MINI-REVIEW

Ciguatera poisoning in French Polynesia: insights into the novel trends of an ancient disease

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Abstract

Ciguatera is a non-bacterial seafood poisoning highly prevalent in French Polynesia where it constitutes a major health issue and a major threat to food sustainability and food security for local populations. Ciguatera results from the bioaccumulation in marine food webs of toxins known as ciguatoxins, originating from benthic dinoflagellates in the genera *Gambierdiscus* and *Fukuyoa*. Ciguatera is characterized by a complex array of gastrointestinal, neurological and cardiovascular symptoms. The effective management of patients is significantly hampered by the occurrence of atypical forms and/or chronic sequelae in some patients, and the lack of both a confirmatory diagnosis test and a specific antidote. In addition, recent findings have outlined the implication of novel species of the causative organisms as well as new vectors, namely marine invertebrates, in ciguatera outbreaks. Another novel trend relates to the geographical expansion of this disease to previously unaffected areas, not only in certain island groups of French Polynesia but also in temperate regions worldwide, as a likely consequence of the effects of climate change.

Keywords: Ciguatoxins, ciguatera poisoning, *Gambierdiscus*, geographical expansion, marine invertebrates, new vectors, symptoms
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Fish products represent a major subsistence resource for French Polynesia populations whose per-capita fish consumption may exceed 100 kg/year in some islands [1]. This heavy reliance on a fish-based diet makes local communities particularly vulnerable to seafood-related poisonings. Among the six poisoning syndromes reported in French Polynesia, including tetrodotoxism (puffer fish), chelonitoxism (turtle), clupeotoxism (clupeids), carchatoxism (sharks) and paralytic shellfish poisoning (crabs) [2,3], ciguatera constitutes the most prevalent form of poisoning, as evidenced by the high incidence rates consistently reported from most of the island groups in French Polynesia (Table 1). Although ciguatera is not a new disease *per se*—early accounts of poisoning incidents are found in Captain James Cook's journal in 1774—significant research progress achieved in the last decade has led to a reconsideration of several of the early paradigms in ciguatera pertaining to, for example, the causative organisms, the vectors involved in ciguatera transmission pathways, and the biogeographical range of this disease.

Clinical manifestations of ciguatera

Ciguatera is characterized by a complex set of polymorphic and non-specific symptoms, resulting from the diversity of the biological targets of ciguatoxins (CTXs) (e.g. voltage-gated sodium and potassium channels) and the negative impacts of CTXs on nerve transmission [4]. These symptoms vary from individual to individual, and also depend on the amount of toxins ingested as well as the geographic origin of the consumed fish: overall, 175 symptoms have been reported in the literature [5], making ciguatera diagnosis particularly challenging, especially in non-endemic regions. Of note, ciguatera does not seem

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to confer any immunity in its victim but often results in increased sensitivity to marine products.

In the absence of confirmatory clinical tests, ciguatera diagnosis is based exclusively on the patient's history, case clusters, suggestive clinical manifestations and differential diagnosis. Ciguatera must be evoked in a non-febrile patient presenting with a combination of gastrointestinal, cardiovascular and neurological disorders [6] in the absence of allergic reactions, developed within 48 hours following the consumption of marine products from tropical/subtropical regions reputed as ciguatera hotspots. Classically, individuals with ciguatera in French Polynesia first suffer from diarrhoea and/or vomiting, possibly associated with a transient hypothermia and cardiovascular symptoms, mostly bradycardia and hypotension (tachycardia and hypertension described to a lesser extent), which may be considered as a criterion of severity [7]. In some instances–for example, poisoning cases following the ingestion of toxic marine invertebrates—atypical symptoms may be observed such as the rapid onset of the disease (within minutes, in some reported cases), and the unusual severity of symptoms including paralysis that sometimes requires the patients' hospitalization [8,9], suggesting that other toxins may potentially be involved in these atypical poisonings. Of note, in exceptionally severe forms, ciguatera can lead to Guillain–Barré syndrome and related neurological disorders [10].

In any case, these initial manifestations usually resolve within a few days giving place to a panel of neurological signs that include extremities/perioral paraesthesia, dysaesthesia (mostly allodynia in response to cold stimuli), muscle weakness, dizziness, headache, visual/balance/concentration and sleep disorders, associated with a pruritus (without cutaneous signs), asthenia, myalgia, arthralgia, oropharyngeal burning, dysgeusia, orofacial pain, and sometimes urogenital discomfort/burning (Table 2). The high predominance of neurological signs in French Polynesian patients is similar to what is observed in the Indian Ocean, except that neuropsychiatric component, such as hallucinations [11], has little been reported in French Polynesia. In all cases, these clinical manifestations spontaneously regress within a few weeks in most patients, however, up to 20% of patients are likely to develop chronic sequelae involving dysaesthesia, paraesthesia, asthenia, general malaise, cognitive/mood disorders and chronic fatigue evocative syndrome, which may persist for months or even years [6,12,13]. Chronic symptoms can express continuously or by short-term peaks, are revived by triggering factors such as food and drinks (marine-related products, meats, foods rich in histamine and protein, nuts), drinks (alcohol, high-energy drinks) and specific circumstances (intense physical activity, cold/hot stimuli, stress) [6]. In most cases, these chronic manifestations eventually resolve in patients with ciguatera, but adopting an eviction diet may help patients to recover more quickly. Regarding ciguatera treatment, the lack of specific and effective antidotes prompts case-by-case symptomatic medical support, although some studies have shown that intravenous mannitol may prove efficient if administered no later than 72 hours post-poisoning [14]. As for chronic symptoms, the biological mechanisms underlying these manifestations are still poorly documented and effective medical solutions are yet to be identified [15]. Of note, many South Pacific communities use traditional remedies, most notably a leaf decoction of the octopus bush *Heliotropium foetherianum*, arguably with great success [16].

Ciguatera causative organisms and related toxins: identification of novel species and toxic compounds

The mode of transmission of ciguatera to humans is well documented: ciguatera results from the consumption of marine products contaminated by sufficiently high concentrations of lipophilic compounds, CTXs. These toxins are produced by a

TABLE 1. Annual incidence rate of ciguatera poisoning cases reported in French Polynesia from 2007 to 2017[a]

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Archipelagos											
Society	3	6	6	7	9	6	4	2	1	3	3
Marquesas	66	125	105	74	87	89	55	50	30	53	87
Tuamotu	121	134	106	104	92	101	60	37	60	220	63
Gambier	539	516	531	591	307	338	77	70	169	345	—[b]
Australes	65	79	236	170	55	47	89	28	72	39	46
Rapa island	0	124	1826	892	270	330	660	194	291	233	0
Animal consumed											
Trochus	0	0	0	0	0	0	0	2 *(10)*	0	0	0
Sea urchin	0	0	2 *(7)*	1 *(2)*	0	0	1 *(2)*	0	2 *(3)*	0	0
Giant clam	0	1 *(1)*	1 *(1)*	1 *(1)*	0	0	1 *(1)*	0	0	0	1*(1)*

Incidence rate expressed in number of cases/10 000 inhabitants). These statistics do not take into account the under-reporting rate, estimated at 31% for the same period. The number of ciguatera-like poisoning events due to consumption of trochus (*Tectus niloticus*), sea urchins (*Tripneustes gratilla*) and giant clams (*Tridacna maxima*) for the same period are also indicated with the number of persons concerned (in italics and in brackets).

[a] Data source: Bureau de Veille Sanitaire, Public Health Directorate of French Polynesia—Institut Louis Malardé (www.ciguatera.pf).

[b] —, no report available for 2017.

benthic dinoflagellate, *Gambierdiscus* spp., and are readily transferred through marine food webs, from algae to herbivorous then carnivorous fish, by grazing and predation respectively, and ultimately to humans. Natural and anthropogenic disturbances are some of the factors likely to exacerbate ciguatera risk in coral reef environments [17] (Fig. 1).

Until 1999, only a limited number of species (six species) were known in the genus *Gambierdiscus* [18,19]. Since 2009, however, the use of genetic data combined with morphological data has dramatically accelerated the detection of multiple novel species, and more species are likely to be discovered in the next few years. Currently the genus *Gambierdiscus* comprises 15 described species plus several ribotypes ([20–22] and references therein) and three sister species in the new genus *Fukuyoa* [23]. Based on the existing literature, most species found in the Pacific are distinct from those in the Atlantic region, although some species clearly show a marked cosmopolitan distribution [24,25]. Field data obtained from risk assessment campaigns indicate that at least six of the described species are present in French Polynesia, namely *Gambierdiscus toxicus*, *Gambierdiscus australes*, *Gambierdiscus pacificus*, *Gambierdiscus polynesiensis*, *Gambierdiscus caribaeus* and *Gambierdiscus carpenteri* [26,27]. To the best of our knowledge, specimens of the genus *Fukuyoa* have not been reported from French Polynesian waters.

Besides CTXs, *Gambierdiscus* also produces several other toxic compounds (e.g. maitotoxins, gambieric acids, gambierol, gambieroxide, and gambierone) [28,29] and references therein), and as significant progress has been achieved in detection techniques, novel compounds are likely to be found in this genus, as exemplified by the recent characterization of a novel maitotoxin compound [30]. However, the ecological relevance of these compounds (e.g. as allelopathic agents) remains elusive, and their potential contribution to ciguatera syndrome still needs to be clarified.

The ability to produce CTXs seems to be genetically determined in the *Gambierdiscus*/*Fukuyoa* complex and reports of the existence of clonal variations ranging from toxic to non-ciguatoxic cells are available in the literature [31,32]. The species- and strain-dependent production of CTXs explains that the presence of *Gambierdiscus* alone in a given area does not necessarily imply a proven poisoning risk, which depends in part on the strains' toxic potential and hence the level of CTXs actually introduced in the marine food web. In terms of risk-forecasting implications, only two species, *G. polynesiensis* and *Gambierdiscus excentricus*, are known to produce substantial amounts of CTXs [31–33], suggesting their potential use as biomarkers of high ciguatera risk in areas colonized by *Gambierdiscus* populations.

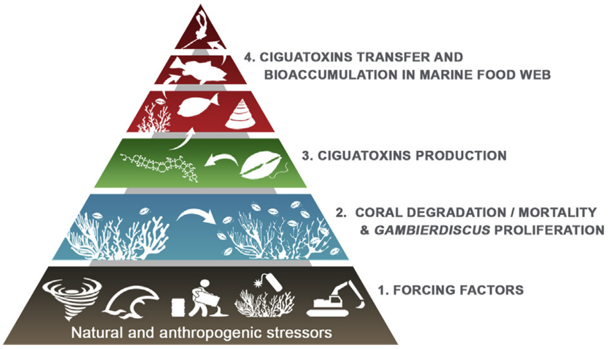

FIG. 1. The trophic chain of ciguatera poisoning.

Ciguatera transmission pathways: implication of novel vectors in French Polynesia

Ciguatera classically results from the ingestion of tropical and subtropical coral reef fish. However, a variety of marine invertebrates that also represent a valuable source of protein and revenue for Pacific island communities, are episodically involved in ciguatera-like poisoning incidents (Fig. 2). The first ever report concerns the giant clam *Tridacna maxima*, which was implicated in a mass-poisoning event in 1964 in Bora Bora Island (Society archipelago) leading to two fatalities [34], and in 2005 in Raivavae Island (Australes) [8]. Of note, a recent study has

TABLE 2. **Prevalence of ciguatera clinical symptoms based on the analysis of 727 declaration forms (ambulatory cases) registered between 2014 and 2017[a] in French Polynesia**

		Neurological		
Digestive	**Cardiovascular**	**Peripheral**	**Central**	**Other**
Diarrhoea (75%) Nausea (44%) Vomiting (37%)	Bradycardia (22%) Hypotension (17%)	Paraesthesia (80%) Cold allodynia (71%) Muscle disturbances (67%) Dysaesthesia (63%)	Dizziness (52%) Headache/migraine (52%) Transient hypothermia (37%) Visual disorder (18%)	Arthralgia (61%) Pruritus/itching (49%) Dysgeusia (42%) Asthenia (26%) Urogenital discomfort/pain (17%)

[a] Data source: Bureau de Veille Sanitaire, Public Health Directorate of French Polynesia—Institut Louis Malardé (www.ciguatera.pf).

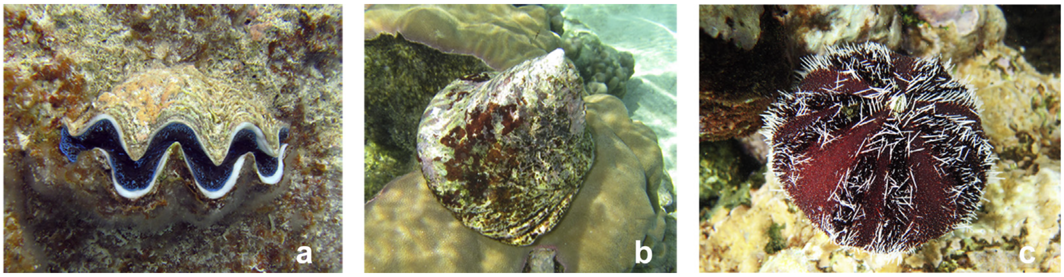

FIG. 2. Marine invertebrates are also susceptible to bioaccumulate ciguatoxins. A) the giant clam *Tridacna maxima* (Tridacnidae, Bivalvia), B) the trochus *Tectus niloticus* (Tegulidae, Gastropoda) and C) the sea urchin *Tripneustes gratilla* (Toxopneustidae, Echinoidea).

provided evidence for the bioaccumulation of CTXs in *Tridacna maxima* experimentally exposed to *Gambierdiscus* cells [35,36]. Toxic incidents following the ingestion of *Tripneustes gratilla* (sea urchin) and *Tectus niloticus* (gastropod) have been documented from Rurutu Island (Australes) and, more recently, from Nuku Hiva Island (Marquesas) [9,26,27,37]. Coincidentally, the affected area in Nuku Hiva Island was also the one with high *Gambierdiscus* densities and high prevalence of toxic fish. At a regional scale, sporadic poisoning cases involving *Tridacna maxima*, *Octopus cyanea* (big blue octopus), *Percnon* spp. (nimble spray crab) and *Dendropoma maxima* (large worm shell) have been reported from the Cook Islands [38], as well as *Panulirus penicillatus* (lobster) and octopus from the Republic of Kiribati [39]. Outside the Pacific region, *Tripneustes esculentus* (sea urchin) has been incriminated in toxic events in the West Indies [40], while two starfish from waters off Madeira, *Ophidiaster ophidianus* and *Marthasterias glacialis*, have been found also to bioaccumulate CTXs [41].

Toxicological analysis using the neuroblastoma cell-based assay and liquid chromatography-tandem mass spectrometry were further performed on *Tectus niloticus* and *Tripneustes gratilla* toxic samples collected from Anaho Bay, a long-standing ciguatera hotspot from Nuku Hiva Island (Marquesas) (http://www.ciguatera.pf/index.php/fr/cartographie-dynamique). They allowed for the unambiguous detection of CTX compounds in these samples [26,27] at levels consistently above the US Food and Drug Administration advisory levels (0.01 equiv P-CTX1 $ng.g^{-1}$) [42]. Based on liquid chromatography-tandem mass spectrometry data, at least five distinct CTX congeners could be detected [26,27], some of which are known to be primarily produced by *G. polynesiensis* in *in vitro* cultures [31]. Interestingly, some of these compounds also corresponded to the CTXs mainly detected in *Tridacna maxima* experimentally fed highly toxic cells of *G. polynesiensis* [35,36]. All these findings, which are consistent with the observation that *G. polynesiensis* is actually the dominant species in Anaho Bay [26,27], suggest that *Gambierdiscus* is the likely source of the CTX compounds that are naturally bio-accumulated in a variety of marine invertebrates.

Considering that most ciguatera mitigation programmes currently rely solely on the survey of *Gambierdiscus* populations and/or the monitoring of CTXs in fish, these data highlight the importance of also extending such surveys to several species of marine invertebrates that are highly prized by local populations, as they actually represent a potential risk for human consumption.

Geographical range of ciguatera: recent expansion to new areas

Another striking feature of ciguatera is its recent expansion to previously unaffected regions [43–45]. Globally, the endemic regions can be superimposed on coral development areas of the Caribbean Sea, and Pacific and Indian Oceans—that is, tropical and sub-tropical areas at low latitudes (between 35°N and 35°S) where the climatology and water conditions are more favourable to the development of *Gambierdiscus* spp. [25]. Rapa Island is located in the southernmost part of the Australes archipelago in French Polynesia, at latitudes near those of temperate locations, and was reputed to be completely free of ciguatera until 2008 when the first cases emerged (Table 1). In 2009, a mass-poisoning event affected half the population following a community fishing party. Clinical records indicated symptoms similar to ciguatera in affected individuals. The unusual severity and magnitude of this outbreak led to two fatalities. Field investigations allowed for the detection of toxic *Gambierdiscus* populations in several sampling sites of Rapa Island, and the presence of CTXs in herbivorous and carnivorous fish at concentrations well above the guidance level [37], confirming the emergence of a novel ciguatera-prone area in French Polynesia. Fortunately, the local population was highly reactive to educational and community outreach interventions, with a significant reduction in incidence rates (Table 1); a result attributable to self-regulating behaviour among the population [19].

More broadly, the case of Rapa Island is emblematic of the current expansion of *Gambierdiscus* spp. and ciguatoxic fish to previously ciguatera-naive regions, most notably to temperate areas, as is the case for several locations in the eastern Atlantic Ocean (Madeira and Canary Islands) where endogenous cases have been reported since 2004 [44,45]. These observations are consistent with the detection of *Gambierdiscus* spp. (including two novel species) in Macaronesian waters, and the confirmation of CTX contamination in indigenous fish [46,47]. Since this date, reports of *Gambierdiscus* spp. and *Fukuyoa* spp. populations are being continually documented from other regions of the globe, such as the Gulf of Mexico, the Mediterranean Sea, Northland New Zealand, Pakistan, the Arabian Gulf and the Red Sea, ([21] and references therein). As a result, our concept of what habitats are suitable for *Gambierdiscus* spp. (e.g. temperature, irradiance, or depth range) is also likely to change [48].

Owing to the high incidence rates reported annually from French Polynesia, ciguatera is not only a major public health issue but also represents a major threat to food sustainability and food security of local communities. Even more alarming, this issue is expected to increase in the context of global change and increased eutrophication in coral reef environments [49], stressing the urgent need for accelerating the implementation of ciguatera mitigation programmes at a global scale. A first significant step towards this goal is the recent request filed by the Codex Committee on Contaminants in Food (www.codexalimentarius.org) to the Food and Agriculture Organization of the United Nations/World Health Organization for scientific advice on the maximum limits for CTXs and for risk management guidelines (http://www.fao.org/fao-who-codexalimentarius/news-and-events/news-details/fr/c/1173604/).

Authors' contribution

MC, CMG, MR and HTD have drafted the article, revised it and approved the final version to be submitted.

Transparency declaration

The authors declare no conflicts of interest.

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