

Clinical Characteristics of Ciguatera Fish Poisoning in Martinique, French West Indies – a case series

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Abstract: Ciguatera fish poisoning (CFP) is one of the most common causes worldwide of marine poisoning associated with fish consumption from tropical areas. Its incidence is underreported. CFP cases seem to increase with grouped cases reported during summer. Exposure to ciguatoxin, the toxin responsible for CFP with sodium-channel agonistic, cholinergic, and adrenergic activities, may result in a large spectrum of manifestations. We aimed to describe the clinical characteristics, management, and outcome of CFP in Martinique, French West Indies. We conducted an observational retrospective single-center study during six years (October 2012 to September 2018) including all CFP patients managed by the prehospital medical services, admitted to the university hospital emergency department, or declared to the regional health agency. One hundred and forty-nine CFP patients (81females/63males; median age, 46 years [interquartile range, 34-61]) were included. Acute features consisted in general (91%; mainly, myalgia pruritus, and asthenia), gastrointestinal (90%; mainly diarrhea, abdominal pain, and nausea), neurological (72%; mainly, paresthesia, dysgeusia, and impairment of hot/cold feeling), and cardiovascular manifestations (22%; bradycardia, hypotension, and heart conduction disorders). Management was supportive. No patient died but symptoms persisted in 40% of the 77 patients with follow-up at day 15. CFP was mainly attributed to the ingestion of trevallies (59%), snappers (13%) and king mackerels (8%) with collective contaminations (71%). Unusual fish (tuna, salmon, and spider conchs) were suspected in rare cases. Ingestion of trevallies was associated with significantly higher persistent symptoms (odds ratio, 3.00; 95% confidence interval, [1.20-8.00]; $p=0.03$). CFP incidence was 0.67 cases per 10,000 patient-years in Martinique over the study period. To conclude, CFP represents an increasing public health issue in Martinique like in other Caribbean islands. Patients present usual but possibly life-threatening features. Outcome is excellent despite frequently prolonged manifestations.

Keywords: Ciguatera; Ciguatoxin; Fish; French West Indies; Martinique; Poisoning

Key Contribution: Our findings enhance understanding on the risks, management and outcome of ciguatera fish poisoning and highlight the resulting public health issue in West Indies.

1. Introduction

Ciguatera fish poisoning (CFP) is one of the most common marine poisonings related to fish consumption worldwide [1-3]. CFP mostly results from accidental ingestion of fish flesh contaminated with the toxins of *Gambier discus spp.*, a unicellular alga. This alga grows on corals with stimulated development if marine environment is disturbed, as more and more frequently observed with cyclones, sand fog, volcanic activity, sargassum waves, pollution, and work on the reefs [3-5]. This alga secretes several toxins including ciguatoxin, a colorless odorless heat-stable non-protein toxin, which finds its way into the food chain. Among fish species likely to transmit ciguatera, large predators such as jacks, groupers, trevallies and barracudas are the most frequently involved.

Incidence of CFP has been determined in various intertropical areas [4-9] (See Supplemental data, Table 1S). Although underestimated with approximately 50,000 to 500,000 annual cases reported worldwide [3], its incidence sharply increased during the last decades in the West Indies. CFP-attributed manifestation are variable and non-specific, mostly beginning within minutes post-exposure with gastrointestinal followed by general, neurological, and cardiovascular disorders [10-12]. They are related to the sodium-channel agonistic, cholinergic, and adrenergic activities of ciguatoxin [1-3]. Management is supportive and outcome favorable.

To date, the incidence and presentations of CFP in Martinique, the largest French island in the West Indies are poorly known. Therefore, we designed this study aiming to describe the clinical characteristics (primary objective) and evaluate management and outcome of CFP patients (secondary objective).

2. Results

During the 6-year study, 149 CFP patients (81 females/63 males; median age, 46 years [interquartile range, 34-61]; history of hypertension, 15%) were included. Overall, 12 patients were managed by the prehospital medical services, 66 patients were admitted to the emergency department, and 117 patients were reported by the RHA. Three patients (2%) had a previous CFP history.

CFP resulted from collective food poisoning in 106/149 cases (71%), involving a median number of three contaminated guests [3-5] per event with fish mainly derived from local Martinique's fisheries (83%). The main involved geographical areas were the counties of Vauclin and Trinité (together accounting for 45% of the cases) (See Supplemental data, Figure 1S).

CFP symptoms occurred 5 hours [3-8] post-fish ingestion. Manifestations were general (135/149, 91%), gastrointestinal (134/149, 90%), neurological (108/149, 72%), and/or cardiovascular (33/149, 22%) (Table 1). Vital parameters available in 66/149 patients (44%) showed body temperature $\leq 36.5^{\circ}\text{C}$ (26/66, 39%), heart rate ≤ 40 bpm (8/66, 12%), and systolic blood pressure ≤ 80 mmHg (8/66, 12%). Electrocardiogram showed cardiac conduction disturbances (9/66 patients, 14%) including first/second-degree atrioventricular

(n=5) and bundle branch blocks (n=4). One additional patient exhibited slow atrial fibrillation. Blood lactate concentration was elevated >2mmol/L in four patients.

Table 1. Clinical manifestations in 149 patients diagnosed with ciguatera fish poisoning in Martinique, French West Indies, in 2012-2018.

Clinical characteristics	Prévalence or value
General manifestations	135/149 (91%)
Body temperature [†]	37.0°C [36.0-37.1]
Myalgia	94/149 (63%)
Pruritus	94/149 (63%)
Asthenia	61/149 (41%)
Hypothermia (temperature $\leq 36.5^{\circ}\text{C}$)*	26/66 (39%)
Arthralgia	54/149 (36%)
Chills	49/149 (33%)
Headaches	42/149 (28%)
Dizziness	34/149 (23%)
Malaise	28/149 (19%)
Sweat	6/149 (4%)
Dyspnea	5/149 (3%)
Limb edema	5/149 (3%)
Gastrointestinal manifestations	134/149 (90%)
Diarrhea	119/149 (80%)
Abdominal pain	102/149 (69%)
Nausea	88/149 (59%)
Vomiting	80/149 (54%)
Neurological manifestations	108/149 (72%)
Paresthesia	77/149 (52%)
Dysgeusia	45/149 (30%)
Impairment of feeling of hot and cold	10/149 (27%)
Touch disorder	37/149 (25%)
Dysuria	25/149 (17%)
Reversal of hot and cold	24/149 (16%)

Balance/coordination/language impairment	24/149 (16%)
Visual disturbance	23/149 (15%)
Behavioral disorder	17/149 (11%)
Pain in cold	11/149 (7%)
Cardiovascular manifestations	33/149 (22%)
Heart rate [†]	69 bpm [50-87]
Systolic blood pressure [†]	112 mmHg [97-130]
Diastolic blood pressure [†]	68 mmHg [59-78]
Bradycardia (heart rate <60 bpm)*	24/66 (36%)
Hypotension (systolic blood pressure <90mmHg)*	10/66 (15%)
ECG abnormalities*	10/66 (15%)
Severe cardiovascular features ^{#,*}	8/66 (12%)
Palpitations	5/149 (3%)
Chronic manifestations**	31/77 (40%)
Chronic pain	20/77 (26%)
Chronic neurological manifestations	15/77 (20%)
Chronic asthenia	11/77 (14%)
Chronic pruritus	10/77 (13%)

[†]expressed as median [interquartile range]; [#]severe cardiovascular features were defined as heart rate <40 bpm or systolic blood pressure <80mmHg on admission; *determined in the 66 patients managed in the emergency department with available vital signs and electrocardiograms; **determined in the 77 patients followed-up at the clinical toxicology consultation (n=39) or by phone call (n=38).

In the 66 patients transported to the emergency department, management was supportive (64%) and included intravenous atropine (10/66, 15%) and mannitol (11/66, 17%) (Table 2). Overall, hospitalization was required (24/149, 16%), mainly in the post-emergency hospitalization unit (20/24, 83%). Length of hospital stay was 1 day [1-2]. Follow-up at day 15 was available in 77/149 patients (52%) including 39 hospital-managed patients followed-up in the clinical toxicology consultation and 38 patients followed-up by phone call. Reported persistent symptoms (31/77, 40%) consisted in pain (20/77, 26%), neurological complains (15/77, 20%), asthenia (11/77, 14%), and pruritus (10/77, 13%). No patient died in relation to CFP.

Table 2. Management in sixty-six patients diagnosed with ciguatera fish poisoning and managed in the emergency department of the university hospital of Martinique, French West Indies, in 2012-2018.

Management at the emergency department	Prevalence or value
Supportive care	42/66 (64%)
Fluids (0.9% NaCl)	11/66 (17%)
20% mannitol infusion	11/66 (17%)
Intravenous atropine administration	10/66 (15%)
Hospitalization	24/149 (16%)
Length of hospital stay [†]	1 days [1-2]
Follow-up at the clinical toxicology consultation	39/66 (59%)

[†]expressed as median [interquartile range]

The incriminated fish species included trevallies (*Carangidae*), snappers (*Lutjanus buccanella*), king mackerels (*Scomberomorus regalis*) and moray eels (*Gymnothorax funebris*) (Table 3). Rare cases were attributed to tunas (*Thunnus atlanticus*). Patients declared to have eaten only the fish flesh (116/149, 78%) but also the head or viscera (25/149, 17%) and the tail (12/149, 8%). Intoxication with trevallies resulted in significantly more frequent acute gastrointestinal manifestations (odds ratio (OR), 3.16; 95% confidence interval (CI) [1.52-6.56]; $p=0.03$) and persistent symptoms (OR, 3.00; 95% CI, [1.20-8.00]; $p=0.03$) (Table 4).

Table 3. Ingested fish that caused ciguatera fish poisoning in 149 patients in Martinique, French West Indies, in 2012-2018.

Incriminated fish	Number of incriminated fish (N=85)	Number of intoxicated patients (N=149)
<i>Carangidae</i> (trevallies)	50	87
<i>Lutjanus buccanella</i> (snapper)	14	19
<i>Scomberomorus regalis</i> (king mackerel)	4	10
<i>Gymnothorax funebris</i> (moray eel)	3	4
<i>Thunnus atlanticus</i> (tuna)	2	6
<i>Coryphaena hippurus</i> (sea bream)	2	3
<i>Syphyraena barracuda</i> (barracuda)	1	9
<i>Epinephelus morio</i> (grouper)	1	1
<i>Strobus gigas</i> (spider conchs)	1	1
<i>Salmo salar</i> (salmon)	1	1
Mixed fish	1	4
Not described	4	4

Table 4. Comparison of clinical characteristics according to the fish responsible for ciguatera poisoning in 145 patients in Martinique[†], French West Indies, in 2012-2018.

Clinical characteristics	Patients intoxicated by trevallies (<i>Carangidae</i>)	Patients intoxicated by other fish species	<i>p</i> -value

	(n=87)	(n=58)	
Fish head or viscera ingestion (N=144)	20/86 (24%)	5/58 (9%)	0.03
Acute vomiting (N=145)	64/87 (74%)	23/58 (40%)	<0.0001
Acute nausea (N=145)	61/87 (70%)	24/58 (41%)	0.001
Acute abdominal pain (N=145)	68/87 (78%)	31/58 (53%)	0.002
Acute hypotension (N=64)	14/35 (40%)	5/29 (17%)	0.05
Mannitol administration (N=63)	8/33 (24%)	2/30 (6%)	0.09
Persistent symptoms (N=74)	19/36 (50%)	9/36 (25%)	0.03

[†]Four patients with unknown ingested fish were excluded from the analysis.

3. Discussion

3.1. Incidence of CFP in the world

Overall, 149 patients were diagnosed with CFP in Martinique from 2012 to 2018, allowing to calculate an incidence of 0.67 cases/10,000 patient-years over the study period in an estimated population of 371,246 inhabitants by the French national institute for statistical and economic studies in 2018.

Epidemiology of CFP is challenging to assess. It has been estimated that less than 20% of CFP cases are reported [4]. In the West Indies, CFP incidence over the 1996-2006 period was estimated at 0.2/10,000 patient-years in Martinique, 0.3/10,000 patient-years in Guadeloupe, 19.9/10,000 patient-years in the British Virgin Islands 34.4/10,000 patient-years in Antigua, and 58.6/10,000 patient-year in Montserrat [4]. An annual incidence of 1.47/10,000 patient-years (95% CI, [1.29-1.66]) was determined in 2016 in Guadeloupe, i.e 5 times the previously reported incidence in 1996-2006 [6]. In the other intertropical French territories, incidence of CFP was estimated at 0.2/10,000 patient-years in 2000-2010 in Reunion (Indian Ocean) [5] and 18/10,000 patient-years in 2016 in the French Polynesia (Pacific Ocean), the most affected territory in France [8]. In the US, Florida is the state with the highest incidence due to its intertropical geographical location, with an estimated incidence of 0.56/10,000 patient-years in 2000-2011 [7].

The incidence reported in our study was 3 times higher than that reported during 1996-2006 (0.2/10,000 patient-years) [4]. Estimate for the 1996-2006 period was based only on RHA reports whereas our study collected data from cases observed in the emergency department. If only cases reported to RHA (n=117)

were taken into account, the incidence would have been of 0.52 cases/10,000 patient-years. The increased incidence of CFP in Martinique, which we reported similarly to Guadeloupe, the second main French island in the West Indies [6], could at least partly be related to the improved data collection. However, it may also correspond to an actual increase in incidence, even if still probably underestimated. Interestingly, tourism in intertropical countries is likely to increase CFP cases in Europe and North America among travelers who have stayed in endemic areas. For instance, six CFP cases involving 20 persons were reported in 2010-2011 in the state of New York, in relation to the consumption of imported fish [13].

Interestingly, collective food poisoning was responsible for 71% of our cases, mainly in summer, compared to 41% in Polynesia [14] and 32% in Guadeloupe over the 2013-2016 period [6]. In our series, 19 CFP cases occurred in 2017 in relation to the consumption of snappers imported from the Indian Ocean area and sold in supermarkets. In August and September 2018, two other episodes of collective food poisoning, attributed to the consumption of fish from local fisheries, involved eight and nine patients, respectively. Grouped cases of CFP are increasingly reported such as thirty-four cases in Germany in 2009-2012 [15,16]; thirteen patients in Italy in 1995-1999 [17]; thirty patients following barracuda ingestion, in 1995 and eighteen others in 1997-2002 in France, especially in the Mediterranean city of Marseille [18].

3.2. Clinical characteristics of CFP

CFP is a polymorphic condition with no specific toxidrome, responsible for ~175 symptoms with marked variable intensity between individuals [19]. CFP presentations in our series were similar to presentations described in other Caribbean studies [4-6,20]. Gastrointestinal manifestations are foremost, including nausea/vomiting, intense abdominal pain, and profuse liquid diarrhea without bloody glair. Cardiovascular impairments may appear rapidly and become life-threatening. They were present in 22% of our patients *versus* 41% in the Guadeloupe's cohort [6] and 12% in the French Guyana series [21]. The relatively high frequency of cardiovascular disorders in our study may be attributed in part to the study design, which mainly included patients admitted to the emergency department, who corresponded to the most severe cases. It is also possible that bradycardia or hypotension were discriminating factors that allowed CFP diagnosis despite a possible underestimation due to the lack of knowledge of this condition by emergency physicians.

Neurological manifestations are polymorphous but suggestive of CFP [22-24]. They usually occur within days following fish ingestion. The main impairments we found were paresthesia (especially perioral), dysesthesia with inversion hot/cold, sensation of metallic taste, and diffuse hyperesthesia. Visual disorders and ataxic disorders have also been described, mimicking a Guillain-Barre syndrome [22]. Psychiatric presentations are rare and may include anxiety, depressive syndrome, phobia, and nocturnal nightmare [23].

Prevalence of hypothermia was also elevated (39%) in our series, consistent with observations from French Polynesia [14,22] and Guadeloupe [6]. Interestingly, hyperthermia is considered in Polynesia as a symptom excluding the diagnosis of CFP [8]. Moreover, ciguatera is named "disease of the dead" by populations from the Marquesas Islands due to CFP-induced body cooling. In addition, joint and muscle disorders such as arthromyalgia affecting the lower limbs are frequently observed, consistent with our series. Similarly, intense pruritus called "la grate" in the Pacific region is characteristic and may induce scratching lesions.

Like in our series, persistent manifestations occurring in ~20% of the patients may be neurological, cutaneous, and/or musculoarticular with almost constant asthenia [25,26]. By contrast, only recurrent neurological manifestations have been reported following the ingestion of non-ciguatoxic food such as poultry, pork, peanuts, and alcohol, or during physical activities including sexual activity [27].

Consistent with the literature [11,12], CFP patient management was mainly supportive in our series. However, due to the absence of institutional guidelines, there was a great disparity in treatments. Atropine was used in poorly tolerated severe bradycardia of <60 bpm, as recommended [28]. Despite evidence of low quality to support its effectiveness to limit neuronal edema and impaired action potentials [29], mannitol was used in the early phase including itching and sensitive neurological syndrome at the request of the physician in charge. If needed, patients admitted to the emergency department were hospitalized shortly.

3.3. Fish involved in CFP

All kinds of fish in Martinique are likely to transmit ciguatera. In our series, we found several CFP cases related to unusual fish species. Mollusks such as lambi (*Strobus gigas*) were shown to transmit ciguatera in Polynesia (Benitiers, Sea Urchins, Trocas) [8,30]. However, the absence of remains of the incriminated lambi prevented us from definitive analytical confirmation. Similarly, salmon (*Salmo salar*) was the source of CFP, although no laboratory confirmation could be obtained. Interestingly, two grouped cases of CFP were related to tuna from local fisheries, causing six analytically confirmed poisonings. To date, this pelagic species is not considered as a ciguatera vector, the unique other CFP case linked to tuna ingestion being reported in Guadeloupe in 2008 [21].

Ciguatoxins are non-protein fat-soluble toxins that accumulate in the fatty parts of fish (head and viscera) [31]. Trevallies seem to have caused more severe intoxication leading to a threefold increase in the risk of developing chronic symptoms (Table 4). Trevallies are cooked traditionally in broth or in blaff, which leads to consume the head and viscera more often, whereas other fish are cooked by grilling or frying with consumption limited to the flesh.

3.4. Study limitations

Our study has limitations related to its retrospective single-center design. Biases in the estimation of ciguatera incidence in Martinique may have resulted from the non-inclusion of patients with mild symptoms who did not consult a medical professional and the uncomplete recovery of hospital cases due to the absence of exact coding in the database. Since the most severe cases were included, severity of CFP may have been enhanced. Missing data were noted in some records, however minimized by the systematic phone call to the patient when possible. Vital parameters at the time of intoxication were not available in RHA declaration forms. Follow-up was limited to 59% of the patients. In the absence of reliable routine bedside screening tests of ciguatoxin, diagnosis was based on history and clinical manifestations suggestive of CFP. No analytical confirmation was obtained, which would have required analysis of the remains of meals in a specialized laboratory [32].

Hence, encouraged by our findings, pieces of fish suspected to be ciguatera-contaminated are now sent systematically for laboratory analysis by the French Directorate of Food, Agriculture & Forestry, and the French Agency for Food, Environmental and Occupational Health & Safety. Implementation of guidelines for CFP management should allow harmonizing the practices and offering optimized management. Our study could also support future preventive actions. We showed the great disparity in species causing CPF in Martinique, including classic species such as snappers and jacks and rarer pelagic species such as tuna and sea bream. Grouped CFP cases observed almost yearly suggest that fish caught in Martinique are potential vectors of ciguatera. The local population should be reminded not to eat the head or viscera of trevallies.

4. Conclusions

CPF is an increasing serious public health issue in Martinique similarly to other West Indies countries. Clinical picture is characterized by predominant gastrointestinal and neurological manifestations with possible life-threatening cardiovascular disturbances. Outcome is excellent despite possible manifestation persistence beyond 15 days.

5. Methods

5.1. Study design and data collection

We performed a retrospective single-center observational study over a six-year period (October 01, 2012 to September 30, 2018) including all CFP patients managed by the emergency medical assistance service (SAMU 972) and/or admitted to the emergency department of the university hospital of Martinique as well as all CFP patients declared to the Regional Health Agency (RHA).

The study was conducted according to the Helsinki principles, declared and approved by our institutional review board. Patients were informed and invited to express their opposition to the use of their anonymized data if desired, but written consent was waived due to the retrospective and non-interventional methodology of the study.

CFP was defined as case of fish consumption followed within 48 hours by gastrointestinal, neurological or cardiovascular manifestations [12]. Symptoms were defined as “persistent” if present after the acute phase that usually lasts 1-14 days after fish ingestion. For analysis, we considered trevallies (*Carangidae*) as a family of ray-finned fish, which includes jacks, pompanos, jack mackerels, runners, and scads.

Patients admitted to the hospital were identified using the electronic database of the hospital medical information department and SAMU 972 (i.e., PMSIpilot, Groupe PSIH, France and Centaure™ software, Inetum, France, respectively). For each patient, the age, gender, history, date of intoxication, incriminated fish species, number of intoxicated persons, clinical manifestations, treatments administered at the hospital, and follow-up data were collected. Of note, patients reported to the RHA received an individual questionnaire accompanied with a systematic phone call to collect all required information. CFP patient follow-up at day 15 post-intoxication and outcome evaluation were performed during the study period by a consultation with a clinical toxicologist at the hospital or by phone call if required.

5.2. Statistical analysis

Quantitative variables are expressed as median [interquartile range] and qualitative variables as numbers (percentages). Univariate comparisons between CFP patients intoxicated by trevallies *versus* other fish were performed using Fisher’s exact tests for qualitative variables and Mann-Whitney U-tests for quantitative variables. ORs and their 95% CIs were calculated. A *p*-value <0.05 was considered as statistically significant.

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Supplemental material

Table 1S- Reported incidence of ciguatera fish poisoning in the world

Region	Period	Incidence (/10,000 patient-years)	Reference
Martinique	1996-2006	0.20	[4]
Reunion (Indian Ocean)	2000-2010	0.20	[5]
Guadeloupe	1996-2006	0.30	[4]
Guadeloupe	2013-2016	1.47	[6]

Florida	2000-2011	5.6	[7]
French Polynesia (Pacific Ocean)	2016	18.0	[8]
Virgin Islands	1996-2006	19.9	[4]
Antigua	1996-2006	34.4	[4]
Montserrat	1996-2006	58.6	[4]
Pacific Island Countries and Territories	1998-2008	194	[9]

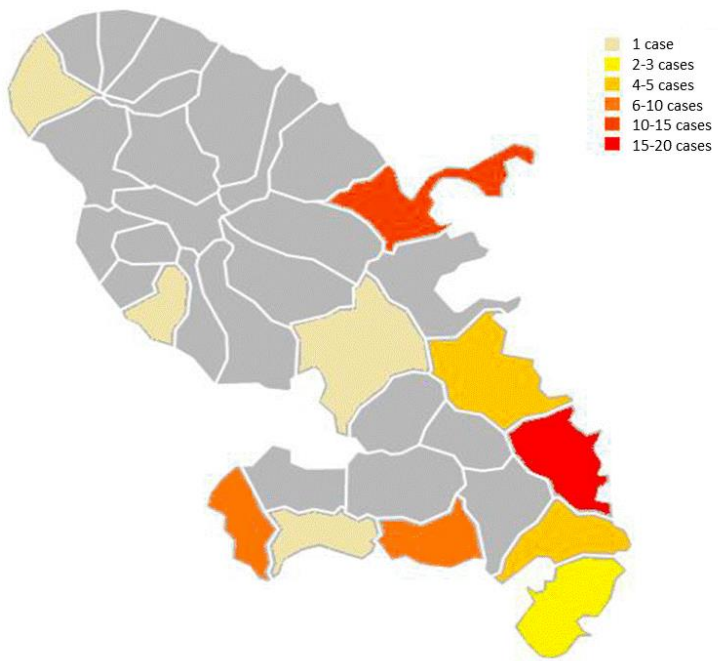


Figure 1S- Map of geographical areas in Martinique where ciguatera fish poisonings were reported in 2012-2018.