v. 2, n. 18, 2022

International Journal of Health Science

CLINICAL MANAGEMENT OF HAFF SYNDROME

Juliany Lins Araújo
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/7085562558589234

Gilmara Carvalho Batista
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/1415145842583207

Berila Beatriz Dias de Almeida
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/6587550313250815

Isabela Avila Fontes Carvalho
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/228938883236132

Fabiana Ramos Viana
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/8282825125807833

Lucas Rocha Barreto de Almeida
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/7289330549199762

Larissa Dantas Sobral
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/0959964907841500

Gabriela Peres de Oliveira Krauss
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/6223909536233030

Larissa Mateus Nascimento Lima
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/1459012548064818

Mariana Soares Faria
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/1386144841025304

Flávia Gabriela Tojal Hora
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/7418072791883050

Maria Clara Santos Souza
Faculdade Tiradentes, Recife
http://lattes.cnpq.br/1015683256157576

Abstract: Introduction: Haff's disease was first reported in 1924 on the Baltic Sea coast. This syndrome is related to a toxin that is still unknown, but can be found in certain freshwater fish when they are contaminated. In the progression of this pathology, a condition called rhabdomyolysis was observed, an aggravating situation that, if not treated immediately, can lead to death. The diagnosis of Haff's disease is based on clinical suspicion, epidemiological history, and elevated levels of muscle necrosis markers. As it is a rare clinical syndrome, underdiagnosed, with an increase in incidence and with a good prognosis if treatment is indicated in a timely manner, this study aims to report what is known about the current clinical management of Haff Syndrome, focusing on greater clarification about of the disease. **Methodology:** This is a literature review in the Scielo, BVS and Google Scholar databases, in addition to the emergency book of the University of São Paulo for comparative purposes. Five articles were selected from 2005 to 2021, in Portuguese, correlated with different aspects of the theme. **Results**: The approach is based on the prevention of acute tubular necrosis and the prompt recognition and correction of electrolyte and acid-base disturbances. In the first 24-48 hours, hydration with isotonic saline must be performed, about 1 to 2 L/h. After the start of diuresis, the volume replacement required is 100 to 200 mL/hour. To increase urinary output, 10g of mannitol and 40 mEq of sodium bicarbonate in 0.45% saline can be considered. If refractory oliguria is present, urgent hemodialysis is indicated. If hyperkalemia, evaluate the use of intravenous glucoinsulin, intravenous sodium bicarbonate, oral exchange resin or even furosemide. If refractory hyperkalemia, also indicate hemodialysis. For hyperphosphatemia, the oral chelator or aluminum hydroxide, avoiding calcium carbonate, are options. Hypocalcemia

must only be corrected in symptomatic cases or in the presence of severe hyperkalemia. Allopurinol may be indicated to control hyperuricemia and also contribute to the elimination of free radicals. As for metabolic acidosis, correction of the other parameters tends to normalize it. If severe acidosis, as in the case of serum bicarbonate less than 15 mEq/L, the use of 50 mEq of intravenous sodium bicarbonate is an alternative. **Conclusions:** Since the disease-causing toxin has not yet been identified and the pathophysiology remains unclear, treatment involves general supportive measures in addition to specific interventions for complications.

Keywords: Haff Syndrome, Black Urine Disease, Rhabdomyolysis, Clinical Management.

INTRODUCTION

Haff's disease was first reported in 1924 in the coastal region of Königsberg Haff, on the Baltic Sea coast. Data released by the Ministry of Health on the epidemiological profile of diseases transmitted by food and water in Brazil, from 2009 to 2018, pointed out, among the foods incriminated in foodborne disease outbreaks, fish as being involved in 2.1% of cases. cases occurring in the country during this period (Brasil, 2018).

This syndrome is related to a toxin that is still unknown, but can be found in certain freshwater fish when they are contaminated. This substance is believed to be thermostable, as it is not inactivated even after cooking. All patients who suffered from Haff's disease reported a history of eating fish within 24 hours of illness onset.

In the progression of this pathology, a condition called rhabdomyolysis was observed, an aggravating situation that, if not treated immediately, can lead to death. Although the causes of rhabdomyolysis are quite diverse, the pathogenesis appears to follow a final common pathway, leading to muscle necrosis and release of muscle components into the cellular interstitium and later into the circulation. Whatever the process determining the onset of rhabdomyolysis, the end result is an increase in cellular permeability to sodium, chloride and water ions, which results in cellular swelling and disruption of the myocyte plasma membrane.

The main mechanism of muscle injury, traumatic and non-traumatic in this condition called rhabdomyolysis, is associated with the reperfusion process. After perfusion is restored to the injured tissue, it is invaded by leukocytes, which increase the damage, releasing more proteases and free radicals at the site. It thus establishes a self-perpetuating myolytic inflammatory reaction that culminates in cell death, with the release of intracellular toxins into the systemic circulation.

It is a sudden onset disease that can lead to death in less than 24 hours due to rhabdomyolysis and multiple organ failure. Striated muscle injury leads to myalgia, muscle weakness and stiffness throughout the body, as well as causing myoglobinuria, which manifests the dark urine for which the disease was popularly known – "black urine disease". Carbon dioxide retention and respiratory failure occur due to weakness of the respiratory muscles. Other findings may include fever, nausea, vomiting, malaise, confusional state (agitation, delirium), and purplish skin discoloration (similar to ecchymosis) in areas of myoedema.

The diagnosis of Haff's disease is based on clinical suspicion, epidemiological history (fish ingestion within 24 hours before the onset of symptoms) and elevated levels of muscle necrosis markers (Table 1), particularly myoglobin and creatine phosphokinase.

Total creatine phosphokinase (CPK)	> 1.000 U/ml and generally exceeds 10,000 U/ml (may be above 100,000 U/ml).
Myoglobin (MB)	It rises, but its value is usually less than 10% of the total CPK. May also manifest myoglobinuria.
Other enzymes	TGO (AST), LDH and aldolase also have their serum levels increased.
Electrolytes	Hyperkalemia, hyperphosphatemia, hypocalcemia.
Acid-base balance	High anion-gap metabolic acidosis (lactic acid + uric acid).
Uric acid	Increased.

Table 1. Laboratory changes in rhabdomyolysis.

The differential diagnosis must include other toxic syndromes in which rhabdomyolysis occurs. As it is a rare clinical syndrome, underdiagnosed, with an increase in incidence and with a good prognosis if treatment is indicated in a timely manner, this study aims to report what is known about the current clinical management of Haff Syndrome, with a focus on greater clarification about of the disease.

METHODOLOGY

This is a literature review, whose search terms were "Haff syndrome", "Black urine disease", "Rhabdomyolysis" and "Clinical management" in the Scielo, VHL and Google Scholar databases, in addition to the book of emergencies at the University of São Paulo for comparative purposes. Five articles were selected from 2005 to 2021, in Portuguese, correlated with different aspects of the theme, as there is still little published material with these descriptors.

RESULTS

Although knowledge about Haff Syndrome is still incipient, the main clinical manifestations related to rhabdomyolysis are well established, and the clinical management of this presentation is well known.

In the case of dark urine disease, it is very important to reduce underdiagnosis through the habit of asking the patient or caregiver about their fish intake in the last few days, especially in the last 24 hours, in the face of a suspected condition of rhabdomyolysis. Validating this diagnostic possibility allows greater scientific reach to understand the real incidence of the pathology, as well as the scientific focus on the identification of the still obscure toxin and even on the correction for a more specific clinical management.

In the face of clinical suspicion, it is necessary to request the dosage of CPK, in addition to other complementary tests if available, such as liver enzymes, lactic dehydrogenase, blood count, myoglobin, electrolytes, uric acid, among others. Some tests may be useful depending on the clinic, such as blood gas analysis and Urine 1. Diagnostic delay may lead to early complications (first 24 hours), which include hydroelectrolytic disorders and liver dysfunction, or late complications (after 24 to 48 hours), such as acute kidney injury, disseminated intravascular coagulation and compartment syndrome.

As for early onset, hyperkalemia and hyperphosphatemia are disproportionate to the degree of kidney injury and oliguria, due to the muscle release of large amounts of potassium and phosphate. Hypocalcemia is due to the precipitation of calcium phosphate in the injured muscle. The release of H+ ions, lactate and uric acid justifies metabolic acidosis with increased anion-gap. Hepatic dysfunction is consequent to injury to hepatocytes induced by muscle proteases released into the circulation.

As for the late ones, acute kidney injury is the most feared because it exacerbates hydroelectrolytic disorders, imposing a risk of life. An important feature is the rapid increase in creatinine relative to urea, due to the direct release of creatine from the injured muscle. Disseminated intravascular coagulation has a laboratory diagnosis, almost always without clinical repercussions (bleeding or thrombosis). Compartment syndrome, on the other hand, can occur due to myoedema, more common in the calf region, requiring urgent fasciotomy.

According to Carvalho et all (2002), the treatment of rhabdomyolysis does not only consist of eliminating the underlying etiological factors, but basically consists of aggressive treatment of hypovolemia, which may require the administration of more than 10 liters of saline per day. This administration is conditioned by a possible associated cardiac pathology, and preparations with lactate and potassium must also be avoided.

The management is based on the prevention of acute tubular necrosis and the prompt recognition and correction of electrolyte and acid-base disturbances, since the main cause of death is cardiac arrest due to hyperkalemia.

In the first 24-48 hours, hydration must be performed with isotonic saline (such as 0.9% saline), approximately 1 to 2 L/h. After the start of diuresis, the volume replacement required is 100 to 200 mL/hour. To increase urine output, mannitol 10g (50 ml) and sodium bicarbonate 40 mEq (40 ml) in 0.45% saline (410 ml) can be considered. If refractory oliguria is present, urgent hemodialysis is indicated.

It is also essential to correct hydroelectrolytic disorders. If hyperkalemia, evaluate the use of intravenous glucoinsulin, intravenous sodium bicarbonate, oral exchange resin or even furosemide. If refractory hyperkalemia, also indicate hemodialysis. For hyperphosphatemia, the oral chelator Sevelamer hydrochloride or aluminum hydroxide, avoiding calcium carbonate, are options. Hypocalcemia must only be corrected in symptomatic cases, such as tetany or convulsions; or in the presence of severe hyperkalemia, to protect against arrhythmias. Allopurinol may be indicated to control hyperuricemia and also contribute to the elimination of free radicals. As for metabolic acidosis, correction of the other parameters tends to normalize it. If severe acidosis, as in the case of serum bicarbonate less than 15 mEq/L, the use of 50 mEq of intravenous sodium bicarbonate is an alternative.

CONCLUSIONS

In short, Haff Syndrome is a disease still being discovered, whose clinical presentation is wide and the etiology is not yet known. Among the main diagnostic aspects, it is essential to investigate the clinical-epidemiological context of the patient, as well as to complement the investigation with tests related to rhabdomyolysis – the main manifestation. Despite the rapid evolution to death in some cases, early clinical management can modify the prognosis. Since the disease-causing toxin has not yet been identified and the pathophysiology

remains unclear, treatment involves general supportive measures, in addition to specific interventions for complications – these are the most studied.

Combating underdiagnosis with the available clinical and laboratory measures must favor the recognition of the incidence of this syndrome, as well as encourage studies on etiopathogenesis and therapy, which are essential in the formulation of protocols.

REFERENCES

CARVALHO, Gabriel Domingos et al. Aspectos relevantes sobre as intoxicações pelo consumo de pescado. 2021.

CULTURAL, Atualiza Associação; FERREIRA, Daise Gomes. Causas, efeitos e tratamento da Rabdomiólise. 2012.

FENG, Gang et al. Doença de Haff complicada por falência de múltiplos órgãos após ingestão de lagostim: estudo de caso. **Revista brasileira de terapia intensiva**, v. 26, p. 407-409, 2014.

GUIMARÃES ROSA, Nuno; RODRIGUES, Fernando; ARAÚJO, José Augusto. Rabdomiólise. 2005.

MARTELLI, Anderson et al. Fisiopatologia da Síndrome de Haff e progressão para rabdomiólise. **Revista Faculdades do Saber**, v. 6, n. 13, p. 1002-1009, 2021.

OLIVEIRA, Frederico Lage de. **Rabdomiólise: revisão bibliográfica com base num caso clinico de etiologia rara**. 2016. Tese de Doutorado.

RAPOSO, José N. et al. Rabdomiólise-breve revisão, a propósito de um caso. **Med Int**, v. 9, n. 1, p. 80-4, 2002.

TOLESANI JUNIOR, Oswaldo et al. Doença de Haff associada ao consumo de carne de Mylossoma duriventre (pacu-manteiga). **Revista Brasileira de Terapia Intensiva**, v. 25, p. 348-351, 2013.

VELASCO, Irineu Tadeu; BRANDÃO NETO, Rodrigo Antonio; SOUZA, Heraldo Possolo de; *et al.* Medicina de emergência: abordagem prática. [S.l: s.n.], 2019.