CHAPTER 34

Fish and Shellfish Poisoning: Toxic Syndromes

Elaine C. Jong

Toxic seafoods are causative agents in a number of gastrointestinal and neurologic illnesses. Historically, these illnesses were seen mainly in specific geographic locations, associated with local seafood products and affecting local resident populations. However, that situation has now changed remarkably: ever-increasing growth in international tourism and the global fish market that emerged over the past two decades have contributed to increased cases of seafood intoxication presenting as unfamiliar toxic syndromes among seafood consumers in non-endemic areas far distant from the seafood's place of origin and in returned international travelers. Thus it is important for all healthcare providers, especially emergency medicine personnel and primary care providers worldwide, to become familiar with the clinical presentations, mechanisms of toxicity, and currently accepted treatments for some of the more common seafood intoxications.

The focus of this chapter is on toxic syndromes in humans resulting from the inadvertent ingestion of toxin-contaminated fish or shellfish. Illnesses that may result from bacterial, viral, or parasitic contamination of food and water are discussed in Chapters 8, 22, 23, and 31-33.

Marine biotoxins are acquired by small herbivorous fish that eat algae; they are concentrated in the skin, musculature, and viscera (i.e., ichthyosarcotoxic), in the reproductive organs (i.e., ichthyotoxic), or in the blood (ichthyohemotoxic). Big carnivorous fish eat the little fish, and the toxin is conserved in increasing concentrations moving up the food chain. Of the nine kinds of ichthyosarcotoxism (based on types of fish), the most important are scombroid, ciguatera, and puffer fish (tetrodotoxin) poisoning. Botulism toxin E intoxication is briefly covered as part of the differential diagnosis of fish poisoning syndromes and is considered in Chapter 33.

Shellfish acquire marine biotoxins from filter feeding on algae. Four major toxic syndromes associated with bivalve mollusk consumption are major health and economic concerns: paralytic shellfish poisoning, neurotoxic shellfish poisoning, diarrhetic shellfish poisoning, and amnesic shellfish poisoning.

A patient's history of a specific seafood ingestion is crucial to establishing the diagnosis of fish or shellfish poisoning. Often patients will not easily recall the inciting meal, as in most cases there is no uniformly reliable appearance, smell, or taste that distinguishes contaminated seafood prior to ingestion and development of symptoms.

SCOMBROID FISH POISONING

Scombroid poisoning is the name given to the histamine-like reaction that occasionally results from the ingestion of improperly cooled and stored tuna and related species in the family Scombridae. These dark-meat fish include the skipjack tuna (*Euthynnus pelamis*), the bonito (*Sarda sarda*), the mackerel (*Scomber scombrus*), and the albacore (*Thunnus alalunga*). A nonscombroid fish, mahi-mahi (*Coryphaena hippurus*), can also become toxic and is actually

a commonly implicated fish in scombroid outbreaks in the United States. The Centers for Disease Control and Prevention reported two outbreaks of scombroid fish poisoning in late 2006, one in Louisiana and one in Tennessee. Both outbreaks were associated with tuna steaks imported from Indonesia and Vietnam, but consumed in Louisiana and Tennessee, respectively.

Fish become toxic after being caught, when inadequate cooling during transport and storage allows for bacterial proliferation. These bacteria (primarily *Morganella morganii* but also other bacteria such as *Escherichia*, *Proteus*, *Salmonella*, and *Shigella* species) degrade histidine present in the musculature of the fish to heat-stable histamine and a histamine-like substance termed saurine. Studies suggest that most symptoms are due to saurine, as histamine when given orally is poorly absorbed and chemically inactivated in the gastrointestinal tract. An exception may occur in patients treated with isoniazid for tuberculosis, as this medication inhibits histaminase in the gut and may make patients more susceptible to the histamine contained in scombrotoxic fish, thus accentuating the symptoms and signs of scombroid poisoning.

Scombrotoxic fish usually appear normal, but toxicity should be suspected if the fish tastes "peppery or sharp." *Within 30 minutes of ingestion of a toxic fish, a systemic histamine-like reaction occurs*. Symptoms and signs include headache, flushing, a burning or peppery taste in the mouth, abdominal cramps with nausea, vomiting, diarrhea, tachycardia, dry mouth, and occasionally urticaria, angioedema, and bronchospasm. Symptoms are transient, rarely lasting over 8-12 hours, and deaths are unusual. Diagnosis is clinical but can be confirmed by measuring the histamine content of the suspected fish, which is generally 20 mg/100 g of fish muscle, or higher (normal histamine content is <1 mg/100 g of fish muscle). Treatment consists of forced emesis and antihistamines. In addition to diphenhydramine (Benadryl), treatment with histamine-2 antagonists such as cimetidine (300 mg intravenous [IV]) or ranitidine (50 mg IV) may provide symptomatic relief. If symptoms are severe, the patient may require IV fluids, antiinflammatory steroids, aminophylline, and epinephrine as used for anaphylaxis-like reactions.

Prevention consists of storing the fish at less than 40°F (4.4°C) at all times between catching and consumption, according to food-safety recommendations.

CIGUATERA FISH POISONING

Ciguatera poisoning presents with acute gastrointestinal and neurologic symptoms following the ingestion of normally edible reef fish that contain ciguatoxins produced by the unicellular marine dinoflagellate *Gambierdiscus toxicus*. Most outbreaks occur in the Caribbean, the Indo-Pacific islands, and the Indian Ocean between 35° North and 35° South latitude. Although more than 425 species of fish are known to be occasionally toxic, the more commonly implicated fish include the barracuda (Sphyraenidae), red snapper (*Lutjanus bohar*), grouper, amberjack (*Seriola dumerili*), sea bass (Serranidae), surgeonfish (Acanthuridae), and moray eel (Muraenidae). Previously, ciguatera poisoning was rarely reported outside local communities within the endemic tropical latitudes; however, increasing numbers of cases are being seen in nontropical countries as the number of international tourists grows each year, and unwary travelers who ingested contaminated fish in endemic areas return home with persistent symptoms. Ciguatera poisoning has become a world health issue as reef fish caught in ciguatera-endemic areas are exported to distant non-endemic areas.

Ciguatoxin (gambiertoxin) is a nonprotein polyether toxin with water-soluble and lipid-soluble fractions. The toxins and their metabolites are accumulated in the musculature, liver, and viscera of herbivorous fish and are concentrated in the food chain when carnivorous fish feed on the smaller herbivorous fish. The toxins become more polar as they undergo oxidative metabolism and pass up the food chain. Increasing polarity of the toxin is associated with increased toxicity, and humans are exposed at the end of the food chain.

The main Pacific ciguatoxin (P-CTX-1) causes ciguatera poisoning at levels of 0.1 mcg/kg or higher in the flesh of carnivorous fish, whereas the main Caribbean ciguatoxin (C-CTX-1) is less polar and 10-fold less toxic than P-CTX-1. Ciguatoxin induces partial

membrane depolarization by enhancing sodium ion permeability in voltage-dependent sodium channels in nerve cell membranes. A recent report suggests that the ciguatoxins and brevetoxin (involved in neurotoxic shellfish poisoning) may have a potent effect on TRPV1 channels, modulating thermal and pain sensation.

Ciguatoxins are not affected by heating, freezing, or drying, and toxic fish have normal taste, texture, and odor. *Symptoms develop 2-6 hours following ingestion of the fish* and last about 1 week but occasionally can extend for months or even years. Typically, patients develop gastrointestinal symptoms such as nausea, watery diarrhea, abdominal cramps, or vomiting. Persistent bradycardia lasting several days has also been reported. Distal paresthesias are common, and the teeth may feel numb or loose. A majority of victims note an unusual hot-cold sensory reversal, in which cold objects "burn" when handled. Asthenia and arthralgias are frequent, and 10-45% of patients develop pruritus, usually 1-3 days after fish ingestion. Erythematous skin rashes that may blister or desquamate can occur in up to 20% of patients. In severe instances, ataxia, paresis, paralysis, or transient blindness occurs, often in association with sinus bradycardia and hypotension. Deaths are generally the result of respiratory depression, coma, and convulsions.

Diagnosis is made clinically but can be verified by assaying for the toxin in the implicated fish, using a bioassay (mouse, cat, mongoose, or brine shrimp), an enzyme-linked immunosorbent assay, or a radioimmunoassay.

Treatment is supportive and consists of forced emesis, IV fluids if volume is depleted, and respiratory support if indicated. IV mannitol (1 gm/kg) was reported to ameliorate neurologic symptoms when given acutely, but subsequent studies did not confirm its efficacy. Other drugs that have been anecdotally reported to give symptomatic relief are amitriptyline (50 mg/day), tocainide (400 mg three times a day), and nifedipine (10 mg three times a day). Another published report described successful treatment of ciguatera poisoning symptoms with gabapentin, a drug structurally related to gamma-aminobutyric acid and usually employed as an antiepileptic or for treatment of chronic pain. Treatment with gabapentin, 400 mg orally three times daily for up to 5 weeks, was reported to relieve neurologic symptoms, pruritus, and sharp, shooting pains in the legs associated with ciguatera poisoning, even though treatment was initiated 1 month after the onset of symptoms.

PUFFER FISH POISONING (TETRODOTOXIN POISONING)

Puffer fish, porcupine fish, ocean sunfishes, and related species in the order Tetraodontiformes are frequently poisonous and may produce a severe neurologic illness following ingestion. This is a particular problem in Japan, Taiwan, and Southeast Asia where puffer fish (*fugu*) is a culinary delicacy. The intoxication has been rarely reported in the United States.

The toxicity is due to the accumulation of tetrodotoxin in the ovaries, liver, intestines, and, to a lesser extent, the musculature of the fish. The toxin is believed to originate from something the puffer fish ingests, but attempts to implicate specific species of algae, jellyfish, sponges, and so forth have not been definitive. A clear correlation does exist, however, between the reproductive season of the puffer fish and its likelihood of being poisonous.

Tetrodotoxin is a nonprotein aminohydroquinazoline compound with a heterocyclic structure. It is water-soluble and heat-resistant and does not alter the taste or appearance of the fish. It appears to be similar, if not identical, to tarichatoxin, present in the California newt, and also to a toxin present in the skin of *Atelopus* frogs in Costa Rica. Physiologically, tetrodotoxin is similar to saxitoxin and (see below) prevents the generation of action potentials by blocking the voltage-sensitive sodium channels in the membranes of nerves and muscle, but it has no effect on potassium conductance.

Most patients experience *signs and symptoms of tetrodotoxin poisoning within 6 hours of ingestion, but a few have experienced a delayed onset of up to 20 hours*. Signs and symptoms include profuse sweating and salivation, hypothermia, headache, tachycardia, and hypotension. Gastrointestinal symptoms of nausea, vomiting, diarrhea, or abdominal pain may or may not be present. The hallmark of puffer fish poisoning is neurologic: paresthesias that frequently progress to numbness, ataxia, tremor, and paralysis involving both cranial and peripheral

nerves. Respiratory compromise and cardiac arrhythmias may result. Occasional patients have complete flaccid paralysis with absent corneal reflexes and dilated pupils but maintain consciousness; these patients require ventilatory support including intubation and mechanical ventilation. Mortality may reach 60%, but the prognosis is good with eventual full recovery if the patient survives the first 24 hours.

Diagnosis is made on clinical grounds. There is no effective antidote. If the patient is seen within 3 hours of ingestion, gastric lavage with 2 L of 2% sodium bicarbonate, followed by instillation of activated charcoal in 70% sorbitol solution, may help to remove toxin from the gastrointestinal tract. Patients require supportive care with special attention to the pulmonary status. Serial vital capacity tests should be done, and early intubation is recommended if there is evidence of inadequate ventilation. There are anecdotal reports of improvement with edrophonium, pralidoxime, and atropine.

Attempts in Japan to prevent the disease have included the requirement of a special license for both restaurants and cooks wishing to serve puffer fish. Only the musculature of the puffer fish can be served and that only during the nonreproductive season (winter months), when the fish are least likely to be toxic. Recreational fishermen in Asian and Southeast Asian waters should be educated as to the identification and potential toxicity of puffer fish and related species.

BOTULISM TOXIN E

Clostridium botulinum bacteria secreting botulism toxin type E have been reported as contaminants of improperly processed or smoked fish and fish eggs. Approximately 24-36 hours after ingestion of contaminated seafood, gastrointestinal symptoms may develop, followed in 3-7 days by cranial nerve dysfunction and symmetric descending weakness. The botulism toxin E blocks acetylcholine release at the neuromuscular junction. The diagnosis is made by clinical presentation and a history of eating preserved fish or fish eggs. Treatment consists of supportive care; heptavalent botulism antitoxin obtained from the CDC should be administered as soon as possible (Chapter 33).

PARALYTIC SHELLFISH POISONING

An unusual neurologic disorder that may follow shellfish ingestion is termed paralytic shellfish poisoning. The disease is primarily associated with the consumption of bivalve mollusks, such as clams, mussels, and oysters, but has also been reported following ingestion of gastropods, chitons, starfish, and crustaceans. Crab, abalone, and fin fish do not appear to be affected. The disease is mainly restricted to temperate climates, with most reported outbreaks in North America, Europe, and Japan, although cases have also occurred in South Africa, Papua New Guinea, and New Zealand.

The toxicity of paralytic shellfish poisoning is due to the accumulation of saxitoxin, a tetrahydropurine base, and related compounds in the shellfish. It does not affect the appearance or taste of the marine mollusks, nor is it effectively inactivated by cooking. Like tetrodotoxin, it blocks action potential generation by preventing sodium ion flow in nerve and muscle cell membranes.

Saxitoxin originates in a unicellular dinoflagellate known as *Gonyaulax*. Since bivalve mollusks are filter feeders, they concentrate the toxins from *Gonyaulax* in their digestive glands (the hepatopancreas). In the Alaska butter clam (*Saxidomus*), the saxitoxin is concentrated in the siphon as well. Toxicity of shellfish correlates with the bloom of this dinoflagellate, known colloquially as "red tide" due to discoloration of coastal waters. Along the Pacific Coast these usually occur between May and October. Toxicity lessens as the dinoflagellate population decreases, but complete detoxification of shellfish may take up to a year.

Symptoms usually occur within 30 minutes after ingestion of contaminated shellfish and include distal and oral paresthesias that may progress to numbness. A sensation of "floating," gross incoordination, and paralysis with respiratory compromise may develop. The case fatality rate is 8.5%.

Diagnosis is clinical, and treatment is supportive, as with other fish poisonings. Suspect shellfish can be analyzed in a mouse bioassay. Toxic shellfish have more than 4 MU (mouse unit)/g wet flesh (1 MU of saxitoxin is the amount that kills a 20-g mouse 15 minutes following intraperitoneal injection of a heated acid extract of the shellfish). Increasing application of liquid chromatography-mass spectrometry methods for the detection of marine biotoxins in seafood safety and surveillance programs will allow for faster analysis of toxic samples.

Prevention of paralytic shellfish poisoning requires public health measures, with routine surveillance and prompt closure of any beach to shellfish collecting when toxic levels of saxitoxin are detected. A Shellfish Safety Hotline (1-800-562-5632) gives information 24 hours a day on harmful algal blooms on Pacific Ocean beaches in Washington state; Oregon maintains its own hotline (1-800-449-2474).

NEUROTOXIC SHELLFISH POISONING (NONPARALYTIC)

Neurotoxic shellfish poisoning affects people who eat mollusks from red tides off the Florida coast. The contaminated shellfish contain brevetoxin from the dinoflagellate *Ptychodiscus brevis* in the red tides. About 1-6 hours after ingestion of contaminated shellfish, the affected person will experience paresthesias, reversal of hot and cold temperature sensation, ataxia, nausea, vomiting, and diarrhea. As mentioned above, both ciguatoxins and brevetoxin may act on TRPV1 channels in nerve cell membranes, affecting thermal and pain sensation. Treatment is symptomatic and supportive. When the toxin is aerosolized in rough surf, exposed people can develop a syndrome consisting of conjunctivitis, rhinorrhea, and a nonproductive cough.

DIARRHETIC SHELLFISH POISONING

Diarrhetic shellfish poisoning can occur in people *hours to days after ingesting contaminated mussels*. A published report of a large outbreak of diarrhetic shellfish poisoning in 2000 involving 120 people in northern Greece who ate mussels harvested from the Adriatic Sea following algal blooms illustrates the international scope of shellfish poisoning outbreaks. Mussels, like other bivalves, are filter feeders and can acquire okadaic acid, a dinophysistoxin-1 from toxic dinoflagellate algae, *Dinophysis acuminata*. The syndrome is characterized by nausea, vomiting, diarrhea, and cramps. Treatment is symptomatic and supportive.

AMNESIC SHELLFISH POISONING

Amnesic shellfish poisoning (domoic acid poisoning, mussel poisoning) is a toxic encephalopathy first described among people who ate contaminated mussels from cultivated beds in Prince Edward Island, Canada in 1989. The mussels contained domoic acid, a marine toxin produced by a marine diatom *Nitzschia pungens*. Environmental factors that favor the proliferation of the algae around certain marine areas allow the toxin to be accumulated by shellfish. Since the original syndrome was described, domoic acid has been detected periodically in razor clams and Dungeness crabs from the Olympic Peninsula in Washington state.

Domoic acid is related structurally to the excitatory amino acid neurotransmitter glutamate. Gastrointestinal symptoms (nausea, vomiting, abdominal cramps, and diarrhea) occur within 24 hours after the toxic ingestion, and neurologic symptoms (headache, seizures, hemiparesis, ophthalmoplegia, abnormal state of arousal ranging from agitation to coma, and antegrade memory loss) become manifest within 48 hours after the ingestion. In the Canadian outbreak, the gastrointestinal symptoms resolved after a day or two. However, after initial widespread neurologic dysfunction, the survivors had persistence of memory deficits and motor neuropathy. Treatment is symptomatic and supportive.

FURTHER READING

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