

SPECIES OF AQUATIC ANIMALS ASSOCIATED WITH THE DEVELOPMENT OF HAFF DISEASE IN HUMANS: A LITERATURE REVIEW

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Abstract: Haff's disease is a syndrome of myalgia and rhabdomyolysis in humans caused by a thermostable toxin of unknown origin present in the muscles and viscera of certain fish and crustaceans and may be associated with the process of aquatic bioaccumulation. The objective of this work is to gather all the vectors associated with Haff disease since its first report until the present moment, in order to better understand its occurrence, distribution and pathogenicity. In 1924, in the Baltic region, the first cases of the disease were recorded after consumption of the fish species Burbot (*Lota lota*), Eel (*Anguilla anguilla*) and Pike (*Esox lucius*). In 1984 in the United States of America, the disease was reported for the first time after consumption of fish of the species Buffalo fish (*Ictiobus cyprinellus*), Red crayfish (*P. rocambarus clarkii*), Salmon (*Salmo spp.*), Grass carp (*Ctenopharyngodon idella*). In 1990, in Japan, cases of Haff Disease were reported after consumption of marine fish Boxfish (*Ostracion immaculatus*) and Roundbelly Cowfish (*Lactoria diaphana*). In China, in 2000, the first record of the syndrome associated with the consumption of red crayfish (*Procambarus clarkii*) was made, this species being the main pathogenic factor of Haff disease in China. In the country there are also reports of the occurrence of the disease through the ingestion of "Pomfret" (*Colossoma brachypomum*). In Brazil, the first cases were registered from 2007 after consumption of Tambaqui (*Colossoma macropomum*), Pacu (*Mylossoma spp.*), Pirapitinga (*Piaractus brachipomus*), Arapaia (*Seriola spp.*) and Whiting (*Mycteroperca spp.*). There is no antitoxin for poisoning by Haff disease, treatment is carried out by relieving symptoms and treating complications, which further demonstrates the importance of studies that seek to deepen knowledge about the toxin and its mechanism of action both in fish as in humans.

Keywords: Crustaceans, Myalgia, Fish, Rhabdomyolysis and Syndrome.

INTRODUCTION

Haff disease is a rare and acute clinical syndrome that results in unexplained myalgia and rhabdomyolysis in humans (Feng et al., 2014) (Chan, 2016). The cause is believed to be a heat-stable toxin of unknown origin, due to the rapid onset of symptoms after consumption (Langley and Bobbitt, 2007). This syndrome is characterized by extreme and sudden muscle stiffness, chest pain, shortness of breath, numbness, weakness, myalgia, and darkened "coffee-colored" urine, associated with elevated serum CPK enzyme (creatin phosphokinase) (Feng et al., 2014).

The first report of Haff disease occurred in 1924, when physicians near the shore of Lake Königsberger, in the Baltic region, recognized an outbreak of a disease characterized by sudden muscle rigidity, casually associated with coffee-colored urine (Feng et al., 2014). Over the next 9 years, similar outbreaks, affecting about 1000 people, occurred in summer and autumn along the shores of the "Haff" (shallow lake), hence the name of the disease. Furthermore, there were reports that seabirds and cats were found dead in the wild after eating these fish (Tolesani et al., 2013). From 1934 to 1984, other outbreaks similar to the disease were described in Sweden and the Soviet Union. In 1984, the first two cases in the United States were reported, in Texas. Then, other cases were reported in Los Angeles and San Francisco (Buchholz, 2000). Then, cases were reported in various places around the world, such as the United States, China and Brazil (Feng et al., 2014). Due to the clearly heterogeneous distribution worldwide, lack of medical awareness can delay diagnosis, having negative impacts on patient outcome, in addition to increasing the risk of relapses.

Therefore, the objective of this work is to

gather reports described in the literature of species of aquatic animals associated with the development of Haff disease in humans.

HAFF'S DISEASE

The etiology of Haff disease is still unknown, however we know that it is associated with the consumption of fish and crustaceans in fresh or salt water, since all cases reported in the literature so far have a history of consumption of this type of food in the 24 hours before the onset of symptoms (Feng et al., 2014) (Tolesani et al., 2013) (Langley and Bobbitt, 2007). Being more associated with freshwater crustaceans than saltwater, diverging from other diseases related to seafood consumption (Zhang et al, 2012). The most common symptoms are, diffuse myalgia, weakness, stiffness of the limbs, chest pain, numbness, dyspnea, loss of strength in the body and coffee-colored urine may occur (Buchholz, 2000).

Notification of cases of this rare syndrome are necessary for further investigation to occur about where it originates, in addition, it is an emerging disease that can be misdiagnosed (Feng et al., 2014) (Huang et al., 2019) (Tolesani et al., 2013). There is no characteristic profile of the involvement of Haff's disease, being reported in different age groups and affecting men and women to the same degree. Greater severity of symptoms is related to greater amounts of fish consumed, which consequently were associated with higher CK levels (Buchholz, 2000).

Some researchers, such as Feng et al (2014) and Tolesani et al. (2013) raise the theory that the possible cause of Haff disease is a thermostable and unknown toxin that tends to accumulate in food. The toxin does not have a different taste or odor, and can originate from algae or smaller fish, being associated with the aquatic bioaccumulation process, since fish and crustaceans feed on various species of microalgae and dinoflagellates,

which may have toxins, and larger fish tend to consume other smaller fish (Tolesani et al., 2013) (Langley and Bobbitt, 2007).

For an accurate diagnosis, it is important to have a clinical suspicion of Haff disease, having a history of fish and crustacean consumption in the last 24 hours of the onset of symptoms, characteristic symptoms and high levels of muscle necrosis markers (Tolesani et al., 2013).

There is no antidote for Haff's disease poisoning, and treatment is completely supportive. After intensive therapy, most patients have complete recovery without residual effects, few have worsening symptoms or die (Diaz, 2015).

SPECIES OF AQUATIC ANIMALS ASSOCIATED WITH THE DEVELOPMENT OF HAFF DISEASE

BURBOT (*Lota lota*) (LINNAEUS, 1758)

The burbot is the only freshwater species of the Lotidae Family. Its most prominent relative is the Atlantic cod *Gadus morhua*. The burbot is carnivorous and has a benthic, nocturnal lifestyle, and its preference for hiding and being a bottom-dwelling fish requires accommodation adaptations, patterns used for most freshwater aquaculture fish (Pietsch et al., 2020).

The adult coastal burbot (*Lota lota* L.) shows a cold stenothermal biology, meaning that they are only found in spawning areas in rivers and estuaries during the winter and reside in the sea during the rest of the year, where temperatures are cooler. stable and cooler (Toivonen et al., 2020). Its first appearance in the literature related to Haff disease is reported in 1924, in the first occurrence of the disease, on the shore of Lake Königsberger, also associated with the species Eel (*Anguilla anguilla*) and Pike (*Esox lucius*)

(Buchholz, 2000).

EEL (*Anguilla anguilla*) (LINNAEUS, 1758)

The European eel (*Anguilla anguilla*) is a catadromous freshwater eel, that is, they spend most of their lives in fresh water until they return to their spawning grounds in the tropics, although part of the population never enters fresh water and, instead, they reside in brackish and marine areas close to the coast. *A. anguilla* travels the longest distances and migrates over 5000 km across the Atlantic Ocean to spawn in the Sargasso Sea (Arai, 2020).

PIKE PIKE (*Esox lucius*) (LINNAEUS, 1758)

Esox lucius is a large, long-lived, iteroparous top-of-chain predatory fish species with a circumpolar distribution that occupies a wide range of aquatic environments (Forsman, 2015). The occurrence of Haff disease due to the consumption of this fish species occurred in 1924, in the first report of the disease, on the coast of the Baltic region (Buchholz, 2000). Previous studies have found that populations of pike in the Baltic Sea harbor local adaptations in various morphological and life history traits such as hatching success and larval survival, growth rate and body size, vertebral count and salinity tolerance (Sunde, Larsson and Forsman, 2019).

BUFFALO FISH (*Ictiobus cyprinellus*) (VALENCIENNES, 1844)

The buffalo fish (*Ictiobus cyprinellus*) is one of the largest freshwater fish endemic to North America, being the largest of all catostomids (Cypriniformes: Catostomidae). It is also the only catostomid with a terminal mouth and planktivorous filter-feeding tendencies (Lackmann et al, 2019). The first cases of Haff disease in the United States (USA) were

reported in Texas in 1984, after consumption of cooked freshwater buffalo fish, *Ictiobus cyprinellus* (Diaz, 2015). As early as March through August 1997, two clusters of cases and one isolated case of Haff disease occurred in the United States involving consumption of buffalo fish in the previous 24 hours (CDC, 1998).

BOXFISH (*Ostracion immaculatus*) (TEMMINCH & SCHLEGEL, 1850)

Occurs near the coast (including semi-enclosed marine areas) on rocky bottoms (Yamada et al., 1995). In Japan, 13 sporadic cases of Haff disease were reported between 1990 and 2008, and all patients had a history of boxfish (*Ostracion immaculatus*) consumption. and (*Lactoria diaphana*) (Shinzato et al., 2008) (Taniyama et., 2009).

ROUNDBELLY COWFISH (*Lactoria diaphana*) (BLOCH & SCHNEIDER, 1801)

It is a marine fish, from brackish water and that is associated with the reef, with a depth range of 8-50 m. Its habitat is usually coral and rocky reefs in coastal areas. It feeds on benthic invertebrates. (Matsuura, K., 2001) Cases of species-associated Haff disease have been reported along with those of boxfish (*Ostracion immaculatus*).

RED CRAYFISH (*Procambarus clarkii*) (GIRARD, 1852)

The Louisiana Red Crayfish (*Procambarus clarkii*) is a species from Louisiana and northern Mexico that has spread to other parts of the planet (Barbaresi and Gherardi, 2000). Despite being a well-known and widespread species, very little is known about the nutritional requirements of *P. clarkii*, both in terms of quality and quantity of food consumed, assuming that they are similar to those of other organisms aquatic animals

(Bardach et al, 1990). In its natural habitat, it can be said that *P. clarkii* is omnivorous, that is, it feeds on live or dead animal and vegetable matter, however it prefers fresh meat when it is available (Correia and Ferreira, 1995).

In the retrospective study by Bai et al. (2015) 1099 reported cases of Haff disease in China from 2016 to 2017 were analyzed, in which a total of 1067 (97.1%) were attributed to crayfish consumption. The study showed that crayfish production and consumption are probably important factors in the epidemiology of Haff disease in China.

One death from Haff disease after consumption of crayfish in Brazil was reported by Feng et al. (2014). This was the first report of the disease complicated by multiple organ failure, and it is believed that it was a consequence of the delay in treatment caused by a first misdiagnosis of lumbar disc disease. Other authors reported the involvement of patients with the syndrome after consuming crayfish, such as Qian and Sha (2018) who reported a case with complication of lung injury, Yang, Fan and Leung (2018); Chan (2016); Zhang et al. (2012) and Huang et al. (2019).

SALMON (*Salmo spp.*) (LINNAEUS, 1758)

Salmon are known for their anadromous migrations in which juveniles migrate from freshwater lakes and rivers to distant oceanic foraging areas and then return to their home location to spawn. Prior to and during this movement, they exhibit many complex physiological, behavioral, and morphological adaptations for seaward migration (McCormick et al. 1998). In 2001, the first case of Haff's disease related to salmon consumption occurred in North Carolina, after consumption of baked fish by a couple, purchased at a local store in the region. Both reported severe muscle aches from the next

day and both said they had no fever (Langley & Bobbitt, 2007).

TAMBAQUI (*Colossoma macropomum*) (CUVIER, 1818)

Originally from South America, from the Amazon and Orinoco river basins, the tambaqui, *Colossoma macropomum* is a species of fish in the class Osteichthyes, subclass Actinopterygii, order Characiformes, family Characidae and subfamily Myleinae (Dairiki & Silva, 2011). According to Lopera-Barreto et al. (2011), the tambaqui is an excellent filter feeder, and in the larval stage its diet is based on the ingestion of zooplankton, starting to consume small seeds and invertebrates in the fry and juvenile stages. Like several native species, tambaqui has a great capacity for adaptation in relation to food, with the capacity to digest protein of animal and vegetable origin (Silva et al., 2003).

Naturally, the tambaqui's diet is primarily composed of fruits and seeds during the flood period. In the ebb season, with the reduction in food availability, it starts to feed on zooplankton, which is why its feeding habit is often called opportunistic omnivore. Macrophytes, insects, algae, molluscs and fish are also part of the diet of the tambaqui (Rodrigues, 2014). In October 2008, the first outbreak of Haff disease in Brazil was reported, with 27 cases of the disease associated with the consumption of *Mylossoma duriventre* (pacu-manteiga), *Colossoma macropomum* (tambaqui) and *Piaractus brachypomus* (pirapitinga), fish from the north from the Amazon region (dos Santos et al. 2009).

FRESHWATER "POMFRET" (*Piaractus brachypomus*) (CUVIER, 1818)

Piaractus brachypomus is native to the Amazon, Solimões, Orinoco rivers and their tributaries. It has an omnivorous feeding habit, naturally feeding on fruits, seeds, leaves

and microcrustaceans (Lima, 2014). On October 27, 2009, 41 people with unexplained generalized myalgia, weakness and fatigue were admitted to a hospital in a small town called Jiubei in China. All patients reported recent consumption of locally purchased freshwater Pomfrets. Experimental studies have indicated that Pomfrets not only cause disease in humans, but also intoxicate laboratory rats. Pomfret, in common with other fish products that have been reported to cause Haff disease, is a bottom feeder that has the potential to accumulate environmental toxins (Huang et al. 2013). Furthermore, Chan, 2016 reported that consumption of Pomfret is associated with a higher incidence of gastrointestinal symptoms when compared to consumption of other species.

GRASS CARP (*Ctenopharyngodon idella*) (CUVIER AND VALENCIENNES, 1844)

The *Ctenopharyngodon idella*, popularly known as Carpa Capim, is a freshwater fish originating in the rivers of China. It is a herbivorous fish that generally feeds on aquatic weeds and when fry on zooplankton. It has a preference for clear waters and grows quickly, reaching a weight of 30-50 kg and a length greater than 1 meter (Sponchiado et al., 2009) (Cudmore et al., 2004). Louis et al., 2016 presented two cases of Haff disease in which patients consumed Grass Carp, both from the same family, in 2014 in the United States.

PACU (*Mylossoma spp.*) (CH EIGENMANN & CH KENNEDY, 1903)

Mylossoma is a herbivorous fish, highly dependent on floodplains and of great economic importance for commercial and sport fishing (Resende, Pereira and Almeida, 1998). In 2013, a case report associated with the consumption of *Mylossoma* occurred in

Brazil, where the patient presented sudden, progressive and excruciating abdominal pain, accompanied by two episodes of vomiting, progressive polymyalgia (predominantly in the lower limbs), asthenia and progressively disabling muscle weakness (Tolesani et al., 2013).

PIRAPITINGA (*Piaractus brachypomus*) (CUVIER, 1818)

Piaractus brachypomus is native to the Amazon, Solimões, Orinoco rivers and their tributaries. It has an omnivorous feeding habit, naturally feeding on fruits, seeds, leaves and microcrustaceans (Lima, 2014). Pirapitingas undergo seasonal spawning migrations, moving from oxbow lakes and lakes at the beginning of the flood season and migrating upstream to spawn in the headwaters. Reported in 2008, during the Haff disease outbreak in Brazil, with 27 cases associated with the consumption of species from the Amazon region, including pirapitinga (Santos et al. 2009).

ARABAIANA (*Seriola spp.*) (CUVIER, 1816)

The Arabaiana (*Seriola dumerili*) is a species of commercially important fish that is distributed along the entire coast of the Northeast Region, where it inhabits depths of up to 200 meters. It is an opportunistic species that feeds on a wide variety of prey that vary throughout its life history. Young individuals less than 8 cm long feed mainly on zooplankton. When they are between 8 and 12 cm long, they enter a transition phase, progressively increasing their predation on larger benthic and neotonic organisms. Once larger than 12 cm in length, they begin to feed exclusively on nectobenthics, finally switching to a piscivorous diet around 20 cm, when they leave the open sea to approach the coast. Adults feed on pelagic fish and cephalopods

(Andaloro and Pipitone, 1997).

Bandeira et al., 2017 described a series of cases of Haff disease that occurred in Salvador, Brazil, between 2016 and 2017. Most of the 15 cases reported in the study clustered between epidemiological weeks 48 and 51 of 2016. outbreak in December 2016, local health authorities began a search and identified other similar cases in local hospitals in Salvador. The species consumed were “Olho de Boi” (*Seriola* spp.) and “Badejo” (*Mycteroperca* spp.). Almeida et al., 2019 also described 2 cases of the disease in a couple that had returned from a trip to the Brazilian Northeast, also with the consumption of *Seriola* spp. a few hours before myalgia episodes. Both patients reported muscle pain and darkened urine.

WHITING (*Mycteroperca* spp.) (GILL, 1863)

Mycteroperca are found on coral reefs and over rocky bottoms at depths between 12 and 200 meters (39 and 656 ft) as adults, while juveniles are found in shallower rocky habitats, in seagrass beds and in estuarine environments. Adults are piscivores, except for species in the rubra species complex that feed on zooplankton. Juveniles feed mainly on crustaceans, although they will eat other invertebrates (Heemstra and Randall, 1993). The consumption of this species was reported during a series of 15 cases of Haff disease that occurred in Salvador, during the period 2016 and 2017, together with the consumption of “Olho de Boi” (*Seriola* spp.) (Bandeira et al., 2017).

FINAL CONSIDERATIONS

Haff’s disease is a syndrome of myalgia and rhabdomyolysis that does not yet have much explanation other than the hypothesis that it is caused by a thermostable toxin. To understand the species involved in this disease is extremely important to understand the

mechanism of action and the possible origin of the toxin that causes rhabdomyolysis, as well as understanding how it affects fish populations and aquaculture itself. Some species drew attention due to their intense relationship with the place where the fish was consumed, raising important epidemiological and environmental questions for the discussion of the cause and mechanism of aquatic bioaccumulation in fish.

There is no antitoxin for Haff disease and treatment is only done to minimize symptoms and other complications caused by the syndrome, so it is important that there is greater awareness about diagnosis, treatment and reporting of it. Because it is an emerging disease and because of its worldwide distribution, it is of great importance in aquaculture and further in-depth studies are needed to characterize the most affected species, in order to better understand the functioning of bioaccumulation in fish and the mechanism of contamination of fish. same.

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