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Ciguatera fish poisoning: A first epidemic in Germany highlights an increasing risk for European countries

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ABSTRACT

Toxin-producing microalgae are thriving worldwide due to coral reef destruction and global warming with major consequences on ecosystems, international trade and human health. Microalgae belonging to the family of flagellate protists, in particular dinoflagellates, secrete a variety of high-molecular-weight polyether toxins that accumulate through the marine food chain to cause disease in humans by acting as sodium channel activator toxins; ciguatera is the most frequent seafood-borne illness worldwide with 50,000 to 500,000 global incidences *per annum* and is usually limited to endemic areas located between 35° northern and 35° southern latitude. The rising global incidence frequency renders it a major human health problem, because no curative treatment is available yet and reliable detection assays are lacking. During the last decade ciguatera has increasingly become endemic in previously unaffected areas for two reasons: first global warming has contributed to the emergence of dinoflagellate species in subtropical and even temperate regions that previously had been constrained to tropical areas and second: in Europe globalization of fishing industry and tourism has led to a progressive increase in the number of ciguatera cases and a lack of awareness among medical personnel contributes to under-reporting. We review, through a recent ciguatera outbreak in Germany, the risk for ciguatera poisoning in Europe and highlight characteristic symptoms, current knowledge about disease pathomechanisms and treatment options.

1. Introduction

1.1. A global public health issue

Ciguatera, a disease associated with a range of heterogeneous symptoms of neurological, gastrointestinal and cardiovascular origin, is contracted by humans through the consumption of fish contaminated by ciguatoxins.

With an increasing global population, food security is becoming difficult to achieve in both emerging and developed countries. Fishery products supply millions of tons of fish worldwide to feed low-income populations of costal and insular areas, and provide an alternative protein source in Europe and America. This demand exerts rising pressure on fishing grounds, and in combination with globalization of trade, is leading to increased import and greater

Abbreviations: CTX, ciguatoxin; C-CTX, Caribbean CTX; I-CTX, Indian Ocean CTX; P-CTX, Pacific CTX.

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consumption of fish sourced from areas where ciguatera is endemic (Achaibar et al., 2007; Garcia and Rosenberg, 2010). Thus, the disease is no longer restricted to the South and Equatorial Pacific, the Caribbean Sea and the Indian Ocean (Bagnis et al., 1979; Lange, 1994), where several hundreds of fish species are known to harbor the toxins responsible for ciguatera.

While the European Union has adopted policies to ensure food safety, global mobility and intensive tourism to tropical and subtropical areas has led to an increased risk of contracting pathologies that rarely occur in temperate latitudes. In addition, the likelihood of contracting ciguatera in endemic areas is also increasing, as a continuous rise in poisoning cases has been reported since 1980 (Skinner et al., 2011). Epidemiological studies estimate that the annual incidence of ciguatera is about 50,000 cases of illness worldwide. However, this evaluation may be greatly underestimated as only 2–10% of cases are estimated to be reported to health authorities worldwide (Lehane and Lewis, 2000). Nonetheless, ciguatera is the most frequent non-bacterial food and seafood-related poisoning, with tourism and fish imports from endemic areas being the main causes for a continuous increase in cases in temperate latitudes (De Haro et al., 2003; Glaizal et al., 2011; Krause et al., 1994; Sanner et al., 1997; From the Centers for Disease Control and Prevention, 2013). To this effect, ciguatera has become a truly global human health concern.

1.2. Ciguatera is increasing worldwide

According to Johnson and Lange, the occurrence of ciguateric fish is restricted to tropical and subtropical marine areas between 35° northern and 35° southern latitude (Johnson and Jong, 1983; Lange, 1987). In subtropical climates, the presence of dinoflagellates is seasonal and likely affected by severe weather events. Worldwide, the Cook Islands in the Pacific appear as the area with the highest incidence (Rongo and van Woesik, 2013). A 2011 study estimated the lifetime risk for Cook Islanders to contract ciguatera as >25% (Skinner et al., 2011). In recent years however, not only an increase in the incidence of ciguatera in endemic areas is observed, but also a higher incidence in subtropical regions and a spread of dinoflagellates into temperate climate zones, with ciguatoxic fish occurring near European coastlines and in the Mediterranean sea (Bentur and Spanier, 2007; Otero et al., 2010). Since 2010 at least three ciguatera outbreaks have been reported in the Canary Islands. These outbreaks coincided with the detection of novel toxin-producing dinoflagellates of the genus *Gambierdiscus* including *Gambierdiscus excentricus* (Fig. 1), and very recently *Gambierdiscus silvae*, which were identified off the Canary Island coastal waters (Boada et al., 2010; Nunez et al., 2012; Fraga and Rodríguez, 2014).

The Caribbean was previously considered as the only endemic area in the Atlantic Ocean, but recently, the occurrence of ciguatera was reported along the West Africa Coast, in particular the coastlines of Cameroon and Senegal (Glaizal et al., 2011; Bienfang et al., 2008). Ciguatera is also on the rise on the Asian continent with toxic micro-algae located on the Korean shorelines and around Jeju Island at 33° northern latitude for the first time in 2011 (Jeong et al., 2012). More recently, there were major outbreaks in temperate climates caused by imported contaminated fish, including 6 outbreaks in New York involving 28 poisoned persons between 2010 and 2011 (From the Centers for Disease Control and Prevention, 2013) and an outbreak in 2012 in northern Germany, where 20 cases were reported.

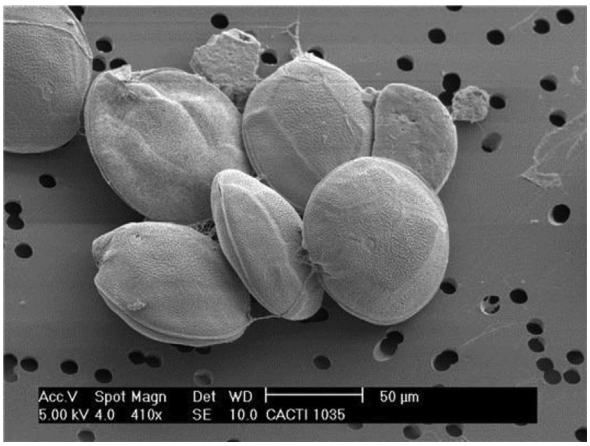

Fig. 1. *Gambierdiscus excentricus*, a novel type of toxic dinoflagellate detected in 2011 in waters off the Canary Islands by researchers at the Instituto Español de Oceanografía (Vigo, Spain). Dinoflagellates of the genus *Gambierdiscus* produce CTXs that accumulate in the food chain. Photography taken by Dr. Santiago Fraga, IEO Instituto Español de Oceanografía©.

1.3. Ciguatoxins – sodium channel toxins in the marine food chain

Marine biotoxins produced by dinoflagellates are the causative agents in human ciguatera poisoning. Dinoflagellates are benthic single-cell organisms residing as epiphytes on damaged corals and contain ciguatoxins as metabolic products. Ciguatoxins (CTXs) are among the most potent neurotoxins. They accumulate through the food chain in herbivorous and carnivorous reef fish and reach highest concentrations in large predatory carnivorous fish. Host fish may be either insensitive to the toxic effects of ciguatoxins, as they appear to be free of symptoms, and instead accumulate the toxins in the flesh, viscera and liver. However, since ciguatera is rarely lethal in humans (<1%), fish carrying particularly high levels of CTXs may be eliminated from the food chain early and thus restrict the doses consumed by humans to sub-lethal exposure. In contrast, freshwater fish appear more sensitive and CTXs can be lethal at lower concentrations (Lewis, 1992). An exception appears to be a reported high death rate (20%) in Madagascar, after consumption of a ciguateric shark (Habermehl et al., 1994).

CTXs are high molecular weight, hydrophobic cyclic polyethers (~1 kDa). CTXs are composed of 11–14 adjacent rings and are grouped in 3 subtypes, depending on their origin from the Pacific (P-CTX), the Indian Ocean (I-CTX) and the Caribbean (C-CTX). The chemical structure of P-CTX-1B is shown in Fig. 2 (Murata et al., 1990; Lewis et al., 1991). In general, P-CTXs are considered the most potent, with humans exhibiting symptoms at 0.1 ppb (0.1 ìg/kg); they are approximately 10-fold more potent than the