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Central pontine myelinosis after treatment of hyponatremia with tolvaptan: a case report

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Abstract

Background: Central pontine myelinosis (CPM) is a demyelinating disorder affecting the pontine white matter. Predisposing conditions include alcoholism, liver disease, malnutrition, and hyponatremia. The purpose of this case report is to highlight the importance of early identification of CPM in patients with hyponatremia undergoing rapid sodium correction.

Case: A 42-year-old male with cirrhosis and refractory ascites with malnutrition was admitted with chronic hypervolemic hyponatremia. He developed acute hypernatremia and osmotic demyelination syndrome due to administration of tolvaptan. We raise the question of optimal dosing of vasopressin antagonists by frequent daily evaluation of sodium levels.

Conclusion: Early diagnosis based on clinical symptoms and timely management decreases morbidity and mortality in patients with liver diseases exhibiting chronic hyponatremia.

Keywords: Central pontine myelinolysis, Hyponatremia correction, Tolvaptan-induced complications

INTRODUCTION

Central pontine myelinosis, a part of osmotic demyelination syndrome (ODS) is a symmetric, non-inflammatory demyelinating disorder. Chronic alcoholics as well as malnourished patients are more susceptible to metabolic deficiencies thereby predisposing them to CPM which eventually leads to pro-apoptosis of glial cells and damage to the pontine white matter tracts.[1,2]

Short-term management with tolvaptan, a competitive antagonist at V2 receptors, antagonist improves dilutional hyponatremia by promoting solute free water clearance.[3] Studies indicate that 25% of patients with severe hyponatremia show neurological symptoms after rapid sodium correction.[4] Our patient presented with cirrhosis, refractory ascites and hyponatremia in a severely malnourished state. After treatment with tolvaptan he developed neurological changes post 12 hours of sodium correction. He was diagnosed with CPM and successfully managed. The purpose of this case report is to highlight the increased tendency of CPM in patients with malnutrition, alcoholic liver disease and those undergoing rapid correction of hyponatremia with tolvaptan.

CASE REPORT

A 42-year-old male patient presented with abdominal distension, discomfort, and yellowish discoloration of eyes since the last 3-4 months. Previously, the patient was treated at a local hospital where therapeutic paracentesis was done.

On admission, he was diagnosed with decompensated cirrhosis and refractory ascites. Laboratory investigations revealed a haemoglobin of 6.2 g/dl, platelet count of 82000 per micro-litre, total leucocyte count of 8400 cells/mm^3, serum sodium levels of 125 mEq/L, serum potassium -4 mEq/L, serum creatinine -0.84 mg/dl, serum bilirubin (total) level -2.5 mg/dl, SGOT- 127 U/L, SGPT -115 U/L, ALP-- 100 U/L, INR 2. In view of hyponatremia (Serum Sodium levels of 125 mEq/L), Tablet Tolvaptan (15 mg dose) was started. After 12 hours, the patient became drowsy, disoriented and unresponsive to verbal commands. Serum sodium (Na) levels were found to be 142 mEq/L so diagnosis of CPM was made and Tolvaptan was immediately stopped. Rest of the treatment course remained unchanged. As the patient's serum

sodium level remained elevated without strict fluid restriction or any other causative drug/factor, we hypothesized that the patient could be highly sensitive to the drug, Tolvaptan.
He was managed with IV fluid dextrose 5% at 30 ml/hour and plain water via nasogastric tube at 75 ml/hour along with other supportive measures. Paracentesis was repeated again the next day. GCS improved on the second day (Na- 130 mEq/L). The patient was fully conscious and oriented when serum sodium levels were 129 mEq/L by the third day. One unit PRC and 2 FFP were transfused on account of severe anaemia (Hb- 6.2 mg/dl). Currently, patient is undergoing follow-up treatment at our hospital.

DISCUSSION

Adams and colleagues were the first to originally report central pontine myelinolysis (CPM) in 1959.[5] In chronic alcoholics, preventive cerebral mechanisms are impaired due to thiamine deficiency and prolonged malnutrition. It causes the oligodendrocytes in the myelin sheaths to vacuolate and undergo myelinolysis. Moreover, they are incapable of synthesizing organic osmoles to maintain the osmotic gradient and Na+/K + ATPase pump activity.[2] If an alcohol addict or malnourished patient develops confusion, quadriplegia, pseudobulbar palsy, or deranged consciousness over a period of several days, CPM becomes one of the strong differentials.
Clinical features of the disease usually appear 1 to 14 days after electrolyte correction. Signs and symptoms reflect injury to upper motor neurons and present in a biphasic manner. Acute encephalopathy and convulsions resolve after restoration of normal sodium levels, followed by clinical deterioration 3-5 days later. Other features include dysphagia, dysarthria, spastic quadriparesis, pseudobulbar paralysis, ataxia, lethargy, tremors, dizziness, catatonia, and in severe cases, locked-in-syndrome and coma[6,7]
Patients with advanced cirrhosis experience dilutional hyponatremia as a result of renal failure preventing the excretion of solute free water. A key contributing factor is the non-osmotic hypersecretion of arginine vasopressin or antidiuretic hormone, from the neurohypophysis along with circulatory dysfunction[8].
Patients with altered sensorium, superadded infections, malnutrition or those with poor oral intake are more likely to suffer hypernatremia.[9,10] Rapid correction of Hyponatremia (at a rate more than 0.5-1.0 mEq /L per hour) is the most common cause of central pontine myelinosis. [11] Other risk factors are included in Table 1. [12]
Tolvaptan, an antagonist drug on V2 receptor on the basolateral membrane of the collecting ducts, obstructs the expression of aquaporin-2 on the apical membrane and hence the production of intracellular cAMP. As a result, there is a noticeable dilution of the excreted urine (aquaresis), which hinders water reabsorption.[13]
Literature indicates that treatment with tolvaptan is a safe and efficient option for patients with refractory ascites. It raises serum sodium concentration, lowers the need for diuretic dosages, and reduces body weight without appreciably raising the risk of major side effects.[14]
Osmotic demyelination can result from tolvaptan's overly rapid correction of hyponatremia (>12 mEq/L/24 hours). Patients with hyponatremia started on AVP-receptor antagonists shouldn't restrict their fluid intake, and monitoring of serum sodium concentration should occur every 6–8 hours to prevent rapid sodium level correction.[15] Currently, reinduction of hyponatremia using hypotonic fluids, such as 5% dextrose water and half normal saline mixed with desmopressin, is the recommended course of treatment for patients with ODS due to hypernatremia.[13] Kinugawa et al in his study reiterated independent factors influencing the development of hypernatremia (Serum sodium levels (≥142 mEq/L), serum potassium levels <3.8 mEq/L and tolvaptan dose of 15mg/day) in patients with heart failure.[16]

CONCLUSION

High sensitivity to TLV coupled with chronically low sodium levels and malnutrition seemed to be the incriminating factors for CPM in our patient. This hypothesis requires further large studies for verification. Effectively using TLV while avoiding its serious side effects remains an urgent problem that needs to be solved. In clinical settings, when treating hyponatremia, TLV can be initiated in the lowest possible dose (7.5 mg daily). Serum electrolytes should be monitored frequently (every 6-8 hours) while keeping a close watch on the patient's symptoms.

TABLE 1 – RISK FACTORS FOR CPM

RISK FACTORS FOR CENTRAL PONTINE MYELINOSIS

Malnutrition Alcoholic liver disease Chronic liver disease Hyperemesis gravidarum Severe hyponatremia (<120 mEq/l for 48 hours) Liberal IV fluid therapy with hypertonic saline

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