Ciguatera is an acute or chronic intoxication syndrome associated with the consumption of marine tropical reef fish. The illness has a short incubation period, and the symptoms typically affect the gastrointestinal and nervous systems. Ciguatera poisoning has been extensively reviewed.1–5 It is endemic in many tropical and subtropical regions, also in the United States,6,5 and Mexico,7 where it accounts for more than half of all outbreaks related to ingestion of fish. In the Caribbean and Indo-Pacific islands, regions where coral reefs are present, the disease is the most common seafood-borne illness. Ciguatera poisoning can occur after the consumption of a wide variety of predatory tropical fish including barracuda, surgeon fish, red-snapper, amber-jack, red-grouper, and king-mackerel. These fish contain heat resistant and acid-stable toxins, mainly ciguatoxin, a lipid-soluble toxin, and maitotoxin, a water-soluble toxin. Both poisons belong to a newly described class of toxins, chemically polycyclic ether compounds, produced by tropical marine microalgae that become attached to the epiphytes of macroalgae, which herbivorous fish consume while foraging. Many small fish succumb to ciguatoxin and are eaten by other fish. Hence ciguatera toxin becomes more biocconcentrated as it passes up through the food chain from large carnivorous fish to larger predatory reef fish and ultimately to humans.

Whereas the toxins are harmless in the host fish, in humans they produce illness. The earliest and commonest symptoms to appear are watery diarrhea, nausea and vomiting, abdominal pain, typically lasting about 12 hours. Usually, 24–48 hours after ingesting the toxic fish, neurologic symptoms follow, including numbness, lip, tongue, and limb paresthesias, severe itching, and cold-to-hot temperature reversal (considered a pathognomonic sign). The illness generally subsides within a week. Neurologic symptoms may last for months or subside and then recur.

Prompted by the growing number of Italian travelers returning from the Caribbean who present to our unit after experiencing symptoms of ciguatera poisoning, we designed this clinical study to assess the clinical outcome in our patients. We also sought to know whether they had received information before departure on the potential risks of ciguatera fish poisoning.

Methods

From the clinical records held in the Department of Infectious and Tropical Medicine we selected for study 13 consecutive patients (10 men and 3 women, mean age 36.4 years) who presented to our department during the period December 1995 to March 1999, for investigation of symptoms compatible with fish poisoning (combination of gastrointestinal and neurologic symptoms), contracted while on holiday in the Caribbean. Of the 13 patients, 5 were admitted to the observation ward, and 8 (2 of whom had been hospitalized overseas) attended our outpatient department. All patients underwent clinical assessment including past and recent medical history, physical examination, and routine laboratory tests.

Case Reports

The series of 13 cases (Table) comprised two clusters. Here we briefly describe the patients, including one patient in whom ciguatera poisoning presented with unusual symptoms to our knowledge not previously reported. The medical history disclosed that before their
departures none of the patients had received information on the risks of ciguatera fish poisoning

**Case 1.** This 34-year-old woman first became ill after eating fish while on vacation in Cuba in December 1995. Unlike most reported cases, she had no initial gastrointestinal symptoms. Her illness began with syncpe followed within hours by muscle weakness, dizziness, and faintness. These symptoms transiently responded to an intramuscular corticosteroid administered by a local physician. The next day the neurologic symptoms recurred, accompanied by tachycardia and another episode of syncpe. While in transit in New York, she consulted a physician who administered an intravenous solution of mannitol. After treatment she remained in good health for a week.

Two weeks after fish poisoning the patient presented to us when she experienced the fourth recurrence of neurologic symptoms (muscle weakness, perioral paresthesias, vertigo, and loss of consciousness) after eating seafood in Rome. She was admitted to our observation ward. The patient's physical examination (Romberg sign, tendon hyporeflexia, and arterial hypotension) and history were compatible with ciguatera poisoning. Some days later, psychic depression developed accompanied by polydipsia, polyuria, and proteinuria, with oval fat bodies in the urinary sediment. In addition, she had slightly elevated serum triglycerides and total cholesterol, with low high-density lipoprotein cholesterol. These findings suggested a transient minimal change disease as part of an idiopathic nephrotic syndrome, successfully treated with a corticosteroid.

In January 1996, after becoming pregnant she experienced transient amnesia and intense muscle weakness. A normal newborn was delivered at term by cesarean section, due to uterine inertia.

**Case 2.** This 32-year-old male became ill in the Caribbean islands, in July 1996 and was admitted to the local hospital. His illness began with acute gastrointestinal symptoms, treated by rehydration, and accompanied by headache and generalized itching. He presented to our unit 3 weeks later because of persisting neurologic and musculoskeletal symptoms accompanied by intense generalized itching. These symptoms gradually disappeared within a month after treatment with a nonsteroidal anti-inflammatory drug.

**Case 3.** This 35-year-old male contracted ciguatera while on vacation in Santo Domingo, in July 1996. The day after the onset of typical gastrointestinal symptoms and hypersalivation, he began to experience odontalgias (loose teeth sensation), lip paresthesias, cold-to-hot temperature reversal, and profuse sweating. The local physician prescribed a nonsteroidal anti-inflammatory drug. He presented to our unit because of persisting neurologic symptoms that resolved within a month.

**Case 4.** This 48-year-old man was also on holiday in the Caribbean islands in August 1996. Five hours after a fish meal, acute gastrointestinal symptoms developed, diagnosed by a local physician as compatible with ciguatera poisoning. Two days later, during the flight home, he began to have disabling myalgias, muscular cramps, and intense headache. When he presented to us by ambulance, he appeared ill and had meningeal signs. A lumbar puncture yielded clear cerebrospinal fluid with increased pressure but normal laboratory findings. The meningeal signs disappeared almost immediately, but the other neurologic signs persisted for almost a month.

**Case 5.** In this 26-year-old woman, who was on holiday in the Caribbean islands, in July 1997, the typical gastrointestinal symptoms of ciguatera, followed by urinary retention, asthenia, anxiety, and depression, developed after ingestion of a fish meal. Knowing that she had acquired a tropical disease she consulted us because of persisting...
neurologic symptoms, and was admitted to our observation ward. The psychiatrist diagnosed depression secondary to fish poisoning that resolved without treatment within 13 months.

**Cases 6 and 7.** These two cases, a honeymoon couple on vacation in Santo Domingo, in August 1997, formed our first cluster. Both persons ate the same fish meal. In the husband symptoms of poisoning began 3 hours after eating the poisoned fish, and in the wife 9 hours afterwards. The husband had gastrointestinal symptoms, weakness, paresthesias, arterial hypotension, intense photophobia, and temperature sensation reversal. His wife had gastrointestinal symptoms followed by weakness and paresthesias, and was treated with intravenous mannitol by a local physician. On return home, they were both admitted to our observation ward and discharged within a few days. The symptoms persisted for a month.

**Cases 8 to 13.** These six patients, sport fishermen who became ill after eating a large fish they had caught on Saint Bartholomew Island, in March 1999, formed our second cluster. Apart from the typical gastrointestinal symptoms, beginning within 3 to 5 hours, most subjects complained of generalized itching, accompanied by weakness (2 cases); paresthesias of the lips and tongue (2 cases); and temperature sensation reversal (2 cases). Two of the fishermen also had bradycardia: Patient 9 with a heart rate of 50 beats/min, and Patient 12, who was hospitalized overseas, 35 beats/min. On their return, the six men came to us for advice on treating mild persistent symptoms. Whereas bradycardia in Patient 12 disappeared in 6 months, the other symptoms all regressed without treatment within a month.

**Discussion**

Most of our patients who suffered ciguatera fish poisoning had the characteristic combination of acute gastrointestinal symptoms lasting approximately 12 hours, and more persistent neurologic manifestations. The presence, prevalence, intensity, and duration of the symptoms differed in each subject (see Table). They differed also between subjects belonging to the same cluster, who consumed the same toxic fish. These characteristics agree well with the many published reports on ciguatera. No seasonality was noted. Male subjects predominated. The incubation period varied between 2 and 9 hours (mean 3.9 hours) well within the range required for a definition of ciguatera poisoning. The species of fish ingested was identified only in the larger cluster; in the other cases it remained unknown.

In nearly all the cases described here ciguatera poisoning began with gastrointestinal symptoms, predominantly diarrhea and nausea rather than vomiting. In line with other reports, neurologic and occasionally psychiatric symptoms began 24–48 hours later. The most frequent neurologic symptoms were weakness (9/13 subjects), and paresthesias (7/13 subjects). The pathognomonic sign of ciguatera poisoning, cold-to-hot reversal of temperature sensation occurred less frequently (2/13 subjects); as did loose-feeling teeth (2/13). Two of the 3 women in our cohort suffered from anxiety and depression. Patient 4, who had headache and musculoskeletal symptoms, also had slightly raised cerebrospinal fluid pressure possibly due to ciguatera poisoning. He recovered completely within a month. Itching, a sign commonly described in ciguatera, was frequent also in our series (8/13 subjects). In our first case, a 34-year-old woman, ciguatera poisoning possibly lead to secondary uterine inertia, but to a normal fetal outcome, an event already described. This incident provides a reminder that ciguatoxin can be sexually transmitted, can cross the placental barrier, can result in spontaneous abortion, premature labor or uterine inertia, and can also be passed in the mother's milk.

The most life-threatening symptom in our series was bradycardia (Patients 9 and 12). Acute fatality, usually due to respiratory failure, circulatory collapse, or cardiac arrhythmias ranges from 0.1% to 12% of reported cases. Most deaths related to ciguatera-contaminated predatory reef fish arise from eating the head, gonads, roe, or other internal organs, because they contain ciguatera toxin in large quantities. Ciguatoxin is a highly potent substance. Even a small dose (1 mg/kg body weight) induces depolarization due to a selective increase in sodium ion permeability in nerve cells and in striated muscle. Ciguatoxin is odorless, colorless, and tasteless, and is not eliminated by cooking, freezing, salting or curing.

The transient signs of renal disease in Patient 1 could have been a minimal change disease in an idiopathic nephrotic syndrome, as has been described, for example, after bee stings. Renal symptoms were an unusual finding, to our knowledge, not previously reported. Damage to the glomerular endothelial cells and to the tubular epithelial cells of the kidneys has been demonstrated in infections with many enteric pathogens, mainly verotoxin-producing *Escherichia coli* 0157:H7, in children and in vitro. No studies have yet investigated renal damage related to ciguatera toxin.

The duration of the illness varied (see Table). In 10 cases it lasted about 1 month. In the remaining cases it took a more chronic course (16 months in Patient 1; 13 months in Patient 5; and 6 months in Patient 12) as others have already noted. In our first patient, the recurrence of neurologic symptoms when she ate small local fish some weeks after returning home presumably confirms reported evidence suggesting increased sensitivity instead of immunity to ingestion of seafood.
In all our cases, ciguatera fish poisoning was diagnosed from the medical history and clinical assessment alone. The available laboratory tests for detecting ciguatera toxin and other marine toxins in fish or food include mouse bioassy, high performance liquid chromatography (HPLC), enzyme- and radioimmune assays, and counter-immunoelectrophoresis. But no diagnostic technique has been definitively approved for use in human clinical pathology.

If ciguatera fish poisoning is identified without delay, in adults and children it generally responds well to treatment with mannitol infused intravenously (20% solution at a dose of 1g/kg body weight). Two patients in our series received mannitol. In one case (Patient 6) the symptoms quickly regressed, but in the other (Patient 1) they persisted for months. Most patients (four in our series) also received corticosteroids, and antidiarrheal agents, (ten in our series); and when necessary antidepressants.

Despite the large yearly consumption of fish per person in Italy, fish poisoning has received scarce attention, apart from a few medical reports. The general public knows little about the problem other than the risk of acquiring diseases such as typhoid, hepatitis A, or cholera from eating uncooked shell fish. It is therefore hardly surprising given the growing interest of Italian travelers in tropical and subtropical destinations that more of them, unaware of ciguatera fish poisoning, now contract the disease. Italy has no coral reefs, and deep-sea fish (for example tuna or swordfish, both common in Mediterranean sea waters) have never been found to carry ciguatoxin. The simplest way to avoid the problem would be for diplomatic travel authorities, travel consultants, and travel agencies offering package tours to ciguatera endemic areas, to include in their brochures, information on the risks of becoming ill after eating meals of local tropical reef fish.

Conclusions

Ciguatera fish poisoning has begun to appear in Italian travelers to the Caribbean islands. Our findings suggest that health authorities should issue travel advisories, for countries where ciguatera poisoning is endemic, with information about this preventable disease. Potential visitors should be given practical information on the dangers of ingesting ciguatera toxins.

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