

# Edematous Hyponatremia Treated with Tolvaptan in a Patient with Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) patients rarely present with either syndrome of inappropriate antidiuretic hormone secretion or generalized edema. Tolvaptan is a selective vasopressin V2 receptor antagonist that produces effective aquaresis, and its use in ALS patients has not been previously reported. A 50-year-old male ALS patient was admitted because of both generalized edema and dilutional hyponatremia. These manifestations were refractory to conventional diuretics and fluid therapy, but a very brisk diuresis was induced by tolvaptan administration. Edema and hyponatremia were also improved, and the patient was able to be discharged without tolvaptan. In this case report, we postulate how edema and dilutional hyponatremia developed in the patient, and discuss the mechanism of tolvaptan in treating hypervolemic hyponatremia. Further experience is necessary to evaluate the usefulness of tolvaptan in patients with neurological disorders.

**Key Words:** Amyotrophic lateral sclerosis, Diuresis, Edema, Hyponatremia, Tolvaptan

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## Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive paralyzing disease, and the mainstay of ALS management is symptomatic treatment and palliative care<sup>1)</sup>. Generalized edema is an unusual manifestation of ALS; however, dependent edema can develop in the limbs of ALS patients as a result of immobility and reduced muscle pumping activity<sup>2)</sup>. In addition, dependent edema may be due in part to the effects of the autonomic nervous system, as sympathetic hyperactivity has been demonstrated in patients with ALS<sup>3)</sup>. Specifically, sympathetic hyperactivity may stimulate the renin-angiotensin-aldosterone system (RAAS), leading to renal sodium retention.

Patients with ALS may also develop renal water retention. Syndrome of inappropriate antidiuretic hormone se-

cretion (SIADH) is the prototype cause of euvolemic hyponatremia, but very rarely accompanies ALS<sup>4)</sup>. However, central nervous system disorders may have the ability to stimulate the release of antidiuretic hormone from the neurohypophysis. Furthermore, severe restrictive respiratory failure requiring mechanical ventilation may cause hypersecretion of antidiuretic hormone in ALS<sup>5)</sup>.

Tolvaptan is a selective vasopressin V2 receptor antagonist (V2RA) that is used to correct dilutional hyponatremia by inducing effective aquaresis. Whereas the use of tolvaptan in patients with congestive heart failure and liver cirrhosis is well known, it is seldom used in patients with other edematous disorders<sup>6)</sup>. Here, we report the case of a 50-year-old man diagnosed with ALS and whose hypervolemic hyponatremia was immediately relieved by tolvaptan administration.

## Case Report

A 50-year-old male visited our emergency room (ER) because of generalized edema. He appeared remarkably swollen during the past week, with associated reduced urine output. There was no history of body weight change as the patient was bed-ridden. Specifically, he previously had no edematous disorders including congestive heart failure, nephrotic syndrome, liver cirrhosis, and hypothyroidism.

Fourteen years earlier, he was diagnosed with ALS when he was admitted due to quadriplegia. Motor neuron disease was confirmed by electromyography and muscle biopsy. Involvement of the autonomic nervous system in the disease process was noted, and tracheostomy and feeding gastrostomy were in place. In addition, the patient was being supported by a home ventilator.

On physical examination, vital signs were stable: blood pressure 144/89 mmHg, pulse rate 90/min, respiratory rate 22/min, and body temperature 35.0°C. Peripheral edema was remarkable at the neck, hands, and feet. Initial laboratory findings were as follows: hemoglobin 10.8 g/dL, white blood cells 17,300/mm<sup>3</sup>, platelet 199,000/mm<sup>3</sup>, blood urea nitrogen 20.8 mg/dL, and serum creatinine 0.25 mg/dL. Urinalysis showed a specific gravity of 1.015, albumin 1+, 5-9 RBCs per HPF, and many white blood cells. Serum



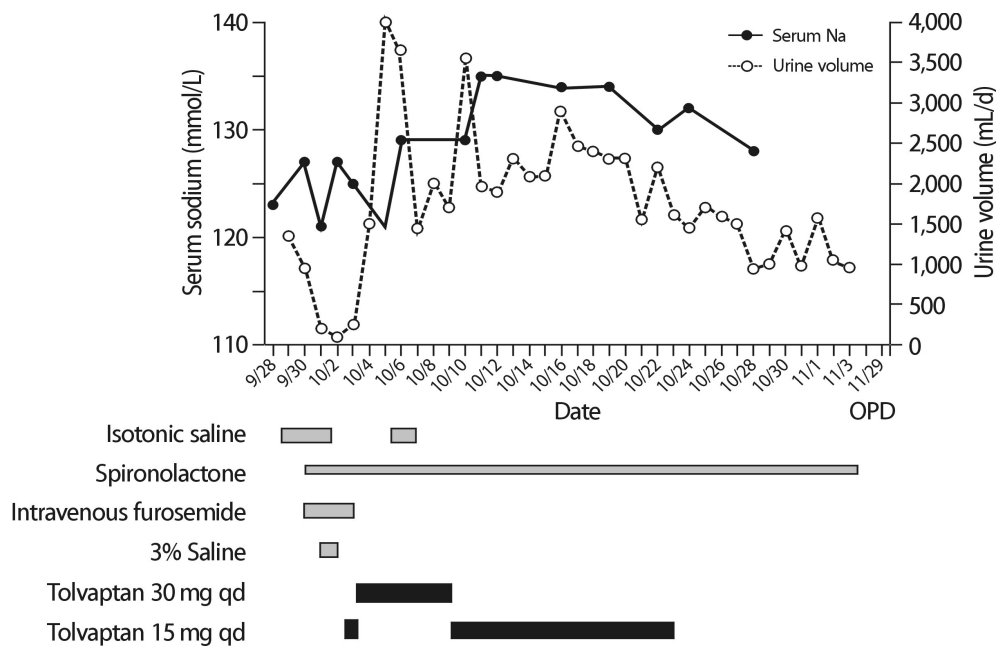
**Fig. 1.** Chest X-ray findings. Partial atelectasis in the lower lobes of both lungs is shown.

sodium was 123 mmol/L, potassium 3.7 mmol/L, chloride 87 mmol/L, and total CO<sub>2</sub> 20.7 mmol/L. Urine sodium was 16 mmol/L, potassium 29 mmol/L, chloride 17 mmol/L, creatinine 6.8 mg/dL, and urea nitrogen 425 mg/dL. Serum and urine osmolality were 268 and 405 mOsm/kg H<sub>2</sub>O, respectively. Chest X-ray showed partial atelectasis of both lower lung lobes (Fig. 1).

In the ER, isotonic saline was infused to treat hyponatremia at a rate of 40 mL/h. Follow-up tests done at admission showed serum sodium 127 mmol/L, urine osmolality 223 mOsm/kg H<sub>2</sub>O, urine sodium 12 mmol/L, urine potassium 8 mmol/L, urine chloride 7 mmol/L, and urine creatinine 2.5 mg/dL. Serum uric acid was 7.3 mg/dL, albumin was 2.8 g/dL, brain natriuretic peptide (BNP) was 93 pg/mL, and C-reactive protein was 33.7 mg/dL. Gram-negative bacilli and Gram-positive cocci were present in the urine, but they were not identified due to low abundance. Thyroid hormones T3 and free T4 were normal, serum adrenocorticotropic hormone (ACTH) was 63 pg/mL, and the peak level of serum cortisol in response to rapid ACTH stimulation was 48.6 µg/dL.

Figure 2 shows the changes in serum sodium concentration and urine volume during the admission. Soon after admission, serum sodium dropped to 121 mmol/L despite isotonic saline infusion. Notably, true oliguria (200 mL/d) was encountered in association with increasing edema. We had to use intravenous furosemide, and a small volume (500 mL) of 3% saline was given once. The patient's oliguria persisted for 3 days, at which time generalized aggravation of the patient's edema was noted, and hyponatremia was not improved by diuretic therapy (Fig. 2). Intravenous furosemide was gradually increased (10 to 60mg) and was finally administered by continuous infusion (240 mg/d).

Furosemide was switched into tolvaptan to treat hypervolemic hyponatremia. The initial dose of tolvaptan 15 mg induced an increase in urine output (1,500 mL/d), while serum sodium remained the same (121 mmol/L). On the following day, polyuria was induced by tolvaptan 30 mg in association with an improvement in hyponatremia (Fig. 2). Urine sodium increased from 12 to 56 mmol/L, and urine osmolality decreased from 223 to 147 mOsm/kg H<sub>2</sub>O. When the serum sodium approached 130 mmol/



**Fig. 2.** Clinical course during the admission. Changes in serum sodium concentration and daily urine volume in response to intravenous fluids, diuretics, and tolvaptan are presented.

L, the daily dose of tolvaptan was reduced to 15 mg. Over the next 2 weeks, the patient's edematous state, urine volume, and hyponatremia were stabilized with continued tolvaptan therapy. Following discharge, having been off tolvaptan for approximately one month, the patient's serum sodium concentration was 132 mmol/L.

## Discussion

We present an unusual case of ALS, in which tolvaptan was used to successfully ameliorate a patient's hypervolemic hyponatremia. The patient had generalized edema in the absence of congestive heart failure, nephrotic syndrome, liver cirrhosis, or hypothyroidism. Drug-induced edema was also excluded. His reduced urine volume and NaCl were compatible with renal sodium avidity likely due to neurohumoral activation. We postulated that in his case, sympathetic over-activity due to ALS may have led to an increase in sodium reabsorption in the proximal tubule of the kidney<sup>7</sup>.

Prior to admission, the patient did not have free access to water intake because he was dependent on a feeding gastrostomy. Despite not having free access to water, his serum sodium concentration was remarkably low. In addition,

because he was overtly edematous, his hyponatremia was dilutional and hypervolemic. His urine osmolality was  $>200$  mOsm/kg H<sub>2</sub>O, suggestive of impaired diuresis or inappropriate antidiuresis. Thus, we suspect that his vasopressin level was inappropriately increased.

SIADH presenting with hyponatremia is rarely associated with ALS<sup>4</sup>. Yoshida et al., proposed that ventilatory failure secondary to the atrophy of respiratory muscle might cause SIADH<sup>5</sup>. Our patient was also in a state of respiratory failure, requiring long-term mechanical ventilation. The association between respiratory failure and SIADH has been investigated by previous studies. Elevated plasma vasopressin levels have been reported in patients with hypoxemia and hypercapnic acidosis<sup>8</sup>. Furthermore, according to Sladen et al., intermittent positive pressure ventilation can cause an increase in intrathoracic pressure, impeding the filling of the left atrium, and thus stimulating vasopressin release<sup>9</sup>. Lastly, ALS can be associated with pain, which is an important non-osmotic stimulus of vasopressin release.

Tolvaptan is effective for correcting hyponatremia in patients with SIADH. On the other hand, tolvaptan has inconsistent effects in patients with edema due to causes other than congestive heart failure and liver cirrhosis<sup>10</sup>.

Generalized edema in patients with ALS has yet to be characterized, and there is no consensus on effective treatments. In our patient, tolvaptan successfully relieved both the patient's edema and hyponatremia. We attributed this result to the ability of tolvaptan to produce natriuresis as well as aquaresis<sup>6</sup>.

It is important to recognize that vasopressin acts on collecting ducts to stimulate water and sodium absorption through the aquaporin-2 water channel and epithelial sodium channel (ENaC), respectively<sup>11</sup>. Specifically, natriuresis is induced by V2RA administration in normal conscious rats<sup>12</sup>, while the expression of ENaC subunits is suppressed by tolvaptan administration in rats<sup>13</sup>.

Neurohumoral activation can be relieved by tolvaptan but not conventional diuretics. In contrast with furosemide, tolvaptan decreases catecholamines and BNP without RAAS enhancement in patients with acute heart failure<sup>14</sup>. These attributes of tolvaptan led to a very brisk increase in urine output in our patient with subsequent improvement of edema and hyponatremia (Fig. 2).

In summary, ALS patients rarely present with either SIADH or generalized edema. Neurologic patients complicated by dilutional hyponatremia and/or neurogenic edema may benefit from use of a V2RA. We report the case of a patient with ALS who presented with both generalized edema and dilutional hyponatremia that promptly improved with tolvaptan treatment. Further experiences will be necessary to evaluate the use of tolvaptan in patients with neurological disorders.

### Conflict of interest

The authors declare no relevant financial interests.

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