

Haff disease in the pandemic COVID-19 period in Brazil

Doença de Haff no período pandêmico de COVID-19 no Brasil

Enfermedad de Haff en el período pandémico COVID-19 in Brasil

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Abstract

Objective: This study describes and characterizes the cases of Haff disease reported in Brazil during the COVID-19 pandemic period. Descriptive and cross-sectional study using public data from the National Center for Strategic Information and Response in Health Surveillance nacional. The Risk Communication number 17 of 09/15/2021 was accessed. The description of suspected cases was extended to all Brazilian states where notifications occurred, from

January 1, 2020, to September 15, 2021. There was an increase in cases of Haff's disease in Brazil, from 2020 onwards, with 46 in the Northeast region of Brazil. Eighty-five cases and three deaths were reported between January and September 2021 in the North, Northeast, South and Midwest regions. Most cases occurred in regions of greater heat such as the coastal region of the Northeast and around regions of the Amazon River Basin. A critical period for coping with the SARS-CoV-2 virus pandemic in Brazil, cases of disease of Haff could be reported in various regions of country. Despite the etiological suspicions, studies, and follow-up of the cases, it is still not possible to affirm that the disease is caused by biomolecules of the Palytoxin-Like Toxins group. The possible identification of the responsible toxin(s) will be essential for a complete understanding of the etiopathogenic mechanism of the disease and adequate development of prevention, treatment, and cure measures.

Keywords: Haff disease; Rhabdomyolysis; Toxins.

Resumo

Este estudo descreve e caracteriza os casos de doença de Haff notificados no Brasil durante o período pandêmico da COVID-19. Estudo descritivo e transversal com dados públicos do Centro Nacional de Informação e Resposta Estratégica em Vigilância Sanitária nacional. Foi acessado o Comunicado de Risco nº 17 de 15/09/2021. A descrição dos casos suspeitos foi estendida a todos os estados brasileiros onde ocorreram notificações, de 1º de janeiro de 2020 a 15 de setembro de 2021. Houve aumento dos casos da doença de Haff no Brasil, a partir de 2020, com 46 na região Nordeste do Brasil. Oitenta e cinco casos e três óbitos foram notificados entre janeiro e setembro de 2021 nas regiões Norte, Nordeste, Sul e Centro-Oeste. A maioria dos casos ocorreu em regiões onde faz mais calor, como a região litorânea do Nordeste e o entorno de regiões da Bacia do Rio Amazonas. Período crítico para o enfrentamento da pandemia do vírus SARS-CoV-2 no Brasil, casos da doença de Haff podem ser notificados em várias regiões do país. Apesar das suspeitas etiológicas, estudos e acompanhamento dos casos, ainda não é possível afirmar que a doença seja causada por biomoléculas do grupo das Toxinas Similares à Palitoxina. A possível identificação da (s) toxina (s) responsável (is) será essencial para o completo entendimento do mecanismo etiopatogênico da doença e para o desenvolvimento adequado de medidas de prevenção, tratamento e cura.

Palavras-chave: Doença de Haff; Rabdomiólise; Toxinas.

Resumen

Este estudio describe y caracteriza los casos de enfermedad de Haff notificados en Brasil durante el período de pandemia de COVID-19. Estudio descriptivo transversal con datos públicos del Centro Nacional de Información Estratégica y Respuesta en Vigilancia de la Salud nacional. Se accedió a la Comunicación de Riesgos con 17 reportes, del 15/09/2021. La descripción de los casos sospechosos se extendió a todos los estados brasileños donde se produjeron notificaciones, desde el 1 de enero de 2020 hasta el 15 de septiembre de 2021. Hubo un aumento en los casos de enfermedad de Haff en Brasil, a partir de 2020, con 46 en la región Nordeste de Brasil. Se reportaron ochenta y cinco casos y tres muertes entre enero y septiembre de 2021 en las regiones Norte, Noreste, Sur y Medio Oeste. La mayoría de los casos ocurrieron en regiones con temperatura mas elevadas, como la región costera del noreste y alrededor de regiones de la cuenca del río Amazonas. Un período crítico para hacer frente a la pandemia del virus SARS-CoV-2 en Brasil, los casos de enfermedad de Haff podrían ser reportados en varias regiones. A pesar de las sospechas etiológicas, estudios y seguimiento de los casos, todavía no es posible afirmar que la enfermedad sea causada por biomoléculas del grupo de toxinas similares a las palitoxinas. La posible identificación de la(s) toxina(s) responsable(s) será esencial para una comprensión completa del mecanismo etiopatogénico de la enfermedad y el desarrollo adecuado de medidas de prevención, tratamiento y curación.

Palabras clave: Enfermedad de Haff; Rabdomiólisis; Toxinas.

1. Introduction

For the first time an outbreak of an unknown disease that occurred along the Baltic coast and near the coast of Königsberg Haff (now Kaliningrad, Russia) in the year 1924 was recognized. A second outbreak occurred a few years later around the shore of the Königsberg lagoon in which about a thousand people developed symptoms of Haff's disease. The most discussed hypothesis is that one or more toxins related to rhabdomyolysis is the cause of the rapid onset of symptoms after ingestion of contaminated fish. However, no theory has yet been fully confirmed and accepted (Jeddeloh e Haffkrankheit, 1939; Júnior et al., 2013).

Clinically, the disease presents variable signs and symptoms, with some cases progressing to death, but with rapid recovery of patients in most cases. It is possible to notice sudden and severe muscle stiffness, sudden, progressive, diffuse, and excruciating abdominal pain, palpitations, vomiting, progressive polymyalgia (which may be predominantly in the lower limbs), physical asthenia, disabling progressive muscle weakness, rhabdomyolysis, and dark-colored urine. However, fever, splenomegaly or hepatomegaly are generally not observed (Jeddeloh e Haffkrankheit, 1939; Júnior et al., 2013; dos Santos et al.,

2009). Rhabdomyolysis is due to injury to the sarcolemma of skeletal muscle cells, and the release of intracellular substances such as calcium, magnesium, enzymes, especially myoglobins (Rosa et al., 2005). In addition to being common in Haff's disease, also known as "black urine disease", rhabdomyolysis can have other causes such as: intense physical activity, use of medications and drugs, infectious diseases, electrolyte changes, etc (Rosa et al., 2005; Qian e Sha, 2018; Yang et al., 2018).

The incubation period of the disease is up to 24 hours, but the signs and symptoms occur after consumption of contaminated fish. Laboratory tests of affected individuals show that occur myoglobinuria, considerable increase in serum creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase enzymes (Pei et al., 2019; Buchholz et al., 2000). The consumption of some types of fish such as pike (*Esox sp.*), burbot (*Lota lota*), eel (*Anguilla anguilla*), Pacupeba/Pacu Manteiga (*Mylossoma duriventre*) from capture or fishing and not from farming systems, were present in meals before the onset of disease symptoms (Júnior et al., 2013; dos Santos et al., 2009).

In Brazil, the first report of an outbreak of Haff disease occurred in 2008, in the state of Amazonas (Northern Brazil), after consumption of the fish species Tambaqui-colossoma of black fin (*Colossoma macropomum*), Pacu-dollar (*Mylossoma spp.*), and freshwater Pirapitinga-pompano (*Piaractus brachypomus*) from the northern region of the Brazilian Amazon (dos Santos et al., 2009). In the State of Bahia, in 2016 and 2017, there were records of cases of the disease after the consumption of fish species "Olho-de-Boi" (*Seriola spp.*) and "Badejo" (*Mycteroperca spp.*). In 2018 there were cases of the disease after the consumption of "Olho-de-boi" fish (*Seriola spp.*) in the state of São Paulo (Pei et al., 2019; SVS-MS, 2021). This study describes and characterize the cases of Haff disease reported in Brazil during the COVID-19 pandemic period.

2. Methodology

Descriptive and cross-sectional study using public data from the National Center for Strategic Information and Response in Health Surveillance (nacional CIEVS), Health Surveillance Secretariat of the Ministry of Health (SVS/MS) and Department of Environmental Health, Worker and Surveillance of Emergencies in Public Health (DSASTE) of Brazil. For data collection, Risk Communication number 17 (CR-17) of 09/15/2021 was accessed. The description of suspected cases was extended to all Brazilian states where notifications occurred, from January 1, 2020 to September 15, 2021. The CR-17 describes the monitoring of cases carried out by the National CIEVS, technical area of the Epidemiological Surveillance of Water and Food Transmitted Diseases – GT DTHA/CGZV/DEIDT/SVS/MS. As well as the descriptions of Informative Note number 35/2021-CGZV/DEIDT/SVS/MS which has guidance on cases of rhabdomyolysis of unknown cause and with possible association with Haff's disease in Brazil. Methodological support to description of this work was executed according to literature (Koche, 2011; Lüdke & André, 1986; A. S. Pereira et al., 2018; Yin, 2014).

3. Results

During the period of the COVID-19 pandemic, there was a growing increase in cases of Haff disease in Brazil, starting in 2020 with 51 cases reported to CIEVS Nacional, from the northeast region of Brazil, with 5 of them subsequently discarded; and 85 notified between January and September 2021, totaling 131 cases in less than 2 years. Of 46 confirmations carried out in 2020, there were 40 cases (86.95%) in the state of Bahia, with almost half of the notifications occurring in the coastal capital city (Salvador, n=17 or 42.5%) and 24 cases (57.5%) were notified in different cities in the interior of the state. The other 6 cases (13.04%) were notified in the capital city of the state of Pernambuco (Recife, n=6) as shown in Table 1.

Table 1. Disease of Haff in the cities of two states in Brazil during the pandemic period of SARS-CoV-2 in 2020.

| | Pernambuco state | Bahia state |
|------------------|------------------|-------------|
| Salvador | - | 17 |
| Camaçari | - | 16 |
| Entre Rios | - | 03 |
| Dias D'Ávila | - | 02 |
| Candiba | - | 01 |
| Feira de Santana | - | 01 |
| Recife | 06 | - |
| TOTAL | 06 | 40 |

Source: Authors.

In the year 2021 cases were reported in almost all regions of Brazil. All cases (n=85) showed classic signs and symptoms to disease and were recorded in 4 of the five regions in which Brazil is divided (North, Northeast, South and Midwest), as shown in Table 2 below. It is possible to observe that the regions where the cases of death, and meanly, of illness registered by Haff disease in the Brazil are widely scattered and distant. The North region had the highest number of cases (82.35%) followed by the Northeast (27.05%).

Most cases registered in Brazil (up to 80%) occurred in November, a period corresponding to the end of spring and proximity to summer, characterizing a seasonal period whose climate is hot in these regions. Were registered three deaths in the north and northeast regions, of which were notified to the national CIEVS, as detailed in Table 2. Most of the registered cases were in the coastal states of the Northeast and regions of the Amazon River Basin (Table 2).

Table 2. Disease of Half and death in the brazilian states during the pandemic period of SARS-CoV-2 in the 2021 year.

| | Cases by state (%) | Death by state |
|-------------------|--------------------|----------------|
| Pará | 06 (7.05%) | 01 |
| Amazonas | 54 (63.52%) | 01 |
| Bahia | 06 (7.05%) | - |
| Ceará | 09 (10.58%) | - |
| Alagoas | 04 (4.7%) | - |
| Pernambuco | 04 (4.7%) | 01 |
| Goiás | 01 (1.17%) | - |
| Rio Grande do Sul | 01 (1.17%) | - |
| TOTAL | 85 | 03 |

Source: Authors.

The cases documented in Brazil occurred with species of saltwater fish, mainly, the arabaiana or bull's eye (*Seriola* spp.) and whiting (*Mycteroperca* spp.). But freshwater species also such as: Pacupeba and butter (*Mylossoma duriventre*), Tambaqui-colossoma with black fin (*Colossoma macropomum*) and freshwater Pirapitinga-pompano (*Piaractus brachypomus*). The signs

and symptoms observed were reddish-brown urine (hypermyoglobinuria due to hypermyoglobinemia), generalized weakness, stiffness and muscle contracture which it is observed in the rhabdomyolysis process. The symptoms of intense myalgia started suddenly and without an apparent cause, affecting mainly the cervical region and trapezius, then it could spread to the arms, back, thighs, calves. The incubation period was less than 24 hours after ingestion of the contaminated food (between 4 and 16 hours after consumption). Other symptoms found in patients are detailed in Table 3 below.

Table 3. Symptoms of disease of Haff in the Brazil during the pandemic period of SARS-CoV-2 between January 1, 2020, up to September 15, 2021.

| Nervous and muscular | Cardiovascular and Respiratory | Gastrointestinal and renal | Autonomic Nervous System |
|-----------------------------|---------------------------------------|-----------------------------------|---------------------------------|
| Lipothymia | Electrolyte changes | Nausea | Xerostomia |
| Generalized Paresthesias | Palpitations | Vomiting | Diaphoresis |
| Allodynia | Heart attack | Gastralgia | |
| Muscle stiffness | Increased Creatine Phosphokinase | Oliguria | |
| Severe myalgia | Increased Aspartate Aminotransferase | Acute kidney failure | |
| Rhabdomyolysis | Increased Lactate Dehydrogenase | Reddish-brown urine | |
| Changes in Muscle enzymes | Increased Aminotransferase | Hypermyoglobinuria | |
| Hypersensitivity | Hypermyoglobinemia | | |
| Physical asthenia | Dyspnea | | |
| Muscle Contractures | | | |

Source: Authors.

4. Discussion

Available data on Haff's disease, including pathophysiological and etiological mechanisms, transmissibility, disease severity, sequelae and potential impact on public health are still scarce in the literature. The Ministry of Health in Brazil recommends notifying those cases of rhabdomyolysis of unknown cause, as it is an unknown disease, and characterizing as a public health event.

The consumption of fish is very important as it presents a source of essential macro and micronutrients for the human body. But fish are among the foods that can cause poisoning and infections, since aquatic organisms may have the capacity to incorporate and biotransform substances. So as micronutrients, vitamins, minerals and various bioactives, toxic or allergenic agents, present in water due to natural processes or arising from planktonic and invertebrate organisms, as well as anthropogenic actions, may be associated with marine toxins. Toxins are substances generated by natural processes, cause deleterious effects, and can be produced by living organisms. Some organisms such as microalgae produce biotoxins (phycotoxins) capable of causing acute poisoning in humans when concentrated in consumed species (Patocka et al., 2015; Boente-Juncal et al., 2020a). According to the findings, the risks remain if the consumption is of fish from capture or fishing.

One of the suspected theories that Haff's disease has its etiopathogenesis in toxins is that there are proliferations of

certain marine and freshwater microalgae that may cause harmful effects to human beings. The levels of phycotoxins in the aquatic environment depend on changes in several factors: temperature, nutrient availability, light intensity, salinity, among others (Vale, 2004). The fish toxins produced by bacteria are transferred and accumulate in the viscera of marine herbivorous fish in coral reefs or environments with algal blooms, transfer to their predators, the deep-sea carnivorous fish, thus reaching the consumer, potentially causing intoxication to humans. Due to the secondary or tertiary origin of fish contamination, the amount of toxins found in fish and invertebrates depends on factors such as: bioaccumulation capacity, fish storage, environmental conditions, and seasonality.

There are few records of human intoxications caused by harmful algae in Brazil, but those due to consumption of bivalve molluscs stand out: diarrheal toxins and amnesic toxins. Intoxications by phycotoxins (ciguatoxin) and bacterial toxins (enterotoxins) were found after consumption of contaminated fish. In the period from 2016 to 2017 there was an outbreak of poisoning (Haff's disease) linked to fish consumption in Pernambuco and Bahia (Bandeira et al., 2017; SES-PE, 2021). But the association with these toxins is still unclear. Although the cause is not yet fully elucidated, it is known that it occurs after ingestion of some species of fish and crustaceans of fresh or salt water. Symptoms corroborate those described in the literature, which contributes to diagnostic confirmation.

Due to the prodromes of ingestion of fish (cooked, fried, roasted, smoked or in natura) or fresh and salt water crustaceans, the fact that such possible toxin is produced or bioaccumulative in the food chain of both aquatic environments is strengthened (Bandeira et al., 2017; Diaz, 2015). Fish related to Haff's disease, may have microalgae such as associated dinoflagellates, since it is found in salt and fresh water (Bandeira et al., 2017; Diaz, 2015; Cardoso e Torgan, 2007). Its toxins: palitoxins (ostreocins) and analogues (ovitoxins) exert similar effects to those described during the disease. Palitoxins are among the largest non-protein molecules of secondary metabolites, find several binding sites and can interact with all cells that have sodium and potassium pumps (Diaz, 2015; Sauviat, 1992; Patocka et al., 2015; Boente-Juncal et al., 2020a; Boente-Juncal et al., 2020b; Habermann, 1989; Caixin et al., 2017).

According to the US Centers for Disease Control and Prevention, there are criteria to distinguish Haff disease: First: Ingestion of aquatic organisms within 24 h (72 h); Second: Serum creatine kinase (CK) levels five or more times above baseline levels; Third: Cardiac creatine kinase (CK-MB) less than 5%. In addition, the contaminated material must not show slow hemolytic activity of the palitoxin and exert less neurotoxic effects, compared to confirmed cases of intoxication by palytoxin (Bandeira et al., 2017; Diaz, 2015).

It has been shown in Japan that urine and serum samples from intoxicated individuals did not show the hemolytic activity of palytoxin (Diaz, 2015). In the United States and China, cases of Haff's disease were analyzed by various chromatographic methods and presented negative results for: okadaic acid, microcystin, nodularin and palitoxins, brevetoxins, saxitoxins, ciguatoxins, tetrodotoxin, domoic acid. However, palitoxins and analogues should not be ruled out as a cause of the disease (Diaz, 2015; Sauviat, 1992; Patocka et al., 2015; Boente-Juncal et al., 2020a; Boente-Juncal et al., 2020b; Habermann, 1989; Chen et al., 2016). However, in infected patients in several regions of Brazil, the absence of fever and gastrointestinal symptoms, and laboratory tests for infections, reinforces the presence of an ingested toxin as etiology main.

In addition to Brazil, several countries around the world had records of occurrence after ingestion of freshwater fish such as pike *Esox* spp., European eel *Anguilla anguilla*, crayfish *Procambarus clarkii* (United States of America - USA and China), damselfish *Lota lota* (Russia), buffalo fish *Ictiobus cyprinellus*, Atlantic salmon *Salmo salar* (USA), and marine species such as Lactoria diaphana cowfish and Ostracion immaculatus cubefish (Japan, after consumption of raw fish). The west and east coasts of Africa, Indian Ocean and China Sea, Sea of Japan, Baltic Sea, Yangtze River basin in China, rivers in the south of the USA have already reported cases (Pei et al., 2019; Buchholz et al., 2000; Boente-Juncal et al., 2020a).

It is not yet possible to say which is the most adequate method to investigate Haff's disease. But at the end of 2020 a report by the Federal Institute of Education, Science and Technology of Santa Catarina, Southern Brazil, detected palytoxin and

ovatoxins in samples of ready-to-eat dishes consumed by intoxicated people in Bahia and Pernambuco. It biological tests and death of animals indicating that cases of food poisoning may be associated with the presence of marine biotoxins were quite suggestive (SVS-MS, 2021). This approaches the most accepted hypothesis for the disease in which one or more toxins may be directly involved with the etiopathogenesis. But a differential diagnostic with significance it is necessary, to clear the subjacent mechanisms (Liu et al., 2018).

Due to the severity and lack of specific treatment, when suspected cases occur in Brazil, laboratory tests and observation of changes and urine color (dark) are recommended, suggesting severe rhabdomyolysis. The main complications of rhabdomyolysis due to Haff's disease are Hyperkalemia, hypo or hypercalcemia, hyperphosphatemia, and hyperuricemia. Early onset intravenous hydration for 48 or 72 hours is important to avoid acute renal failure related to major damage to the nephrons as seen in the renal tubules. It is recommended not to use anti-inflammatory drugs. Serum electrolytes and renal function should be monitored in conjunction with ongoing treatment. There is a recommendation to alkalinize the urine, which contributes to increase the excretion of toxic acid substances.

5. Final Considerations

In the years 2020 and 2021, a critical period for coping with the SARS-CoV-2 virus pandemic in Brazil, many cases of disease of Haff could be reported in various regions of the country. Cases of illness and death occurred in different Brazilian regions, from states in the North to the South of the country. Despite the etiological suspicions, studies, and follow-up of the cases, it is still not possible to affirm that the disease is caused by biomolecules of the Palytoxin-Like Toxins group. But both freshwater and saltwater fish can be vectors to develop of Haff's disease. The possible identification of the responsible toxin(s) will be essential for a complete understanding of the etiopathogenic mechanism of the disease, as well as the adequate development of prevention, treatment, and cure measures. On the other hand, even with the incidence records of cases in 2021, it is believed that there is an underreporting to the national CIEVS and underdiagnosis.

Further works are very needed to improve our comprehension and approaches about the etiology underlying Haff disease, which will help to understand the chain of transmission and, consequently, prevention of the disease. On the other hand, early therapy, correct patient management and public health education measures to society are fundamental conducts to prevent illness, disease worsening and mortality.

Declaration of Interests

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