Mielinólise Pontina Central após Transplante Hepático: o Sódio É o Único Vilão? Relato de Caso*

Central Pontine Myelinolysis after Liver Transplantation: is Sodium the Only Villain? Case Report

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RESUMO

Morais BS, Carneiro FS, Araújo RM, Oliveira RB, Araújo GF - Mielinólise Pontina Central após Transplante Hepático: o Sódio É o Único Vilão? Relato de Caso.

JUSTIFICATIVA E OBJETIVOS*: A ocorrência de sintomas neurológicos em pacientes gravemente enfermos é comum e, muitas vezes, um desafio propedêutico. Descrita há cerca de 50 anos, a desmielinização dos neurônios da região pontina é uma alteração patológica associada a quadros neurológicos e psiquiátricos após transplante hepático. O objetivo deste relato foi apresentar a mielinólise pontina central diagnosticada no pós-operatório de transplante hepático e discutir sua fisiopatologia.*

RELATO DO CASO*: Paciente do sexo feminino, 29 anos, submetida a transplante hepático devido insuficiência hepática fulminante. No pós-operatório apresentou quadro neurológico característico de Síndrome Locked In e lesões compatíveis com mielinólise pontina central à ressonância nuclear magnética. A paciente não apresentou oscilações exageradas do sódio plasmático, íon frequentemente incriminado como agente causal, evoluindo com melhora significativa em algumas semanas.*

CONCLUSÕES*: A mielinólise pontina central tem etiologia multifatorial e atenção especial deve ser dada ao grupo de pacientes com maior risco, tais como aqueles submetidos a alterações abruptas da natremia, transplantados de fígado, etilistas crônicos e desnutridos. É importante reconhecer que as síndromes desmielinizantes osmósticas podem surgir em pacientes com níveis séricos de sódio baixo, normal ou elevado, evidenciando a contribuição de outros fatores desencadeantes.*

Unitermos: CIRURGIA, Transplante: fígado; COMPLICAÇÕES: mielinólise central da ponte.

SUMMARY

Morais BS, Carneiro FS, Araújo RM, Oliveira RB, Araújo GF – Central Pontine Myelinolysis after Liver Transplantation: Is Sodium the Only Villain? Case Report.

BACKGROUND AND OBJECTIVES: *Critically ill patients frequently develop neurologic symptoms, which frequently become a clinical challenge. Described approximately 50 years ago, pontine neuronal demyelination is a pathologic change associated with neurologic and psychiatric problems after liver transplantation. The objective of this report was to present a case of central pontine myelinolysis diagnosed after liver transplantation and to discuss its pathophysiology.*

CASE REPORT: *A 29 years old female patient underwent liver transplantation for fulminant hepatic failure. Postoperatively, she developed neurologic symptoms characteristic of the Locked In Syndrome and the MRI showed changes compatible with central pontine myelinolysis. The patient did not develop dramatic changes in sodium plasma levels, which is frequently incriminated as the causal agent, and improved considerably within a few weeks.*

CONCLUSIONS: *The etiology of central pontine myelinolysis is multifactorial, and special attention should be given to the group of patients at greater risk, such as those with sudden changes in the plasma levels of sodium, liver transplantation, chronic alcoholics, and malnourished. It is important to recognize that osmotic demyelination can develop in patients with low, normal, or elevated plasma levels of sodium, indicating the contribution of other trigger factors.*

Keywords: COMPLICATIONS: central pontine myelinolysis; SURGERY, Transplantation: liver.

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INTRODUCTION

Central pontine myelinolysis (CPM) is a rare and severe neurologic complication characterized by acute central pontine

neuronal demyelination along with severe and occasionally irreversible manifestations [1]. Although it is believed that fast correction of the plasma levels of sodium is the main cause [2], this report supports the presence of other factors related to the development of CPM.

CASE REPORT

This is a 29-year old female, 1.65 m, 58 kg, MELD 40, who underwent orthotopic liver transplantation from a dead donor by reason of a fulminant liver failure. The patient was transferred to the ICU intubated and on mechanical ventilation for 48 hours due to worsening of her neurologic condition and hemodynamic instability.

The patient was monitored with electrocardiogram, pulse oximeter, intra-arterial blood pressure, pulmonary artery catheter with continuous measurements of the cardiac output and mixed venous oxygen saturation. Thromboelastography, erythrogram, coagulogram, blood electrolytes, and arterial blood gases were done periodically during the surgery. She was maintained with balanced general anesthesia and continuous infusion of noradrenaline to maintain mean arterial pressure above 60 mmHg. Ringer's lactate, 5% albumin, and blood products were administered according to the results of serial exams. The patient evolved with hemodynamic stability and transplant viability. She was extubated 48 hours after the transplant, when she developed neurologic changes with quadriplegia and anarthria. She followed movements with horizontal eye movements, but she did not followed commands, and Babinski sign was positive bilaterally. After 24 hours, and magnetic ressoance imaging (MRI) of the head showed central pontine demyelination (Figure 1), confirming the diagnosis of CPM. The patient recovered in a few weeks, being discharged from the hospital with mild dysarthria and dysmetria. She presented good recovery of the muscle strength and was walking normally. Neurologic follow-up continued throughout the postoperative period.

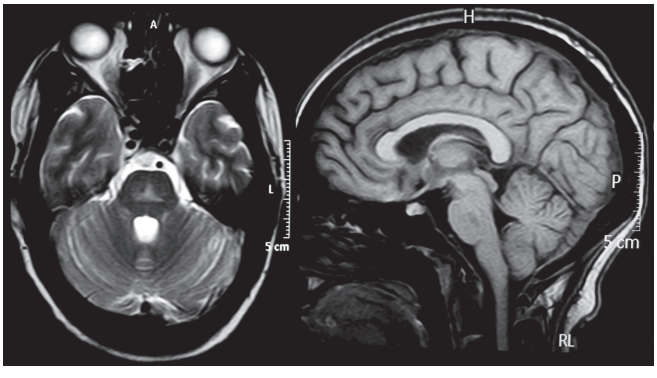

Figure 1 – MRI of the Head. Hyperdense image on T2 (axial) and hypodense in T1 (sagittal), triangular and without capture, at the geometric center of the pons. Bat-wing shape seen on axial view.

Table I – Perioperative Evolution of Sodium Serum Levels

Period	Sodium Levels ($mEq.L^{-1}$)
Day before surgery	138
Pre-anhepatic phase	133
Anhepatic phase	136
Neohepatic phase	138
D 1 postoperative	138
D 2 postoperative	142
D 3 postoperative	139

During the entire perioperative period, the patient did not develop sudden changes in the plasma levels of sodium, as shown in Table I.

DISCUSSION

Neurologic complications are frequent after liver transplantation, with an incidence between 8% and 47% [1,3-8]. Those complications, which include encephalopathies, cerebrovascular disorders, infections, immunosupressor-induced neurotoxicity, and peripheral nerve lesions can influence considerably survival and quality of life of patients [1].

Central pontine myelinolysis was first described in 1959 [9] and in 1978 reported after liver transplantation [10]. It has an incidence that ranges from 1.2% to 10% in liver transplant recipients, with a high mortality rate [8,11]. By definition, it is a non-inflammatory, frequently symmetrical central pontine demyelination. However, in 10% of the cases demyelination also affects extra-pontine areas, and the term osmotic demyelination syndrome (ODS) was proposed for such cases [2,12]. Osmotic demyelination syndromes are rapidly progressive and usually fatal. Central pontine myelinolysis is the most severe post-liver transplantation neurologic complication with a mortality rate higher than 50% in the first two weeks and 90% in six months. When patients survive most of them have neurologic deficits [13-15].

The etiology of osmotic demyelination is not well understood. Although rapid correction of serum sodium levels in hyponatremia have been implicated as the main cause, alcohol abuse and liver transplantation are strong independent risk factors [16]. Other risk factors such as adrenal insufficiency, mal nutrition, chronic renal failure and hemodialysis, sepsis, and neoplasms are being identified and it can develop in the absence of fluctuations in sodium serum levels [17,18].

Central pontine myelinolysis is a clinical syndrome characterized by quadriplegia and pseudobulbar paralysis, and it is frequently associated with loss of consciousness [19]. Progressive lethargy, quadriparesis, dysarthria, ophthalmoplegia, dysphasia, ataxia, and changes in reflexes develop two to seven days after the onset of the treatment of the underlying

disease or correction of hydrolelectrolytic imbalance [12]. As a consequence, a typical pseudocoma, also known as the locked-in syndrome (quadriplegia, anarthria, a capacity to follow the examiner with the eyes but not to follow command, bilateral Babinski sign) develops [19]. Although it can be reversible the patient usually dies after several days or weeks [19].

Radiological confirmation is necessary to exclude other diagnosis and to determine the exact extension of the demyelination. Computed tomography can underestimate the real extension of the disease. Magnetic resonance imaging plays a fundamental role in the determination of the number and extension of the lesions showing acute, symmetrical demyelinating lesions, with hypointensity in T_1 and hyperintensity in T_2 in the subacute phase due to microhemorrhages secondary to endothelial damage. Lesions are visible on MRI a few days or weeks after the onset of the symptoms [15].

Osmotic demyelinating syndromes are characterized by the dissolution of myelin shafts, sparing the axons. Surprisingly, inflammation is absent suggesting that cell death is by apoptosis [2]. Glial cells vulnerable on CPM play an important role in controlling the extracellular osmolality of the neurons they support using glucose as a metabolic substrate. During hyponatremia, in an attempt to reduce cellular edema, cells expel osmotically active particles such as taurine to reduce the amount of intracellular water [16]. In the reverse process, glial cells activate Na^+-K^+ATPase pumps to import electrolytes at the expense of a high metabolic cost using all glucose available [16]. This metabolic stress results in the release of glutamate and other excitatory modulators that cause the opening of calcium channels, which, along with the increased production of free radicals by the mitochondria, start the process of apoptosis [16]. In patients with liver failure, glial cells do not have adequate glucose or glycogen supply and, therefore, small derangements lead to energy depletion and cell death [2]. Organic osmolytes protect the brain from sudden changes in serum osmolality. Patients with liver disease have a deficiency of myo-inositol, an important osmolyte, becoming susceptible to CPM. Besides, those patients present negative nitrogen balance decreasing the amount of amino acids available to form essential organic osmolytes (taurine, creatine) [8]. Hypocalcemia represents an additional risk factor because it increases the action potential against which ATPAse has to work [16]. Animal models demonstrated that brain levels of phosphocreatine, creatine, myo-inositol, glycerophosphorylcholine, taurine, glutamate, and glutamine decrease 24 hours after the beginning of hyponatremia, but accumulate again slowly during corrective treatment independently of the rate of correction of sodium levels. This explains why normal sodium levels do not exclude the diagnosis of ODS [15].

Osmotic demyelinating syndromes have a predilection for the pons because in this structure neurons and glial cells are arranged in a strict linear configuration forcing cells to lose more osmolytes as an adaptive mechanism, since they cannot become edematous. This set up also limits glucose storage and transportation due to greater metabolic needs and worse perfusion, since it is done only by perforating branches of the basilar artery.

Specific treatments capable of interrupting or reverting the progress of ODS do not exist. Although isolated reports that corticosteroids, thyrotropin releasing hormones, and plasmapheresis [12,20] can be useful, those treatments need more support, since there are no randomized studies proving their efficacy. Several guidelines [11,15,16,21] on adequate sodium administration to hyponatremic patients have been published and one should avoid raising it above 12 $mEq.L^{-1}$ in the first 24 hours. A proper approach would be to administer 0.5 to 1.0 $mEq.L^{-1}.h^{-1}$ without exceeding sodium levels of 130 $mEq.L^{-1}$ in the first 48 hours. Although the patient presented here did not develop important hyponatremia, sodium changes were lower than 10 $mEq.L^{-1}$ in 24 hours throughout hospitalization. Recommendations on treating individuals with normal serum levels are lacking.

Currently, treatment consists basically on preventing osmotic demyelination. The predominating view (based mainly on case reports) is that individuals with one or more risk factors (severe systemic disease, alcoholism, liver transplantation, malnutrition) should undergo frequent neurological exams, along with imaging exams. The diagnosis of osmotic demyelinating syndrome should be considered in patients who do not recover as expected from a severe disease or in patients who develop new psychiatric symptoms after being severely ill.

Avoiding metabolic stress with administration of thiamine and if necessary slow correction of the serum levels of sodium are recommended in high-risk patients. Strict control of glucose levels, preoperative dialysis in patients with renal failure, and correction of electrolytes levels and other exacerbating factors are recommended [2].

Central pontine myelinolysis has a multifactorial etiology, partly related to neuronal and glial osmotic stress, and partly to deficiencies on glial/neuronal energy supply and use culminating in the process of cellular apoptosis [16]. Slow correction of chronic hyponatremia is fundamental for the prevention of this disorder; however, special attention should be given to the group of patients with higher risk factors like liver transplantations, alcoholism, and mal nutrition. It is important to recognize that ODS can affect patients with low, normal, or elevated serum levels of sodium.

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RESUMEN

Morais BS, Carneiro FS, Araújo RM, Oliveira RB, Araújo GF - Mielinólisis Pontina Central después del Transplante Hepático: ¿Es el sodio el único villano? Relato de Caso.

***JUSTIFICATIVA Y OBJETIVOS**: El aparecimiento de síntomas neurológicos en pacientes gravemente enfermos es común y muchas veces, es un reto propedéutico. Descrita hace cerca de 50 años, la desmielinización de las neuronas de la región pontina, es una alteración patológica asociada a cuadros neurológicos y psiquiátricos posteriores al transplante hepático. El objetivo de este relato, fue presentar la mielinólisis pontina central diagnosticada en el postoperatorio de transplante hepático y discutir su fisiopatología.*

***RELATO DEL CASO**: Paciente del sexo femenino, 29 años, sometida a transplante hepático debido a un fracaso hepático fulminante. En el postoperatorio, presentó un cuadro neurológico característico de Síndrome Locked In y lesiones compatibles con la mielinólisis pontina central a la resonancia nuclear magnética. La paciente no presentó oscilaciones exageradas del sodio plasmático, que es el ión frecuentemente acusado de ser el agente causador, y evolucionó con una mejoría significativa en algunas semanas.*

***CONCLUSIONES**: La mielinólisis pontina central tiene una etiología multifactorial, y una atención especial debe dársele al grupo de pacientes con mayor riesgo, tales como los sometidos a alteraciones abruptas de la natremia, transplantados de hígado, etilistas crónicos y desnutridos. Es importante reconocer, que los síndromes de desmielinización osmósticos pueden surgir en pacientes con niveles séricos de sodio bajo, normal o elevado, evidenciando la contribución de otros factores desencadenantes.*