JAOA

REVIEW ARTICLE

Ciguatera: Current concepts

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Ciguatera poisoning develops after ingestion of certain coral reef–associated fish. With travel to and from the tropics and importation of tropical food fish increasing, ciguatera has begun to appear in temperate countries with more frequency. The causative agents are certain varieties of the protozoan dinoflagellate *Gambierdiscus toxicus*, but bacteria associated with these protozoa may have a role in toxin elaboration. A specific "ciguatoxin" seems to cause the symptoms, but toxicosis may also be a result of a family of toxins. Toxicosis develops from 10 minutes to 30 hours after ingestion of poisoned fish, and the syndrome can include gastrointestinal and neurologic symptoms, as well as chills, sweating, pruritus, bradycardia, tachycardia, and long-lasting weakness and fatigue. More severe features are rare. In this review, the pathophysiologic features and symptoms of ciguatera are reviewed and compared with those of other seafood-related syndromes. Although no definitive therapy is known, the most promising treatment for ciguatera is intravenous administration of mannitol. Physicians should warn patients who are traveling to endemic areas about this toxicosis.

(Key words: Ciguatera, ciguatoxin, fish, mannitol, seafood, shellfish, temperature reversal)

Worldwide, ciguatera is the most common toxicity borne by fish. Its group of symptoms is bizarre, and unless the physician is familiar with the strange manifestations of ciguatera, unraveling the diagnosis may prove difficult. Although the syndrome has been known for at least hundreds of years, its mechanisms are only beginning to be elucidated. Effective treatments have just begun to emerge.

Ciguatera is a major public health problem in the tropics, with probably more than 30,000 poisonings yearly in Puerto Rico and the US Virgin Islands alone. The endemic area is bounded by latitudes 37° north and south. Ciguatera in temperate countries is a concern because people returning from business trips, vacations, or living in the tropics may have been poisoned through food they had eaten. The development of worldwide marketing of fish from a variety of ecosystems creates a danger of ciguatera intoxication in climates far removed from sandy beaches and waving palms. Outbreaks have been reported in Vermont, Rhode Island, New York State, Montreal, and British Columbia. In Canada alone, ciguatera costs more than $3 million a year in medical and indirect costs.[1]

Means of toxicosis

Ingestion of any one of more than 400 species of tropical or subtropical reef fish can cause ciguatera. Larger reef-associated carnivorous fish such as barracuda, some groupers, jacks, and snappers are most likely to cause toxicosis, but many other fish are implicated as well (*Table 1*).

Ciguatoxin (CTX) itself has been identified as a lipid polyether with several hydroxyl groups and a molecular weight of 1112, one of the most potent nonproteinaceous poisons known. Controversy exists as to whether toxicosis results from one toxin or from many. Through research in the past 5 years, the picture regarding the causative agent has actually become less clear. (Yet another example of just how right Heisenberg really was! The closer we get to a subject,

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Table 1
Some Fish Implicated in Cases of Ciguatera Poisoning

Herrings	Goatfish
Tarpon	Mullet
Anchovy	Triggerfish
True eels	Snappers
Flying fish	Porgies
Squirrelfish	Jacks
Sea perch	Parrotfish
Dolphins	Surgeonfish
Sailfish	Grunts
Bass	Tunas
Grouper	Swordfish

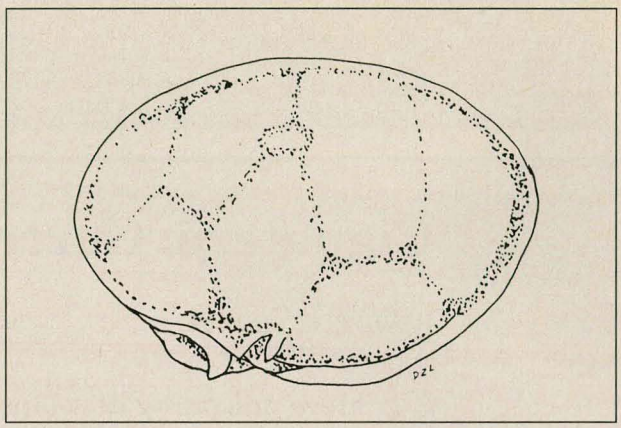

Figure. *Author's drawing of* Gambierdiscus toxicus, *a benthic dinoflagellate involved in ciguatera poisoning. (Source: "Ciguatera in the North Eastern Caribbean," Datos Marinos, No. 7A, Department of Marine Sciences, UPR-RUM, Mayaguez, PR [undated])*

the less we seem able to understand it.) It may be that toxicosis results from a family of toxins rather than from one specific ciguatoxin.[2]

Ciguatoxin(s) are evolved by certain varieties of the protozoan dinoflagellate *Gambierdiscus toxicus* (*Figure*). Recently, it has been suggested that they may also be elaborated by another strain of dinoflagellate, *Ostreopsis lenticularis*, which is found associated with *G toxicus*. To complicate matters even further, recent research indicates that certain bacteria are found symbiotically associated with dinoflagellates and seem to have a role in the elaboration of toxins by the symbiont dinoflagellates. Bacteria found associated with dinoflagellates include strains of *Pseudomonas* (most common), *Nocardia, Vibrio, Aeromonas, Flavobacterium,* and *Moraxella*.[3,4]

Dinoflagellates are responsible for several other known toxins, as well as the infamous "red tides." It has been suggested that *G toxicus* flourishes where reef ecology has been disturbed by construction, pollution, military activity, or natural causes.[5] The organism attaches itself to macroalgae and is eaten by herbivorous reef fish. These herbivores are eaten by carnivores, and these carnivores are preyed upon by larger carnivores, passing on—and concentrating—the toxin. When humans are at the top of this food chain, they become vulnerable to ingestion of ciguatoxin and other benthic (sea-bottom)–associated) marine toxins.

Clinical characteristics

The symptoms of ciguatera are unique (*Table 2*), although ciguatera has nausea, vomiting, diarrhea, and abdominal pain in common with other food poisonings. Onset is 10 minutes to 30 hours after ingestion of a toxic meal, and this gastrointestinal aspect of the intoxication usually resolves in 24 to 48 hours. Arthralgia and myalgia are common. The neurologic symptoms are the most bizarre and are also most specific to ciguatera as an entity. The patient may have dizziness, oral and circumoral paresthesia, headache, paresthesia of the extremities, and taste disturbance. Chills and profuse sweating are relatively common. Whole-body pruritus or pruritus limited to the palms and soles can be extremely distressing. Bradycardia and hypotension or tachycardia and mild hypertension may occur.

The "signature" of ciguatera is hot/cold reversal. The patient perceives cold sensations as hot (for example, interpreting a cool breeze as burning hot) and vice versa (*Table 2*). In very rare cases, delirium, coma, cardiac and respiratory failure, and death may occur, but no deaths from ciguatera have occurred in North America. Persistent weakness and fatigue are the symptoms most responsible for loss of working days.[6] Discomfort may lead to severe insomnia.

Differential diagnosis

Most other forms of seafood poisoning should be reasonably easy to distinguish from ciguatera (*Table 3*). Scombroid poisoning usually results from ingestion of tuna or mackerel that has been inadequately refrigerated. The disorder is histamine mediated and resembles other histamine reactions. Patients may experience

Table 2
Signs and Symptoms of Ciguatera

General	Gastrointestinal	Neurologic
Weakness (especially lower extremity)	Nausea	Oral and circumoral paresthesias
Malaise	Vomiting	Acral paresthesias
Fatigue	Diarrhea	Dizziness
Myalgia	Abdominal pain	Temperature reversal
Arthralgia		Pruritus
		Ataxia
		Chills

flushing, coryza, severe headache, dizziness, burning of the mouth and throat, abdominal cramps, nausea, vomiting, diarrhea, and pruritus.[7] Paralytic shellfish poisoning and neurotoxic shellfish poisoning result from ingestion of dinoflagellate-contaminated shellfish. Neurotoxic shellfish poisoning is typically a mild syndrome involving the usual gastrointestinal symptoms, as well as varying paresthesias and cerebellar symptoms. It is limited to a few days' duration.[8] (Temperature reversal has also been noted with this syndrome, which somewhat complicates the diagnosis of ciguatera.) Paralytic shellfish poisoning, as the name would suggest, carries more potential morbidity and mortality, and is usually encountered in the summer. An initial neurologic symptom, circumoral paresthesia, may be followed by cerebellar symptoms, cranial nerve involvement, and motor paralysis including respiratory failure. Treatment is supportive, and patients usually recover within a week.[9]

Laboratory evaluation

In ciguatera poisoning, physical examination and routine laboratory analyses show no abnormalities. A laboratory means of objectively determining whether a patient has ciguatera poisoning is not currently available.

Several biological assays for determining which fish are toxic have been in use for some time. An enzyme-linked immunoassay using monoclonal antibodies has been developed by Yoshitsuro Hokama, PhD, and his associates at the University of Hawaii Medical School. The test uses coated bamboo sticks that are stabbed into the flesh of the suspect fish. The stick is then treated with several reagents. If the fish is toxic, the coating turns a deep blue-purple.[10] The assay has been used very successfully by commercial fisherman in Hawaii, according to Dr Hokama (personal telephone communication, 1992).[11] It has been argued, however, that the test is inadequately specific and has been tested only in Hawaii, where ciguatera is reportedly not a major problem, and that therefore the appearance of success may be caused by the Hawthorn effect. (T.R. Tosteson, PhD, conversation, December 1992). The patent for the stick test was sold by the University of Hawaii to a California corporation (Ciguatect, Hawaii Chemtect International, Pasadena, Calif). Apparently it has been developed for commercial marketing, but release has been delayed indefinitely pending litigation between the company and the University of Hawaii (Robert Goldsmith, MA, Hawaii Chemtect International, personal telephone communication, February 1995). It is hoped that the stick test, if proved practical, will soon be available again and that its cost will not prohibit its use in poorer areas where ciguatera is endemic.

Pathophysiologic features

The mechanism of ciguatera is beginning to come to light. The toxin seems to open (activate) voltage-dependent sodium channels, affecting a global array of body functions.[12] It has been reported that Schwann cells surrounding peripheral nerve axons become edematous,[12] possibly modifying or impeding neural transmission. The marked array of symptomatic responses to ciguatera may result in part from metabolic changes in the toxin both within the host fish and within the human target. A.L.

Hupka, PhD, has stated that ciguatoxin itself appears to have different fractions, which may account for variability in symptoms (conversation, 1992). *Gambierdiscus* elaborates another toxin, maitotoxin, which also may be responsible for variability in clinical presentation.[14]

Treatment

Numerous treatment regimens for ciguatera have been advocated,[15-23] but several that seem to have real promise have emerged in the last 5 years. It seems reasonable that if ciguatera affects sodium channels, agents that stabilize these membrane channels should be effective. It has been noted for some time that intravenously administered lidocaine alleviates symptoms[15] and, consequently, tocainide, an oral analog of lidocaine, has been tested in several cases of toxicosis, with encouraging results (dosage and duration of treatment not known).[16] Another stabilizer of sodium channels, amitriptyline, 25 mg twice or three times daily, has been reported to work well in some cases and not at all in others.[17,18] It has also been recommended in one report as the best treatment for the chronic effects of ciguatera.[19]

The most promising therapy, intravenously administered mannitol therapy, seems to rapidly reverse ciguatera toxicity, but its mechanism is unknown. The drug is inexpensive and relatively safe. The 20% solution (1 g/5 mL) is administered intravenously at a dose of 1 g per kilogram of body weight, over 30 to 45 minutes. Often, the symptoms begin to abate within minutes. The treatment sometimes needs to be repeated.[20-23] It has been suggested that the mechanism of mannitol's efficacy in ciguatera poisoning may be related to reversal of periaxonal Schwann cell edema, but if this is the situation, similar results might be expected with other diuretics. This has not been the case.

It is important to correct fluid and electrolyte imbalances resulting from diarrhea or vomiting (or both) before initiation of mannitol therapy. Mannitol is a powerful osmotic diuretic and can cause potentially serious fluid shifts.

Recovering patients should be cautioned to avoid eating fish or shellfish for 6 months after the intoxication. Relapses—sometimes as severe as the original attack—have occurred in patients who ate fish that were not ciguatoxic. Likewise, patients should avoid alcohol, mayonnaise, seeds, and nuts. Avoidance of cosmetics, epoxies, resins, glues, and solvents is also recommened, but these admonitions appear impractical, if not impossible.

Educating the traveler

Physicians should inform patients preparing for travel to endemic areas that ingestion of fish carries the risk of ciguatera. Travelers should be cautioned to inquire of personnel at eating establishments, local fisherman, or local health officials about potentially toxic varieties of fish in their area and should avoid those fish that may be dangerous. Admittedly, this may not be a simple task. Restaurant workers may not know, or may be unwilling to risk their jobs by being frank. Officials may downplay possible risk to avoid a perceived adverse effect on tourism by admitting that the local delicacies could make people extremely ill. Travelers should avoid eating larger specimens (weighing more than 5 pounds) of most tropical fish and completely avoid barracuda, moray eels, fish roe, fish heads, and viscera.

Comments

Ciguatera is the most common toxic fish poisoning worldwide and is increasing in incidence, prevalence, and distribution as the world increasingly becomes a "global village." The presentation of ciguatera is usually distinctive, which facilitates identification. The most promising treatment seems to be intravenous administration of mannitol, but the drug's mechanism in reversal of the syndrome remains a mystery.

Ciguatera is at least annoying and at worst disastrous to the patient. For people living in tropical countries who depend on fish for their subsistence, the potential effects are wider. In a fascinating article, Nancy D. Lewis,[24] of the University of Hawaii, discusses the impact further. She points out that ciguatera also limits the development of export fisheries and may adversely affect tourism. She states that an increase in ciguatera makes islanders more dependent on imported foods, which decreases self-sufficiency and forces native populations into a cash economy and away from traditional means of subsistence. This leads to greater dependence on industrialized countries.

Ciguatera may spread when reef ecology is disturbed. It has been hypothesized[5] that it increases with dredging, shoreline development, and pollution. If this is the case, physicians, to be effective in the broadest possible sense, must take a proactive role in issues affecting the

Table 3
Common Syndromes Associated With Seafood Consumption

	Ciguatera	Scombroid	Paralytic shellfish poisoning	Neurotoxic shellfish poisoning
Most common sources	Reef-associated fish	Tuna, mackerel, jacks, and others	Raw or cooked shellfish	Shellfish (probably both raw and cooked
Chemical mediator	Ciguatoxin	Histamine	Saxitoxin and other toxins associated with Gonyaulax (dinoflagellate)	Brevetoxin associated with Ptychodiscus (dinoflagellate causing red tide)
Onset	30 min to 30 h	Minutes to hours	Usually within 30 min	1 h to 3 h
Signs and symptoms	Perioral, oral, and acral aresthesias; emperature reversal; headache; dizziness; fatigue/weakness; arthralgias; myalgias; pruritus; vomiting/diarrhea; abdominal pain; coma (rare); death (rare); hypotension	Flushing (especially face, neck, upper trunk); headache; dizziness; pruritus; coryza; urticaria; bronchospasm; vomiting/diarrhea; abdodminal pain; tachycardia; hypotension	Oral, facial, and acral paresthesias; "floating sensation"; ataxia; vertigo; muscle weakness; paralysis cranial nerve dysfunction; nausea/vomiting; diarrhea; respiratory collapse (rare)	Similar to those of ciguatera but milder
Treatment*	Mannitol, IV Amitriptyline, PO	Diphenhydramine, IM Cimetidine, IV	Supportive gastric lavage; activated charcoal; catharsis sodium bicarbonate, IV	Supportive symptomatic
Recovery	Days to years	12 h to 24 h	Days to weeks	Days

*IM, intramuscularly; IV, intravenously; PO, orally.

environment as well as an active role in treating the individual patient.

Acknowledgments

Many thanks to Barbara Shipman, MA, of the Ingham Medical Center Library, Lansing, Mich, for her skilled and eternally cheerful assistance, and to Yoshitsuro Hokama, PhD, of the University of Hawaii; Arthur L. Hupka, PhD, of the Ponce School of Medicine, Ponce, Puerto Rico; and T.R. Tosteson, PhD, of the University of Puerto Rico, for their time and invaluable help.

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