Medical Case Reports and Reviews

Case Report ISSN: 2517-7214

The Syndrome of Inappropriate Antidiuretic Syndrome (SIADH) in association with Riluzole and SSRI treatment in an ALS patient

Efrat Zamir[1], Talia Alster[1] and Raymond Farah[1,2]*

[1]Department of Internal Medicine B, Ziv Medical Center, Safed-Israel

[2]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

Abstract

Amyotrophic Lateral Sclerosis (ALS) currently has a single approved drug proven to impact survival, Riluzole, which is associated with several adverse effects, e.g. asthenia, nausea and elevated liver enzymes.

Few cases found in medical literature report the association of the Syndrome of Inappropriate Antidiuretic Syndrome (SIADH) with Amyotrophic Lateral Sclerosis (ALS). When reported, the association is often mentioned in association with respiratory deterioration and impending respiratory failure, eventually requiring mechanical ventilation.

We hereby report a patient with ALS presenting initially with severe hyponatremia secondary to SIADH, following one-month of treatment with Riluzole and Fluoxetine, later deteriorating to respiratory failure and requiring mechanical ventilation

Introduction

Amyotrophic Lateral Sclerosis (ALS), also known as Motor Neuron Disease (MND) is a progressive neurodegenerative disease of both upper and lower motor neurons, classically affecting adults around the ages 45-63, for which no cure is currently available [1-5].

Riluzole is the first FDA-approved medication for ALS, known to modestly increase survival in patients [2,6]. Although its mechanism of action is poorly understood, it is speculated to reduce glutamatergic neurotransmission by blocking voltage-gated sodium channels. Riluzole is considered relatively safe, with common adverse effects including an increase in liver enzymes and asthenia, as well as rare descriptions of hepatic failure and pancreatitis [2,4].

Few reports in literature describe single cases in which ALS patients presented with, or developed, hyponatremia with features compatible with a diagnosis of SIADH [1,7-10]. These cases were commonly associated with progressive respiratory deterioration, eventually leading to respiratory failure requiring mechanically ventilating the patient. Although the mechanism remains incompletely understood, proposed mechanisms suggest the following: 1) SIADH secondary to hypoxia and hypercapnia, 2) an intrathoracic circulation dysfunction leading to SIADH, and 3) emotional factors and physical stress contributing to eventual SIADH development [6,10].

Fluoxetine is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class, commonly used as first line treatment for major depressive disorder, as well as other diagnoses. It is considered to have a high safety index, with major adverse effects generally classified to emotional effects (anxiety, insomnia, etc.), sexual-dysfunction related (i.e. abnormal ejaculation) and systemic symptoms (e.g. dry mouth, dyspepsia, flu-like symptoms) [3]. Cases of SIADH associated with fluoxetine treatment are commonly reported in literature as single case reports, mostly in the elderly patient population [10].

Case report

We report a 61-year-old male patient diagnosed with familial ALS three months prior to the current reported event. Prior to his diagnosis, the patient had a medical history significant for hypertension, treated medically. He worked a full-time job in manual labor, completing 12-hour work shifts in a near-by factory.

Diagnosis was suspected following two years of symptoms including progressive muscle weakness, night cramps, breathing difficulties and finally, difficulty expectorating sputum. Concomitantly with his diagnosis, the family of the patient reported increasingly low fluid intake and constipation, as well as symptoms of depression. Following diagnosis by a neurologist, the patient was started on a regimen of Riluzole (Rilutek 50 mg x 1/day), as well as Fluoxetine (20 mg X 1/day) and Zopiclone (Imovane 7.5 mg X 1/day).

Two months after commencing the above-mentioned medical treatment, the patient performed routine blood tests in the community setting, revealing hypo-osmolar (true) hyponatremia in serum measuring 122 mEq/L sodium. The patient himself was without symptoms and was subsequently sent to the ED by his GP.

In the ED the patient was alert and fully cooperative, with no cognitive impairment. Physical and neurological exam was

Correspondence to: Raymond Farah, Department of Internal Medicine B, Ziv Medical Center, Safed-Israel, Tel: 97246828946; Fax: 97246828116; E-mail: raymond.F@ziv.health.gov.il

Key words: *SIADH, ALS, hyponatremia, riluzole*

Received: January 16, 2019; **Accepted:** January 23, 2019; **Published:** January 25, 2019

unremarkable aside from known muscle weakness in limbs. Laboratory results were significant for a low measured serum sodium 117.5 mEq/L with hypo-osmolar serum measurements. Urine studies showed urine osmolality within normal range (i.e. low, since relative to serum osmolarity) with a urine sodium concentration of 74.5 mEq/L (i.e. higher than expected for serum sodium), indicating a state of SIADH.

The patient was subsequently admitted for follow-up and treatment in the Internal Medicine ward, with instructions for limitation of fluid intake and serial blood chemistry measurements. However, consecutive blood chemistry studies revealed worsening hyponatremia despite treatment, reaching 108.1 mEq/L. All medications (Riluzole and Fluoxetine) were consequently discontinued and the patient was started on a regimen of IV fluids containing 3% Sodium Chloride (hypertonic saline).

Shortly after the initiation of IV fluids, the patient presented with signs of shock including clinically cold periphery, sweating, dyspnea and severe lethargy. Blood pressure was rapidly reducing, and the patient presented with signs of impending respiratory failure, due to which mechanical ventilation was commenced on the patient. Following stabilization of the patient, a Synacthen test was performing ruling out Addisonian Crisis as the cause of the patient's current state. TSH and thyroid hormones were normal.

Following eight days of mechanical ventilation in combination with IV fluid treatment containing sodium chloride at hypertonic, and later eutonic concentrations, the patient's blood work showed return to normal serum sodium and osmolarity levels.

The patient himself could not be weaned off of mechanical ventilation later during his hospitalization period despite ongoing discontinuation of his medications, and although he was able to maintain hemodynamic stability and was found to have normal chemistry studies. A permanent tracheostomy operation was eventually performed on him.

Discussion

Single case reports exist (up to 8 cases including the current one, to the best of our knowledge), concerning the association between ALS patients and presentation with SIADH, occasionally additionally in association with respiratory distress and impending failure leading to mechanical ventilation [1,7-10]. Several mechanisms have been suggested to explain the correlation, including hypoxia and hypercapnia, intrathoracic circulation dysfunction, and emotional factors and physical stress [6,10].

No case reports in literature were found mentioning the association of treatment with Riluzole with hyponatremia or a state of SIADH, however post-marketing data does mention it as an infrequent side effect [6]. Conversely, reports do exist about the association of Fluoxetine with SIADH, but exceedingly more so in the elderly and geriatric population, a demographic which our patient does not match [3,11].

In relation to our patient, it would be challenging to definitively determine the exact cause of SIADH he presented with. ALS in of itself could have been the cause of the electrolyte imbalance, especially when considering the rapid respiratory failure leading to mechanical ventilation in the patient. However, since both Riluzole and Fluoxetine showed previous association with a hyponatremic state (albeit Fluoxeine did so for a different population demographic than the case mentioned here), it cannot be ruled out as an additional possible explanation. It cannot be ruled out that his state of SIADH was due to a combination of all the above-mentioned.

No data to date, to our knowledge, shows a causal relation between SIADH and eventual respiratory failure, other than being a leading sign for the upcoming. Despite this, the multiple risk factors for SIADH with which our patient presented, and his eventual respiratory failure leading to mechanical ventilation emphasizes the delicate metabolic and respiratory balance in ALS patients. The increased risk for SIADH in this patient population requires careful use of medications and fluids that may further raise their risk of metabolic imbalance, mainly reduction in serum sodium levels.

Conclusion

To conclude, with this case report we further emphasize the clinical importance of further investigation of the association between ALS and SIADH. Additionally, we raise awareness to the need for careful use of medications associated with a hyponatremic state such as SSRIs in ALS patients, especially those treated with Riluzole, and serial monitoring of serum sodium levels to prevent electrolyte imbalance, as well as possible respiratory deterioration.

References

1. Arakawa K, Nishio T, Sunohara N (1997) Two cases of MND/ALS developing the syndrome of inappropriate secretion of antidiuretic hormone. *Acta Neurol Cand* 96: 262-265.
2. Bensimon G, Lacomblez L, Meininger V (1994) A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med* 330: 585-591.
3. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG (2014) Antidepressants and the risk of hyponatremia: a class-by-class review of literature. *Psychosomatics* 55: 536-547. [Crossref]
4. Falcão de Campos C, de Carvalho M (2017) Riluzole-induced recurrent pancreatitis. *J Clin Neurosci* 45: 153-154. [Crossref]
5. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, et al. (2017) Amyotrophic lateral sclerosis. *Nat Rev Dis Primers* 3: 17071.
6. Miller RG, Mitchell JD, Moore DH (2012) Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) *Cochrane Database Syst Rev* 14: CD001447.
7. Inoue Y, Murakami T, Nakamura T, Morita K, Kaneda D, et al. (2017) Syndrome of inappropriate antidiuretic hormone secretion associated with amyotrophic lateral sclerosis in a patient developing carbon dioxide narcosis. *Intern Med* 56: 797-803.
8. Koyama S, Aizawa H, Haga T, Nakatani-Enomoto S, Kikuchi K (2002) An autopsy case of amyotrophic lateral sclerosis accompanied by syndrome of inappropriate secretion of antidiuretic hormone. *Intern Med* 41: 395-397.
9. Motoo Y, Ohta H, Okai T, Sawabu N (1992) Amyotrophic lateral sclerosis associated with the syndrome of inappropriate secretion of antidiuretic hormone. *Intern Med* 31: 1023-1025.
10. Yoshida Y, Kato B, Mizushima Y, Arai N, Matsui S, et al. (1999) Syndrome of inappropriate secretion of antidiuretic hormone associated with amyotrophic lateral sclerosis in respiratory failure. *Respirology* 4: 185-187.
11. Raphael K, Tokeshi J (2002) Hyponatremia associated with sertraline and fluoxetine: a case report. *Hawaii Med J* 61: 46-47. [Crossref]