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Letter to the Editor

A case of Ciguatera poisoning with paradoxical dysaesthesia and degenerative features at skin biopsy

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Dear Editor,

Ciguatera poisoning is a widespread seafood-toxic illness, endemic in the tropical and subtropical regions of Caribbean and Indo-Pacific. It is the most frequently reported marine toxin-related poisoning globally. The climate and environment changes together with the international commerce and consumption of frozen fish species are responsible for an increasing number of Ciguatera poisoning also in temperate regions [1]. Ciguatoxins are produced by dinoflagellates of the Gambierdiscus species, bottom-dwelling single-cell organisms living in the coral reef. Ciguatoxins are lipophilic, soluble, heat-stable polycyclic polyethers, which are stored in finfish viscera and concentrate and bioaccumulate up the food chain from small reef fish to the large carnivorous species. They are grouped in 3 variants, depending on their origin from the Pacific (P-CTX), Caribbean (C-CTX) and Indian Ocean (I-CTX) [2].

Typically, Ciguatera poisoning induces acute gastrointestinal signs and symptoms within 6–12 h after fish ingestion. Up to two-three days after exposure, neurological and cardiovascular symptoms begin. Neurological involvement includes distal diffuse paresthesias, metallic taste and numbness in the oral region, itching, myalgia, arthralgia, headache and dizziness. The pathognomonic symptom is the so-called “paradoxical dysaesthesia” or cold allodynia, a reversal of thermal perception in which touching mild cool or cold surfaces produces a burning pain. Cardiac acute symptoms, such as hypotension and bradycardia may appear in the early stage of poisoning. Fatigue, difficulty in concentration, depression, irritability and anxiety are sometimes associated. Rarely, after the visceral organs' consumption, the clinical features could include respiratory failure, dehydration, focal neurological signs or coma, leading to death. There are currently no available biomarkers for ciguatoxins exposure in humans. The diagnosis is therefore based on history (fish intake in or from appropriate geographical regions), clinical manifestation and time course consistent with Ciguatera poisoning [3–5].

The pathophysiology of paradoxical dysaesthesia is still unclear, but it is likely secondary to improper sodium channel activation. Ciguatoxins bind quasi-irreversibly sodium channels and modulate membrane depolarization through activation of the Nav1.8 subunit in TRPA1-positive neurons leading to peripheral sensitization to cooling [6].

We report on a patient who suffered from Ciguatera poisoning after a holiday in Cuba. Diagnosis was based on the history of recent fish, epidemiological criteria and typical clinical manifestations. The patient underwent a skin biopsy that revealed axonal swelling of epidermal fibers.

A 63-year-old man, with unremarkable medical history, came to our attention for enduring cold allodynia (cold objects, especially cold drinks, felt unpleasantly burning hot). He also reported metallic taste, oral tingling and the sensation that flat water felt like sparkling. A month earlier, while on holiday in Cuba, he had eaten two portions of a large local fish, cooked and sold on a rural beach and identified as a dog snapper. He had dinner by himself, he had not consumed other types of seafood (shellfish or raw fish) nor alcoholic drinks during the meal. He denied any food allergy. About 24 h after fish consumption, the patient had sought medical advice for the acute onset of perioral and tongue burning sensations and cold skin sensation on his limbs. He reported that his hands felt “burning” when he washed them with cold water and he experienced “burning hot” feet while walking barefoot on cold floor. The symptoms of temperature reversal were prominent when he ate or drank and when he showered. The clinical manifestations were not influenced by other potential triggers (such as the assumption of peanuts, alcohol or caffeine). He did not complain of gastrointestinal symptoms. At the time of our examination, burning sensations had only partially decreased with gabapentin that was given by the family doctor. The patient still complained of lingual paresthesias and burning pain when drinking cold drinks.

Neurological examination confirmed only the presence of burning dysaesthesias. Nerve conduction studies and needle electromyography at four limbs were negative. Hematologic work-up showed no abnormalities. Based on the distinctive history and clinical presentation, a diagnosis of Ciguatera poisoning was presumed. The accurate description of the eaten fish, the suggestive geographical context, the detailed history provided by the patient and his persistent indicative symptoms let us to rule out other possible causes including food poisoning, seafood allergy, neurotoxic shellfish poisoning, pesticide poisoning or alcohol intoxication. Two months after symptoms onset, the patient underwent skin biopsy that was analyzed at Skin Biopsy, Peripheral Neuropathy and Neuropathic Pain Laboratory of “Carlo Besta” Neurological Institute in Milan. The laboratory is equipped with physicians and biologists trained to evaluate the skin nerve fibers.Specifically, one physician and one biologist independently evaluated the specimen,

Quantification of epidermal innervation density resulted normal (3.8 IENF/mm; age and sex-adjusted normal value > 2.8) while diffuse axonal swellings were observed (Fig. 1). Lamotrigine, a sodium

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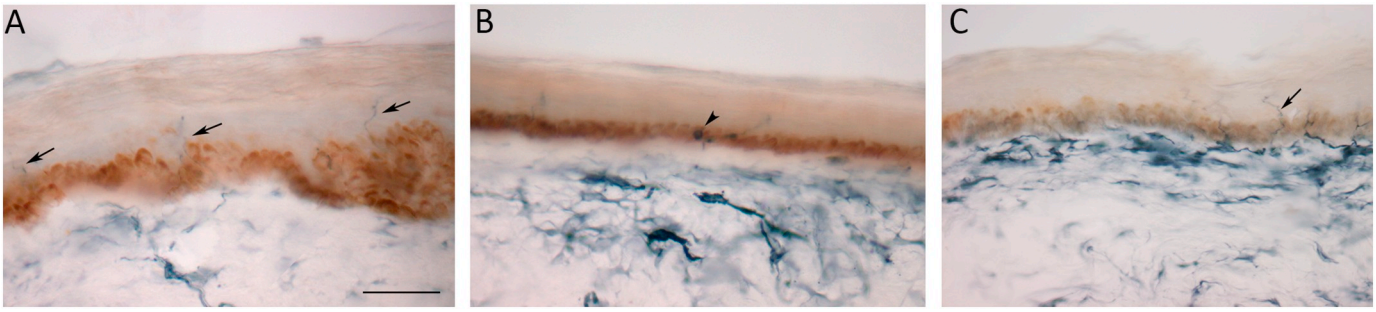

Fig. 1. Bright field immunohistochemical study with polyclonal anti-protein gene product 9.5 antibody in 50-μm sections from skin biopsies taken at the distal leg in the patient (A and B) and a healthy subject (C). Note the intraepidermal nerve fibers (A; arrows) with normal density but diffuse swellings (B; arrowhead). Original magnification 40×. Bar is 50 μm.

channel-blocker, was prescribed with progressive improvement up to complete recovery and drug discontinuation 4 months later.

Diagnosis of Ciguatera poisoning is challenging, since biomarker of Ciguatoxins in humans are lacking. Ciguatoxins are tasteless, odorless and heat stable to cooking temperature, and may stable for months also at freezing temperatures, so poisoning can occur also in temperate areas. Symptoms and signs may significantly vary, depending on the individual susceptibility, the dose and the Ciguatoxin variant received. Although the mean duration of clinical manifestations is 8 days, sensory and motor signs may persist for months. However, neurological and neurophysiological examination may be completely normal and mild forms of ciguatera poisoning are usually characterized by almost exclusively subjective complaints. Thus, the diagnostic "gold standard" includes the detection of Ciguatoxins in the fish by appropriate analytical testing, in addition to a recent fish-eating history, signs, symptoms and time course consistent with Ciguatera intoxication [4,5].

Pathophysiology of Ciguatera poisoning is still little known. In vitro and in vivo studies had demonstrated that ciguatoxins are powerful mammalian voltage-gated sodium channel activators [6]. Injection of P-CTX-1 in fact elicits cold allodynia in mice by targeting specific Nav 1.8 and TRPA1-expressing unmyelinated and myelinated primary sensory neurons. The toxin activates voltage-dependent sodium channels, resulting in sustained membrane depolarization via TRPA1-dependent calcium influx [7]. Furthermore, the intracutaneous injection of P-CTX-1 induces the release of the calcitonin gene-related peptide (CGRP) that causes a transient cold allodynia and a long-lasting axon reflex flare in human skin. CGRP release seems to be responsible of long-lasting symptoms of ciguatera through chronic activation of the immune system [8].

Previous studies and cases reports demonstrated the presence of axon demyelination, axonal degeneration with edema and a marked reduction of myelin fiber density in sural nerve biopsies of patients with ciguatera-induced peripheral neurological symptoms [9]. Furthermore, the chronic neurological disturbances could be related to the delayed functional recovery of peripheral nerves due to the inhibition of regenerative regrowth by the ciguatoxin [10].

In our patient, skin biopsy revealed axonal swellings that represent pre-degenerative changes of nerve ending processes. The epidermal nerve density was normal possibly because the time elapsed since toxin exposure has allowed their regeneration. Alternatively, based on the relatively mild clinical presentation of our patient, ciguatoxins might have affected the function of primary nociceptors altering the activity of sodium channels without causing the degeneration of their peripheral endings.

Declarations of Competing Interest

None.

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