repeatedly reminded to avoid eating the CTX-rich parts (viscera and head) of reef fish since the amounts of CTX exposures and the risk of severe ciguatera will be much higher.⁵⁴ Many fatal cases in the past were related to ingestion of reef fish viscera (Table 2). In Hong Kong, fish are gutted before cooking at home or in the restaurants also because viscera do not taste or smell nice. It is not surprising that symptoms of brain dysfunction, convulsions, coma, and respiratory paralysis have not been reported so far.¹² Severe bradycardia and prolonged hypotension requiring ICU care remains the most important life-threatening complications.⁵⁶

Reef destruction caused by hurricanes or typhoons can be followed by increase in toxicity of reef fish and incidence of ciguatera.⁵⁷ This was seen in Dominica in 1980 and Puerto Rico in 1981 1 year after the passage of hurricanes, resulting in deaths.^{39–41} Particularly after hits by disastrous storms, it is important to monitor the toxicity of reef fish and the incidence rates of ciguatera.⁵⁷

To prevent mass ciguatera fish poisoning in gatherings and parties,^{31,42} the most ciguatoxic fish species (e.g., *Gymnothorax* species) and potentially toxic fish species must be avoided.

CONCLUSIONS

Ciguatera-related deaths, although rare, have been reported from the Pacific, Caribbean, and Indian Ocean regions. The clinical features were generally dominated by convulsions and coma, with various focal neurological signs. Other evidence of severe brain damage, brain dysfunction, respiratory failure, and respiratory depression could also be present. On the basis of the cases reviewed, several contributory factors could be identified, including consumption of CTX-rich fish parts (viscera and head) in larger amounts, the most ciguatoxic fish species (e.g., *G. flavimarginatus*) and

reef fish with increased toxicity collected after storms. Individuals' susceptibility must also be important, since many subjects sharing the same fish had milder symptoms and recovered. Mass ciguatera fish poisoning with mortalities also occurred when *G. flavimarginatus* and other ciguatoxic fish species were shared in gatherings and parties.

Coma, convulsions, focal neurological signs, and other serious brain dysfunction features characteristic of fatal ciguatera fish poisoning must be recognized early, so that immediate life support followed by management in the ICU can be provided. The public should be repeatedly reminded to avoid eating the most ciguatoxic fish species (e.g., *G. flavimarginatus*) and the CTX-rich parts (viscera and head) of reef fish. To prevent mass ciguatera fish poisoning in gatherings and parties, the most ciguatoxic fish species and potentially toxic fish species must be avoided. Particularly after hits by disastrous storms, it is important to monitor the toxicity of reef fish and the incidence rates of ciguatera.

Received September 18, 2015. Accepted for publication December 8, 2015.

Published online January 19, 2016.

Financial support: This work is supported by research funding from the Centre for Food and Drug Safety, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong, China.

Authors' addresses: Thomas Y. K. Chan, Division of Clinical Pharmacology and Drug and Poisons Information Bureau, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China, and Centre for Food and Drug Safety, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China, E-mail: tykchan@cuhk.edu.hk.

REFERENCES

1. FAO, 2004. Ciguatera fish poisoning. *Marine Biotoxins*. FAO Food and Nutrition Paper 80. Rome, Italy: Food and Agriculture Organization of the United Nations, 185–218.
2. Friedman MA, Fleming LE, Fernandez M, Bienfang P, Schrank K, Dickey R, Bottein MY, Backer L, Ayyar R, Weisman R, Watkins S, Granade R, Reich A, 2008. Ciguatera fish poisoning: treatment, prevention and management. *Mar Drugs* 6: 456–479.
3. Mak YL, Wai TC, Murphy MB, Chan WH, Wu JJ, Lam JCW, Chan LL, Lam PKS, 2013. Pacific ciguatoxins in food web components of coral reef systems in the Republic of Kiribati. *Environ Sci Technol* 47: 14070–14079.
4. Chan TYK, 2013. Ciguatera caused by consumption of humphead wrasse. *Toxicon* 76: 255–259.
5. Chan TYK, 2014. Large outbreaks of ciguatera after consumption of brown marbled grouper. *Toxins (Basel)* 6: 2041–2049.
6. Chan TYK, 2015. Ciguatoxic potential of brown-marbled grouper in relation to fish size and geographical origin. *Am J Trop Med Hyg* 93: 1117–1121.
7. Vernoux JP, Lahlou N, Abbad el Andaloussi S, Riyeche N, Magras LP, 1985. A study of the distribution of ciguatoxin in individual Caribbean fish. *Acta Trop* 42: 225–233.
8. Chan TYK, 2015. Ciguatera fish poisoning in East Asia and Southeast Asia. *Mar Drugs* 13: 3466–3478.
9. Gingold DB, Strickland MJ, Hess JJ, 2014. Ciguatera fish poisoning and climate change: analysis of National Poison Center Data in the United States, 2001–2011. *Environ Health Perspect* 122: 580–586.
10. Litaker RW, Vandersea MW, Faust MA, Kibler SR, Nau AW, Holland WC, Chinain M, Holmes MJ, Tester PA, 2010. Global distribution of ciguatera causing dinoflagellates in the genus *Gambierdiscus*. *Toxicon* 56: 711–730.
11. Dickey RW, Plakas SM, 2010. Ciguatera: a public health perspective. *Toxicon* 56: 123–136.

12. Chan TYK, 2014. Epidemiology and clinical features of ciguatera fish poisoning in Hong Kong. *Toxins (Basel)* 6: 2989–2997.
13. Oshiro N, Yogi K, Asato S, Sasaki T, Tamanaha K, Hiram M, Yasumoto T, Inafuku Y, 2010. Ciguatera incidence and fish toxicity in Okinawa, Japan. *Toxicon* 56: 656–661.
14. Rongo T, Bush M, van Woesik R, 2009. Did ciguatera prompt the late Holocene Polynesian voyages of discovery? *J Biogeogr* 36: 1423–1432.
15. Chinain M, Darius HT, Ung A, Fouc MT, Revel T, Cruchet P, Pauillac S, Laurent D, 2010. Ciguatera risk management in French Polynesia: the case study of Raivavae Island (Australes Archipelago). *Toxicon* 56: 674–690.
16. Skinner MP, Brewer TD, Johnstone R, Fleming LE, Lewis RJ, 2011. Ciguatera fish poisoning in the Pacific Islands (1998 to 2008). *PLoS Negl Trop Dis* 5: e1416.
17. Tester PA, Feldman RL, Nau AW, Kibler SR, Wayne Litaker R, 2010. Ciguatera fish poisoning and sea surface temperatures in the Caribbean Sea and the West Indies. *Toxicon* 56: 698–710.
18. Celis JS, Pineda M, Ernesto J, 2015. Historical analysis of ciguatera incidence in the Caribbean islands during 31 years: 1980–2010. *Boletín de Investigaciones Marinas y Costeras* 44: 7–32.
19. Radke EG, Grattan LM, Cook RL, Smith TB, Anderson DM, Morris JG Jr, 2013. Ciguatera incidence in the US Virgin Islands has not increased over a 30-year time period despite rising seawater temperatures. *Am J Trop Med Hyg* 88: 908–913.
20. Radke EG, Reich A, Morris JG Jr, 2015. Epidemiology of ciguatera in Florida. *Am J Trop Med Hyg* 93: 425–432.
21. Quod JP, Turquet J, 1996. Ciguatera in Reunion Island (SW Indian Ocean): epidemiology and clinical patterns. *Toxicon* 34: 779–785.
22. Chan TYK, Wang AYM, 1993. Life-threatening bradycardia and hypotension in a patient with ciguatera fish poisoning. *Trans R Soc Trop Med Hyg* 87: 71.
23. Lewis RJ, 2006. Ciguatera: Australian perspectives on a global problem. *Toxicon* 48: 799–809.
24. Tonge JJ, Battey Y, Forbes JJ, Grant EM, 1967. Ciguatera poisoning: a report of two outbreaks and a probable fatal case in Queensland. *Med J Aust* 2: 1088–1090.
25. Hamilton B, Whittle N, Shaw G, Eaglesham G, Moore MR, Lewis RJ, 2010. Human fatality associated with Pacific ciguatera contaminated fish. *Toxicon* 56: 668–673.
26. Yasumoto T, Raj U, Bagnis R, 1984. Symposium on Seafood Toxins in Tropical Regions. Symposium on Seafood Toxins from Tropical Regions, 1–74. Laboratory of Food Hygiene, Faculty of Agriculture, Tohoku University, Sendai, Japan.
27. Bagnis R, 1970. Concerning a fatal case of ciguatera poisoning in the Tuamotu Islands. *Clin Toxicol* 3: 579–583.
28. Bagnis R, Kuberski T, Laugier S, 1979. Clinical observations on 3,009 cases of ciguatera (fish poisoning) in the South Pacific. *Am J Trop Med Hyg* 28: 1067–1073.
29. Gatti C, Oelher E, Legrand AM, 2008. Severe seafood poisoning in French Polynesia: a retrospective analysis of 129 medical files. *Toxicon* 51: 746–753.
30. Anderson BS, Sims JK, Wiebenga NH, Sugi M, 1983. The epidemiology of ciguatera fish poisoning in Hawaii, 1975–1981. *Hawaii Med J* 42: 326–334.
31. Khlentzos CT, 1950. Seventeen cases of poisoning due to ingestion of an eel, *Gymnothorax flavimarginatus*. *Am J Trop Med Hyg* 30: 785–793.
32. Ralls RJ, Halstead BW, 1955. Moray eel poisoning and a preliminary report on the action of the toxin. *Am J Trop Med Hyg* 4: 136–140.
33. Inoue A, Edward A, 1995. The growth of *G. toxicus*, a toxic dinoflagellate in Pohnpei Island and Ant Atoll, the Federated States of Micronesia. *Kagoshima Univ Res Center S Pac Occasional Papers* 26: 25–29.
34. Rapson AM, 1968. *Ichthyosarcotoxism (Fish Poisoning) in New Guinea*. SPC Seminar on Ichthyosarcotoxism, 16–22 August, 1968. Available at: http://www.spc.int/DigitalLibrary/Doc/FAME/Meetings/Meetings_on_Ciguatera/Seminar_Ichthyosarcotoxism_68/WP10.pdf. Accessed November 30, 2015.
35. Hsieh CH, Hwang KL, Lee MM, Lan CH, Lin WF, Hwang DF, 2009. Species identification of ciguatera-carrying grouper implicated in food poisoning. *J Food Prot* 72: 2375–2379.
36. Lin WF, Hwang DF, 2012. Analysis of poisoning cases, monitoring and risk warning for marine toxins (TTX, PSP and CTXs) in Taiwan. *J Food Drug Anal* 20: 764–771.
37. Sierra-Beltrán AP, Cruz A, Núñez E, Del Villar LM, Cerecero J, Ochoa JL, 1998. An overview of the marine food poisoning in Mexico. *Toxicon* 36: 1493–1502.
38. Pumariega RBH, Mullings AOH, Escandón AS, del Corral García J, 2005. *Evolución fatal por ciguatera. A propósito de un brote*. Available at: <http://www.bvsde.paho.org/bvsacd/cd27/ciguareta.pdf>. Accessed November 30, 2015.
39. Taylor FJR, 1984. Human and domestic animal fatalities as well as skin reactions associated with the 'rough triggerfish', *Canthidermis maculatus* (Bloch) in Dominica, West Indies, following Hurricane David. *Rev Int Océanogr Méd* 73/74: 35–40.
40. Caribbean Fishery Management Council, 1985. *Fishery Management Plan, Final Environmental Impact Statement, and Draft Regulatory Impact Review for the Shallow-Water Reefish Fishery of Puerto Rico and the U.S. Virgin Islands*. Available at: <http://www.caribbeanfmc.com/fmp%20REEF%20FISH/RF%20FMP.pdf>. Accessed November 30, 2015.
41. Ghigliotti J, 1981. Death at the dinner table. In: *Sunday Magazine*. San Juan, Puerto Rico: The San Juan Star, 2–6.
42. Doorenbos N, 1984. Ciguatera toxins: where do we go from here? Ragelis EP, ed. *Seafood Toxins*. Washington, DC: American Chemical Society, 69–73.
43. Wasay M, Sarangzai A, Siddiqi A, Nizami Q, 2008. Ciguatera fish poisoning with elevated muscle enzymes and abnormal spinal MRI. *Southeast Asian J Trop Med Public Health* 39: 307–309.
44. Habermehl GG, Krebs HC, Rasoaivo P, Ramialiharisoa A, 1994. Severe ciguatera poisoning in Madagascar: a case report. *Toxicon* 32: 1539–1542.
45. Boisier P, Ranaivoson G, Rasolofonirina N, Andriamahefazy B, Roux J, Chanteau S, Satake M, Yasumoto T, 1995. Fatal mass poisoning in Madagascar following ingestion of a shark (*Carcharhinus leucas*): clinical and epidemiological aspects and isolation of toxins. *Toxicon* 33: 1359–1364.
46. Rege UG, Tilve GH, Juvalé NI, Jayakar VV, Nair KG, 1979. Ciguatera (a variety of fresh fish poisoning) (a case report). *J Postgrad Med* 25: 112–114.
47. Copeland NK, Palmer WR, Bienfang PK, 2014. Ciguatera fish poisoning in Hawaii and the Pacific. *Hawaii J Med Public Health* 73 (Suppl 2): 24–27.
48. Olsen DA, 1988. The impact of ciguatera fish poisoning within a changing Caribbean environment. *Popul Environ* 10: 14–31.
49. Chan TYK, 2015. Emergence and epidemiology of ciguatera in the coastal cities of Southern China. *Mar Drugs* 13: 1175–1184.
50. Gillespie NC, Lewis RJ, Pearn JH, Bourke AT, Holmes MJ, Bourke JB, Shields WJ, 1986. Ciguatera in Australia. Occurrence, clinical features, pathophysiology and management. *Med J Aust* 145: 584–590.
51. Pennotti R, Scallan E, Backer L, Thomas J, Angulo FJ, 2013. Ciguatera and scombroid fish poisoning in the United States. *Foodborne Pathog Dis* 10: 1059–1066.
52. Cooper MJ, 1964. Ciguatera and other marine poisoning in the Gilbert Islands. *Pac Sci* 18: 411–440.
53. Katz AR, Terrell-Perica S, Sasaki DM, 1993. Ciguatera on Kauai: investigation of factors associated with severity of illness. *Am J Trop Med Hyg* 49: 448–454.
54. Chateau-Degat ML, Huin-Blondey MO, Chinain M, Darius T, Legrand AM, Nguyen NL, Laudon F, Chansin R, Dewailly E, 2007. Prevalence of chronic symptoms of ciguatera disease in French Polynesian adults. *Am J Trop Med Hyg* 77: 842–846.
55. Chan WH, Mak YL, Wu JJ, Jin L, Sit WH, Lam JC, Sadovy de Mitcheson Y, Chan LL, Lam PK, Murphy MB, 2011. Spatial distribution of ciguatera fish in the Republic of Kiribati. *Chemosphere* 84: 117–123.
56. Chan TYK, 2013. Severe bradycardia and prolonged hypotension in ciguatera. *Singapore Med J* 54: e120–e122.
57. Lewis ND, 1986. Epidemiology and impact of ciguatera in the Pacific: a review. *Mar Fish Rev* 48: 6–13.