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Overview of the State of the Art of Ciguatera Fish Poisoning

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Abstract

Ciguatera Fish Poisoning (CFP) is the most frequently seafood-toxin illness in the world, with big substantial physical and functional impact. Toxins produced by Dinoflagellates are often found associated with Macrophyte Algae and dead Corals. Herbivorous fishes become toxic after ingesting macroalgae or parts of dead coral. Herbivorous fishes are preyed upon by carnivorous fishes which in turn become toxic. Man becomes infected by eating fish and poisoned herbivores and carnivores. CTX (Ciguatoxin) is odourless and tasteless, resists cooking. It caused gastrointestinal, neurologic and/or cardiovascular symptoms which last days to weeks, or even months. The purpose of this review of literature about the toxins, just to clarify causes, species and symptom, treatment, method of analysis, research of quick test and provide information about management and prevention of CFP.

Keywords: Ciguatera; *Gambierdiscus; Fukuyoa; Phyrophyta*; Cigueatera Therapy

Introduction

Ciguatera fish poisoning (CFP) is a frequent seafood borne-illness caused by the bioaccumulation of lipophilic ciguatoxins (CTX) in coral reef fish and invertebrates, and their subsequent consumption by humans [1]. These phycotoxins are produced by tropical epiphytic dinoflagellates belonging to the genera *Gambierdiscus* and *Fukuyoa*, which live on a variety of macrophytes, as well as on dead corals and sand. The disease is of significant concern in many tropical areas where it has been known since centuries. Although mortality from CFP is low, morbidity is high and symptoms may be debilitating and prolonged. Ciguatera produces characteristic gastrointestinal, neurological, and to a lesser extent, cardiovascular symptoms. Though the symptoms are relatively well documented, the disease often goes unreported or misdiagnosed [2-6]. The toxins are ingested by and accumulate in herbivorous fishes that, when consumed by humans, ultimately cause CFP. CTX has also been found in farmed fish fed with fishmeal obtained from ciguatoxin intoxicated fish [7].

The first report of CFP dates back to the 16th century (1555) by historian Peter Martyr de Anghera, who described the phenome-

non in the Indian and Pacific Ocean area. In the Pacific area, ciguatera intoxication in Spanish sailors was also reported as early as 1606 [8]. However, the best-known case dates back to the 18th century (1774) and involved the crew of Captain Cook's vessel, who became intoxicated after eating fish meat belonging to the Lutjanidae family. The term "Ciguatera" is of Iberian origin and derives from the name used in the 18th century to indicate intoxication caused by the ingestion of the marine mollusc *Livona pica*, known in the Spanish Antilles with the Cuban name of "Cigua" which means snail. Being phytophagous, this species can accumulate toxins in its meat and transfer them along the food chain [9]. The onset of the disease occurs after the consumption of fish caught between 35° north latitude and 36° south latitude, although minor cases have been described after the consumption of seafood fished even outside these coordinates. In 2008, cases were described in the Iberian Peninsula both in the Mediterranean and in the Canary Islands and in the Azores and Madeira [10]. Large fish, once poisoned, can remain poisonous for years, as has been shown in some experiments. The size of the fish is linked to the risk of intoxication because they have the possibility of accumulating the toxin. Contaminated fish weighing more than 5 - 6 kg are considered dangerous.

The species of fish involved in CFP are more than 400. Generally, only a few of them are regularly involved in CFP. The most common species are: *Carcharhinus leucas (Carcharhinidae), Lutjanus sp. (Lutjanidae), Gymnothorax spp. (Muraenidae), Seriola fasciata (Carangidae), Chlorurus microrhinos (Scaridae), Epinephelus merra (Serranidae), Epinephelus multinotatus (Serranidae), Plectropomus leopardus (Serranidae), Variola louti (Serranidae), Epinephelus spilotoceps, (Serranidae), Pagrus pagrus (Sparidae), Balistes vetula (Balistidae), Balistapus undulatus (Balistidae) Sphyraena barracuda (Sphyraenidae), Scarus altipinnis (Scaridae), Kyphosus cinerascens (Kyphosidae), Liza vaigiensis (Mugilidae), Pterois volitans (Scorpaenidae), Scomberomorus commerson (Scombridae).*

Also invertebrate species are known to be involved in CFP, including *Tridacna maxima, Tectus niloticus, Octopus cyanea* (big blue octopus), *Percnon spp.* (nimblespray crab), *Dendropoma maxima, Panulirus penicillatus* (lobster), *Tripneustes esculentus* (sea urchin), *Ophidia sterophidianus, Marthasterias glacialis, Livona pica* [11].

Distribution

The CFP is specific to tropical regions, from three great oceans: Pacific Ocean (French Polynesia, New Caledonia, Australia, Vanuatu, Hawaii, Japan), Atlantic Ocean and Indian Ocean. It is also found in Florida, and recently (2003) it was founded in the Mediterranean Balearian islands, Greek coast (Crete), Atlantic Ocean especially in Madera and the Canary [10]. Within the EU, only countries with outermost regions, located in the tropics and very far from the European continent, have been exposed to ciguatera, in particular, Portugal (Azores and Madeira), France (Guadeloupe, Saint Martin, Guyana, Martinique and Réunion. Mayotte) and Spain (Canary Islands). To date, the EU has not indicated a regulatory threshold or specified feasible analytical methods for CTXs [12]. Nevertheless, the European Food Safety Agency has specified that a dose of 0.01 µg P-CTX1 equivalent/kg shell meat would not cause adverse effects in humans [12].

Global warming of the ocean surface is expected by the middle of the 21st century with an increase in temperatures of 0.4 - 1.4°C. Causing the increase in the spread of many dinoflagellate genera of tropical and subtropical origin which are harmful to health such as *Gambierdiscus*, *Fukuyoa* and *Ostreopsis*. An exception to this trend will occur in the tropical area where the exceeding of the thermal tolerances will bring the water to a temperature of around 30 - 31°C. Above these temperatures, growth and diffusion will suffer a significant slowdown [13].

Ciguatoxin intoxication had not been described in the West Africa coast until (2004). In 2008 and 2009 two episodes were described in Canary Island [10].

At the end of the 80' (1989) cases of ciguatera intoxication were reported in Israel [14].

Mechanism of action of toxins

The dinoflagellates are widespread on macrophytes and dead corals and are ingested by herbivorous fish or gastropods or crustaceans that accumulate the toxin in their body becoming toxic, these phytophagous or detritivores animals can be consumed by humans who become intoxicated or be preyed upon by carnivorous fish, which in turn become toxic. By eating carnivorous fish, man becomes intoxicated. A mechanism of accumulation of toxins is known which reach toxic levels for humans in fish weighing more than 1.5 kg. The local health authorities of Pacific islands recom-

mend above all to tourists but also to indigenous populations not to consume fish larger than 1.5 kg. The first works on CFP starting in 1958 [15], (1963) [16], and. (1971,1976) [17]. They made a correlation from disc-shaped dinoflagellates in stomach of fishes (i.e., Surgeonfish *Ctenochaetus striatus*) contents with toxins from viscera extracts. The collection of Dinoflagellates found on calcareous algae and dead corals at the Gambier Islands and the subsequent extraction of compounds produced chemical and toxicological similar fractions with those extracted from ciguatoxic fish. The laboratory cultivation of Dinoflagellate samples collected in nature allowed to confirm the benthic bond with ciguatoxins [17]. Dinoflagellate belonging to the Phyrophyta division has been classified with new or genus and species, *Gambierdiscus toxicus*. After this discovery, new species *Gambierdiscus belizeanus*, *Gambierdiscus yasumotoi*, *Gambierdiscus pacificus, Gambierdiscus australes* and *Gambierdiscus polynesiensis* were further found and added to the Genus. However a work taking a cue from detailed sequencing of rDNA suggests the hypothesis of a single cosmopolitan species of *Gambierdiscus tossicus*. Genetic clustering suggests that a wide-ranging complex of multiple cryptic species exists" [18]. Respect from the better known open-water "red-tide" that form big face blooms, *Gambierdiscus spp*. are often found in sparse population only in particular conditions (i.e. protected areas) form dense populations. Exist a correlation from toxin productions and Genus".

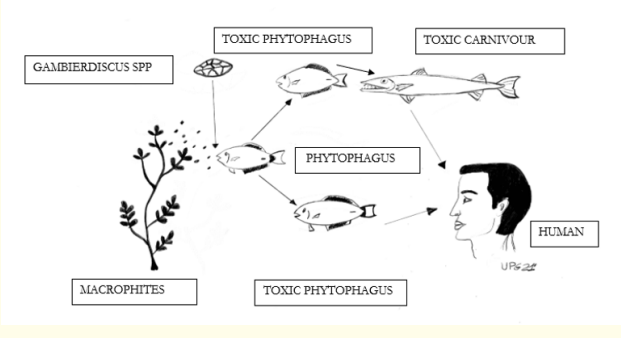

Figure 1: CTX transmission mechanism.

CTX phycotoxins are lipophilic neurotoxins, polyethers having a molecular weight of 1110 Da, characterized by 10 to 14 cycles transfused by ether bonds. Exist a regional difference in ciguatera toxin profiles associated with fish and the symptoms reported in outbreaks in the three major ciguatera-endemic regions, (Caribbean Sea, Pacifica and Indian Oceans)" [18]. They are divided into three families according to their origin: "The P-Ctxs (Pacific Ocean), C-CTX (Caribbean) and I-CTX (Indian Ocean). Toxins accumulate through the trophic chain, starting from the algae that are consumed by herbivorous fish, carnivorous fish, before reaching humans (Figure 1). More than 400 species have been considered as carriers of these toxins responsible for Ciguatera (CFP). The mechanism of action is the same as that of brevotoxins, binding to the S5 site on the Cnavd (Kd - 0.04-4 nM). This powerful bond between the toxin and the channel exerts a powerful and direct action on the neuromuscular junctions, a depolarization is induced on the sensory neuronal membranes by inducing the selective opening of the sodium channels in tension dependent on normal resting potential. Symptoms appear within 10 - 30 minutes of ingestion. The syndrome is characterized by several symptoms in combination each other acting mainly at the gastrointestinal level, neurological and cardiovascular. Gastrointestinal disorders usually subside and disappear in 1 - 2 days, like cardiovascular ones which subside in 2 - 5 days. The most persistent seem to be the neurological and sensory ones which act for 2 - 3 weeks. Fatal outcome (death) can occur from direct cardiovascular collapse, hypovolemic shock, or respiratory paralysis. The most typical and tell-tale symptom of the syndrome appears to be the temperature inversion, in which the patient mistakes heat for cold. Human tests involving the biopsy of nerve tissues revealed swelling of Schwann cells with axonal compression and vesicular degeneration of the myelin. The toxin is sexually transmitted, significantly harming the foetus with an often-fatal outcome (abortion) [12].

Another toxin produced by Gambierdiscus dinoflagellate is maitotoxin (MTx) in addition to ciguatoxin is the most common toxin involved in ciguatera fish poisoning (CFP), Maitotoxin (MTx) is one of the potent polyether toxins produced by the dinoflagellate *Gambierdiscus toxicus* and, besides ciguatoxin, is the most common toxin involved in ciguatera fish poisoning (CFP). There is little evidence that maitotoxin can cause behavioral and morphological changes maitotoxin in fish, and its accumulation in the flesh of surgeonfish or other fish, can result in its death [19]. Despite the widespread occurrence of maitotoxins in the benthos (at the bottom of the sea), maitotoxins are unlikely to cause human poisoning because of their poor accumulation might impose an upper limit on the levels they can in fish flesh and their relatively low oral potency [19].

Symptoms

Actually the diagnosis of CFP is based on clinical sign and the recent eating history of the patients. This is due to the fact that don't exist human biomarker for CFP. The main CFP 'symptoms are associated with cardiovascular, gastrointestinal neurological and neuropsychiatric symptoms and signs. Cardiovascular symptoms include: arrhythmia, hypertension, bradycardia emerged in the early phases and when include hypotension and bradycardia may necessitate urgent medical care. Gastrointestinal symptoms include: diarrhoea, nausea, vomiting, abdominal pain. These symptoms usually occur after 6/24 hours fish ingestion and often resolve spontaneously after 1-4 days. Neurological symptoms include: Extremity Paraesthesia, circumoral paraesthesia, temperature, Dysesthesia, Myalgia, Arthralgia, Pruritis, Headache, Vertigo, Weakness (Asthenia), Dental Pain/Feeling like teeth are loose or falling out, Dysuria, Chills/Sweating. They are present within the first few days of illness, after the GI symptoms, particularly in CFP from fish came from Caribbean waters. Exist a neurologic symptoms variation among patients including paraesthesia (numbness and tingling) in the extremities of body (feet and hands) and oral region, generalized pruritis (itching), myalgia (muscle pain), arthralgia (joint pain), and fatigue. A symptom often reported by many patients is an alteration or "reversal" of hot/cold temperature perception, in which cold surfaces are perceived as hot to the patient, or produce dysesthesia (unpleasant, abnormal sensation). This temperature-related dysesthesia is considered characteristic of CFP, although not all patients report experiencing this symptom. Temperature-related dysesthesia has been reported even in other intoxication from seafood (e.g. Neurotoxic Shellfish Poisoning (NSP). Neuropsychiatric symptoms include depression and memory loss, anxiety, hallucination and giddiness, incoordination or ataxia, coma, these last especially appear to be specific to CFP in Indian and Pacific Ocean. These geographical differences in symptom patterns may be attributable to the presence of different suites of CTX or toxin precursors in these different areas. Gastrointestinal symptoms are predominating in the acute phase (first 12 hours), in the Caribbean, followed by prominence of neurologic, especially peripheral neurologic symptoms. The neurological symptoms and signs predominate in the Pacific area with severe neurologic effects including coma. In the Indian Ocean, CFP is always associated with mental status alterations, neurological disturbs like depression, hallucinations, giddiness, incoordination, loss of equilibrium. CFP is rarely reported as fatal itself. Death may occur in some cases due to severe and fast symptoms like cardiovascular shock especially in the early initial illness phase, severe dehydration, respiratory failure from paralysis of the respiratory musculature. Last but not least, the environmental factor also contributes to the fatal outcome, due to the lack of supportive health machinery (respiratory), rehydrating solutions, specific medications. Even the parts of toxic fish consumed can contribute to the fatal outcome of intoxication. Viscera and gonads usually contain more toxins than muscles (fillets). Cases of chronicity was recorded, after the acute illness some patients suffer from weakness generally last a few days to several weeks or months. Other neurologic symptoms such as paraesthesia in the extremities, pruritis, and neuropsychiatric symptoms such as malaise, depression, generalized fatigue, headaches. Symptom recurrence and sensitization [20]. The persistence of nervous symptoms (movements a snap, gaze), for irreversible nerve damage. Due to widespread in the Caribbean area. The chronic form of Ciguatera in that area it is believed to occur in part inspired, the popular traditions on the "living dead" (Zombie). Recently also bacteria (genus Pseudomonas, Vibrio, Aeromonas) living in symbiosis with microalgae have been considered possible toxinogens [21].

Therapy

Despite that Ciguatera intoxication is the world most prevalent foodborne disease, with 50,000 to 500,000 incidences per year, the mortality rate remains very rare with deaths estimated at < 0.1%. The popularity for tourism reasons of tropical and sub-tropical regions with seafoods' exportation, make this disease a global health problem. Actually, no antidote is available. Mannitol' treatment remains symptomatic but is the most effective remedy that leads to a regression of symptoms) [22]. Even the local medicine (Polynesian area) based on plant extract (*Heliotropium foertherianum*) (Boraginaceae) and rosmarinic acid can be have good effects [20].

Diagnosis

Actually, no valid biomarkers exist to confirm exposure to CTX in humans. The current CFP diagnosis is based on history to eaten reef fish and importantly", the exclusion of other diagnoses that could have common symptoms with CFP, like Paralytic and Neurotoxic Shellfish Poisonings, scombroid and pufferfish toxicity, botulism, enterovirus, and bacteraemia, as well as organophosphate pesticide poisoning, eosinophilic meningitis, multiple sclerosis, and other neurologic conditions" [23].

"Several methods have been developed to screen for the presence of CTXs in fish tissue prior to consumption. In vivo whole-ani-

mal detection methods are now superseded by in vitro assays that have greater sensitivity, including receptor-binding assays (RBAs), cell-based assays (CBAs), Enzyme-Linked Immunosorbent Assays (ELISA), capillary electrophoresis (CE)-based immunoassays, electrochemical immunosensors (ECS), and liquid chromatography tandem mass spectrometry (LC-MS/MS). Present methods for CTX analysis, in general, are labour-intensive, time-consuming, and require laboratory facilities with well-trained technicians. To date, these methods have not been properly validated. At present it is difficult to obtain strong standard CTXs as reference calibrants, impeding corroboration and widespread application of these analytical techniques [24].

Other diagnostic methods include the cultivation and harvesting of CTX in the phase of maximum development, the extraction of toxins that are analysed with immunosensitivity tools with magnetic bead (MB) -based immunosensing tools (colorimetric immunoassay and electrochemical immunosensor). This method is used for this diagnosis for the first time and allows to determine the presence of toxins and the screening between Gambierdiscus and Fukuyoa strains, but also the ability to discriminate between two series of congeners (CTX1B and CTX3C) [25]. Recently a portable electrochemical immunosensor for the detection of CTXs is presented. It's based on a sandwich configuration type [26].

From November 2012 to January 2015, an EU-funded project called "Ciguatools" was developed which, through the creation of a consortium made up of experts in marine toxins, determined a search and identification of toxins and related profiles widespread in the Union's waters. European Union, consequent study and production of reference standards. Creation of a simple, fast method to determine the presence of CTX in the meat of marine animals intended for human consumption. The phases of the project included: Cultivation under controlled conditions of Gambeirdiscus, relative extraction of toxins from cultures, their purification, characterization as a standard for the toxin and subsequent use for the production of antibodies for an ELISA type kit and development of PCR techniques for the identification of toxins in the water column. With regard to the possible production of ELISA KITs, further investigations will be required.

Conclusion

The RASSF (Rapid Alert System for Food and Feed) site that collects all food and no food warnings, registered 5 warnings in the years from 2012 to 2020 (Table 1). The countries involved in this intoxication were France (2 cases) Germany (2 cases), Netherland (1 case). The origin of toxic fish products was India (3 cases) and Vietnam (2 cases) The species most involved was Lutjanus spp. and in particular *Lutjanus bohar* and *Acanthocybium solandri*. All five cases triggered a national health alert.

Date of case	Reference	Notyfing country	Subject	Product category	Type	Risk decision
01/6/2020	2020.2254	Netherland	Ciguatera poisoning suspected to be caused by frozen red snapper steaks (Lutjanus bohar) from India, via France	Fish and fish products	Food	Serious
05/3/2019	2019.0875	France	Ciguatera poisoning suspected (4 out of 4 samples) to be caused by frozen wahoo loin fillets (Acanthocybium solandri) from Vietnam	Fish and fish products	Food	Serious
17/3/2017	2017.0345	Germany	Ciguatera poisoning suspected to be caused by frozen red snapper fillets (Lutjanus bohar) from Vietnam, via Denmark	Fish and fish products	Food	Serious
14/7/2016	2016.0932	France	Ciguatera poisoning suspected to be caused by frozen red snapper (*Lutjanus spp.*) from India, via the Netherlands	Fish and fish products	Food	Serious
16/11/2012	2012.1602	Germany	Ciguatera poisoning suspected to be caused by fresh red snapper fillets (*Lutjanus spp.*) from India			
16/11/2012	2012.1602	Germany	Ciguatera poisoning suspected to be caused by fresh red snapper fillets (*Lutjanus* spp.) from India	Fish and fish products	Food	Serious

Table 1: Rapid alert system for food and feed (RASSF) alert notification for Ciguatera.

Tourist travels to tropical destinations, the globalization of food habits, the tropicalization of the seas, have contributed to the spread of this pathology, which has begun to be at the centre of diagnostic studies. These studies have allowed us to understand the cause, the diffusion system, the mechanism of toxicity in human cells. Currently there is no specific and official therapy, the indigenous people who have known the problem for centuries have resorted to phytotherapy. Modern science is based on substances that induce contrast mechanisms of a biochemical nature. The approach towards this biotoxin should be oriented on the use of a rapid approach that allows an immediate diagnosis, especially since the intoxications usually occur in places with poor first aid facilities. Prevention (consuming fish weighing less than 1.5 kg), Early diagnosis and proper supportive therapy can help to fight this emerged bio intoxication.

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