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Original article

Reset osmostat

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Abstract

Introduction: Reset osmostat (RO) is a common syndrome, making up about 30 % of patients with hyponatremia.
Objective: Conduct a comprehensive review of osmostat reset, describing its clinical, pathophysiologic, diagnostic, and therapeutic aspects.
Methodology: A narrative review was conducted based on the main articles published in the medical literature.
Results: Reset osmostat has a low plasma osmolality threshold, which consequently leads to an elevation in antidiuretic hormone at a lower plasma osmolarity, along with normal water load excretion and intact urine diluting ability, while maintaining normal sodium balance. Reset osmostat can be observed in pregnancy, older age, quadriplegia, psychosis, cerebral hemorrhage, encephalitis, dementia, alcoholism, malnutrition, malignancy, and particular infectious diseases.
Conclusions: Reset osmostat often resets to normal if it is the consequence of a reversible clinical setting; however, this normalization might not happen if it is secondary to an irreversible condition. In such cases, treatment is required similar to that of any hyponatremia in order to avoid its negative consequences.

Keywords: Hyponatremia, Reset osmostat, Diagnosis, Osmolar concentration, Vasopressins, Communicable diseases.

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Reset del osmostato

Resumen

Introducción: el reset del osmostato (RO) es un síndrome común que representa aproximadamente el 30 % de los pacientes con hiponatremia.

Objetivo: realizar una revisión exhaustiva sobre el reset del osmostato, describiendo sus aspectos clínicos, fisiopatológicos, diagnósticos y terapéuticos.

Metodología: se realizó una revisión narrativa basada en los principales artículos publicados en la literatura médica.

Resultados: el reset del osmostato tiene un umbral de osmolalidad plasmática bajo que, en consecuencia, conduce a una elevación de la hormona antidiurética y a una osmolaridad plasmática más baja, junto con una capacidad intacta para diluir la orina y mantener el equilibrio normal de sodio. El reset del osmostato se puede observar en el embarazo, la vejez, la cuadriplejía, la psicosis, la hemorragia cerebral, la encefalitis, la demencia, el alcoholismo, la desnutrición, las enfermedades malignas y en determinadas enfermedades infecciosas.

Conclusión: el reset del osmostato a menudo se restablece a la normalidad si ha sido inducido por una enfermedad reversible; sin embargo, puede no normalizarse si lo induce una condición irreversible. En tales casos, se requiere un tratamiento similar al de cualquier hiponatremia para evitar sus consecuencias negativas.

Palabras clave: hiponatremia, reset del osmostato, diagnóstico, concentración osmolar, vasopresinas, enfermedades transmisibles.

Introduction

Reset osmostat hyponatremia is a common syndrome, making up about 30 % of patients with low serum sodium. It is characterized by a low plasma osmolality threshold (usually 280 mOsm/kg), high vasopressin, and low sodium serum levels. Despite the alterations, patients maintain an intact ability to dilute urine and a normal sodium balance, this latter feature being a fundamental characteristic that distinguishes this type of hyponatremia from others [1–14]. This condition consists of a dysfunction of the hypothalamic region in its ability to maintain the plasma osmolarity value in the normal range (290±5 mOsm/L), thus usually inducing hyponatremia. However, reset osmostat can induce, although infrequently, hypernatremia [15]. Clinical settings that can induce reset osmostat are numerous and diverse, including physiological, neurological, muscular, hepatic, metabolic, nutritional, oncological, infectious, and transplant-related conditions [1–15] (see Table 1).

Table 1. Conditions reported as associated to reset osmostat

Physiological
Pregnancy

Neuromuscular
Rhabdomyolysis
Quadriplegia
Psychosis
Cerebral hemorrhage
Encephalitis
Seizures
Parkinson disease, dementia
(Lewy bodies)
Digestive
Diarrhea
Cirrhosis
Alcoholism
Type 2 diabetes mellitus
Malnutrition
Oncologic
Gastric carcinoma
Colonic carcinoma
Oat cells carcinoma
Metastatic uterine cancer
Metastatic pancreatic cancer
Infectious
Tuberculosis pneumonia
Pneumocystis carinii
Pneumonia
Miscellaneous
Renal transplant
Senescence

Reset osmostat pathophysiology

The proposed pathophysiology behind the frequent detection of reset osmostat in severely malnourished patients involves an alteration in the osmoreceptor cells' metabolism.

Moreover, successfully treating malnourished patients, as well as other reversible reset osmostat-inducing diseases (like pneumocystis pneumonia), can successfully correct this reset [15].

As specified above, pregnancy might induce reset osmostat. Despite the partially unknown mechanism of its induction, it appears that the fetal-placental unit is an absolute requirement for its appearance. Additional supporting data indicate that other factors also contribute to this osmotic adjustment during pregnancy. For instance, one paper observed that the human chorionic gonadotropin secreted by the placenta of molar pregnancies is a risk factor for the generation of reset osmostat [16]. In addition, congenital reset osmostat has been associated with midline birth defects –such as cleft lip and palate– as well as corpus callosum agenesis and hypothalamic cysts [15].

Regarding the pathophysiology of the reset osmostat, which can be observed in weakened patients, the proposed mechanism revolves around a primary disturbance of osmoreceptor neuronal cells, known as "sick cell syndrome". This condition could be triggered by metabolic or nutritional cell dysfunctions and alterations of the plasma membrane permeability. The concept of sick cell syndrome consists of a membrane transport failure (sodium-potassium ATPase pump dysfunction), which leads to lower sodium excretion and lower potassium incorporation into the cells, resulting in increased intracellular sodium and decreased intracellular potassium levels.

This phenomenon, which reduces sodium concentration in the intravascular compartment, induces hyponatremia in severely ill patients. In this sense, it has been proposed that the sick cell phenomenon could be responsible for inducing hyponatremia in these patients by leading osmostat cells to change plasma osmolality threshold in order to adapt the whole organism to a new status of body salt and water handling.

Finally, another hypothesis postulates that a reset osmostat could result from the interruption of inhibitory pathways to the hypothalamus, which could induce vasopressin release, either by autonomic neuropathy or by carcinomatous invasion [17, 18].

Reset osmostat and hypernatremia

As it was mentioned above, although reset osmostat is classically identified as a cause of hyponatremia, it has also been described in the clinical context of hypernatremia, a condition known as "essential hypernatremia". This entity should be suspected in those patients who present stable hypernatremia regardless of variations in sodium and water intake.

Essential hypernatremia is usually associated with hypothalamic-pituitary structural lesions or the absence of a "posterior pituitary bright spot" on T1 imaging on magnetic resonance imaging. The posterior pituitary bright spot is a neurohypophyseal T1 hyperintense signal in the sella behind the adenohypophysis, which has been interpreted as proteins, phospholipid vesicles, or vasopressin hormone accumulation. The absence of a posterior pituitary bright spot has been associated with conditions such as craniopharyngioma, diabetes insipidus, and Langerhans cell histiocytosis.

The relation between the loss of the posterior pituitary bright spot and essential hypernatremia leads to the hypothesis that the hypernatremia could be due to damage in the thirst and osmoregulatory centers secondary to ischemic events (such as small vessel disease or stroke) or to autoimmune damage [15].

Reset osmostat diagnosis

Since reset osmostat can be suspected in patients presenting hyponatremia with normal extracellular volume, it should be distinguished from other causes of hyponatremia with similar volume status, such as the classical syndrome of inappropriate antidiuretic hormone secretion, as well as from mild forms of hyponatremia with low extracellular volume, such as renal salt wasting states. The diagnostic criteria for reset osmostat are as follows [15, 19–25]:

- Normal serum volume and low serum sodium level that maintains a sodium balance without correcting hyponatremia when salt was provided.
- Kidneys that retain their ability to excrete diluted urine. A reset osmostat patient shows normal water loading tests by excreting >80 % of the water load within 4 hours. However, it is worth noting that it is not recommended to perform this test in hyponatremic patients who have hyponatremia $\leq$ 125 mmol per L.
- Normal urinary ability to concentrate urine in response to fluid restriction.
- Normal values of serum uric acid (4-7.5 mg/dl) and normal values of fractional excretion of uric acid (4-11 %), in the absence of psychogenic polydipsia. It is worth mentioning that fractional excretion of uric acid can be increased when glomerular filtration rate is reduced (serum creatinine higher than 1.5 mg %), thus reducing the diagnostic efficacy of fractional excretion of uric acid in this setting.

As previously mentioned, a normal fractional excretion of uric acid value is an important indicator of reset osmostat, regardless of urine osmolality or serum uric acid levels, and it aids in distinguishing reset osmostat from classical syndrome of inappropriate antidiuretic hormone secretion and renal salt wasting, since both conditions typically have low serum

uric acid levels (<4 mg/dL), and elevated fractional excretion of uric acid (>11 %).

On the other hand, low fractional excretion of uric acid (<4 %) is usually evident in hyponatremic patients with real hypovolemia (e.g., Addison disease) or effective hypovolemia (e.g., cardiac failure, cirrhosis, etc.). Additionally, even though hyponatremic patients with psychogenic polydipsia have normal fractional excretion of uric acid values, they can be differentiated from reset osmostat by their large intake of water, polyuria, and excretion of very diluted urine (urine osmolarity usually <100 mOsm-L) [15, 18–20].

Reset osmostat clinical presentation

Regarding the clinical presentation of reset osmostat, early papers reported it as an asymptomatic condition. However, more recent studies show that most patients with hyponatremia are symptomatic (overt or paucisymptomatic). It has been reported that chronic hyponatremia can induce osteoporosis, as well as an elevated incidence of falls, and bone fractures. Moreover, psychomotor delay associated with reset osmostat hyponatremia has been documented. Therefore, the current view is that all hyponatremic patients should be treated [26–32].

Reset osmostat diagnostic algorithm

The reset osmostat diagnoses should be taken into account as a potential low serum sodium- inducing mechanism in patients suffering from hyponatremia with normal extracellular volume. Thus, based on the characteristics described above, the following diagnostic steps can be delineated for achieving reset osmostat diagnosis (see Figure 1):

- The first diagnostic step consists of evaluating the patient serum osmolality. If serum osmolality is <290 mmosl/L, then it is discarded as a normal serum osmolality hyponatremia (pseudohyponatremia) and a high serum osmolality hyponatremia (e.g., hyponatremia secondary to hyperglucemia). Therefore, this hyponatremia could be considered hypotonic.

- The second diagnostic step consists of evaluating the patient's serum uric acid level. If the level is normal (4-7.5 mg/dl), proceed to the third diagnostic step

- The third diagnostic step consists of evaluating the patient's fractional excretion of uric acid value, if the fractional excretion is 4-11 %, then the probability of reset osmostat diagnosis is very high.

- The fourth diagnostic step consists of identifying the condition inducing the reset osmostat, which means evaluating whether the reset osmostat is primary or secondary to

a particular disease. For this purpose, if the patient's medical record and antecedents—such as diabetes mellitus, alcoholism, or kidney transplant—are not sufficient to answer this question, then the following complementary studies should be performed:

- Nutritional evaluation: to rule out cachexia.
- TC scan (cerebral, thoracic, abdominal-pelvic) to rule out cirrhosis or oncologic disease.
- Gastrointestinal endoscopy to rule out digestive oncologic disease.

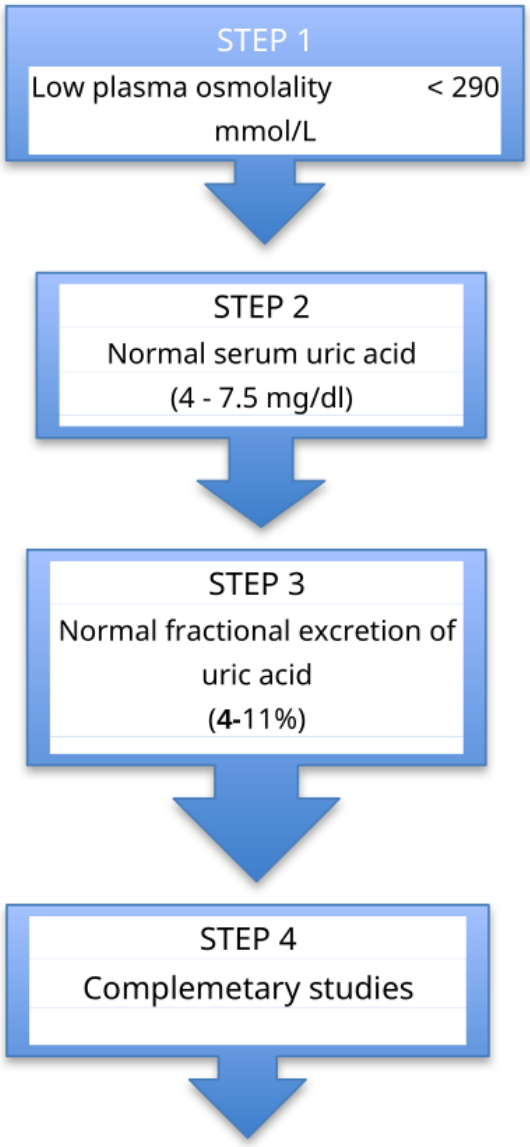

Figure 1. Reset osmostat diagnostic steps

Source: Author's elaboration.

- Neuromuscular evaluation to rule out stroke, dementia, parkinsonism, encephalitis and/or myopathies.

Reset osmostat treatment

Based on the above-mentioned negative consequences of chronic hyponatremia, it is clear that there is a need to treat hyponatremic patients with reset osmostat. This can be achieved by applying some of the following therapeutic strategies [8, 15, 32]:

1. Water restriction (the main treatment)
2. Salt supplementation (with limited effectiveness)
3. Use of V2 antidiuretic hormone receptor inhibitors (e.g., tolvaptan)
4. Hypertonic saline (depending on the patient's symptomatology)

Points 3 and 4 raise the question of osmotic demyelination; therefore, the rate of correction should be kept below 6 mmol/L within 24 hours to reduce the likelihood of such complication. It is worth pointing out that with water intake, the patient should avoid bouts of acute intake of large quantities of water to prevent acute hyponatremia with its dire consequences. The ingestion of a larger quantity of water could lead to seizures and even death. The use of tolvaptan can be limiting, mainly due to its cost when administered over a prolonged period of time. Finally, reset osmostat often resets to normal if it is the consequence of a reversible illness, for instance pneumonia.

Conclusion

Reset osmostat is one of the hyponatremia-inducing mechanisms, representing about 30 % of this condition. It is characterized by a low serum osmolality threshold, which consequently induces an antidiuretic hormone elevation at a lower plasma osmolarity while maintaining intact the capability of diluting urine and keeping sodium balance. Reset osmostat can be observed in some physiological (pregnancy) or pathological settings, reversible (infections, etc.) or irreversible (dementia, etc.) conditions, requiring always to be treated in order to avoid chronic hyponatremia complications.

Ethical statement

All authors declare no ethical conflicts or conflicts of interest.

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Authors contribution

Flavia P. Avallay: Data curation, Formal analysis, Writing – original draft, Writing – review & editing; Victoria P. Musso-Enz: Data curation, Formal analysis, Writing – original draft, Writing – review & editing; Gustavo Aroca-Martinez: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing; Carlos G. Musso: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

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