

## The first case of levetiracetam-induced and tolvaptan-resistant hyponatremia

### Levetirasetama bağlı tolvaptana dirençli hiponatremili ilk olgu

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**Summary**– Hyponatremia is frequently seen in heart failure patients and has a high mortality rate. If not treated adequately, acute and chronic hyponatremia may worsen the prognosis of heart failure. Despite its high incidence in heart failure patients, other underlying conditions that possibly lead to the incidence of hyponatremia may be underestimated, thus making its treatment more difficult. In this case study, we describe a rare case of levetiracetam-induced and tolvaptan-resistant hyponatremia.

Hyponatremia is frequently seen in congestive heart failure (CHF) due to increased volume retention, and is an independent predictor of mortality in patients with CHF. Additionally, diuretics, such as furosemide, may cause or worsen hyponatremia. Heart failure (HF) patients are generally older and have comorbidities like neurological problems, chronic kidney disease and arrhythmia. Multidrug use may easily increase side effects by causing electrolyte imbalance. Therefore, close follow-up of metabolic parameters in these patients is mandatory. Although the literature contains many drug-related hyponatremia cases, very few have been related with the use of levetiracetam. Levetiracetam is frequently prescribed for elderly patients who have neurological comorbidities and heart failure. In the current study, we describe a patient using levetiracetam for epilepsy for two years with a low level of serum sodium (Na) at hospitalization that could not be restored with oral tolvaptan treatment. Interestingly, the serum Na levels returned to normal after discontinuing levetiracetam. Although levetiracetam-induced hyponatremia is rarely reported, this side effect should be kept in mind, especially in

**Özet**– Hiponatremi kalp yetersizliği bulunan hastalarda sık görülen ve mortalitesi yüksek bir durumdur. Akut ve kronik hiponatremi tedavi edilmediği takdirde kalp yetersizliğinin prognozunu da kötüleştirmektedir. Kalp yetersizliği bulunan hastalarda sık görülmesi geri döndürülebilir başka nedenlerin kolaylıkla gözden kaçmasına ve hiponatreminin tedavisinin zorlaşmasına yol açar. Bu yazıda, literatürde oldukça nadir görülen, levetirasetama bağlı olup tolvaptana dirençli olan hiponatremili bir olgu sunuldu.

patients with heart failure. The resistance to tolvaptan was another striking point in this case, and one which we believe should be shared in the literature.

#### Abbreviations:

|       |  |
|-------|--|
| CHF   | Congestive heart failure               |
| HF    | Heart failure                          |
| Na    | Sodium                                 |
| SIADH | Syndrome of inappropriate antidiuretic |

#### CASE REPORT

A 74-year-old male patient was admitted to the cardiology department for worsening of heart failure symptoms and severe hyponatremia. The patient had a history of CHF and valvular heart disease (mechanical aortic valve), diagnosed 10 years previously. He was using chronic HF treatment (carvedilol 12.5 mg 2x1, furosemide 40 mg 1x1, trandolapril 0.5 mg 1x1, spiroloactone/hydrochlorothiazide 25/12.5 mg 1x1) and warfarin. The patient had also been diagnosed with epilepsy 2 years previously and was prescribed levetiracetam 500 mg twice daily. He had been hospitalized many times for decompensation and hyponatremia. In the previous hospitalization when the patient was decompensated, his blood pressure was

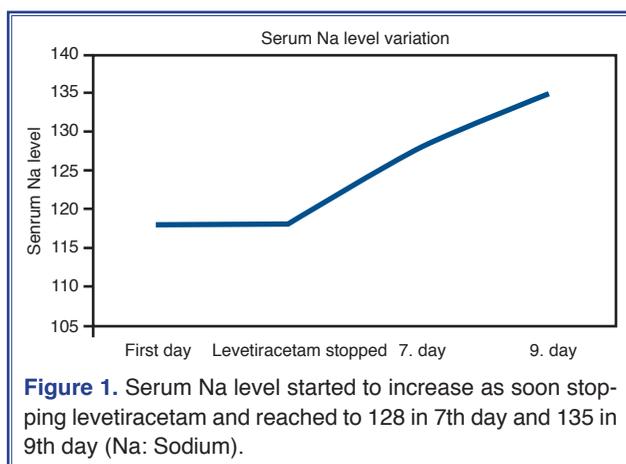
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**Figure 1.** Serum Na level started to increase as soon stopping levetiracetam and reached to 128 in 7th day and 135 in 9th day (Na: Sodium).

100/60 mmHg and heart rate 85 bpm. The patient had positive bilateral pretibial edema. At the current admission, the patient's blood Na level was 118 mmol/l, and his serum osmolality 250 mosm/l. He was lethargic, confused and pale. Intravenous furosemide was administered for congestion, and serum electrolyte levels were followed up daily. The resulting urine Na level was 143 mmol/l and urine osmolality increased to 650 mosm/l. At the follow up, the pretibial edema regressed, but despite hypertonic saline infusion, his blood Na level persisted at 118-120 mmol/l. The patient's lethargy, confusion and appetite loss also persisted. Due to the continual normovolemic hyponatremic condition, we decided to stop hypertonic saline and start 15 mg tolvaptan, an oral vasopressin V2 receptor antagonist, according to both American and European Heart Association guidelines. Despite regular daily treatment with increasing doses of tolvaptan, the hyponatremia continued for 7 days. With confusion and lethargy persisting, neurologists were consulted, and the symptoms attributed to hyponatremia.

The patient's Na level decreased to 115 mmol/l during this period. Since the patient was refractory to both diuretics and tolvaptan, we suspected causes other than CHF for the hyponatremia. The decreased blood Na and osmolality and increased urine Na and osmolality were indicative of Syndrome of Inappropriate Antidiuretic (SIADH). Monitoring of cortisol and thyroid stimulating hormones indicated levels within the normal range, and the patient did not have any malignancy. The patient was not hypervolemic either, since his diuretic response was very good. Although there are very few cases in the literature concerning levetiracetam-induced hyponatremia due to SIADH, we suspected levetiracetam was the cause of this patient's tolvaptan-resistant hyponatremia. Therefore, we discontinued its use, and the patient was initiated to sodium valproate. After discontinuing levetiracetam, the patient's Na levels started to increase gradually. At the end of the seventh day, his blood Na was 128 mmol/l, and on the ninth day, 135 mmol/l (Figure 1). Meanwhile, the patient showed regression of dyspnea and pretibial edema, and was discharged from the hospital with an optimal medical treatment. At his 3-month follow up, no recurrence of severe hyponatremia was observed.

## DISCUSSION

Hyponatremia is the most common electrolyte abnormality in hospitalized patients, especially those with chronic diseases like CHF and cirrhosis. Both dietary restrictions and multidrug use may worsen hyponatremia. It is associated with increased morbidity as in cognitive impairment, falls, fractures and osteoporosis. Hyponatremia is defined as Na concentration of less than 135 mEq/l.<sup>[1]</sup> Although hyponatremia may

**Table 1.** Causes of hyponatremia\*

| Hypovolemic hyponatremia     | Euvolemic hyponatremia   | Hypervolemic hyponatremia |
|------------------------------|--|---------------------------|
| Cerebral salt wasting        | Drugs (Diuretics, barbiturates, chlorpropamide, clofibrate, opioids etc) | Cirrhosis                 |
| Salt losing nephropathy      | Syndrome of inappropriate ADH secretion                                  | Heart failure             |
| Diuretics                    | Hypothyroidism   | Acute kidney dysfunction  |
| Mineralocorticoid deficiency | Adrenal insufficiency as in Addison disease                              | Chronic kidney disease    |
| Ketonuria                    | Primary polydipsia   | Nephrotic syndrome        |

\* Adapted from "Sahay M, Sahay R. Hyponatremia: a practical approach. Indian J Endocrinol Metab 2014;18:760-771. doi:10.4103/2230-8210.141320."

cause malaise, headache, nausea, vomiting, lethargy, stupor, seizure and coma depending on its severity, patients are generally asymptomatic, especially in the chronic period, and hyponatremia frequently goes undiagnosed and untreated.<sup>[2]</sup> Along with hyponatremia, the most common electrolyte abnormalities observed in heart failure patients are hypokalemia and hypomagnesemia.<sup>[3]</sup> In CHF, renin, angiotensin II and aldosterone secretions rise above normal and water reabsorption increases. Angiotensin II itself stimulates thirst leading to enhanced water intake, causing hypervolemic hyponatremia. Besides these, both diuretic and non-cardiac drug use may worsen hyponatremia. Hyponatremia is an important prognostic factor in HF that is associated with mortality and morbidity.<sup>[4,5]</sup> Tolvaptan, the first FDA-approved oral vasopressin V2 receptor antagonist, has been recommended in the ESC heart failure guidelines for use especially in patients with resistant hyponatremia and HF.<sup>[6]</sup> Tolvaptan increases the blood Na level by blocking Arginine Vasopressin (AVP) water reabsorption in kidneys. Several randomized trials have evaluated the effect of tolvaptan in CHF patients. Konstam et al. compared tolvaptan with placebo in 254 CHF patients, and reported that tolvaptan administration led to a reduction in body weight and edema and normalization of Na in hyponatremic patients, with no significant changes in heart rate, blood pressure, serum potassium level and renal function.<sup>[7]</sup> Schrier et al. reported the effectiveness of tolvaptan on serum Na concentration at day 4 and day 30 of treatment.<sup>[8]</sup> Although tolvaptan is very effective in increasing serum Na level in hyponatremic patients without affecting other metabolic and physiological parameters, two systematic reviews showed no significant reduction in the risk of death.<sup>[9,10]</sup> In our clinical experience, tolvaptan has been used extensively for resistant hyponatremia in CHF patients, and the condition was easily corrected in many patients. However, unlike in other cases, hyponatremia persisted in the patient described in this case report despite the use of tolvaptan. Detailed investigations also ruled out all other causes of hyponatremia. In elderly patients hospitalized with HF, clinical conditions that frequently lead to hyponatremia include diuretic use, hypothyroidism and SIADH (Table 1).<sup>[11]</sup> The main issue in SIADH is excess water, and hyponatremia is dilutional in nature. Central nervous system disturbances, malignancies, pulmonary diseases, surgery and use of drugs like carbamazepine,

chlorpropamide, amiodarone, haloperidol may cause SIADH.<sup>[12]</sup> The patient described here was using levetiracetam for epilepsy. Levetiracetam use has many side effects, but hyponatremia is very rarely seen. In the literature, only 3 cases of levetiracetam-induced hyponatremia have been described. The authors attributed hyponatremia to levetiracetam-induced SIADH, and recovery was observed as soon as the drug was discontinued.<sup>[13-15]</sup> The laboratory findings were consistent with SIADH in our patient. Fluid restriction, intravenous saline and vasopressin receptor antagonists are the main steps in the treatment of SIADH.<sup>[16]</sup> However, despite increasing the dose of tolvaptan and adequate diuresis, the hyponatremia persisted. When levetiracetam was discontinued, serum Na level rose to the normal range. When hyponatremia is diagnosed in patients with chronic diseases, especially in multi-drug users,, we should therefore carefully investigate and dismiss other underlying causes that may reverse the condition before correcting blood Na. The case described here is a rare incidence of levetiracetam-induced and tolvaptan-resistant SIADH that warrants sharing in the literature.

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- Key words:** Congestive heart failure; hyponatremia; levetiracetam; syndrome of inappropriate antidiuretic; tolvaptan.
- Anahtar sözcükler:** Konjestif kalp yetersizliği; hiponatremi; levetiracetam; uygunsuz antidiüretik hormon salınımı sendromu; tolvaptan.