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CASE REPORT

# Terlipressin-induced hyponatremic encephalopathy in a noncirrhotic patient

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**Abstract** Terlipressin, an analogue of vasopressin, is frequently used for the management of esophageal varices bleeding and hepatorenal syndrome. Terlipressin therapy in portal hypertensive patients is frequently associated with hyponatremia, but is rarely accompanied with serious neurological manifestations. A 39-year-old female with pancreatic neuroendocrine tumor, liver metastasis, main portal vein thrombosis, and a history of esophageal varices presented to the emergency room because of hematemesis. Terlipressin was given with a loading dose of 2 mg followed by 1 mg every 6 hours. After a total of 6 mg terlipressin injection, she suffered from acute delirium. Pertinent examinations showed there was no gross brain lesion by computed tomography, whereas her serum sodium level dropped from baseline (136 mmol/L) to 116 mmol/L with a serum osmolality of 256 mOsm/kg. At that time, urine sodium and urine osmolality were 142 mmol/L and 488 mOsm/kg, respectively. Under the tentative diagnosis of terlipressin-induced hyponatremic encephalopathy, terlipressin was withheld and hypertonic saline infusion was given. Within 12 hours, her serum sodium level recovered to 130 mmol/L and she gradually regained her cognitive functions. Although symptomatic

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hyponatremic encephalopathy is a rare complication of terlipressin treatment, close monitoring of serum electrolyte level is warranted in patients receiving terlipressin.


## Introduction

Terlipressin, an analogue of vasopressin with powerful agonistic activity on arginine vasopressin type 1 receptor (AVPR1), can cause splanchnic vasoconstriction to result in a significant (around 30%) decrease of hepatic blood flow and portal venous flow in portal hypertensive patients. It is an efficient treatment for variceal bleeding and hepatorenal syndrome, two major serious complications, in patients with cirrhosis [1,2]. Terlipressin can also act on arginine vasopressin type 2 receptor (AVPR2) to enhance the water permeability of renal tubules by 8—10-fold to cause antidiuresis [3], leading to water retention and potentially hyponatremia.

Hyponatremia is a frequently encountered electrolyte disorder in advanced cirrhotic patients secondary to the nonosmotic release of antidiuretic hormone. Therefore, terlipressin-induced asymptomatic hyponatremia can be easily ignored in cirrhotic patients during terlipressin therapy. In one recent prospective study, Solà et al. [4] showed that patients who developed terlipressin-induced hyponatremia had less advanced liver disease than those who did not develop hyponatremia. In addition, genetic defect at AVPR2, which augments the vasopressin function and results in excessive water retention [5], is suggested as a precipitating factor for terlipressin-induced hyponatremia.

We report the occurrence of terlipressin-induced hyponatremic encephalopathy in a noncirrhotic patient. The observation highlights the importance of carefully monitoring plasma sodium level in patients receiving terlipressin therapy.

## Case report

A 39-year-old female with pancreatic neuroendocrine tumor with liver metastasis and main portal vein thrombosis presented to our emergency department with hematemesis and black stool over the past 2 days. She had no history of hepatitis B or C infection, and previous study showed no radiological evidence of cirrhosis. However, esophageal varices and gastric varices were noted on previous esophagogastroduodenoscopy (EGD) examination. On arrival, physical examination revealed the following details: blood pressure 105/74 mmHg, heart rate 86 beats/min, respiratory rate 16 breaths/min, and body temperature 36.3°C. Pertinent laboratory tests showed positive fecal occult blood test, hemoglobin 7.6 g/dL, white blood cell count 10,800/μL, platelet count 104,000/μL, prothrombin time 11.3 seconds (international normalized ratio: 1.11), aspartate aminotransferase 32 IU/L, alanine aminotransferase 36 IU/L, total bilirubin 0.5 mg/dL, albumin 4.04 g/dL, serum creatinine 0.52 mg/dL, blood urea nitrogen 10 mg/dL, serum sodium 136 mmol/L, and serum potassium 3.7 mmol/L. Under the tentative diagnosis of variceal bleeding, terlipressin was initiated with a bolus loading dose of 2 mg, followed by 1 mg every 6 hours after admission. Thirty-six hours later, the patient appeared in an acute delirium state with cognitive deficits and severe disorganization of behavior. An emergent computed tomography scan of the brain revealed neither apparent intracranial lesion nor brain edema. However, blood biochemistry examination showed hypoosmotic hyponatremia (serum sodium 116 mmol/L, serum osmolality 256 mOsm/kg) with natriuresis and antidiuresis (urine sodium 142 mmol/L, urine osmolality 488 mOsm/kg), a profile resembling syndrome of inappropriate antidiuretic hormone (SIADH), and hyperammonemia (126 μg/dL). This patient did not have ascites, and no diuretic was used prior to or during the hyponatremic period. Under the diagnosis of terlipressin-induced hyponatremic encephalopathy, terlipressin was immediately withheld and hypertonic saline infusion was given.

Within 12 hours after terlipressin withdrawal and hypertonic saline infusion, the patient gradually recovered from the delirium state and serum sodium level was also found to increase dramatically to 130 mmol/L. Hypertonic saline infusion was stopped when the patient's consciousness had improved. Her serum sodium further improved to 140 mmol/L with full recovery of consciousness within the next 24 hours (Fig. 1). Brain magnetic resonance imaging with gadolinium diethylenetriaminepentaacetic acid enhancement showed no evidence of acute infarction, hemorrhage, or space-

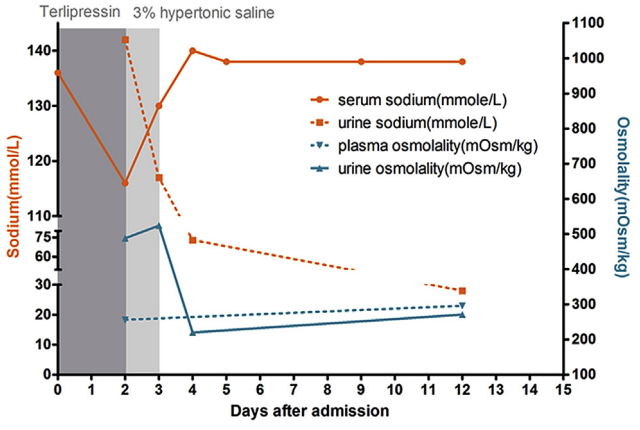


**Figure 1.** Clinical course with series serum and urine electrolyte changes in the patient reveals a drastic increase of natriuresis with a drop in serum sodium level after terlipressin administration, and diminishing of urine sodium excretion with prompt recovery of serum sodium level after withholding terlipressin administration.

occupying lesions on images. No central pontine myelinolysis, as a complication of acute change in serum sodium level in chronic hyponatremia, was detected by brain magnetic resonance imaging, even though the serum sodium level had once increased to more than 10 mmol/L within 12 hours. The patient underwent esophagogastroduodenoscopy 3 days after recovery, and esophageal and gastric varices were found. Varices were suspected to be the bleeder for this upper gastrointestinal bleeding episode. The patient's general condition was stable after recovery from hyponatremia. No apparent sequelae or complications were found prior to her discharge and during follow-up at our outpatient clinic for the consecutive 24 weeks. To investigate the mechanism of such drastic antidiuretic and natriuretic responses to terlipressin therapy in this patient, a genetic testing for AVPR2 mutation was performed after a signed informed consent was given. In brief, we collected her peripheral blood mononuclear cells, extracted the genomic DNA, and performed polymerase chain reaction and sequencing of the AVPR2 coding region. However, we did not find any mutation, variant, or single-nucleotide polymorphism in this patient (Fig. 2).

## Discussion

The arginine vasopressin analogue, terlipressin, is the treatment of choice for variceal bleeding. The mechanism is to reduce portal venous inflow by mediating splanchnic vasoconstriction through acting on the AVPR1 receptor. However, terlipressin may concurrently activate the AVPR2 receptor, which enhances aquaporin-2 incorporating to the luminal membrane in the renal collecting duct. Therefore, free-water clearance and serum sodium level are decreased [3], and hypervolemic hyponatremia and/or water intoxication may happen as a result.

Many studies have shown that the development of hyponatremia is not uncommon in patients treated with terlipressin. A double-blind controlled trial by Feu et al. [6] reported that hyponatremia occurred in 6% of patients treated with terlipressin; and in another multicenter controlled trial, which enrolled 106 cirrhotic patients treated with terlipressin, there were four cases with hyponatremia [7]. Previous studies found rapid recovery from hyponatremia after terlipressin withdrawal, and this phenomenon strongly suggested that terlipressin could be the cause of hyponatremia during the treatment for variceal bleeding [4,8]. In this study case, the clinical and laboratory evidence strongly suggested that terlipressin was the cause of hyponatremia. It could be further confirmed by rechallenge with terlipressin, but for safety considerations, this is not allowed.

Terlipressin-induced hyponatremia is theoretically caused by activating the renal AVPR2 receptor, which increases reabsorption of water from the renal collecting duct and leads to a decrease in plasma osmolality and serum sodium [9]. In our case, we found both antidiuretic and

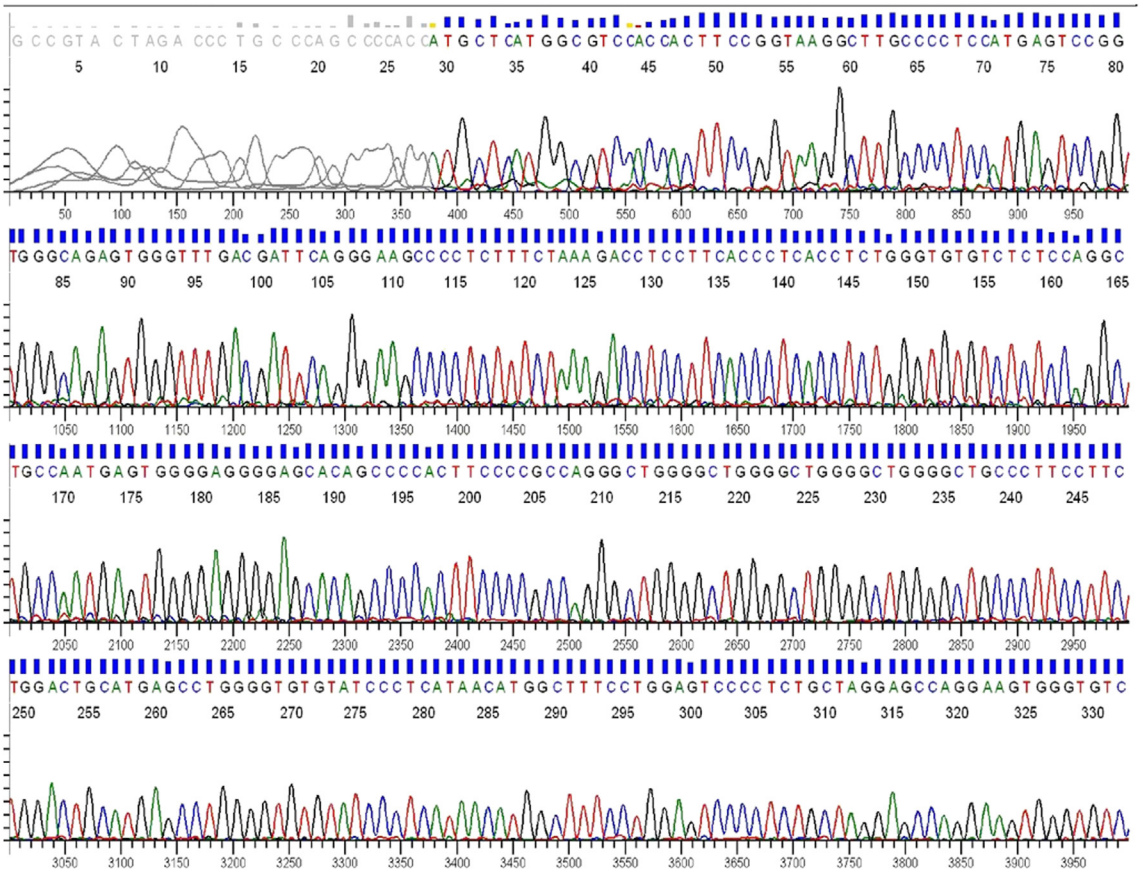

**Figure 2.** Genomic DNA sequencing shows no variant or single nucleotide polymorphism in the patient's arginine vasopressin type 2 receptor coding sequence.

natriuretic effects during terlipressin treatment. When this patient suffered from delirium, initial laboratory tests showed both natriuresis and antidiuresis, including hypoosmotic hyponatremia (plasma osmolality, 256 mOsm/kg) with relative high urine osmolality (urine osmolality, 488 mOsm/kg), relative high urine sodium (142 mmol/L), and fractional excretion of sodium (FeNa, 1.8%). Withdrawal of terlipressin resulted in immediate recovery of serum sodium, urine osmolality, and urine sodium (Fig. 1). These findings strongly suggested the association between hyponatremia and terlipressin in this case. In handling this patient, the unanticipated rapid recovery in serum sodium is attributed to the dual effect of hypertonic saline and withdrawal of terlipressin. Fortunately, central pontine myelinolysis did not occur in this patient, and even the speed of correction was more rapid than the usual recommendation. According to this experience, more frequent monitoring of serum sodium level during the treatment of terlipressin-induced hyponatremia still needs to be emphasized.

Solà et al. [4] reported that the reduction in serum sodium was related to baseline serum sodium and Model for End-Stage Liver Disease (MELD) score. Patients with low MELD scores and normal or near-normal baseline serum sodium concentration had the highest risk [4]. Our patient initially had a normal serum sodium level (136 mmol/L) and a low MELD score (6 points), which was compatible with the result of Solà et al. [4]. Other risk groups in developing hyponatremic encephalopathy are patients who suffer a hypoxic event and premenopausal women [10]. More importantly, physicians should be aware of the early sign of hyponatremic encephalopathy (such as headache, nausea, and vomiting) in susceptible patient groups during terlipressin treatment, even if their serum sodium level is greater than 130 mmol/L at that time [11].

Cirrhotic patients are prone to suffer hyponatremia. The plasma level of vasopressin is higher in cirrhotic patients than in healthy individuals, and the vasopressin level increases in parallel with the stage of cirrhosis [12]. In healthy individuals, the escape from vasopressin-induced antidiuresis can be observed by the downregulation of the kidney aquaporin-2 channel and AVPR2 despite high plasma AVP levels [13]. Therefore, mutations of AVPR2 may induce hyponatremia, which has been reported as nephrogenic syndrome of inappropriate antidiuresis (NSIAD) [14—16]. NSIAD has the same clinical picture as SIADH except for undetectable AVP levels. We performed polymerase chain reaction and sequencing of the *AVPR2* gene coding region in an attempt to demonstrate a possible mutation of AVPR2 to explain the exaggerated result of water retention effect of terlipressin, but no variant or single nucleotide polymorphism was found in our case.

In summary, terlipressin-induced hyponatremia is easily ignored and hyponatremic encephalopathy is life-threatening. This may happen in the absence of AVPR2 mutation. Serum sodium level during terlipressin treatment should be frequently monitored, even in noncirrhotic patients.

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