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Recurrent rhabdomyolysis secondary to hyponatremia in a patient with primary psychogenic polydipsia

Rabdomiólise recorrente secundária à hiponatremia em doente com polidipsia psicogênica primária

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ABSTRACT

Rhabdomyolysis is characterized by the destruction of skeletal muscle tissue, and its main causes are trauma, toxic substances and electrolyte disturbances. Among the latter is hyponatremia-induced rhabdomyolysis, a rare condition that occurs mainly in patients with psychogenic polydipsia. Psycogenic polydipsia mostly affects patients with schizophrenia, coursing with hyponatremia in almost 25% of the cases. It is also in this context that rhabdomyolysis secondary to hyponatremia occurs most often. In this article, the case of a 49-year-old male with a history of schizophrenia, medicated with clozapine, and brought to the emergency room in a state of coma and seizures is described. Severe hypoosmolar hyponatremia with cerebral edema was found on a computed tomography examination, and a subsequent diagnosis of hyponatremia secondary to psychogenic polydipsia was made. Hyponatremia correction therapy was started, and the patient was admitted to the intensive care unit. After the hyponatremia correction, the patient presented with analytical worsening, showing marked rhabdomyolysis with a creatine phosphokinase level of 44.058UI/L on day 3 of hospitalization. The condition showed a subsequent progressive improvement with therapy, with no occurrence of kidney damage. This case stresses the need for monitoring rhabdomyolysis markers in severe hyponatremia, illustrating the condition of rhabdomyolysis secondary to hyponatremia induced by psychogenic polydipsia, which should be considered in patients undergoing treatment with neuroleptics.

Keywords: Polydipsia, psychogenic; Water intoxication; Hyponatremia; Rhabdomyolysis; Clozapine; Myelinolysis, central pontine; Case reports

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INTRODUCTION

Rhabdomyolysis is a clinical entity characterized by the lysis of myocytes in the skeletal muscle tissue and the release of their cell components, such as myoglobin, the main cause of the toxic effects of rhabdomyolysis. The leading causes are trauma and toxins (which include medications), but rhabdomyolysis can also occur due to electrolyte disturbances, and the most often involved ion is potassium.[1]

The first rhabdomyolysis case associated with hyponatremia was described in 1979 by Peter Browne, and since then, several cases have been documented; nonetheless, it has remained a relatively rare disease. Some of the factors contributing for the occurrence of this clinical condition are psychogenic

polydipsia (PP), certain drug therapies (thiazides and proton pump inhibitors), endocrine disorders (thyroid or adrenal disease) and iatrogeny (particularly after prostate surgery or preparation for colonoscopy with mannitol).[2]

PP often occurs in patients with psychiatric disorders, especially schizophrenia, and hyponatremia occurs in 25% of the cases.[2] It is also in this clinical context that most cases of rhabdomyolysis associated with hyponatremia occur. In this same patient group, rare cases of rhabdomyolysis associated with hyponatremia correction are described in the literature - most of these patients under psychiatric therapy (antipsychotic or selective serotonin reuptake inhibitors - SSRIs).

The authors describe here the case of a patient with hebephrenic schizophrenia admitted to the intensive care unit for severe hyponatremia associated with marked rhabdomyolysis, which was the second episode in the patient.

CASE REPORT

A 49-year-old male with a history of schizophrenia, treated with clozapine and risperidone, was brought to the emergency room in a coma (Glasgow coma scale 7 - E2M4V1) with generalized tonic-clonic seizures. Tracheal intubation and mechanical ventilation were performed, and the seizures were controlled with phenytoin perfusion. After initial stabilization of the patient, further diagnostic tests were performed, which revealed hypoosmolar hyponatremia (sodium 110mEq/L and osmolarity 220mOsm/L) and increased creatine phosphokinase (CPK; 2.356UI/L) without other significant alterations. A craniocerebral computed tomography scan was performed, which showed slight to moderate cerebral edema. Given the severe and symptomatic hyponatremia, correction was initiated with 3% sodium chloride, and the patient was admitted to the intensive care unit. At the first ionic re-evaluation, a higher than expected increase in sodium was observed (increase of 10 mEq in 6 hours); therefore, the sodium correction was suspended, and close monitoring of natremia was maintained. In the first 12 hours after admission, the patient experienced an increase of 15mEq, with natremia normalization on the third hospitalization day, approximately 48 hours after admission. At that point, the craniocerebral computed tomography was repeated, which showed clear improvement of the cerebral edema. From a neurological point of view, sedation suspension was possible approximately 24 hours after its introduction, with recovery of consciousness and no associated neurological deficits, excluding the hypothesis of osmotic demyelination syndrome. However, a progressive worsening of the rhabdomyolysis present at admission was observed, occurring more acutely on the 3rd day of hospitalization with a maximum CPK value of 44,065UI/L. The analytical progression of the patient is shown in table 1.

After ruling out neuroleptic malignant syndrome (apyrexia without autonomic dysfunction or altered state of consciousness) and drug iatrogeny, fluid therapy was increased to prevent nephropathy. The patient showed progressive improvement in the rhabdomyolysis parameters with no acute kidney damage. After normalization of the rhabdomyolysis parameters, risperidone (the previous medication) was introduced to the patient therapy without a recurrence of rhabdomyolysis.

The patient was discharged to psychiatric services on the 6th day of hospitalization, and his routine therapy was changed (clozapine was suspended). He was referred to a nursing facility due to the need for monitoring and surveillance. When analyzing his personal history, a previous admission to the intensive care unit was found for the same reason: severe hyponatremia in a PP context with rhabdomyolysis complications, and at the time, he was also medicated with clozapine and risperidone.

DISCUSSION

PP is a disease that can be described as having three stages: the first stage is polydipsia and polyuria, which evolves into hyponatremia in the second stage, and in the third stage, it becomes "water intoxication", a term

Table 1 - Progression of analytical parameters during hospitalization

	0 h (D1)	12 h (D1)	36 h (D2)	60 h (D3)	84 h (D4)	106 h (D5)	132 h (D6)
Sodium (mmol/L)	110	125	130.9	137.4	138.6	139.9	137.8
CPK (UI/L)	2,356	3,441	9,470	44,058	14,930	5,766	759
Urea (mmol/L)	-	3.1	4.2	4.0	5.6	5.7	5.0
Creatinine (µmol/L)	-	74.3	78.9	48.9	62.9	75.2	56.7
GOT/GPT (UI/L)	-	60/59	72/46	268/55	155/40	-	43/38

h - hour; D - hospitalization day; CPK - creatine phosphokinase; GOT - glutamic oxaloacetic transaminase; GPT - glutamic pyruvic transaminase.

first used in 1993, which can manifest by worsening of psychiatric symptoms, nausea, vomiting, ataxia, delirium, seizures or coma.[2]

This disease appears to be associated with certain individual characteristics, namely male gender, chronic disease, heavy smoking, alcohol abuse and even certain psychiatric illnesses, such as schizophrenia and cognitive deficits.[3]

Ingestion of large amounts of water alone does not induce hyponatremia; however, it may occur in situations with a concurrent increase of antidiuretic hormone (ADH) secretion or kidney damage. In fact, a 2001 study concluded that hyponatremia is more likely to occur in patients with certain characteristics including comorbidities (such as kidney failure), abnormal levels of potassium or certain therapeutics, such as diuretics, calcium channel blockers and tricyclic antidepressants.[4] The administration of neuroleptics and SSRIs is equally associated with more severe hyponatremia through mechanisms that are not yet fully known but could be related to the activation of serotonin receptors (5-hydroxytryptamine-A2), which result in increased cell permeability.[4]

Only approximately 17 to 25% of PP patients develop hyponatremia or water intoxication.[5] As previously mentioned, most PP cases occur in psychiatric patients, particularly schizophrenics, which may be due to a greater sensitivity to ADH, changes in osmoregulatory mechanisms or even increased ADH secretion.[5]

In the case described, the patient was treated with clozapine for several years without evidence of rhabdomyolysis until the first hospitalization (6 months before the current episode). In both hospital admissions, water intake in large amounts was reported (above 5L per day) in the days prior to hospital arrival. Similarly, in both cases, the patient had severe symptomatic hyponatremia (seizures and coma) at admission. This patient presented several risk factors classically associated with the development of hyponatremia in PP, including an underlying disease (schizophrenia), male gender and chronic use of atypical neuroleptics (clozapine).

Since the first report of rhabdomyolysis associated with hyponatremia, these situations have been described occasionally, with only small case series reporting this pathology. This situation seems to be more common in patients under the effect of various medications, especially thiazide diuretics, proton pump inhibitors and trimethoprim-sulfamethoxazole.[6]

The mechanism by which hyponatremia induces rhabdomyolysis seems to be dysfunction of the sodium/calcium pump, which leads to the activation of the proteases and lipases that are responsible for cell lysis.[4,6] There is another theory arguing that the decrease in the osmolarity of the extracellular fluid leads to the outflow of potassium from the cells, resulting in its consequent depletion and cell destruction.[7] This last mechanism, reflecting the inability of regulating cell volume, suggests an explanation for the occurrence of rhabdomyolysis, both in hyponatremia and in its correction, which is another situation that has been recently identified. It also justifies the importance of speed in hyponatremia correction in the clinical condition of rhabdomyolysis, as shown by a study by Morita et al.; the only factors directly associated with rhabdomyolysis in hyponatremia were the rate of sodium correction per hour and an increase in the amount of sodium in the first 24 hours. Several other factors were evaluated, and no relationship seemed to exist among them (age, gender, previous alcohol consumption, psychotropic drug overdose, Glasgow score, initial sodium, potassium, chloride or glucose levels, plasma osmolarity and seizures as the initial manifestation).[8] Nevertheless, the risk of rapid correction of hyponatremia is lower than the risk caused by a delay in the correction of symptomatic hyponatremia. Hyponatremia guidelines have been recently revised, and an increase of 5mEq in the first hour is currently recommended. Through the use of hypertonic saline (3% NaCl) and subsequently normal saline (0.9% NaCl), a target of 10mEq in the first 24 hours can be reached, and thereafter, the goal is 8mEq/L per day.[9] Higher corrections increase the risk of pontine myelinolysis, which can lead to death.

In the case described, the identified rhabdomyolysis presented several possible etiologies. It is not always easy to distinguish the causes of rhabdomyolysis, especially in cases that include hyponatremia (or its correction), seizures or neuroleptics. However, the time profile, peak CPK elevation and clinical condition can facilitate the etiological diagnosis. With regard to generalized tonic-clonic seizures or the epileptic illness states (the condition presented by the patient at the initial phase), the CPK increase starts at 3 hours and has a maximum peak classically described between 18 and 24[10] and 36 and 40 hours,[11,12] with CPK increasing 8 to 12 times.[13] Higher values are reached in specific clinical situations, such as trauma, prolonged surgeries with associated ischemia,[14] and toxins and drugs,[15,16] in addition to rhabdomyolysis caused by ionic or toxic disorders.[17] In rhabdomyolysis due to hyponatremia, the peak is reached at 48 to 96 hours, very often with values between 18,000 - 98,000UI/L, and in rhabdomyolysis due to hyponatremia correction, the peak is further delayed and often reached

after 96 hours.[17] Rhabdomyolysis secondary to direct toxic effects of neuroleptics on myocytes may arise after a few administrations or up to two years after the beginning of medication administration.[18] In the case described, the patient had been medicated for over 5 years with clozapine without having ever presented rhabdomyolysis, which works against this hypothesis. Although it is not possible to exclude the important role of the seizures in this case, the late peak (between the 3rd and 4th day of hospitalization - 48 and 60 hours) with an extremely high amount of CPK (more than 200 times the upper limit of normality) highly suggested that hyponatremia was the main cause of rhabdomyolysis, possibly aggravated by its rapid correction.

Recurrence of rhabdomyolysis due to hyponatremia is very uncommon and has been described in the literature, to the best of the authors' knowledge, in only three articles. In the case described, the patient was admitted to the intensive care unit for the second time for severe hyponatremia secondary to PP, leading to rhabdomyolysis, and the patient was treated with neuroleptics (clozapine) in both hospitalizations. This is a classically described added risk factor, which is why neuroleptic treatment was suspended in the current hospitalization.

The treatments of rhabdomyolysis and hyponatremia by PP are in direct contrast; in fact, rhabdomyolysis must be treated with fluid therapy and eventual alkaline diuresis, while symptomatic hyponatremia requires, in most cases, fluid restriction and 3% sodium chloride. An interesting finding is the occurrence of a lower percentage of acute kidney damage in rhabdomyolysis due to hyponatremia secondary to PP than rhabdomyolysis due to other causes, leading some authors to propose the hypothesis of a possible "hypervolemia" protective effect.

CONCLUSION

This article stresses the importance of frequent monitoring of muscle enzymes in hyponatremia and its correction to quickly identify hyponatremia related rhabdomyolysis, provide appropriate treatment and avoid complications.

RESUMO

A rabdomiólise é caracterizada por destruição de tecido muscular esquelético, sendo as suas principais causas o trauma, os tóxicos e os distúrbios hidroeletrolíticos. Entre esses últimos, inclui-se a rabdomiólise induzida por hiponatremia, uma situação rara, que ocorre principalmente em doentes com polidipsia psicogênica. Esta acomete maioritariamente doentes com esquizofrenia, cursando com hiponatremia em quase 25% dos casos. É também nesse contexto que a rabdomiólise secundária a hiponatremia ocorre mais frequentemente. Neste artigo, descreveu-se o caso de um homem de 49 anos, com antecedentes de esquizofrenia, medicado com clozapina, trazido ao serviço de urgência por quadro de coma e convulsões. Foi objetivada hiponatremia hiposmolar grave, com edema cerebral em tomografia computorizada, sendo feito posteriormente o diagnóstico de hiponatremia secundária à polidipsia psicogênica. Foi iniciada terapêutica de correção de hiponatremia e internado em unidade de terapia intensiva. Feita correção de hiponatremia, contudo apresentou analiticamente marcada rabdomiólise, de agravamento crescente, com creatinofosfoquinase de 44.058UI/L no 3º dia de internação. Houve posterior redução progressiva com a terapêutica, sem ocorrência de lesão renal. Este caso alerta para a necessidade de monitorização dos marcadores de rabdomiólise na hiponatremia grave, ilustrando um quadro de rabdomiólise secundária à hiponatremia induzida por polidipsia psicogênica, situação a considerar em doentes sob terapêutica com neurolépticos.

Descritores: Polidipsia psicogênica; Intoxicação por água; Hiponatremia; Rabdomiólise; Clozapina; Mielinólise central da ponte; Relatos de casos

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