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Letter to the editor

Rhabdomyolysis following fish consumption: a contained outbreak of Haff Disease in São Paulo

Dear Editor:

Haff disease is characterized by myalgia and rhabdomyolysis following fish consumption, symptoms starting within 24 h after eating contaminated fish.[1] The disease was first reported in 1924 in Prussia and Sweden and other cases were later described in Brazil, China, Japan, and US.[1–4] Nevertheless, Haff disease remains a rare condition and lack of awareness contributes to delayed diagnosis.

A 38-year-old male (patient 1) and his 39-year-old wife (patient 2) presented to an emergency department in São Paulo (Brazil) complaining of intense diffuse myalgia that had started that same day. The symptoms were recurring: both had complained of mild to moderate muscle pain four days before which had resolved with analgesics. They also noted a darkening urine before admission (patient 1 presented with dark yellow and patient 2 had red brownish urine). They had no substantial past medical history and denied fever, headache, upper airway symptoms, or skin changes. They also denied using new medications or drugs and having any trauma or performed high-intensity exercise. The couple had returned from a trip to Northeast of Brazil 10 days before onset of symptoms.

Physical examination of patient 1 was remarkable for severe and disabling muscular pain in the back, thighs, legs, arms, thorax, and abdomen. Patient 2 was unable to walk and presented with more weakness and disabling pain in her lower limbs. Vital signs were stable, and the rest of their physical examination was otherwise unremarkable.

Diagnosis of rhabdomyolysis was suspected and confirmed by laboratory tests showing highly elevated creatinine phosphokinase (CPK) (Patient 1: CPK = 11,286 U/L; Patient 2: CPK = 2921 U/L; Reference: 55–170). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also elevated (Patient 1: AST = 108 U/L and ALT = 111 U/L; Patient 2: AST = 80 U/L and ALT = 75 U/L; Reference: AST = 17–59 and ALT = 21–72). At admission, both patients had normal complete blood cell count and serum creatinine, but urine dipstick was positive for blood and protein.

At this point, the couple was enquired about their recent food intake. They recalled having eaten cooked fish, a species called 'Olho-de-boi' (*Seriola spp*) (Fig. 1), a few hours before both episodes of myalgia. The fish had been bought in their vacation to the Northeast of Brazil, packed in a styrofoam during the flight, manually washed by patient 1 and stored in the refrigerator. It was later discovered that patient 1's mother, who had also eaten the fish, developed mild diffuse myalgia as well. A diagnosis of Haff disease was made and confirmed by excluding other potential infectious causes of rhabdomyolysis (CMV, HIV, Epstein–Barr, dengue, yellow fever, zika virus, parechovirus, enterovirus, and hepatitis). The patients were initially managed with aggressive fluid therapy and opioids for pain. They also received bicarbonate solution in order to prevent acute kidney failure. Their CPK continued to increase and peaked 24–36 h later (Patient 1: CPK = 28,571 U/L; Patient 2: CPK = 73,391 U/L at 36 and 24 h after admission, respectively). Similarly, AST/ALT levels rose up to 1134/375 U/L (patient 1) and 1128/546 UL/L (patient 2) two days after admission. Although their renal function remained stable, both developed bilateral parenchymal nephropathy with normal corticomedullary ratio on ultrasound. After the third day of hospital admission, both patients showed marked clinical and laboratory improvement and were asymptomatic at discharge, seven days after admission.

Haff disease has been described following the ingestion of cooked or uncooked crayfish, freshwater and marine fish.[2] Previously reported species associated with Haff disease include crayfish *Procambarus clarkii*, Badejo (*Mycteroperca* spp.), Atlantic salmon (*Salmo salar*), and Buffalo fish (*Ictiobus cyprinellus*), among others.[2–4]

The disease is believed to be caused by an unknown thermostable toxin, which is not destroyed by cooking the fish; however in a previous outbreak of Haff disease (2016–2017) in Salvador, Brazil, samples of raw fish were sent to the Food and Drug Administration for toxin analysis and no conclusion was drawn on the etiology of the disease.[3] Therefore, Haff disease remains a clinical diagnosis that should be suspected when other frequent causes of rhabdomyolysis (infections, drugs, electrolyte imbalance, trauma or heatstroke) have been excluded. In this situation, enquiring after recent fish consumption and investigating whether other people have developed similar symptoms is essential not only for a precise diagnosis, but also because disease outbreaks may occur.[3]

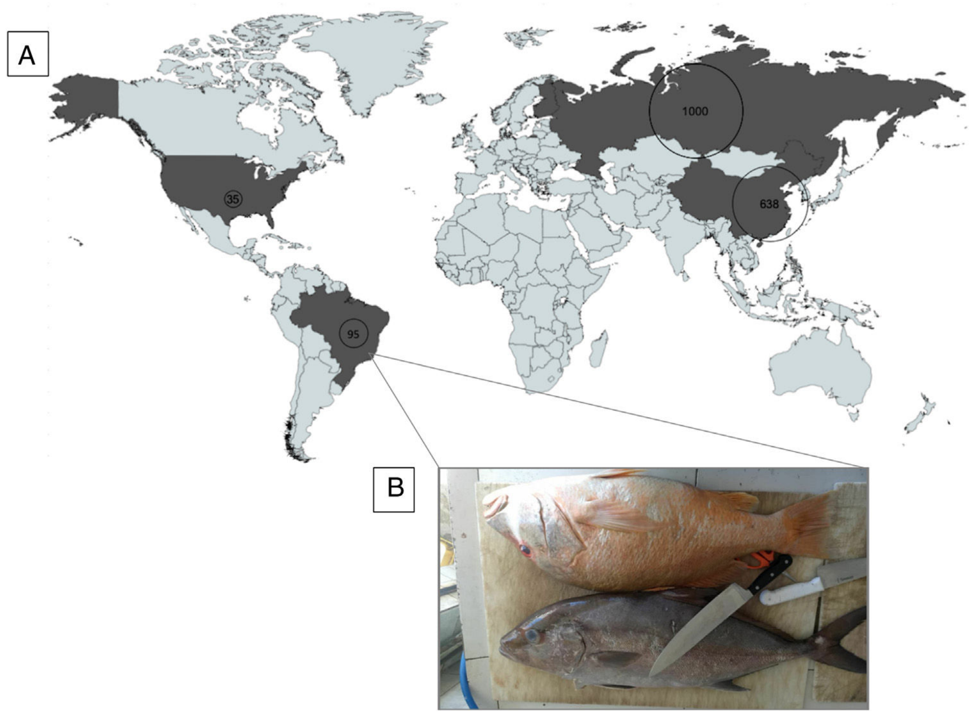

Fig. 1 – (A) Global incidence of Haff Disease (1942–2019). (B) Fish bought by the patients. They had eaten the gray one below ('Olho-de-boi' – *Seriola spp*) before developing the symptoms of Haff disease.

In order to have a better understanding of the epidemiology of the disease, we searched PubMed and LILACS databases from inception to March 2019. Since its discovery in 1924, 1768 cases of Haff disease have been reported around the world[1–5] (Fig. 1), most of which occurred in Northern and Eastern Europe (56.56%). There were also 638 cases in Asia (36%) and 35 in the US (1.94%). In Brazil, 95 patients (5.4%) have been diagnosed with Haff disease, mostly due to outbreaks in the North and Northeast.[3] Although no previous cases had been reported in Southeast of Brazil, it is noteworthy that both described patients ingested a fish brought from the Northeast.

Because the distribution of the disease is clearly heterogenous throughout the world and even within individual countries, lack of physician awareness might delay the diagnosis, with negative impacts on patient outcomes and increased risk of outbreaks. As an example, in 2013, a 66-year-old Chinese patient with Haff disease was misdiagnosed as having lumbar disk disease and was discharged home with analgesics. One day later he was readmitted with severe rhabdomyolysis and died after developing multiple organ failure.[5] Having said that, prompt identification of the disease is necessary to rapidly initiate treatment, which is mainly supportive and focused on prevention or reversion of acute organ failure. Aggressive fluid therapy and correction of electrolyte imbalances are the mainstay, along with avoiding drugs which could potentially worsen rhabdomyolysis, such as non-steroid anti-inflammatory medications.

In addition, once a diagnosis of Haff disease is made, health care providers should do their best to identify the source of contaminated fish and report the case to health authorities, so that outbreaks can be contained and at-risk populations could be alerted about the need to seek help in case they develop similar symptoms.

In conclusion, given the globalized world we have today, it is important to reinforce the need to investigate a history of recent fish consumption when assessing causes of rhabdomyolysis, even in regions where the disease has not been reported. Consequently, reporting new cases is essential to improve the knowledge on the disease epidemiology and increase physician awareness, hopefully allowing patients to be diagnosed earlier and containing outbreaks sooner.

Disclaimers

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Brazilian Society of Infectious Diseases or the institutions with which the authors are affiliated. The authors have no competing interests to declare.

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Conflicts of interest

The authors declare no conflicts of interest.

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