

Case Report

A Case Report of an Effective Treatment for Syndrome of Inappropriate Secretion of Antidiuretic Hormone with Integration of Western Medicine and Traditional Chinese Medicine

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Abstract

Background: Syndrome of Inappropriate secretion of Antidiuretic Hormone (SIADH) is a group of disorders in which free water excretion is impaired due to increased Arginine Vaso Pressin (AVP) secretion in the absence of renal or endocrine dysfunction, which in turn leads to hypotonic hyponatremia. In this case report, we describe the diagnostic process of a patient with SIADH and the treatment with integration of Western and Chinese medicine.

Case Presentation: A 69-year-old man was admitted to our hospital for intermittent hand tremors. He was diagnosed with hyponatremia based on laboratory tests. However, after 2 weeks of sodium supplementation, his condition did not improve. Combined with Pituitary MRI, 24h urine sodium and other laboratory tests, he was diagnosed with SIADH. After taking oral tolvaptan and traditional Chinese medicine Rehmanniae Decoction of Six Ingredients granules, his symptoms were alleviated and the serum sodium normalized. Conclusion: SIADH could be as an etiology for hyponatremia that is difficult-to-correct, and traditional Chinese medicine may have some efficacy and advantages.

Keywords: SIADH; Hyponatremia; Tolvaptan; Rehmanniae decoction of six ingredients

Introduction

Hyponatremia is a pathophysiological state in which serum sodium is less than 135 mmol/L and is a relatively common clinical fluid-electrolyte imbalance. One of the major causes of hyponatremia is Syndrome of Inappropriate secretion of Antidiuretic Hormone (SIADH), which is characterized by water retention, increased urinary sodium and hyponatremia. SIADH has an insidious onset, and the common cause is malignancy. It is often ineffective when given conventional sodium replacement treatment and may be life-threatening if left untreated. There are few case reports of SIADH and the treatment is mainly based on water restriction and oral tolvaptan tablets. Here we report the diagnostic process of a patient with SIADH and an excellent treatment with a combination of traditional Chinese medicine and Western medicine. We hope to provide some ideas for physicians who encounter patients with refractory hyponatremia in clinical practice.

Case Presentation

A 69-years-old man was admitted to our hospital on June 1, 2020, mainly for intermittent hand tremors. We learned that eight years ago, he visited the Third Hospital of Hebei Medical University for “confusion” and was diagnosed with “hyponatremia and Parkinson’s syndrome” after examination. He was treated with oral sodium valproate tablets (1g/day) and then his symptoms were relieved. After discharge from the hospital, his conditions recurred. Over the years, he has been admitted to several hospitals for intermittent hand tremors and seizures, and is now taking oral oxcarbazepine tablets (0.9g/day). Due to the poor treatment results, he was then gone to our hospital for further treatment. Post-admission examination: temperature 36.3°C, pulse 88/min, respiration 18/min, blood pressure 107/62 mmHg. He had normal muscle tone and muscle strength grade V. His biceps and triceps tendon reflexes and knee tendon reflexes were normal on both sides. He also had negative Hoff-

mann's sign, Babinski's sign, and Kerning's sign. Hematological examination revealed lower sodium levels of 126 mmol/L, oxcarbazepine metabolites 5.4, decreased blood creatinine and blood uric acid (creatinine 45.8 $\mu\text{mol/L}$, uric acid 177.7 $\mu\text{mol/L}$), normal levels of liver function, glycated hemoglobin, homocysteine, parathyroid hormone, testosterone, estradiol, progesterone, folliculopoietin, luteinizing hormone and prolactin. Additionally, abdominal ultrasound, chest CT and cranial MRI did not show any significant abnormalities. On admission, he complained of involuntary trembling of the hands, weakness of the waist and knees, fatigue, sweating, coughing, insomnia and dreaminess, occasional night sweats and a long history of constipation. His tongue was dark red with thin white coating and his pulse was stringent. He denied history of other chronic diseases such as diabetes mellitus, infectious diseases such as hepatitis, tuberculosis, typhoid, etc. A history of major trauma, blood transfusion, drug and food allergies and a family history of hereditary diseases were also denied. Based on the symptoms and the examination, he was preliminarily diagnosed as follows: Traditional Chinese medicine (TCM) diagnosis: epilepsy, deficiency of kidney essence. Western medicine diagnosis: electrolyte metabolism disorder, hyponatremia. He was treated with oral salt capsules (3g/day) and intravenous infusions of 3% sodium chloride injection to correct hyponatremia. His mental status was also closely observed as too rapid an elevation of serum sodium can lead to central demyelinating lesions.

Electrolytes were rechecked after treatment and sodium was 125.2 mmol/l on June 6, 118.2 mmol/l on June 9, and 121.4 mmol/l on June 13, indicating that his hyponatremia remained uncorrected. Together with the persistence of his symptoms, we performed further examinations for him. Pituitary MRI showed small cystic lesion between anterior and posterior lobes of pituitary gland, which was considered a Rathke's cyst. Serum sample showed 22.76 pg/ml of adrenal stimulating hormone, and 5.36 $\mu\text{g/dl}$ of serum cortisol. Urine sample showed 305.2 mmol/24h of urine sodium, 348.25 mmol/24h of urine chloride, and 802.20 nmol/24h of urine cortisol. Although there was no obvious trigger, the above examinations were most consistent with the diagnosis of SIADH. After communication, he was informed of the adverse effects of tolvaptan tablets and took oral tolvaptan tablets, while sodium supplementation was discontinued and fluid intake was restricted. At the same time, we closely monitored his blood pressure, heart rate changes, 24-h access. His liver and kidney function and electrolytes were regularly rechecked. In terms of TCM, his symptoms such as thirsty, soreness of waist and knees, fatigue, coughing, insomnia, night sweating, tongue coating and pulse are all signs of kidney essence deficiency and imbalance of yin and yang. Therefore, the principle of treatment was to benefit the kidney, fill the essence and balance yin and yang. We prepared the Rehmanniae Decoction of Six Ingredients granules for him and the formula was as follows: radix rehmanniae, 15 g; prepared rehmannia, 15 g; moutan bark, 12 g; cornus officinalis, 15 g; poria cocos, 12 g; rhizoma dioscoreae, 12 g; alisma orientalis, 9 g; astragalus, 30 g; ophiopogon japonicus, 15 g; Hempseed, 30 g; angelicae sinensis, 10 g; schisandra chinensis, 6 g; semen cuscudae, 15 g. The above herbs were processed as no-decoction granules, 1 dose/day, which he took in the morning and evening separately.

On June 17, one week after treatment, the laboratory tests showed normal serum sodium levels of 135.3 mmol/L, which indicating the hyponatremia have been corrected. He was advised to continue to take oral tolvaptan tablets and Chinese medicine granules and to review electrolytes regularly. On June

23, our patient presented no hand tremors with alleviation of his symptoms such as weakness, sweating, insomnia, cough, sputum and constipation, In addition, he had a good appetite and sleep. Laboratory examination showed 138.1 mmol/L of sodium, 159.40 mmol/L of urinary sodium concentration, 366.62mmol/24h of urinary sodium, all of which were in the normal range. In combination with these results, the western medical diagnosis was revised to a) SIADH; b) pituitary cyst. He was discharged with improved symptoms and normal serum sodium levels. At regular visits, it was learned that his serum sodium had not dropped again and that he had no more episodes of hand tremors.

Discussion

SIADH is a group of disorders caused by abnormally increased secretion of endogenous antidiuretic hormone (ADH), also known as arginine pressor hormone, which leads to water retention, increased urinary sodium excretion and dilutional hyponatremia [1]. SIADH usually has an insidious onset and may be life-threatening if the disease progresses further. The most common causes of the disease are malignancy, central system disorders, pulmonary infections, drugs and other factors such as surgery [2]. SIADH is difficult to diagnose, and there is no urine or plasma biomarker with high enough sensitivity and specificity to independently assess and diagnose. The diagnostic criteria for SIADH include: 1) serum sodium <130 mmol/L; 2) plasma osmolality <270 mOsm/L, urinary osmolality is greater than plasma osmolality; 3) normal blood volume; 4) urinary sodium >20 mmol/L; 5) no abnormalities in heart, liver, kidney, adrenal function and thyroid function [3]. In this case, the patient came to our hospital with a diagnosis of moderate hyponatremia based on serum sodium of 126 mmol/L and was treated with oral salt capsules as well as intravenous rehydration with hypertonic salt. However, after treatment, his serum sodium did not improve significantly. Considering his persistent serum sodium <130 mmol/l, increased urinary sodium, blood volume manifestations (decreased blood creatinine and blood uric acid), and progressive decrease in serum sodium level even after intravenous rehydration, which are all typical features of SIADH, we restricted his fluid intake and administered tolvaptan and TCM. After treatment, his serum sodium level returned to normal, which further confirmed his diagnosis of SIADH.

After the diagnosis of SIADH, it is vital to actively identify the underlying cause and instruct optimal treatment. Pseudohyponatremia could be excluded in our patient because his blood glucose, lipid and total protein levels were within the normal range. Hyperalgesia was not considered because his cortisol level and rhythm were normal. In addition, his thyroid hormones were all normal, so hypothyroidism could be excluded too. Pituitary MRI showed pituitary cysts, which can indirectly enhance ADH release and lead to SIADH, so pituitary cysts complicated by SIADH could be a possibility [4]. Moreover, it has been shown that oxcarbazepine can directly inhibit the secretion of ADH from the posterior pituitary gland, lowering the equilibrium point of ADH secretion and causing hyponatremia [5]. In this case, the possibility of a rule for oxcarbazepine in the pathophysiology of SIADH cannot be excluded since he had taken oxcarbazepine orally for about four years and the level of oxcarbazepine metabolite was measured as 5.4.

In terms of treatment, the first step was to address the etiology. Since he had a small pituitary cyst, with no significant headache or vision loss, and roughly normal pituitary hormone levels, there was no intervention was made and pituitary MRI

will be reviewed periodically. In addition, he was discontinued from oxcarbazepine upon admission and its metabolites will be reviewed after one month. The next and most important treatment was for SIADH. Saline intravenous infusion generally cannot correct the hyponatremia of SIADH and may even exacerbate it if the urine osmolality is greater than 500 mOsm/kg [6]. Selective vasopressin receptor blockers, such as tolvaptan, are now widely used in clinical practice and have been shown to be effective. Tolvaptan is an orally administered selective non-peptide ADHV2 receptor antagonist approved by the US FDA in 2009. It can significantly improve the prognosis of SIADH by targeting the specific pathological mechanism. Specifically, it competitively blocks the binding of ADH to V2 receptors to inhibit water reabsorption of ADH in the kidney, and promotes the excretion of excess water from the urine without affecting sodium reabsorption, thereby correcting serum sodium concentration [7]. However, safety concerns remain due to its severe hepatotoxicity and the tendency to overcorrect hyponatremia associated with long-term use. Furthermore, the high price limits its widespread use. In recent years, TCM has played an increasingly important role in the treatment of difficult cases as it can provide personalized treatment based on the patients' symptoms and constitution. Moreover, TCM has the advantages of low price and less toxicity and side effects. After detailed questioning of the symptoms as well as physical examination, we prescribed Chinese medicine as a complementary treatment for him.

According to TCM, SIADH can be classified as "epilepsy", "syncope", "deficiency labor", "headache" and "sweating" depending on the clinical manifestations. In this case, the TCM diagnosis was "epilepsy" as his main symptom was hand tremors. The pathogenesis of epilepsy is a nutrition deficiency of the limbs caused by exogenous or internal injuries. Internal injuries are due to congenital deficiency, weak endowment, acquired deficiency and depletion of essence, which can result in kidney essence deficiency. Exogenous injury refers to qi stagnation, blood stasis, phlegm and dampness, which eventually leads to loss of nourishment of the collaterals, resulting in shivering of the limbs and difficulty in sleeping [8]. In this case, our patient is old, with deficient kidney qi and decreased kidney's sealing function. Therefore, the essence is excreted from the urine, resulting in elevated urinary sodium (electrolytes can be attributed to the essence as discussed in TCM). Kidney essence deficiency leads to lack of nutrition in the limbs which in turn causes hand tremors. In addition, kidney essence produces marrow, and the brain is the container of marrow, so the marrow is the material basis of the connection between the brain and the kidney. Inadequate kidney essence and loss of nourishment of the marrow can lead to brain disorders such as pituitary cysts. Therefore, kidney-tonifying should be the principal of treatment for our patient. Rehmanniae Decoction of Six Ingredients is a representative formula for tonifying the kidney, which can benefit the kidney, fill up the essence, and balance yin and yang [9]. Specifically, radix rehmanniae, prepared rehmannia, moutan bark, cornus officinalis, poria cocos, rhizoma dioscoreae and alisma orientalis can nourish the liver and kidney. The kidney stores essence and the liver stores blood. Essence and blood are homologous and can be transformed into each other, so the above herbs can also replenish the essence and blood while tonifying the kidney. The astragalus is a great tonic for vital energy, generates heart energy to help spread essence, and generates kidney essence to promote sealing function. The ophiopogon japonicus and schisandra chinensis can astringent lung qi, nourish

kidney qi, generate fluid and stop sweating, calm the mind and help sleep. The semen cuscutae can tonify yang and make yin rise with yang, just like spring water source inexhaustible. The angelicae sinensis tonifies and harmonizes the blood, so that the essence and blood can produce each other. The hempseed moistens the intestines and ease-constipation. The combination of the above herbs can benefit the kidney, fill the essence and balance yin and yang. Because our patients need to restrict fluid intake, we gave him herbal formula granules to take orally rather than decoction. After treatment, his symptoms of thirst, weakness, sweating, cough and insomnia were significantly relieved, and his serum sodium level normalized. Since he received a combination of Chinese and Western medicine, the specific effects of Rehmanniae Decoction of Six Ingredients in SIADH disease needs further studied. We share here the his prescription in the hope of providing physicians with some ideas for Chinese medicine use.

Hyponatremia is a common disorder of water-electrolyte balance, which is even life-threatening in severe cases. Timely clarification of the cause of hyponatremia can effectively improve the correction rate of the disease and reduce complications. SIADH can cause hyponatremia, and conventional sodium replacement therapy is often ineffective, so it is important to raise awareness of the disease and provide timely and clear diagnosis. Because of the lack of clinical experience in treating SIADH, the patient in this case was diagnosed more than 10 days after the onset of hyponatremia. Although he was eventually treated effectively without serious consequences, the condition was actually delayed. Our experience emphasizes the significance of considering SIADH as an etiology for hyponatremia that is difficult-to-correct. In terms of treatment, Chinese medicine, which is focused on kidney tonification, may have some efficacy and advantages.

Author Statements

Ethics Statement

Written informed consent was obtained from the patient to publish this case report.

Author Contributions

All authors listed have significantly contributed to the investigation, development and writing of this article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Data Availability Statement

Data will be made available on request.

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