

Sylwester MATWIEJCZUK
Miroslawa PÜSKÜLLÜOĞLU
Aneta L. ZYGULSKA

Oncological emergencies: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Stany nagłe w onkologii: Zespół nieadekwatnego uwalniania wazopresyny

Klinika Onkologii Szpitala Uniwersyteckiego w Krakowie
Kierownik:
Doc. dr hab. Krzysztof Krzemieniecki

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Excessive secretion of vasopressin in the course of Syndrome of Inappropriate Antidiuretic Hormone Secretion is a common cause of hyponatremia in cancer patients. Clinical symptoms depend on the cause, rate of change of sodium level and their absolute values. Treatment options include fluid restrictions, intravenous administration of hypertonic sodium chloride solutions, loop diuretics and vaptans. The sodium level should not be adjusted too fast, because it may lead to irreversible brain damage. The article presents pathophysiology, diagnostics and recommendations of management of this oncological emergency.

Nadmierne wydzielanie wazopresyny w przebiegu zespołu Schwartz-Barttera jest częstą przyczyną hiponatremii wśród pacjentów onkologicznych. Obraz kliniczny zależy od przyczyny, szybkości spadku poziomu sodu oraz bezwzględnych wartości hiponatremii. Do głównych metod leczenia zaliczamy restrykcje płynowe, dożylny wlew hipertonicznego roztworu soli, diuretyki pętlowe oraz vaptany. Poziom sodu nie powinien być korygowany zbyt szybko, ze względu na ryzyko nieodwracalnego uszkodzenia mózgu. W artykule przedstawiono patofizjologię, diagnostykę oraz leczenie tego onkologicznego stanu nagłego.

Introduction

The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), otherwise known as the Schwartz-Bartter syndrome, is characterized by excessive release of ADH (antidiuretic hormone, vasopressin) from the posterior pituitary gland or ectopic source [1,2].

The first description of SIADH was made in 1957. It was based on the cases of two lung cancer patients. The most important was the fact that despite the dramatic reduction in the serum sodium concentration, urine osmolality remained consistently hypertonic to the plasma. This discovery, taken together with the evidence of normal volume status and blood pressure, as well as normal kidney and adrenal function, suggested that the syndrome was caused by inappropriate ADH secretion [3].

Epidemiology

Hyponatremia in the course of SIADH is one of the most common metabolic disorders in cancer patients. It may accompany or precede the diagnosis of the underlying disease [2]. Even mild hyponatremia is associated with an increased risk of death in hospitalized patients [4,5]. According to a Belgian study, the incidence of hyponatremia, being defined as serum sodium level less than 130 mmol/L, in cancer patients was 3.7% [6].

Etiology

Lung cancer is the most common cause of SIADH in the cancer patients. Small-cell lung cancer (SCLC) is responsible for

approximately 75% of cases in this group of patients. Other cases are associated with non-small-cell lung cancer (NSCLC), breast cancers, head and neck cancer and haematological malignancies [7]. Active infection, anticancer drugs such as cisplatin, high doses of cyclophosphamide, melphalan and vinca alkaloids, which can stimulate the secretion of ADH, are non-cancer causes of SIADH [8]. Occasionally SIADH may be increased after chemotherapy, because ADH is released from the dead tumor cells. The most important causes of SIADH are included in Table I [6].

Pathophysiology

The pathophysiological mechanisms leading to the development of hyponatremia in the course of SIADH run in two stages. Hyponatremia is primarily induced by water retention caused by the influence of ADH in the collecting ducts. The consequent increase in the volume of extracellular fluid triggers secondary mechanisms for maintaining euvoolemia, resulting in increased excretion of water and sodium. For this reason, in the course of SIADH sodium loss is much more pronounced than water retention [9].

Symptoms

Most patients with SIADH are asymptomatic. Not only the degree of hyponatremia, but also the rate of change contribute to the severity of the symptoms. Early symptoms are non-specific. These include anorexia, nausea, vomiting and weakness. With further decrease of the sodium level, confusion, seizures, and coma appear. The decrease

Adres do korespondencji:

Sylwester Matwiejczuk
ul. Śniadeckich 10, Ilp., 31-531 Kraków
Tel. 124248912, fax 124248910
e-mail: sylwester.matwiejczuk@gmail.com

of sodium level below 110 mmol/L results in the inhibition of deep tendon reflexes. Notably, although the patients may present serious symptoms, they are euvoletic and have no orthostatic hypotension or edema. Typical symptoms of SIADH are listed in Table II [2].

Diagnosis

SIADH should be differentiated from other causes of hyponatremia, which are presented in Table III. The criteria for the diagnosis of SIADH are [8,10]:

- Low plasma osmolarity (grades of hyponatremia are included in Table IV)
- Inappropriately elevated urine osmolarity (> 100 mOsm/kg, usually > 300 mOsm/kg)
- The sodium concentration in urine usually > 30 mmol/L
- Relatively low plasma levels of urea and creatinine
- Normal function of adrenal gland and thyroid gland

Treatment

The basis for treating hyponatremia in cancer patients should be the treatment of the underlying disease [11]. If treatment of cancer is insufficient or impossible, the choice of therapy depends on such factors as the degree of hyponatremia, the presence or absence of symptoms and, in some cases, urine osmolarity. There are many opportunities to correct hyponatremia in the course of SIADH. These are: fluid restriction, the administration of hypertonic sodium chloride solutions, loop diuretics, administration of ADH receptor antagonists and demeclocycline.

Fluid restriction

Fluid restriction is the basis for therapy in most patients with SIADH. Suggested daily fluid intake should not exceed 800 ml [12]. Due to negative water balance, sodium concentration increases. Fluid restriction also prevents decline in sodium level in patients being treated chronically.

Intravenous administration of hypertonic sodium chloride solutions

Hypertonic solutions of sodium chloride are administered in severe symptomatic or fluid restriction resistant cases. It is of major importance to remember that to increase the osmolarity of the plasma, the solution with osmolarity higher than both plasma and urine osmolarity should be administered [13].

To illustrate the importance of administration of sodium chloride solutions in an appropriate osmolarity, let us consider a case of a patient with a baseline sodium concentration of 115 mmol/l and urine osmolarity of 462 mOsm/kg. If 1000 mL of isotonic saline is given, serum sodium will initially rise, but eventually it will drop to an even lower level than before. This is due to the fact that the concentration of ADH in patients with SIADH does not depend on the amount of ingested water, urine osmolarity is relatively constant and its volume depends on the amount of excreted electrolytes. The excretion of all the administered saline requires about 670 ml of water. The remaining 330 ml of water will exacerbate hyponatremia [14].

Table I

Main causes of SIADH (acc. 7,8,29).

Główne przyczyny SIADH (wg 7,8,29).

CNS disturbances	stroke, hemorrhage, infection, trauma, psychosis
Malignancies	small-cell lung cancer (SCLC), non-small-cell lung cancer (NSCLC), head and neck cancer, breast cancers, olfactory neuroblastoma, extrapulmonary small cell carcinomas, haematological malignancies
Drugs	chlorpropamide, carbamazepine, oxcarbazepine, high doses of cyclophosphamide, selective serotonin reuptake inhibitors (SSRI), vincristine, vinblastine, vinorelbine, cisplatin, thiothixene, thioridazine, haloperidol, amitriptyline, monoamine oxidase inhibitors, melphalan, ifosfamide, methotrexate, opiates, nonsteroidal antiinflammatory agents, interferon-alpha, interferon-gamma, sodium valproate, bromocriptine, lorcaidine, amiodarone, ciprofloxacin, high-dose imatinib, and "ecstasy" (methylene-dioxyamphetamine)
Other	active infection, surgery, pulmonary disease, hormone deficiency, hormone administration, HIV infection, hereditary SIADH

Table II

Typical symptoms of SIADH (acc. 2)

Typowe objawy SIADH (wg 2).

Symptoms of SIADH	
Early symptoms	- anorexia - nausea - vomiting - weakness
Severe symptoms	- confusion - seizures - coma - inhibition of deep tendon reflexes

Table III

Causes of hyponatremia (acc. 30)

Przyczyny hiponatremii (wg 30).

Causes	The volume of extracellular fluid		
	Hypovolemia	Euvoolemia	Hypervolemia
Causes	diarrhea, vomiting, heavy sweating, diuretics	SIADH, hypothyroidism, adrenal insufficiency	congestive heart failure (CHF), cirrhosis, nephrotic syndrome
Plasma osmolarity	Low	Low	Low
Urine osmolarity [mOsm/kg]	> 500	> 100	> 100
Urine valume	Usually increased	Variable	Usually increased
Urine sodium concentration [mmol/l]	< 20	> 40	< 20
Response to administration of saline solution	Biochemical and clinical improvement	No change or deterioration	Small change

Table IV

Grades of hyponatremia according to Common Terminology Criteria for Adverse Events (CTCAE) v 4,03 (acc. 10).

Stopnie hiponatremii zgodnie z Common Terminology Criteria for Adverse Events (CTCAE) v 4,03 (wg 10).

Grade	Sodium concentration in the blood
1	<LLN* - 130 mmol/L
2	----
3	<130 - 120 mmol/L
4	<120 mmol/L (with life-threatening consequences)
5	Death related to adverse event

*Lower limit of normal

Loop diuretics

The use of loop diuretics is particularly useful in patients whose urine osmolarity twice exceeds the plasma osmolarity and who cannot tolerate fluid restriction for various reasons. Their mechanism of action involves inhibition of uptake of sodium chloride in the core part of the nephron loop, resulting in a reduced ability of the kidneys to concentrate urine, thereby increasing the excretion of free water. The usual dose of furosemide is 40 mg per day, in two doses of 20 mg. Du-

ring treatment, it is urgent to monitor serum potassium level, and if necessary, it should be combined with potassium or potassium-sparing drugs [15,16].

Receptor antagonists to ADH

Renal vasopressin receptors (V2) are located on the cells forming renal collecting ducts. Their activation increases water permeability of collecting ducts, thus allowing water reabsorption for more concentrated urine. Medicines that are antagonists of

these receptors (vaptans) have been used to treat patients with SIADH [17].

Conivaptan is a non-selective antagonist of the ADH. It is administered in intravenous infusion, which means it can be used in hospitals only. Administration of conivaptan among patients with euvoletic and hipovolemic hyponatremia, at a dose of 40 mg daily for 4 days, significantly increased plasma sodium concentration. The main side effects include injection site reactions, hypotension and excessive rate of sodium level increase [18,19].

Tolvaptan is an oral, selective V2 receptor antagonist. Patients at the implementation of treatment should be hospitalized in order to evaluate the clinical response and monitoring of side effects. Due to increased thirstiness, tolvaptan is not recommended for patients who are not able to control the amount of fluid intake [20,21].

The effect of vaptans is difficult to predict and it varies between patients, for this reason vaptans are less useful than hypertonic sodium chloride solutions in the treatment of patients with severe, symptomatic hyponatremia, where quick results are essential [22].

Other

Demeclocycline acts on the collecting tubule cell to decrease its responsiveness to ADH, which leads to nephrogenic diabetes insipidus. It may be useful in the treatment of SIADH, but in some countries, such as Poland, it is not registered, which limits its availability [23].

Treatment according to the severity of the symptoms

Symptomatic hyponatremia with severe neurological symptoms

Severe symptoms of hyponatremia, such as convulsions or coma, occur most frequently when the sodium level fell below 120 mmol/l in less than 48 hours, which can further lead to potentially fatal cerebral edema [24].

Based on clinical data, administration of hypertonic sodium chloride is the only reasonably quick way to increase serum sodium level and improve neurological function in patients suffering from severe symptomatic hyponatremia [25]. It is recommended to administer 100 mL of 3% sodium chloride solution as a bolus, which should increase the plasma sodium level with about 2 mmol/L for women and 1.5 mmol/L for men [16].

If the patient's condition does not improve, it is permissible to administer the following two doses of 100 mL of 3% sodium chloride solution as a bolus, at intervals of 10 minutes. To minimize the risk of complications caused by an excessive rate of increasing the sodium concentration in the plasma, it is recommended not to correct hyponatremia faster than 6-8 mmol/L within 24 hours, 12-14 mmol/L within 48 hours, and 14-16 mmol/L within 72 hours [16,26].

Symptomatic hyponatremia with mild to moderate neurological symptoms

Less severe neurological symptoms, such as dizziness, gait disturbances, memory problems, confusion, may occur when the

sodium level falls below 120 mmol/L within more than 48 hours, or in patients with less severe hyponatremia that occurred during less than 48 hours. In this group of patients, treatment should not be as aggressive as the above-mentioned. For mild symptoms, fluid restriction constitutes sufficient treatment. Within patients suffering from bothersome symptoms, hypertonic saline can be used. For the first three to four hours the sodium concentration should be increased with a rate of 1 mmol/L per hour. Then, the rate of correction should be decreased not to exceed the daily standards mentioned above [27].

Asymptomatic patients

Within asymptomatic patients, serum sodium is usually chronic in the range from 120 to 129 mmol/L. Treatment for most patients is fluid restriction; if that is not enough, and urine osmolality is more than twice than the plasma osmolality, then loop diuretics may be considered. Although the symptoms do not seem to occur among these patients, studies prove that patients suffering from chronic hyponatremia demonstrate a higher probability of falls, possibly associated with impaired gait and concentration [28]. Confirmation of asymptomatic hyponatremia impact on psychomotor performance is the improvement of the results of mental, motor, and social tests after tolvaptan administration in patients with baseline serum sodium below 130 mmol/L [21]. For this reason, proper treatment must be carefully considered in patients with asymptomatic hyponatremia because it may affect their quality of life.

Summary

Excessive secretion of ADH in the course of SIADH is a common cause of hyponatremia in cancer patients. Small-cell lung cancer (SCLC) is the most common cause of SIADH in this population. Physicians should always consider SIADH in cancer patients with a low level of sodium. The basis for treating hyponatremia in cancer patients should be the treatment of the underlying disease. If it is insufficient or impossible, appropriate symptomatic treatment should be implemented. Clinical management depends mainly on the clinical picture. The sodium level should not be adjusted too fast, because it may lead to irreversible brain damage.

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