Best Practice & Research Clinical Endocrinology & Metabolism 26 Suppl. 1 (2012) S1–S6

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Hyponatraemia: an overview of frequency, clinical presentation and complications

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Keywords:
hyponatraemia
syndrome of inappropriate antidiuresis (SIAD)
syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
sodium

Hyponatraemia (defined as a serum sodium concentration <136 mmol/L) is the most frequently encountered electrolyte disturbance in clinical practice. It is classified according to volume status (hypovolaemia, hypervolaemia or euvolaemia), reflecting the relative proportions of water and sodium within the body. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most common cause of euvolaemic hyponatraemia. Although hyponatraemia is associated with poor prognosis and increased length of hospital stay, it is often poorly managed and sometimes underdiagnosed and undertreated. This article provides an overview of the frequency, pathophysiology and complications associated with this common clinical condition.

1. The European Hyponatraemia Network

The European Hyponatraemia Network is a pan-European educational programme driven by a steering committee comprised of nephrologists and endocrinologists from across Europe, who have clinical and research interests in hyponatraemia (Appendix 1). The primary aim of the European Hyponatraemia Network is to facilitate the exchange of ideas and to disseminate knowledge about the investigation and management of hyponatraemia between physicians from different specialties across Europe. In doing so, it is hoped to improve the diagnosis and treatment of hyponatraemia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). It should be noted that this condition may also be referred to as the syndrome of inappropriate antidiuresis (SIAD). This new term has been proposed in order to include rare patients with clinical features consistent with the presence of SIADH

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This supplement was commissioned by Otsuka Pharmaceutical Europe Ltd.
The European Hyponatraemia Network Academy meeting was organised and supported by Otsuka Pharmaceutical Europe Ltd.

who have no elevation in vasopressin levels due to the presence of gain-of-function mutations in the V_2 vasopressin receptor.[1] However, throughout this supplement we have used the term SIADH.

The inaugural European Hyponatraemia Network Academy Meeting was held on the 24th and 25th February, 2011, in Barcelona and was attended by approximately 40 nephrologists and endocrinologists. This supplement contains the proceedings of this meeting, in which issues surrounding the management of hyponatraemia, such as differential diagnosis, perspectives on hyponatraemia management and the treatment of hyponatraemia secondary to SIADH across Europe were addressed.

2. Frequency of hyponatraemia

Hyponatraemia, defined as a serum sodium concentration ($[Na^+]$) <136 mmol/L, is the most common electrolyte disturbance encountered in clinical practice. Mild hyponatraemia (serum $[Na^+]$ 130–135 mmol/L) has been estimated to occur in up to 30% of hospitalised patients[2] and moderate-to-severe hyponatraemia (serum $[Na^+]$ ≤125–129 mmol/L) is estimated to occur in up to 7% of hospitalised patients.[3,4]

The incidence of hyponatraemia can vary between hospitals and departments. A study performed in the Netherlands reported an increased incidence of hyponatraemia in the departments of surgery, internal medicine and intensive care (32%, 36% and 38%, respectively), compared with all other departments ($p < 0.05$).[4] Furthermore, the risk of developing hyponatraemia can increase with age compared with ambulatory patients, as reported in a study of 118 nursing home residents;[5] 18% of the nursing home residents were hyponatraemic compared with 8% of the similarly aged ambulatory patients ($n = 60$).

3. Pathophysiology and classification of hyponatraemia

Sodium is the principle cation in the extracellular fluid; thus the plasma concentration of sodium is the principal determinant of serum osmolality.[6] Hyponatraemia represents an excess of water relative to total body sodium, arising as a result of impaired water excretion by the kidneys or the depletion of sodium in excess of water. Hypotonic (dilutional) hyponatraemia is classified by the extracellular volume status into hypo-, eu- and hyper-volaemic hyponatraemia (this classification is summarised in Fig. 1).[7–9] Although this classification is useful, it should be emphasised that the clinical assessment of the extracellular fluid volume is difficult.[10,11]

- In hypovolaemic hyponatraemia both total body water and total body sodium are decreased. The relative decrease in total body sodium is greater compared with the decrease in total body water and this leads to hyponatraemia.
- In euvolaemic hyponatraemia total body sodium remains close to or slightly below normal while total body water is increased, leading to hyponatraemia. As this increase in total body water is distributed across the intracellular and extracellular fluid compartments, the patient will remain clinically euvolaemic.
- In hypervolaemic hyponatraemia there is an increase in both total body water and total body sodium, with hyponatraemia resulting from a relatively greater increase in total body water.

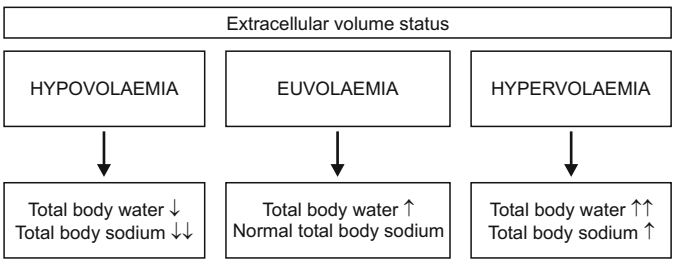

Fig. 1. Classification of hyponatraemia according to extracellular volume status. The lower tier of boxes illustrates the relative proportion of sodium and water within the body.

Under normal circumstances, serum [Na^+] and osmolality are maintained in a narrow range, between 136 to 145 mmol/L and 280 to 295 mOsm/kg of water, respectively.[12,13] This regulation is achieved through the secretion of vasopressin (also known as antidiuretic hormone) from the posterior pituitary and through the perception of thirst, both of which occur in response to increases in serum osmolality.[8] An increase in serum osmolality of 1–2% stimulates the release of vasopressin. Vasopressin facilitates the reabsorption of water by the kidneys into the bloodstream, restoring serum osmolality and therefore serum [Na^+].[8,14]

In SIADH, vasopressin secretion is unregulated and secreted despite hypotonicity of the serum.[15] This leads to retention of water by the kidneys and hypotonic euvolaemic hyponatraemia; SIADH is the most common cause of euvolaemic hyponatraemia.[16]

4. Clinical presentation and complications of hyponatraemia

The signs and symptoms of hyponatraemia can vary depending on the severity and duration of the condition; they include headache, nausea, vomiting, muscle cramps, disorientation, depressed reflexes, seizures and coma.[7,9] The symptoms, and any complications which may develop as a result, reflect the underlying cerebral pathophysiology of the hyponatraemia.[7,17]

Following the onset of hyponatraemia, water moves into the brain down an osmotic gradient leading to swelling of the brain (cerebral oedema). A few hours after the onset of hyponatraemia, the brain undergoes a process of volume adaptation, in which intracellular and extracellular solutes are extruded, inducing water loss and ameliorating brain swelling (illustrated in Fig. 2).[7,18]

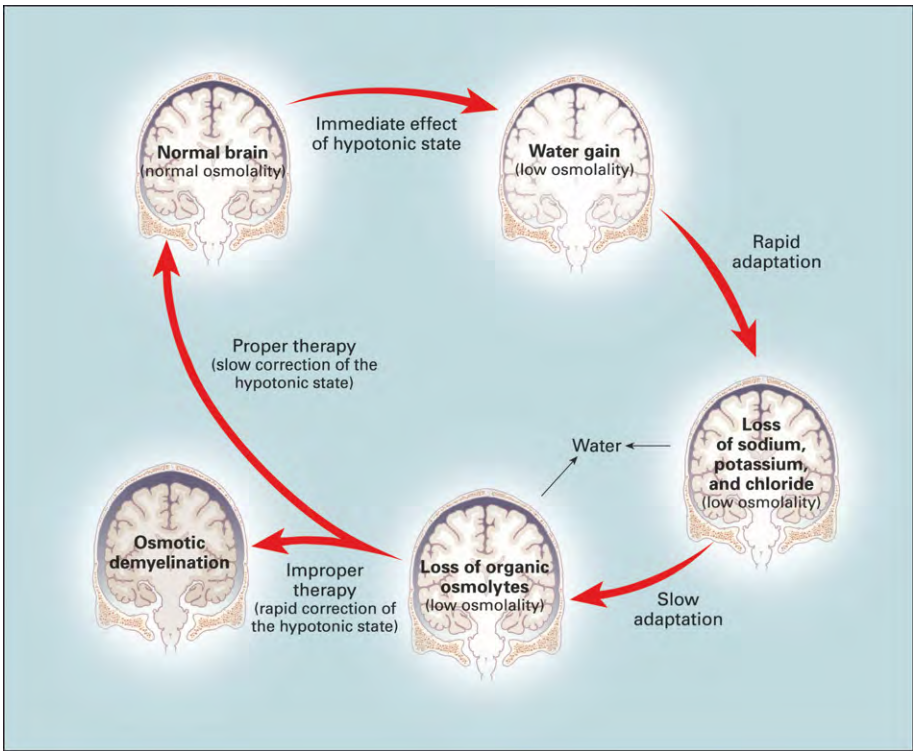

Fig. 2. Schematic diagram of brain volume adaptation to hyponatraemia. Under normal conditions, brain osmolality and extracellular fluid osmolality are in equilibrium. Reproduced with permission from Adrogué HJ et al. *N Engl J Med* 2000; **342**: 1581–1589.[7]

4.1. Rapid onset (acute) hyponatraemia

In cases of rapid onset hyponatraemia (i.e., developing in <48 hours), volume adaptation in the brain may not have time to take place. Severe neurological symptoms may appear because the swelling of the brain is limited by the cranium.[18] The complications of rapid onset hyponatraemia mainly reflect a failure of the volume adaptation process and continued swelling of the brain. In extreme cases this can lead to Cheyne-Stokes respiration, seizures, coma and herniation of the brainstem.[9]

4.2. Gradual onset (chronic) hyponatraemia

In gradual onset hyponatraemia (i.e., developing in >48 hours) the loss of solute from the cells within the brain is accompanied by a loss of fluid, which returns the volume of the brain towards normal.[18] Previously, mild, gradual onset hyponatraemia has often been thought to be asymptomatic; however, further investigation into this patient population has revealed complications associated with mild hyponatraemia (serum [Na^+] 130–135 mmol/L), which have not been addressed until recently. These complications include gait instability, falls, attentional deficits[19] and increased risk of fracture occurrence.[20–22] Furthermore, there is increasing evidence that hyponatraemia is associated with an elevated risk of osteoporosis compared to normonatraemia as a result of increased osteoclast activity and mobilisation of sodium stored within the bone matrix.[23,24]

5. The challenge of managing hyponatraemia

Despite the frequency of hyponatraemia in clinical practice, and the potential severity of some of its associated complications, the underlying cause of hyponatraemia is often unrecognised and consequently undertreated.[4,25,26] For example, although SIADH was first described over 50 years ago[27] it continues to be under-diagnosed by physicians, often as a result of a failure to order sufficient diagnostic tests.[25] Moreover, physicians treating patients with hyponatraemia may not fully understand the condition and the implications of different treatment options available to manage the condition. Conventional treatments such as water restriction are less targeted towards the underlying cause of hyponatraemia and may sometimes demonstrate limited efficacy and may also be challenging to use.[3,7,28] However, the recent availability of vasopressin receptor antagonists (also known as vaptans), which offer a targeted approach to the treatment of hyponatraemia secondary to SIADH, has stimulated renewed interest in the management of hyponatraemia. This interest has highlighted the need for improved education amongst physicians regarding the diagnosis of this condition and the clinical application of these therapies.

6. Summary

Despite being the most common electrolyte disorder encountered in clinical practice, hyponatraemia is sometimes underdiagnosed and undertreated. This may be compounded by that fact that conventional treatment options may exhibit limited efficacy and can be challenging to use. Therefore, there is an urgent need for improved education regarding the diagnosis and management of this important condition. The European Hyponatraemia Network is a pan-European programme with the aim of promoting discussion and facilitating the exchange of knowledge regarding the management of hyponatraemia between physicians from across Europe.

7. Acknowledgements

This supplement was commissioned by Otsuka Pharmaceutical Europe Ltd. and summarises the proceedings of a meeting organised and supported by Otsuka Pharmaceutical Europe Ltd. The authors have not received any honorarium in relation to this supplement. Otsuka Pharmaceutical Europe Ltd. has had the opportunity to comment on the medical content and accuracy of the article and editorial support has been provided by Otsuka Pharmaceutical Europe Ltd.; however, final editorial content resides with the authors and *Best Practice & Research: Clinical Endocrinology & Metabolism*.

Practice points

- Hyponatraemia is defined as a serum [Na^+] <136 mmol/L.
- Moderate-to-severe hyponatraemia is defined as a serum [Na^+] <130 mmol/L.
- Hyponatraemia is classified according to volume status, which reflects the relative proportion of total body water and total body sodium.
- SIADH is the most frequent cause of euvolaemic hyponatraemia.
- Despite the condition first being described almost 50 years ago, SIADH is underdiagnosed.

8. Conflict of interest

Prof. Thompson is on the Otsuka Pharmaceutical advisory board for tolvaptan and has received honoraria from Otsuka Pharmaceutical for speaking at symposia. Dr. Hoorn has received consulting fees from Otsuka Pharmaceutical.

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Appendix 1. Steering committee members of the European Hyponatraemia Network and guest speakers

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