Rhabdomyolysis And Delirium Tremens In An Alcoholic Patient: Case Report

Rabdomiólise E Delirium Tremens Em Paciente Alcóolatra: Relato De Caso

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RESUMO
A síndrome de abstinência alcoólica é uma importante causa de internações. Em seus diferentes estágios de gravidade, o paciente pode cursar com alterações psíquicas até delirium tremens. Todavia, o abuso de álcool desses pacientes pode cursar clinicamente com até rabdomiólise. Neste sentido, este artigo visa relatar o caso de um paciente brasileiro com o diagnóstico de rabdomiólise e delirium tremens associado ao uso de álcool. O paciente abriu o quadro com uma fratura transtrocanteriana à esquerda, apresentando durante a internação delirium e rabdomiólise, não condizentes com a fratura. Diante da investigação clínico-laboratorial foi evidenciado um quadro de insuficiência renal aguda AKIN III, oriunda de lesão renal por rabdomiólise alcoólica, e delirium tremens pela classificação CIWA-AR. Portanto, este trabalho mostra a dificuldade do diagnóstico, a necessidade de uma abordagem multidisciplinar no tratamento e que há necessidade de mais estudos para aprender mais sobre esta correlação sindrômica para uma melhor abordagem terapêutica ao paciente.

Palavras-chave: Abstinência de Álcool, Rabdomiólise, Delirium por Abstinência Alcoólica.

ABSTRACT
Alcohol withdrawal syndrome is an important cause of hospitalizations. In its different stages of severity, the patient may develop psychic changes up to delirium tremens. However, alcohol abuse in these patients can be clinically accompanied by even rhabdomyolysis. In this sense, this article aims to report the case of a Brazilian patient diagnosed with rhabdomyolysis and delirium tremens in association with alcoholism. The patient first recorded the incident with a left transtrocanteric fracture, presenting with delirium and rhabdomyolysis during hospitalization, not consistent with the fracture. In the clinical and laboratory investigation, AKIN III acute renal failure, resulting from kidney injury due to alcoholic rhabdomyolysis, and delirium tremens according to the CIWA-AR classification, were evidenced. Therefore, this work shows the difficulty of diagnosis, the need for a multidisciplinary approach to treatment and that there is a need for further studies to learn more about this syndromic correlation for a better therapeutic approach to the patient.

Keywords: Alcohol Abstinence, Rhabdomyolysis, Alcohol Withdrawal Delirium.

1 INTRODUCTION
According to the World Health Organization (2018), more than 3 million people died from harmful alcohol use in 2016. Overall, harmful alcohol use causes more than 5% of the global disease burden. In this context, given the reality of hospitals and wards, an important cause of hospitalization is alcohol withdrawal syndrome (AWS).1
The AWS has different levels of severity, ranging from an eminently psychic condition (insomnia, irritability, worsening cognitive functions) to others, markedly autonomic, with delirium and seizures.²,³

AWS can be assessed according to some predictors of severity: a past history of severe AWS, high blood alcohol levels with no signs and symptoms of intoxication; high blood alcohol (300mg / dl); concomitant use of sedatives; comorbidities and advanced age. However, when the patient has AWS, it is advisable to apply the Clinical Withdrawal Assessment Revised (CIWA-Ar). With this scale, which has 10 items, it is possible to classify the severity of AWS and the therapeutic management.⁴

In this context, AWS can be classified as Level I, or also mild and moderate. It appears in the first 24 hours after the last dose ingested by the patient. It affects about 90% of patients, with symptoms such as agitation, anxiety, fine extremity tremors, altered sleep, sense-perception, mood, interpersonal relationship, appetite, sweating in outbreaks, increased heart rate, pulse and temperature. However, at this level, hallucinations are rare.⁵,⁶ Already Level II or severe AWS affects approximately 5% of patients, after 48 hours of the last dose, being an evolution from level I to II. Autonomic signs are more intense, generalized tremors, present auditory and visual hallucinations and temporospatial disorientation.⁶,⁷

In an even more severe stage, some patients with AWS level II arrive at Delirium tremens (DT), 72 hours after the last dose. DT is the most serious manifestation of alcohol withdrawal, however, it occurs in approximately 5% of hospitalized patients with alcohol dependence and has a reported mortality rate of approximately 15%.⁸

In addition, current diagnostic criteria for TD include disturbance of consciousness, change in cognition or perceptual disorder that develops in a short period and symptoms appear during or shortly after withdrawal from heavy alcohol intake. DT usually lasts for approximately 5 to 7 days, with a prolonged course being rare. The latter usually only occurs if there are underlying medical causes.⁹,¹⁰

In another context, rhabdomyolysis, conceptually, is seen as post-traumatic muscle injury.¹¹ However, this pathology can also come from non-traumatic causes that include occlusion or hypoperfusion of vessels that supply the muscle during prolonged immobilization as in a lithotomy position, electric current, hyperthermia, metabolic myopathies, drugs and toxins (including alcohol), infections, electrolyte abnormalities, endocrine disorders and polymyositis.¹² Among medications, rhabdomyolysis is most
commonly seen with HMG-CoA reductase inhibitors, but it can also be seen with the use of antimalarials, diuretics and fibrates, proton pump inhibitors, levofloxacin, caffeine, mefloquine, pregabalin and sildenafil.\textsuperscript{13,14,15,16,17,18}

Nevertheless, alcohol has also been an important cause. The adverse effects of ethanol on muscles have been experimentally described for several decades. Alcohol can induce rhabdomyolysis by inhibiting the accumulation of calcium in the sarcoplasmic reticulum, disrupting muscle cell membranes and inhibiting the sodium-potassium ATPase pump, which helps maintain cell integrity.\textsuperscript{19} Other causes can coexist in the same patient, thus increasing the probability of rhabdomyolysis. These include delirium tremens, alcohol withdrawal seizures, muscle hypoxia due to prolonged immobilization and limb compression, hypoperfusion after volume depletion and hypokalemia and hypophosphatemia that frequently occurs in malnourished alcoholic patients.\textsuperscript{20} Liver dysfunction in alcoholism produces systemic vasoactive factors, which increase renal failure.\textsuperscript{21}

\textbf{2 CASE REPORT}

V.A.C. patient, male, 60 years old, unemployed, from Conquista, Minas Gerais. He arrived at Mário Palmério Hospital Universitário, in Uberaba, Minas Gerais, in the orthopedics sector, for the correction of a left transtrochanteric fracture. During the pre-surgical investigation, laboratory tests showed urea results of 134 mg / dL (reference value - VR - 19 to 43 mg / dL), creatinine 8.31 mg / dL (VR 0.7 to 1, 2 mg / dL) and glomerular filtration rate (GFR) 6 ml / min (VR> 90 ml / min), which led to the elucidation of the diagnostic hypothesis of acute renal failure (AKI) AKIN III classification or acute chronic kidney disease. In view of the laboratory results, the patient was transferred to the medical clinic ward for investigation, stabilization and treatment of impaired renal function.

Upon the first assessment made by the team, the patient was in regular general condition, with poor hygiene conditions, confused, with visual delusions, agitated, self and psychologically disoriented. Since the patient's arrival at the service, no family member has been present to research the trauma history, background, habits and living conditions prior to hospitalization. On physical examination, he had 2 + / 4 + pale mucous, 2 + / 4 + dehydrated, anicteric and acyanotic mucous membranes. Isochoric pupils, photoreagents and the presence of horizontal nystagmus. Abdomen, respiratory and
cardiovascular systems unchanged. Palpable liver in costal topography. Left lower limb was turned to the side and shortened, with the presence of ecchymosis at the fracture site. Patient at all times with diffuse tremors throughout the body. Missing asterisks. The medical clinic team elucidated the confusional syndrome as a possible new diagnostic hypothesis. To investigate the syndrome’s etiology, new requests for laboratory and imaging tests were made.

In the exams, the following altered results were found that aroused attention: Urea 224 mg / dL (VR 19 to 43 mg / dL); Creatinine 9.3 mg / dL (VR 0.7 to 1.2); GFR 5 ml / min (VR> 90 ml / min); Aspartate aminotransferase (TGO) 6929 U / L (VR 15 to 46 U / L); Alanine aminotransferase (TGP) 1423 U / L (VR <50 U / L); GT Range (GGT) 78 U / L (VR 15 to 73 U / L); Normochromic normocytic anemia, with hemoglobin of 6.4 g% (VR 14 to 18 g%); Creatinophosphokinase (CK-NAC) 12368 U / L (VR 55 to 170 U / L); Computed tomography of the skull with brain volume reduction and microangiopathy.

Tests for serology of hepatitis B, syphilis, hepatitis C and human immunodeficiency virus were negative. The electrolytes, blood culture, urine culture and urine routine also had no significant changes.

It was possible to get in touch with the patient’s family, who reported that he lived in the back of his mother's house, and that he spent most of the day on the street. He was an alcoholic of about two liters of spirits a day and a smoker of marijuana and paper cigarettes (unknown smoking load). The family did not recognize any illness prior to admission.

After talking to the patient's family and examining the exams, the diagnosis of AKI III ARI, resulting from kidney injury due to alcoholic rhabdomyolysis, was closed. The transtrochanteric fracture was not consistent with the exaggerated increase in CK-NAC to assert that the cause of rhabdomyolysis was trauma. As for the confusional syndrome, the hypothesis of alcohol withdrawal syndrome, delirium tremens and uremia was raised.

On the seventh day of hospitalization, during the physical examination, the heart rate was measured at 122 beats per minute. Together with this data, CIWA-Ar was applied, with a result greater than 15 points. Thus, the diagnosis of delirium tremens was closed.
3 DISCUSSION

Rhabdomyolysis, the degradation of skeletal muscle fibers that leads to the leakage of muscle content into the circulation, is defined as an increase in creatine phosphokinase (CPK) of 5 to 10 times the upper limit of normal. It is a syndrome capable of generating early complications (such as severe hyperkalaemia, which may progress to arrhythmia and cardiac arrest) and late complications (such as acute renal failure, which affects up to 15% of patients), presenting a potential risk of life. Therefore, the institution of early diagnosis and treatment is essential.22,23

Several rhabdomyolysis etiologies have been described: (1) drugs, such as alcohol, cocaine, amphetamine, opioid, clofibrate, lovastatin; (2) strenuous physical exercise for sports, military training, seizures and myoclonus; (3) direct muscle injury by electric shock, freezing, burning and “Crush Syndrome” - including pressure necrosis induced by immobilization; (4) ischemic necrosis, due to vascular occlusion or external compression; (5) metabolic disorders, such as diabetic ketoacidosis / non-ketotic hyperosmolar coma, hypothyroidism, water intoxication, electrolyte disturbances - hypokalemia, hypophosphatemia; (6) malignant hyperthermia; (7) bacterial or viral sepsis; (8) inflammatory myopathy - polymyositis, infectious myopathy; (9) toxins - tetanus, typhoid, staphylococci, insect toxins; (10) hereditary disorders, such as glycogenolytic enzyme deficiencies - MacAdle’s syndrome, deficiencies in lipid metabolism - carnitine-palmitotransferase, and miscellaneous - malignant hyperthermia / neuroleptic malignant syndrome.24

Alcohol intoxication is the main etiology of non-traumatic rhabdomyolysis and is frequently associated with seizures, delirium tremens or muscle compression. In this context, rhabdomyolysis is usually triggered in periods of severe alcohol intake, with plasma levels above 100 nM.25 According to the review “Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse”, alcohol was the substance most consumed in an abusive way, being implicated in 54% of the cases.26

The pathophysiology of alcohol-induced rhabdomyolysis is not yet fully understood, but it differs between short- and long-term alcohol poisoning. In the first situation, immobilization and coma are the main causal factors, while in the second, acid-base and electrolyte disorders (hypokalemia, hypophosphatemia, hypomagnesaemia and hypocalcemia) stand out.22
The literature suggests that the direct toxic effect of ethanol on skeletal muscles may be determinant in the disintegration of these fibers, by disrupting the function of the adenosine triphosphatase pump, breaking the muscle membrane, altering the sarcoplasmic reticulum and / or inducing cytochrome P450.22

The diagnosis of rhabdomyolysis consists of determining CPK activity and the presence of myoglobinuria.27 The classic triad of rhabdomyolysis, however uncommon (<10% of cases), includes myalgia, transient muscle weakness and pigmenturia. The prognosis depends on the etiology and complications. The mortality rate varies between 8 and 10% and is even higher if the patient develops acute renal failure (either due to mechanical obstruction of the renal tubules by myoglobin, by renal vasoconstriction, hypovolemia or by the direct renal toxic effects of myoglobin).22

To prevent acute renal failure, you should: (1) Administer fluids in the first 6 hours of muscle damage, for at least 24 hours, maintaining a urine output of at least 300 mL / h; (2) Administer intravenous sodium bicarbonate only if necessary - to correct systemic acidosis or to reach a urinary pH of 6.5 in order to eliminate myoglobin; (3) Administer mannitol only if necessary - to maintain the desired urine output. In cases of rhabdomyolysis induced by resistant alcohol coexisting with polymyositis, systemic corticosteroids can be used as a second line of treatment.22

Alcoholism is a primary chronic disease, which can be predisposed by genetic, psychosocial components and environmental factors. It is defined by the 10th edition of the International Classification of Diseases (ICD-10), of the World Health Organization (WHO), as a set of behavioral, cognitive and physiological phenomena that develop after repeated use of alcohol, such as the strong desire drinking, difficulty controlling consumption, continued use despite the negatives, priority given to the use of alcohol in relation to other activities, increased tolerance and sometimes a state of physical abstinence.38

Alcoholic Withdrawal Syndrome (AWS) is a set of symptoms that appears when an individual who abuses alcoholic beverages suddenly reduces or ceases consumption. In general, the symptoms of AWS start 1 to 4 days after the interruption of alcohol use.31 This is because alcohol interferes with the communication of nerve cells, since chronic consumption of alcohol in high doses triggers the increase in the density of NMDA receptors (N-Methyl – D-Aspartate), which is excitatory in the central nervous system (CNS) and decrease in gamma-aminobutyric acid receptors (GABA), which is an
inhibitory neurotransmitter. Therefore, as ethanol acts as an antagonist of NMDA receptors and agonist of GABA receptors, with short action, withdrawal symptoms usually begin within 8 hours after the reduction of blood alcohol levels, peak at around 72 hours and are markedly reduced from the 5th to the 7th day of abstinence.

In this scenario, as the patient in abstinence is in a state of hyperexcitation of the nervous system, the most common symptoms are tachycardia, increased blood pressure, hyperthermia, muscle stiffness, convulsions, agitation, tremors, nausea, vomiting and changes in humor. Although some patients may have a mild condition, there are those who develop symptoms and serious complications, which can culminate in death. Thus, when diagnosed with AWS, the patient should be classified according to the severity of the symptoms and investigated for possible complications and comorbidities related to alcoholism.

When AWS is suspected, it is advisable to apply the Clinical Withdrawal Assessment Revised (CIWA-Ar), which refers to a scale with 10 items, whose final score classifies the severity of AWS and provides subsidies to plan the management of the patient. In CIWA-Ar, the score ranges from 0 to 20 points, with 0 to 9 points mild AWS, 10 to 18 moderate AWS and more than 18 severe AWS, the items that make up the scale are diaphoresis, tremor, anxiety, agitation, nausea/vomiting, itching, headache, orientation, visual, auditory and tactile disorders.

The severity of AWS can be divided into Level I (mild/moderate) and Level II (severe). At Level I, the predominant signs and symptoms are tachycardia, anxiety, changes in blood pressure and sweating. However, approximately 5% of the cases present as Level II, which is a severe impairment and, therefore, with a more exuberant autonomic response, in addition to complications such as seizures, hallucinations and Delirium Tremens (DT).

Delirium Tremens is a serious complication of alcohol withdrawal syndrome, in which the patient has hallucinations, changes in the level of consciousness and disorientation, in addition to other symptoms characteristic of AWS. Studies indicate that the risk of death is reduced in patients with DT who receive adequate medical and pharmacological assistance. In this context, it is essential that the patient receives diagnosis and treatment as soon as possible.

Delirium is defined as an acute confusional condition, and DT is a specific condition of delirium, related to alcohol withdrawal. Delirium is a common cause of
altered behavior in people with some physical disease that has not been diagnosed or treated adequately.\textsuperscript{30} In this sense, it is important to identify the main etiologies of this disease as possible differential diagnoses in order to provide adequate therapy to the patient that presents this picture. Examples of possible causes of delirium tremens simile: Dementia, post-surgical patients, burns / dehydration, abrupt discontinuation of other drugs, malnutrition, chronic liver disease, dialysis, Parkinson's disease and HIV infection.\textsuperscript{32}

Regardless of whether the diagnosis of DT is clinical, in the initial approach of the patient, it is necessary to complement the evaluation with laboratory tests to properly investigate the organic changes caused by alcohol dependence, and which can negatively interfere in the patient's evolution. Thus, considering that the places most affected by chronic alcohol use are the liver, blood, immune and neurological systems, and that, the alcoholic patient usually presents and is in a state of malnutrition, it is convenient to order liver function tests, electrolytes and blood count, as well as imaging tests that can contribute to the management of the case.\textsuperscript{31, 39} In addition, the agitation and seizures, when causing an acute increase in muscle metabolism, can generate destruction of myocytes and culminate in a rhabdomyolysis event, therefore, the dosage of creatinophosphokinase (CPK) may also be relevant.

Most studies show that 3 to 5\% of patients hospitalized for alcohol withdrawal meet criteria for the diagnosis of delirium due to withdrawal, and around 1 to 4\% of those who have suffered delirium due to withdrawal die.\textsuperscript{33} Therefore, the TD must be treated as a clinical-psychiatric emergency. In view of this, the management of AWS involves supportive measures to help keep patients safe, hydrated and nourished, in addition, it is important to make Tiamine replacement, since its levels are usually low in chronic drinkers and its deficiency can lead to development of Wernicke's encephalopathy, another serious complication with neurological manifestations. However, for patients complicated with TD, the basis of treatment involves high doses of benzodiazepines, such as Diazepam, and if necessary, antipsychotic drugs, such as low doses of haloperidol, can also be used.\textsuperscript{35, 36}

4 FINAL CONSIDERATIONS

Alcohol withdrawal syndrome arises after the sudden interruption of alcohol consumption in patients who were alcohol abusers. It is responsible for a large portion of
hospital admissions. Its most serious manifestation, delirium tremens, presents itself through hallucination, alteration of the level of consciousness and disorientation. Early treatment of this condition using benzodiazepines and antipsychotics is necessary to reduce mortality.

The main non-traumatic etiology of rhabdomyolysis is alcohol. Its pathophysiology is not completely understood, requiring further studies, but it is believed that there is a direct toxic effect of alcohol on skeletal muscle fibers, leading to its disintegration. Alcohol intoxication leads to rhabdomyolysis due to seizures due to alcohol withdrawal, muscle hypoxia induced by limb immobilization and compression, malnutrition and liver dysfunction.

Acute renal failure is a possible complication of rhabdomyolysis, which is present in the patient in this report. To prevent this condition, it is necessary to administer fluids, correct hydroelectrolytic disorders and, if polymositis is identified, administer systemic corticosteroids.
REFERENCES


