

Illnesses Caused by Marine Toxins

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Marine toxins are produced by algae or bacteria and are concentrated in contaminated seafood. Substantial increases in seafood consumption in recent years, together with globalization of the seafood trade, have increased potential exposure to these agents. Marine toxins produce neurological, gastrointestinal, and cardiovascular syndromes, some of which result in high mortality and long-term morbidity. Routine clinical diagnostic tests are not available for these toxins; diagnosis is based on clinical presentation and a history of eating seafood in the preceding 24 h. There is no antidote for any of the marine toxins, and supportive care is the mainstay of treatment. In particular, paralytic shellfish poisoning and puffer fish poisoning can cause death within hours after consuming the toxins and may require immediate intensive care. Rapid notification of public health authorities is essential, because timely investigation may identify the source of contaminated seafood and prevent additional illnesses. Extensive environmental monitoring and sometimes seasonal quarantine of a harvest are employed to reduce the risk of exposure.

These ye shall eat of all that are in the waters: all that have fins and scales shall ye eat: And whatsoever hath not fins and scales ye may not eat; it is unclean unto you.

—Deuteronomy 14:9–10

The Biblical injunction would have limited consumption by the ancient Israelites of all shellfish and various species of fish, including puffer fish, found in the Near East; one may speculate whether the injunction was based on empirical experience of illness. In the contemporary United States, the rate of consumption of seafood is increasing. The annual per capita consumption of fish and shellfish in the United States was 7.4 kg in 2003; the annual per capita consumption of shrimp increased from 6.4 kg to 1.82 kg between 1980 and 2003 [1]. Long-chain polyunsaturated n-3 fatty acids, found in seafood, significantly reduce the risk of cardiovascular diseases [2] and possibly other disorders, including cancers [3]. International trade has dramatically increased the year-round availability of assorted seafoods, many of which come from distant geographic locations.

In the United States, 2.2 billion kg of imported seafood were consumed in 2003 [1].

Intoxications from seafood, which are relatively uncommon but likely underreported, are due to algal or bacterial toxins that accumulate in shellfish, fish, and rarely crustaceans (e.g., lobster and crab) or to the production of histamine by spoilage bacteria in fish. These toxins are not detectable by sight or smell, and the seafood in which they are found appears normal. Marine toxins are heat stable and largely unaffected by cooking. Diagnostic tests for any of the marine toxins are not available in health care clinics, nor does an antidote exist for any toxin except histamine [4]. Accordingly, diagnosis is based on clinical presentation and a history of seafood consumption in the preceding 24 h, and treatment is essentially supportive. For patients affected by marine toxins that may cause rapid death, a high index of suspicion and placement in an intensive care unit are essential. Suspected cases should be reported immediately to local or state health departments, because rapid investigation may result in the identification of the contaminated food and the prevention of additional illnesses.

Prevention of illness is accomplished by extensive monitoring of toxin concentrations in seafood samples [5–9]. In some lo-

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cations, harvesting is restricted during certain months or when toxic algal concentrations exceed a specified level. Detailed protocols exist for testing of seafood for the presence of marine toxins associated with specific environments, and detected “action levels” of toxin result in a ban of harvesting [5, 10].

ALGAL TOXINS

Algae constitute most of the biomass of the oceans. Of ~5000 species of algae, ~40 species, of which most are dinoflagellates (*Pyrrhophyta* division), produce potent toxins [11]. These algae are a main source of food for shellfish and the larvae of crustaceans. Algae are also an important food source of small herbivorous fish, which may be consumed by larger fish that are, in turn, eaten by humans.

Under appropriate environmental conditions, algae can reproduce with extraordinary rapidity, even to the point of discoloring the sea, producing algal blooms that include “red tides” [12]. Toxin may be so concentrated in waters under these circumstances that it can be aerosolized by surf and cause a transient syndrome of inhalational intoxication in humans [11]. Red tides are associated with increased toxin levels in shellfish and fish, and commercial fishing is usually prohibited when they occur; but not all red tides are caused by toxin-producing dinoflagellates, and high toxin concentrations can be found in shellfish and fish in the absence of a red tide. Red tides are a natural phenomenon and are apparently increasing in frequency and extent, possibly because of ecological changes that include increased nitrogen and phosphorous content in coastal waters caused by aquaculture and agricultural runoff, global warming, the introduction of algae to new environments in ship-ballast water, or the introduction of foreign shellfish stocks [12].

Paralytic shellfish poisoning. Paralytic shellfish poisoning is a severe disease with rapid onset that may be life threatening (table 1). The syndrome is exclusively neurological. The illness is caused by saxitoxin and closely related marine toxins. Saxitoxin is a water-soluble, heat-stable tetrahydropurine that is produced by certain dinoflagellates and possibly other algae and bacteria [11]. Common exposures are mussels, scallops, and clams, but illness has been related to ingestion of crustaceans, gastropods, and fish. Toxin-containing shellfish are encountered principally in cold water regions on the coasts of the northwestern and northeastern United States, southern Chile, and Japan and in the North Sea; large-scale monitoring programs monitor toxin levels in shellfish in various countries [6–8]. Harvest areas are closed when toxin levels exceed defined action levels [10]. Dangerous levels of saxitoxin are encountered relatively frequently, but illness rarely occurs, suggesting that control strategies are effective. The mode of action of saxitoxin is blockage of voltage-gated sodium channels in nerve and muscle cell membranes, blocking nerve signal transmission [11].

Symptoms usually commence within 30 min after exposure. Tingling or numbness begin periorally and spread to the neck and face and are followed by headache, nausea, vomiting, and diarrhea [6, 13]. Death may result from respiratory muscle paralysis, and ingestion of a large dose of toxin may be followed by respiratory arrest and death within 2 h after onset of symptoms [14]; in one outbreak affecting 187 persons, 70% were hospitalized, and 14% died [13]. No antidote exists, and supportive treatment, including artificial ventilation (when necessary), is the mainstay of therapy. The definitive diagnostic test is a mouse bioassay of suspected food or waters, which is not clinically available; diagnosis, therefore, is based on clinical presentation and a history of seafood consumption in the preceding 24 h. Between 1998 and 2002, there were 7 outbreaks reported in the United States that affected a total of 43 persons, 13 of whom were hospitalized and none of whom died (Centers for Disease Control and Prevention [CDC], unpublished data). Saxitoxin intoxication can also be caused by consumption of puffer fish, which is the classic food vehicle of tetrodotoxin poisoning (see below) [15].

Diarrheic shellfish poisoning. Diarrheic shellfish poisoning is a rapid-onset, self-resolving illness with exclusively gastrointestinal symptoms (table 1). Symptoms are typically severe, but always self-limiting. The illness is caused by okadaic acid and possibly related toxins produced by certain dinoflagellates. Okadaic acid is a lipophilic polyether that inhibits eukaryotic protein phosphatases and is thought to cause diarrhea by phosphorylation of control proteins that results in sodium release by intestinal mucosal cells [11]. The illness is most common in Japan, and outbreaks have occurred in Europe [16]; no cases have been reported in the United States. Symptoms usually occur within 30 min after exposure and include diarrhea and abdominal cramps that typically resolve within 3–4 days after onset; hospitalization of affected persons is rare [6]. Okadaic acid and related toxins are potent tumor-growth promoters and immunosuppressants in animals, but the effect of acute or chronic exposure in humans is unknown [11]. The standard toxin test—a bioassay in mice of suspected food and waters—is not clinically available; diagnosis depends on clinical presentation and a history of seafood consumption.

Amnesic shellfish poisoning. Amnesic shellfish poisoning is a rare illness with symptoms ranging from gastrointestinal disturbance to severe and unusual neurological manifestations (table 1). It is caused by domoic acid, a water-soluble, heat-stable amino acid that is produced by certain algal diatoms of *Pseudo-nitzschia* species. The disease was first documented and its etiologic agent was ascertained during a large outbreak in Canada in 1987 [17], in which 107 persons developed a distinct illness after consuming contaminated mussels; 19 persons were hospitalized and 4 persons died [18]. Gastrointestinal symptoms, including vomiting, cramps, and diarrhea, occurred

Table 1. Select characteristics of syndromes caused by marine toxins [6–8].

Syndrome	Symptoms	Time to onset of symptoms after exposure to toxin	Treatment	Toxin and source	Mechanism of toxin action	Food source	Main geographic distribution in environment
Paralytic shellfish poisoning	Facial and perioral paresthesias, headache, dizziness, muscular weakness, ataxia and dysmetria, mental status changes, nausea and vomiting, respiratory compromise, and death	30 min–4 h	Supportive care and mechanical ventilation	Saxitoxin produced by dinoflagellates	Blocks sodium channels	Shellfish and other fish	Northwest and northeast United States, southern Chile, the North Sea, and Japan
Diarrheic shellfish poisoning	Diarrhea, nausea and vomiting, abdominal cramps, and chills	30 min–12 h	Supportive care	Okadaic acid produced by dinoflagellates	Inhibits protein phosphatases	Shellfish	Japan, Europe, and the coast of Africa
Amnesic shellfish poisoning	Nausea and vomiting, abdominal cramps, diarrhea, headache, visual disturbances, weakness, mental status changes, cranial nerve palsies, autonomic nervous dysfunction, amnesia, pain, seizures, coma, and death	Gastrointestinal, <24 h; neurological, <48 h	Supportive care	Domoic acid produced by diatom alga	Stimulates glutamate receptors	Shellfish	Eastern Canada, and northeastern and western United States
Ciguatera	Facial and perioral paresthesias, headache, reversed temperature perception, arthralgia, rash, cyanosis, insomnia, myalgia, extremity pain, loss of hair and nails, motor disturbances, coma, and death	3–30 h; may recur or be induced later	Supportive care and treatment with mannitol	Ciguatoxin, maitotoxin, and other toxins produced by dinoflagellates	Ciguatoxin opens sodium channels; maitotoxin opens calcium channels	Large predatory reef fish, such as barracuda, snapper, grouper, kahala, and others	All tropical areas
Neurotoxic shellfish poisoning	Paresthesias, abdominal pain, dizziness and diplopia, diarrhea, gait disturbance, chills, reversed temperature perception, headache, musculoskeletal pain, and respiratory difficulty	3–6 h	Supportive care	Brevetoxins produced by dinoflagellates	Opens sodium channels	Shellfish and other fish	Western Florida and the Caribbean
Scombroid fish poisoning	Bright pruritic facial and truncal rash, flushing and sweating, perioral tingling, peppery taste in mouth, headache, facial and lingual swelling, wheezing, cramps, nausea and vomiting, diarrhea, dizziness and blurred vision, tachycardia, and circulatory compromise	Minutes to hours	Antihistamines and supportive care	Histamine and possibly other factors	Histaminic action	Tuna, mahi-mahi, blue fish, mackerel, skipjack, and other fish	Worldwide; in places with poor conditions of storage of fresh fish
Puffer fish poisoning	Numbness of face and extremities, sensation of detachment or doom, ascending paralysis, respiratory failure, circulatory collapse, and death	30 min–3 h	Supportive care and mechanical ventilation	Tetrodotoxin produced by bacteria; saxitoxin produced by dinoflagellates	Blocks sodium channels	Puffer fish	East Asia, especially China and Japan

within 24 h after exposure, and neurological symptoms began within 48 h after exposure. Gastrointestinal symptoms were prevalent in patients aged <40 years, and neurological symptoms were prevalent in patients aged >50 years. Nearly one-half of the patients experienced neurological symptoms, the most common of which were severe headache and short-term memory loss. Twelve patients experienced severe symptoms, including agitation, seizures, coma, profuse respiratory secretions, and circulatory instability. Most of these 12 patients were >65 years old or had chronic comorbidities. Crude estimates of the ingested amount of toxin indicated a dose-response relationship with the presence and severity of neurological symptoms [18], whereby the severity of symptoms increased with an increased dose of ingested toxin. Four to 6 months after onset of acute illness, 12 of 14 severely ill patients still demonstrated anterograde amnesia, and several demonstrated retrograde amnesia [19]. Neuropathologic examination of tissue specimens obtained from patients who died within 4 months after the start of the outbreak revealed neuronal necrosis and degeneration in the hippocampus and amygdala [19]. Animal studies have shown acute brain toxicity following domoic acid exposure that corresponded with findings of human postmortem examination [17]. Domoic acid strongly stimulates glutamate receptors and would disrupt neurochemical transmission in the brain [17]. Domoic acid-producing algae have been isolated worldwide [7]; monitoring programs have been instituted in many countries.

Ciguatera. Ciguatera is typically a self-limiting illness manifesting combinations of gastrointestinal, neurological, and cardiovascular symptoms (table 1) [20]. It is the one of the most common forms of seafood intoxication, with an estimated 20,000–50,000 cases occurring annually worldwide [6, 8]. Illness is caused by 2 dinoflagellate toxins. Ciguatoxin and closely related toxins are lipophilic, heat-stable polyethers that open voltage-sensitive sodium channels at the neuromuscular junction, resulting in membrane hyperexcitability, spontaneous repetitive neurotransmitter release, blockage of synaptic transmission, and depletion of synaptic vesicles [11]. Maitotoxin is a water-soluble molecule that opens calcium channels of the cell plasma membrane; it is the most toxic nonproteinaceous molecule known [11]. Both are produced by certain dinoflagellates that are consumed by small herbivorous fish that are in turn consumed by carnivorous fish, resulting in bioconcentration of the toxin along the food chain. Consequently, unlike the shellfish poisoning syndromes, ciguatera is caused by consumption of large tropical reef-dwelling carnivorous fish from the oceans between latitudes 35° north and south of the equator. Hundreds of fish species have been implicated in ciguatera outbreaks; the most common include barracuda, grouper, sea bass, snapper, and amberjack [6, 8, 9]. Symptoms typically begin 6 h after exposure, but the incubation period may be up

to 30 h. Diarrhea, vomiting, and cramping occur in about one-half of affected persons, and when they are present they precede neurological symptoms. Cardiovascular symptoms include hypotension, bradycardia, and tachycardia. Neurological symptoms are present in 90% of cases (table 1). The classic reversal of temperature perception is striking; affected persons describe cold objects as producing a sensation of heat, burning, or “dry ice.” Gastrointestinal and cardiovascular symptoms typically resolve within a few days after onset; neurological symptoms persist for several weeks. Severe cases manifest symptoms for months or years, which may subsequently recur under conditions of stress or following exposure to fish, shellfish, alcohol, or nuts. The overall mortality rate is ~0.1% [6–9, 21–23]. There has been a convincing report of sexual transmission of ciguatera [24]; ciguatoxin has been observed in breast milk [21], and in pregnant women it can cause premature labor and abortion [23]. In the absence of clinical tests, diagnosis is based on clinical presentation and a history of seafood consumption. No antidote exists. In uncontrolled trials, intravenous treatment with mannitol administered early after the onset of illness has been reported to produce resolution of symptoms [25]. A more recent double-blind controlled trial showed no benefit [26], but clinical opinion remains divided, and some authorities advocate this treatment. Otherwise, treatment is supportive. Between 1998 and 2002, there were 101 outbreaks reported in the United States that affected a total of 374 persons, 30 of whom were hospitalized and 1 of whom died (CDC, unpublished data). Prevention would require avoiding reef fish, especially barracuda, which has such a high risk that its sale and distribution have been banned by some jurisdictions in the United States.

Neurotoxic shellfish poisoning. Neurotoxic shellfish poisoning produces a transient illness characterized by gastrointestinal and neurological symptoms (table 1). Illness is caused by members of the brevetoxin family of toxins, which are lipophilic polyethers that, like ciguatera, open voltage-sensitive sodium channels [11]. The toxin is produced by the dinoflagellate *Gymnodinium breve*, which is found principally in the Gulf of Mexico, the Caribbean, and New Zealand [11]. The dinoflagellate produces red tides in Florida that may result in massive fish kills; aerosolization of the toxin from sea water produces a transient, self-resolving inhalational syndrome in humans. Symptoms include perioral paresthesias, diarrhea, gait deficits, and the reversal of temperature sensation noted so prominently in persons with ciguatera. Symptoms typically resolve within 48 h after onset; hospitalization of affected persons is rare; and no deaths have been reported to be associated with the illness [6–9]. Diagnosis is based on clinical presentation and a history of seafood consumption. Treatment is supportive. Between 1998 and 2002, there were 2 outbreaks reported in the United States that affected a total of 4 persons, 1 of whom

was hospitalized and none of whom died (CDC, unpublished data).

TOXINS FROM OTHER SOURCES

Scombroid fish poisoning (histamine fish poisoning). Scombroid fish poisoning is probably the most common seafood-related intoxication and is mostly caused by consumption of fish with high histamine levels, and symptoms are essentially the same as those associated with histamine toxicity. "Scombrotoxin" as such does not exist (table 1). The syndrome has been classically described as being associated with both fresh and processed fast-swimming, deep-sea fish of the Scombroidea family, such as tuna, bonito, and mackerel, which have high levels of tissue histidine. It is also caused by consumption of nonscombroid fish, such as blue fish, sardines, anchovies, amberjack, and mahi-mahi. High histamine levels in fish result from postmortem spoilage bacteria that proliferate when the catch is not adequately refrigerated. These bacteria catalyze the decarboxylation of histidine to histamine, which is heat stable. Scombroid fish poisoning from fish with low histamine levels does occur, and the action of nonhistamine vasoactive amines or histamine potentiators has been proposed as the cause [6, 27]. The disease occurs worldwide. Very high histamine levels can exist in fish without perceptible changes in the appearance or smell of the fish. Adequate refrigeration from the time the fish is hooked or netted until cooking is the key to prevention [28]. Symptoms include tingling and burning sensations around the mouth, headache, facial flushing, palpitations, profuse sweating, truncal rash and pruritis, abdominal cramps, nausea, and diarrhea [29]. In most persons, these symptoms, although alarming, are self-limiting, but circulatory collapse, shock, and acute pulmonary edema have been described. The condition may be confounded by an allergic reaction [30, 31]; misdiagnosis of symptoms as those of coronary heart disease may result in inappropriate medical interventions. For most mild cases, prompt antihistamine treatment is effective. Diagnosis is based on clinical presentation and a history of food consumption. Food-safety laboratories in the public health system can confirm the diagnosis by demonstrating elevated histamine levels in leftover fish. Between 1998 and 2002, there were 167 outbreaks reported in the United States that affected 703 persons, 38 of whom were hospitalized and none of whom died (CDC, unpublished data).

Puffer fish poisoning. Puffer fish poisoning is a lethal intoxication resulting from consumption of toxic species of the puffer fish, which is also known as fugu, globefish, or blowfish and which resides in shallow waters of tropical and temperate seas (table 1). The causative agent is tetrodotoxin, a heat-stable, water-soluble molecule that acts by blocking sodium channels and interfering with axonal nerve transmission in skeletal muscle [32]. Tetrodotoxin is produced by bacteria concentrated in

the viscera (i.e., gonads, liver, and spleen) and skin of the fish; the highest levels of tetrodotoxin are observed in female puffer fish at the peak of reproductive season [33]. Puffer fish consumption is culturally sanctioned in Japan, where it is served in ceremonial meals prepared by expert chefs trained to remove the tetrodotoxin-containing tissues. Despite the attendant precautions, several dozen Japanese puffer fish-eaters die each year [32]. Outside Japan, most illnesses are probably due to consumption of the fish by noncommercial fishermen unaware of the risk [33] or by sale of processed toxic fish to the public (a consequence of inadequate government controls) [34]. The disease is exceedingly rare in the United States; 1 outbreak was caused by fish imported in a traveler's luggage [35].

Symptoms usually begin within 30 min after exposure and completely resolve within 24 h after onset. They begin with perioral paresthesia, which may spread to the entire body, and could possibly be followed by vomiting, lightheadedness, dizziness, and a sensation variously described as "floating" or doom-laden. Ascending paralysis has been reported in the majority of case studies [32]. In fatal cases, progression is precipitous, with death due to respiratory muscle paralysis occurring within 6 h after onset of symptoms [36]. Fatality rates in the early twentieth century were ~60%, but a large case series study from the 1970s reported a rate of 37% [37], and a case series study from the 1990s reported a fatality rate of 14% [33]. Survival depends on the immediate provision of intensive care; because the severity of illness is proportional to the ingested dose of toxin, gastric lavage and activated charcoal administration have been recommended [35]. Diagnosis is based on clinical symptoms and a history of food consumption, and treatment is supportive. Public health authorities may be able to arrange testing of food samples, samples of stomach contents, or biological specimens.

Although the designation puffer fish poisoning refers to illness from tetrodotoxin, in some regions puffer fish contain saxitoxin, the causative agent of paralytic shellfish poisoning, and consumption of them has caused human illness [15].

NEW AND EMERGING MARINE TOXINS

Paralytic shellfish poisoning, ciguatera, scombroid fish poisoning, neurotoxic shellfish poisoning, and puffer fish poisoning have been known for centuries, although their toxins were only recently described [11]. Diarrhetic shellfish poisoning was recognized in the 1960s, and amnesic shellfish poisoning was recognized in the 1980s. A new human toxin syndrome, azaspiracid poisoning, came to light in the 1990s [38]. Symptoms closely resemble those associated with diarrhetic shellfish poisoning. Within a few years of its discovery, cases of human illness from several European countries were attributed to this toxin, and azaspiracid-producing dinoflagellates were isolated in extensive regions of northern European waters [39].

In 1993, a total of 188 persons were admitted to a hospital in Madagascar after consuming a shark with symptoms of burning perioral pain, parasthesias, ataxia, cranial nerve palsies, coma, convulsions, and respiratory distress. Fifty patients (27%) died. On the basis of clinical findings, 1 report diagnosed the illness as ciguatera, attributing the high mortality rate to very high toxin levels in the shark [40]. A separate investigation, however, reported identification of novel toxins [41].

Given the ubiquity of algal species, the increasing consumption of seafood by humans, and the acceleration of ecological changes, it is possible that new syndromes may emerge. Familiar syndromes may become associated with new species of seafood; for example, saxitoxin poisoning might emerge from consumption of recreationally caught puffer fish in Florida [15], or toxin-producing algae might spread to new environments, as demonstrated by a lethal outbreak of paralytic shellfish poisoning in Guatemala [13].

CONCLUSIONS

In the absence of readily available clinical tests, diagnosis of marine toxin poisoning is based on clinical findings and a history of food consumption. Obtaining a history of seafood consumption, and possibly a history of illness in people exposed to shared seafood, may be critical in determining a diagnosis. Puffer fish poisoning and paralytic shellfish poisoning can be rapidly fatal, and antidotes do not exist. These syndromes may not be readily distinguishable from those produced by the more benign marine toxins. Immediate placement in an intensive care unit and provision of artificial ventilation (when needed) are the keys to survival in severely affected patients. Rapid reporting to public health authorities is critical for identification of the source of contaminated food and prevention of additional illnesses. Public health may be able to provide results of delayed confirmatory testing of clinical specimens and food samples.

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