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CIGUATERA POISONING: PACIFIC DISEASE, FOODBORNE POISONING FROM FISH IN WARM SEAS AND OCEANS. Review

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ABSTRACT

Purpose: The review is provoked because of lack of awareness of the medical practitioners in Bulgaria concerning of the ethnology, pathogenesis, clinical symptoms and treatment of the ciguatera fish poisoning (CFP). This can be a source of prolonged diagnostic delays, as some cases reporting in another country in Europe, for example Germany, Spain and UK. Varna is the sea town with many sailor crews returning from tropical and subtropical regions, or CFP can affect people who travel to the Pacific and Caribbean or ate exotic fish from supermarket. The information of this fish food-borne poisoning is part of student's education in discipline "Marine medicine" in Medical University, Varna.

Materials and methods: To present better information from different authors and last scientific data, we made review of published materials of 58 issues to construct definition, history, etiology, pathogenesis (toxins and mechanisms of action), clinical symptoms, treatment and prevention of the Ciguatera or ichtyosarcotoxicosis, a wide spread food-born poisoning.

Results: Ciguatera poisoning is ichtyosarcotoxicosis, a wide-spread foodborne poisoning in people after consumption of flesh of different kinds of fishes in which toxins produced by poisonous microorganisms (Dinoflagellates) have accumulated. The poisoning develops by accumulating toxins higher up the food chain starting with toxin producing dinoflagellates (species: *Gambierdiscus toxicus*, *Prorocentrum concavum*, *Pr. lima*, *Ostreoposis lenticularis*, *Ostr. Siamensis* and others), continuing with the poisoned algae (species: *Portieria*, *Halymenia*, *Turbinaria*, *Sargassum*), and after that involving small crustacea and small fishes to greater fishes (vector fishes, genus *Herbivores* and *Carnivores*), in which the toxins have been stored in amount, great enough to cause foodborne poisoning in humans. This poisoning is widespread in tropical and subtropical regions, but because of its delayed toxic effects, lasting for months and years, there is a possibility that every medic can encounter its unusual symptoms, requiring specific treatment. The following toxins cause the poisoning: ciguatoxin, meitotoxin, ostreotoxin, domoic acid and some other unspecified toxins. They are lipid soluble, thermo stable and cannot be decomposed by culinary processing. These toxins have neurotoxic, cardiotoxic, hemolytic properties and cause diarrheic syndrome. Clinical presentation is characterized by average latent period of 12 hours after the consummation, vomiting and diarrhea next 24 hours and neurological symptoms that appear at the beginning of the poisoning with paresthesias along the body, changing feeling of hot and cold, strong myalgia. Disturbances in cardiac rhythm and conduction, strong dehydration or shock are possible in severe cases. Light cases pass over in several days, but, more often the poisoning has a chronic course – from 3-4 months to 1 year, with prevalence of neurologic symptoms: myalgia, paresthesias, skin itching with scratches, depression. The management is not specific and includes stomach lavage with activated charcoal, fluids replacement during the first 24 hours, corticosteroids, antiallergics, high doses of vitamins from group B (Vit. B1, Vit. B6, Vit. B12), mannitol IV, nootropic medicaments, antidepressants and other symptomatic medicaments. The prophylaxis is done by examining every fish with specific test for detecting ciguateratoxin.

Key words: ichtyosarcotoxicosis, dinoflagellates, ciguatoxin, meitotoxin, domoic acid, ciguatera poisoning

INTRODUCTION

Definition:

Ciguatera poisoning is a ichtyosarcotoxicosis, a wide spread foodborn poisoning in people after consumption of flesh of different kinds of fishes in which toxins produced by poisonous microorganisms (Dinoflagellates) have accumulated. The poisoning develops by accumulating toxins higher up the food chain: microorganisms develop on algae which serve as food to crustaceae and little fishes which serve as food to bigger fishes. Toxins accumulate in greater quantities in the flesh of bigger fishes and enter human organism after consumption of these fishes [1-7]. This poisoning is widespread in tropical and subtropical regions, but because of its delayed toxic effects, lasting for months and years, there is a possibility that every medic can encounter its unusual symptoms, requiring specific treatment.

History:

According to some authors [3, 5, 6, 8, 9], every year between 20000 and 50000 people annually fall sick after consumption of flesh of fishes caught in tropic and subtropic seas and oceans (width 35°N-35°S). Ciguatera poisoning is most frequent in Caribbean, Indian Ocean, Maldives, Seychelles, Solomon islands, Guam islands, Fortuna islands, Williams islands etc. The impact of climatic changes on coral reefs can lead to widening or change of the endemic regions of this poisoning [2, 4, 7, 8, 10-15]. Once caught in tropic waters fishes can get in every supermarket all over the world because of the easy trade nowadays. Fifteen cases of this poisoning were reported in USA in 2010 year, some cases were reported in Canada [16] and new 28 cases in 2011. A cluster of reports of neurological and cardiovascular symptoms among people eating reef fish (barracuda and grouper) bought from supermarkets in New York city distributed from Florida have been reported [17]. In 2012, several cases of ciguatera occurred in Germany due to sale of contaminated fish products originating from the Indian Ocean [18, 19]. CFP outbreaks have been reported in France, Italy, Germany and the Netherlands [20]. European sailors are an occupational group at risk for ciguatera fish poisoning due to potentially unsafe food sources during international travel. In 2006 in Avonmouth, UK, outbreak of ciguatera poisoning occurred among returned crew, related to a white snapper fish from the Caribbean [21]. In 2009 in Hamburg 15 sailors fell ill after they ate fish from a catch in the Caribbean 2 weeks earlier [22]. Global warming has contributed to the emergence of dinoflagellate species in subtropical and even temperate regions. In 2004, 2008 and 2009 has been described three outbreaks of ciguatera poisoning in Canary Islands, Spain. Caribbean ciguatoxin-1 (C-CTX-1) was confirmed in fish samples by LC-MS/MS [23].

The term «cigua» does not mean any specific kind of fish. It derived from poisoning with sea periwinkle «cigua», reported for the first time in 1601 in Indian Ocean. The symptoms were similar to those of fish poisoning, so later the Pacific disease was called ciguatera poisoning. The fishes that are connected to this poisoning are more than 420 kinds. They are so called vector fishes genus *Herbivores* and *Carnivores*. Most often these are the fishes from the kind grouper, snapper, moray eels, barracuda. They are big fishes that consume enough quantities of toxins along the food chain; they accumulate in their flesh and can cause poisoning in people. The fish itself does not die from this poison [24]. The first description of this poisoning was in 1555 year from West India [1]. In 1770 Fernandez de Quiros described poisoning of a whole ship crew in South Pacific. In their diaries captain Cook and captain Forster (1776) noted fish poisoning cases with fish from Pacific Ocean. Some cases were registered in French Polynesia in 1792 [1, 2].

RESULTS AND DISSCUSSION

Etiology:

The fishes that cause this poisonings do not possess a poisonous apparatus and do not synthesize poison. For a long time it has been considered that the poison comes from poisonous algae. Today it is known that the poisoning is caused by a microscopic sea plancton, unicellular sea organisms called dinoflagellates. They are organisms of one cell (protozoa), similar to algae and phytoplancton but do not contain chloroplasts and can not photosynthetise. There are many kinds of dynoflagellates. The toxins they synthetise are only 2% from the cell contents but the affected algae become poisonous. Several kinds of algae are hosts of the dynoflagellates most frequently so they are often called poisonous algae because of the accumulated dinoflagellate toxins. This algae are from the kind *Portieria*, *Halymenia*, *Turbinaria*, *Sargassum*. Dynoflagellates supply algae with food substances as nitrogen and phosphorus, which leads to abundant algae florescence which changes the color of the water to red, brown or mahogany. When huge fields of algae die they deplete the oxygen and cause hypoxia or anoxia thus affecting a lot of organisms in the ecosystem. Fishes, caught in such colored currents, can be poisonous because they have eaten poisonous algae. The reproduction of algae depends to great extent on human activities, especially on the water pollution. The increase of Dynoflagellate population and of some bacteria growing on algae is a critical factor for the poisoning of the flesh of fishes [2, 25-27]. Several kinds of Dynoflagellates are associated with ciguatera poisoning: *Gambierdiscus toxicus* [25, 28], *Prorocentrum concavum* [3, 29, 30], and *Prorocentrum lima*, *Ostreoposis lenticularis*, *Ostreoposis siamensis* [15]. All of these Dynoflagellates synthesize different kinds of toxins. The prevalence of some of these toxins in the flesh of the consummated fish creates variety in clinical presentation of this intoxication. Most often ciguatera poisoning is associated with *Gambierdiscus toxicus*, which synthesizes ciguatoxin and maitotoxin. They are lipid soluble neurotoxins and cause the neurotoxic symptoms that can last months after the consummation of the fish. Dynoflagellates of the kind *O. Lenticularis* also synthesize neurotoxin, called ostreotoxin. Dynoflagellates of the kinds *Prorocentrum concavum*, *Prorocentrum lima* and *P.hoffmanium* synthesize the toxin okadaic acid, which causes diarrhea. Some more kinds of Dynoflagellates are associated with ciguatera poisoning but they have less importance for the course of this intoxication and have not been studied well yet: *P. mexicanum*, *O. ovata*, *O. Siamensis*, *O. heptagona*, *C. Monotis*. They synthesize toxins which cause hemolysis of mouse and human erythrocytes [1, 2, 3, 11, 25, 26, 31]. The toxins of dynoflagellates are accumulated in algae. Smaller fishes that use poisonous algae for food on their turn become food for bigger fishes. Toxins are accumulated in the flesh of bigger fishes and most of all – in inner organs and roe. The smell, taste and appearance of the fish are not changed. The toxins are thermo stable, so cooking by boiling; stewing, baking or roasting does not change the toxicity.

Toxins and mechanisms of action:

Ciguatoxins (CTXs) are neurotoxins. They are lipid-soluble polyether compounds made up of 13 or 14 rings fused into rigid ladder-like structures. Multiple forms of CTX with small structural differences have been described and there are important geographic differences. The Pacific

ciguatoxin-1 (P-CTX-1) is the most potent and its structure is slightly different from that of the Caribbean ciguatoxin-1 (C-CTX-1). These differences are also reflected in the symptoms produced [20].

LD_{50} of C-CTX-1 for guinea pigs intraperitoneally is 0.45 ng/kg. A dose of 0.1 ng causes intoxication in humans. The toxin is lipid soluble that is why it is accumulated and stored in the flesh of fishes. The mechanism of action is connected to opening of the voltage dependent sodium channels in neuronal cell membrane. The toxin induces membrane depolarization there. That causes symptoms of neural excitation with consequent neural blockade or damage, which require restoration of the neural tissue. Maitotoxin (MTT) is a neurotoxin. It is called after the fish maito (Ctenochaetus striatus), from Tahiti region, from which it was isolated. LD_{50} maitotoxin 0.15 ng/kg ip. LD_{50} for humans by mouth is 50 ng/kg. Maitotoxin is water soluble. The mechanism of its toxicity is connected to disturbance in calcium balance in the cells. Maitotoxin increases the influx of calcium in the cell through the excitable membrane, thus increasing the cytosol Ca^{2+}. That leads to activation of the cell death cascade by augmentation of the membrane permeability. The toxin activates the cytosol calcium activated proteases calpain-1 è calpain-2 which cause necroses. The toxin îstreotoxin is a neuromuscular toxin. It causes spontaneous muscular contractions. Like ciguatoxin it attacks the voltage dependent sodium channels (prolongs the time of opening of the channel) and leads to depolarization of the muscle membrane and contractions. The toxin okadaic acid causes diarrhea syndrome [16, 32, 33].

Clinical presentation of the poisoning:

The initial symptoms appear between the 4th and the 12th hour (on the average 12 hours) after the consumption of fish with preserved taste qualities. Three main clinical syndromes develop: gastrointestinal, neurologic and cardiocircullatory. The first complaints are from abdominal pain, nausea and vomiting. The neurologic symptoms, which generally present within the first few days of illness, often become prominent after the GI symptoms. Tingling of arms, sense of pins and needles, formication, tingling of teeth, disturbed vision; blurred images appear. Changing feeling of cold and hot is a pathognomonic symptom of this intoxication. Neuropsychiatric symptoms in CFP may include anxiety [34], depression and subjectively reported memory loss [35]. More marked mental status changes such as hallucinations, giddiness, incoordination or ataxia [36, 37], and coma [1] have been reported, but appear to be specific to CFP in Indian and Pacific Ocean regions. Cardiotoxicity include: cardiac bradycardia, arrhythmias or cardiac block appear. The intensity and duration of symptoms are different in different individuals and regions, where the poisoning had taken place. This difference is explained by the kind and quantity of the ingested toxins as well as the individual sensitivity [6, 7, 9, 17, 38-41]. Lethal cases were reported with frequency from 0.1% to 12%. The lethal exit is associated to consumption of the most toxic parts of the fish – liver, other internal organs, roe. The death occurs from acute respiratory failure due to depression of the respiratory center in the brain, acute circulatory failure (shock), extreme cardiac arrhythmia – tachycardia or asystolia [35, 42-44].

The duration of ciguatera intoxication is different. The lightest clinical form lasts from several days to a week. Diarrheic syndrome, allergic symptoms like obstinate itching and neurologic symptoms like diastesia and paresthesia of the body, general weakness are observed. More severe forms are characterized by neurologic symptoms that continue several months. If the symptoms persist for more than three months a chronification of ciguatera intoxication is accepted. Cases with duration of one year have been described. These chronic forms are characterized by neurologic symptoms with different severity like psychic disturbances, general dyscomfort, depression, headache, strong muscle pains, unusual sensations in extremities. Symptoms are worsened by consumption of alcohol and coffee. Cases of ciguatera poisoning have been described in a newborn baby and a breast – fed baby, because the lipid soluble ciguatoxin can pass through placentar barrier and mother‘s milk [6, 7, 16, 38, 39].

Diagnosis: There are currently no reliable biomarkers that can be used to confirm exposure to CTX in humans. At present, CFP diagnosis is based on the presenting symptoms and time course, the history of having eaten a reef fish importantly, the exclusion of other diagnoses that could account for the symptoms. Differential diagnosis is made with: (1) Paralytic syndrome after consumption of reef clams, shrimps (mollusks), a poisoning caused by other kinds of Dynoflagellates that synthetize paralytic toxin; (2) Botulism (from consumption of smoked fish); (3) Scombroid (histamine) poisoning after consumption of mackerel, tunny, belted bonito; (4) Eosinophylic meningitis (consumption of crabs, clams and some fishes infected by the helmynths *Angiostrongylus cantonensis*); (5) Organophosphosphorus intoxication [2, 6, 39].

Treatment:

There is no specific antidote for ciguatera poisoning. Treatment is largely supportive and symptom driven. If performed within 3-4 hours of toxin ingestion, gastric decontamination with activated charcoal may help. Antiemetics (Metoclopramid) and H2 blockers may control nausea and vomiting. Corticosteroids and antihistamines help relieve pruritus. Many authors recommended amitriptyline to diminish severity of residual symptoms (eg, chronic pruritus, pain syndromes and depression). Atropine is suitable to apply in case of bradyarrythmia. Control hypotension with volume replacement and pressor agents, i.e. dopamine in case of shock. Neurological symptoms treat with vitamins from group B (B1, B6, B12). Calcium antagonists appear to be useful because of meitotoxin action on calcium membrane permeability. The long lasting neurological complaints are treated with Gabapentin, Analgesics and Nonsteroidal anti-inflammatory drugs [6, 7, 15, 17, 24, 39]. The most important is mannitol therapy for two primary goals: reduction of acute symptoms (especially neurologic) and possible prevention of chronic neurologic symptoms.The effect of mannitol infusion is thought to be mediated by the osmotic reduction of neuronal edema [45-47]. Intravenous mannitol is

administered at 0.5 to 1.0 g/kg body weight over a 30-45 minute period. It is suggested that it be given within 48-72 hours of ingestion of toxic fish [48, 49], although beneficial effects have been observed even up to several weeks after intoxication [50-52]. Also, mannitol may act as a scavenger of free radicals generated by the CTX molecule, and may reduce the action of CTX at sodium and/or potassium channels [53]. Opposite, at least one prospective, controlled study, found no difference between mannitol and normal saline in the treatment of ciguatera poisoning [54]. One group in Japan has reported developing a strategy to use monoclonal antibodies to treat ciguatera toxicity. Possibly an effective treatment will be available in the near future [55].

Prevention:

Prevention requires educating people to the risk of eating coral reef fish such as barracuda, grouper, snapper, amberjack, and surgeonfish that are caught in areas known to be contaminated, such as the waters off Pacific, south Florida and the Caribbean. Because the toxins are colorless, odorless, and tasteless and are not destroyed by cooking, they are difficult to detect. CTXs can be detected using a number of techniques following extraction and purification techniques. The most widely used test method is a mouse bioassay, but biomolecular assay methods, such as cytotoxicity, receptor binding and immunoassay can also be applied. An ELISA-based method for CTX detection has recently been developed. The difficulty of detecting CTXs in fish, plus their stability, severely limits the control options available. The presence of ciguatoxin is confirmed by liquid chromatography - mass spectrometry [3, 6, 9, 56, 57].

Risk for Bulgarian citizens:

In the EU, including Bulgaria, legislation covering fishery products states that "Fishery products containing biotoxins such as ciguatera toxins" cannot be placed on the market, but no methods of analysis are given [58]. The risk group in Bulgaria, suspected for ciguatera poisoning, can be people who ate fish from Caribbean's or Pacific Ocean (sailor crews, travelers, and consumers ate exotic fish from supermarket). There are no reports of CFP in Bulgaria, but missing right diagnosis can be observed in some cases. Confirmation of poisoning requires sending samples of suspected contaminated fish to a laboratory, however in Bulgaria there are no labs equipped with specialized testing capabilities.

CONCLUSION

CFP is associated with consumption of coral reef fish from tropical and subtropical waters in the Pacific and Indian Oceans and the Caribbean Sea and is considered to be a significant public health problem. In former times, CFP was restricted to indigenous populations in areas where CTXs are endemic, but this has changed in recent years with the increase in global travel and the increasing importation of exotic food fish species into developed countries. Education of this disease with lasting neurological symptoms must include medicals students and doctors, toxicologists, neurologists and other practitioners.

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