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Hyponatremia and the syndrome of inappropriate antidiuretic hormone secretion
Old topic, new perspectives

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Despite hyponatremia being common, and of interest to general practitioners, physicians and surgeons, it is often poorly managed because of lack of a systematic approach to its investigation and treatment. New insight is now available into the effects of chronic hyponatremia on, for example, subtle neurological dysfunction, falls, osteoporosis, osteoporotic fractures and mortality. Approximately half of the cases of chronic hyponatremia are due to the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). It is crucial that this diagnosis is considered and a diagnostic algorithm is strictly followed prior to initiating treatment for hyponatremia, because the therapeutic approach for SIADH differs from that for other forms of hyponatremia. Moreover, once treatment has been initiated it becomes difficult to make sense of some of the tests commonly used to diagnose SIADH. V_2-receptor antagonists have revolutionized the treatment of SIADH, and experience of the use of these agents has now been documented. These agents are not indicated for the majority of forms of hyponatremia, and their use must be restricted to the selected population with confirmed SIADH.

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Περίληψη στο τέλος του άρθρου

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1. INTRODUCTION

Hyponatremia is the most common electrolyte imbalance. In ambulatory, randomly selected, healthy, elderly people living in the community, its prevalence is approximately 4%. This figure is much higher (up to 53%) in elderly institutionalized populations. The incidence of newly diagnosed hyponatremia in hospitalized patients is high and depends on the underlying diagnosis; e.g., 8% in pneumonia, and 10–56% in neurosurgical patients. Approximately 50% of chronic hyponatremia is due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Despite hyponatremia being common and of interest to general practitioners, physicians and surgeons, it is often poorly managed because of lack of a systematic approach to its investigation and treatment.[1] New insight into the effects of chronic hyponatremia is now available, on for example, subtle neurological dysfunction, falls, osteoporosis and mortality. V_2-receptor antagonists have revolutionized the treatment of SIADH and experience of the use of these agents has been documented, but they are not indicated for the majority of forms of hyponatremia, and their use must be restricted to a selected population with confirmed SIADH.

2. DIAGNOSIS

SIADH refers to the presence of inappropriately concentrated urine (urine osmolality >100 mOsm/kg) in the presence of plasma hypotonicity and hyponatremia. It is a diagnosis of exclusion, which is of great importance, as when the diagnosis of SIADH is made mistakenly, inappropriate or unnecessary treatment may be instituted. We suggest 12 points that should be considered prior to the diagnosis of SIADH, as shown in table 1. It should be emphasized that, although free water excretion is impaired in SIADH, sodium handling is intact, as both the renin-angiotensin-aldosterone system and atrial natriuretic peptide function

Table 1. 12-point check list for diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Parameter	Comments
Plasma sodium	Low
Plasma osmolality	Low; <275 mOsm/kg
Urine osmolality	High; >100 mOsm/Kg
Urine sodium	High; >30; usually >40 mOsm/kg; provided dietary salt and water intake is normal
Thyroid axis	Normal
ACTH/cortisol axis	Normal
Diuretics	Discontinued; washout period is 2/52†
Renal function	Normal*
Potassium	Normal or low normal
Uric acid	Low
Triglycerides and total protein	Normal
Glucose	Normal

† This is more of an issue with thiazide rather than loop diuretics
* Urine volume is usually reduced; conversely acid-base balance is intact
ACTH: Adrenocorticotropic hormone

normally. Natriuretic mechanisms are activated secondarily following initial volume expansion, with resultant sodium and water loss in urine and restoration of near-euvolemia. As a general rule, most cases of hyponatremia are associated with plasma hypotonicity. Based on clinical criteria a stratification can be made between hypovolemia (e.g., with salt-losing nephropathy, diarrhea and vomiting), euvolemia (e.g., with SIADH, severe hypothyroidism, Addison's disease and pregnancy) and hypervolemia (e.g., with congestive cardiac failure, nephrotic syndrome and liver cirrhosis). In the case of plasma hypervolemia, excessive water intake (e.g., with primary polydipsia) or reduced solute intake (e.g., with excessive beer consumption) may be the cause. The first step recommended in the management of such patients, given the poor diagnostic accuracy of the routine clinical examination on assessing the fluid balance status, is urine osmolality; with a value of urine osmolality ≤100 mOsm/kg, relative excess water intake is the likely cause whereas with a value of >100 mOsm/kg simultaneous measurement of urine sodium is required; if urine sodium is ≤30 mmoL/L low effective arterial volume is a likely culprit, whereas a concentration of >30 mmoL/L points to either diuretic use, or a SIADH-like picture or SIADH *per se*.[2]

Measurement of lipids and total proteins is indicated, as hyperlipidemia and hyperproteinemia can cause pseudohyponatremia; they induce *in vitro* interference, resulting in apparent hyponatremia and with a normal measured (but not estimated) plasma osmolality (osmolal gap). Conversely, hyperglycemia can cause hyperosmotic hyponatremia. In clinical practice many cases are encountered of SIADH coupled with hyperglycemia, which when treated (e.g., with insulin) results in an increase of sodium levels; the degree that the hyponatremia is due to glucose can be estimated using relevant tables and equations.[3] Finally, both low cortisol and thyroxine appear to impair renal free water excretion, inducing an SIADH-like picture, as cortisol appears to impair secretion of antidiuretic hormone (ADH); these hormones should always be tested for and deficiencies that are identified should be promptly treated. We therefore recommend measuring free T4, thyroid stimulating hormone (TSH) and 9am cortisol in all such patients; the short Synacthen test is reserved for suspicious cases or those with a low morning cortisol level.

2.1. Subtypes of SIADH

As a general rule, plasma ADH (vasopressin) is difficult to measure and is not used in routine clinical practice, but its measurement in the research setting has improved the understanding of this heterogeneous condition and made possible the current classification of the different types of SIADH. Specifically, type A SIADH refers to fluctuating and unregulated ADH that varies widely and bears no relation to the plasma osmolality, while in type B SIADH there is a fixed but modest elevation of ADH. Type C SIADH refers to a "reset osmostat" phenomenon; serum sodium is constantly mildly lowered (e.g., 125–135 mmoL/L) and the ADH response for this level of sodium is normal; it behaves and responds appropriately, as if the sodium was within the normal range. It is important for type C to be thought of and identified, as an attempt to raise the sodium in such instances is unnecessary. It should be suspected when the sodium is mildly reduced but does not alter with changes in the intake of water and salt. Lastly, type D SIADH involves appropriate ADH secretion, according to the plasma osmolality, but with concentrated urine. One way that this occurs is via an activating V_2-receptor germ cell mutation,[4–6] which causes the transit of aquaporins in the apical membrane of the collecting tubules and therefore water reabsorption. Similarly, post-receptor defects have been described that also cause this pattern. It should be considered in young patients with unexplained hyponatremia, in which case a water load test with vasopressin measurements is a reasonable screening test, while AVPR2 sequencing provides the definitive molecular genetic diagnosis.[6] When the diagnosis is confirmed, long-term water restriction is usually effective in controlling this condition.

3. CAUSES

The causes of SIADH are summarized in table 2. It is of note that we have seen many cases of hyponatremia and SIADH as the first presentation of small cell lung carcinoma. In such patients, hyponatremia surveillance can be used as a "tumor marker" of disease recurrence. The medication history of these patients should be carefully interrogated to identify drugs that can cause hyponatremia with/without SIADH. SIADH has been reported in the post-operative state and is a common scenario on days 6–7 after transsphenoidal pituitary surgery, often following a bout of diabetes insipidus. In this scenario the possibility of partial ACTH deficiency should be entertained. Genetic causes have been described, as above, and also polymorphisms in the hypothalamic osmoreceptor transient receptor potential vanilloid type 4 (TRV4) have been linked with mild hyponatremia.[7] Although idiopathic SIADH has been described in ambulatory geriatric populations,[8] medical practitioners should be alert to the possibility of an occult tumor (e.g., small cell lung cancer) and rarer entities, such as temporal arteritis.[9]

4. COMPLICATIONS

4.1. Neurocognitive dysfunction and falls

Even mild hyponatremia can lead to cognitive deficits and gait disturbances. In a case-control study, one third of elderly patients (>65 years) who had an in-patient fall were hyponatremic; low sodium was associated with an adjusted odds-ratio of 3.7 for falls.[10] A prospective study demonstrated improved nerve conduction velocities of the left peroneal nerve when profound hyponatremia (Na <125 mmoL/L) was corrected.[11] An increase in sodium following 30 days of oral administration of tolvaptan (see the management section) was accompanied by significant improvement on the physical component scores of the SF-12 general health survey questionnaire (physical function, body pain, general health and physically limited accomplishment) and borderline significant improvement on the mental component scores (vitality, social function, calmness, sadness and emotionally limited accomplishment).[12]

4.2. Osteoporosis and fractures

A recent meta-analysis revealed a 60–100% increase in the risk of osteoporosis and fractures in individuals with hyponatremia compared to normonatremic control subjects.[13] The underlying mechanism has not yet been fully described, but there is some evidence of reduced bone quality in these patients, and subtle cognitive defects and an increased risk of falls may be contributing factors.

4.3. Mortality

Hyponatremia has been associated with reduced survival in breast cancer, colorectal cancer, lung cancer and lymphoma, and a trend towards reduced progression-free survival in all cancers.[14] A similar association between hyponatremia and increased mortality has been confirmed in a wide spectrum of patient groups, including hospitalized patients,[15] patients with respiratory problems, such as chronic obstructive pulmonary disease (COPD)[16] or pulmonary infections,[17] patients with cirrhosis,[17] chronic kidney disease and those on hemodialysis,[18] and patients with heart disease, such as decompensated heart failure[19] and myocardial infarction.[17] Overall, a sodium level of <130 mmoL/L exhibits good discriminatory power for predicting mortality.[16,17]

Table 2. Causes of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Category	Main culprit conditions
CNS disease	Vascular (e.g., infarction and hemorrhage), infections (e.g., meningitis and encephalitis), inflammatory (e.g., SLE, demyelination), psychosis
Pulmonary disease	Infections (bacterial, viral, fungal and TB), asthma, pneumothorax, bronchiectasis, mechanical ventilation
Malignancy	Small cell lung cancer, mesothelioma, head and neck tumors, hematological malignancies, extrapulmonary small cell carcinomas
Drugs	SSRIs, TCAs, MAOIs, antipsychotics, carbamazepine, sodium valproate, nicotine, opiates, (high-dose) cyclophosphamide, amiodarone, ecstasy, oxytocin, NSAIDs
Others	Acute intermittent porphyria, post-CVA, severe pain, AIDS, post-operatively, pituitary surgery, nausea, hereditary
Idiopathic	

CNS: Central nervous system, SLE: Systemic lupus erythematosus, TB: Tuberculosis; SSRIs: Selective serotonin reuptake inhibitors; TCAs: Tricyclic antidepressants, MAOIs: Monoamine oxidase inhibitors, NSAIDs: Non-steroidal anti-inflammatory drugs, CVA: Cerebrovascular accident, AIDS: Acquired immune deficiency syndrome

5. MANAGEMENT

Identification and treatment of the underlying cause, whenever possible, is paramount. As a general principle, acute hyponatremia (developed within the past 48 hours) can be corrected more "acutely" (i.e., faster) than chronic hyponatremia, which should be reversed in a more "chronic" (i.e., slower) fashion. Fluid restriction to, for example ≤750 mLs per day, has traditionally been the first step; this is often, but not always, an effective strategy in correcting hyponatremia, but it is usually difficult to implement in acutely ill and hospitalized patients. Moreover, fluid restriction is unlikely to correct the hyponatremia if the urine osmolality is high, e.g., >500 mOsm/kg. The addition of salt tablets, at a dose of 9 g per day, can increase solute output in urine, with consequent sodium and free water loss and a resultant rise in plasma sodium. This can, however, be difficult to implement in patients with cancer. Furosemide (e.g., 20 mg bid) can be added if hyponatremia is resistant to the aforementioned measures; it is effective when the urine osmolality is at least twice as high as plasma osmolality. Urea can also enhance urine solute output, but it is not readily available, although it has, surprisingly, re-emerged in the recent European guidelines on this topic.[1] In a retrospective review of 29 patients with chronic SIADH it was observed that about one third of the patients could be treated with mild water restriction (1.5–2 L per day) alone; all these patients had initial urine osmolality of <400 mOsm/kg.[20] The rest were also effectively managed with mild water restriction coupled with urea (at 15–30 g per day).[20]

Another option is demeclocycline, which works by inducing a partial diabetes insipidus state, and can be used in addition to fluid restriction at a dose of 300 mg bid or tds escalating to 1.2 g per day if necessary; it is usually slow to act. Side effects of demeclocycline include nausea and vomiting, acute kidney injury and photosensitivity. Lithium works in a similar fashion and can be used as an alternative to demeclocycline, but given its narrow therapeutic range and adverse effects profile, it is not an agent we tend to use for SIADH in everyday clinical practice.

The new development in recent years is the use of selective V_2-receptor antagonists (e.g., tolvaptan) for the treatment of SIADH. These function by blocking the action of ADH and impairing the expression of aquaporins in the collecting tubules of the kidneys, with consequent free water loss. It is an expensive medication, but our experience is that it aids the earlier discharge of patients from hospital and thus may incur indirect savings. The sodium increment that it induces may also permit the initiation of definitive therapy for the underlying cause, such as chemotherapy for small cell lung carcinoma. The recommended starting dose is 15 mg per day and the dose can be slowly escalated if the targets are not achieved. Our own experience on the use of this medication has been based on half that dosage, at 7.5 mg, which we have found to be safe and effective.[21] One of the major concerns with these medications is overcorrection of hyponatremia, which would predispose to central pontine myelinolysis, which has been reported on rare occasions in patients exposed to tolvaptan.[22] A rapid increase in sodium levels (a rise in sodium by >12 mmoL/L in the first 24 hours) is seen in 2–4% of patients taking these medications, although this proportion is likely to be higher with the more recent, stricter criteria.[2] With a dose of 7.5 mg this complication appears to be less common.[21] We suggest the key to successful utilization of this medication is supervision of the management by an experienced endocrine team, with close monitoring of sodium. In phase III clinical trials, tolvaptan has not been utilised with serum sodium levels of less than 120 mmoL/L. It is sensible to follow this criterion in clinical practice, and as a general rule to prefer hypertonic saline in such instances of severe hyponatrenia. Another point to emphasize is that tolvaptan can increase the thirst and thus it is recommended to allow all patients receiving these medications free access to water. It should be avoided in confused patients and those with a reduced level of consciousness (and hence we recommend avoidance, or at least extreme caution with its use for patients in intensive care). If demeclocycline has been trialled prior to the use of tolvaptan, a washout period of about two days should suffice.

Another development is the extent to which the "vaptans" improve neurocognitive function. The well-designed randomized placebo-controlled SALT trials demonstrated some improvement in neurocognitive abilities in patients receiving tolvaptan (alongside overall improved sodium levels).[23] These findings, however, were limited by a short follow-up period, and other studies have not yet reproduced the results. Another concern was raised when tolvaptan was investigated for use in autosomal dominant polycystic kidney disease;[24,25] its observed association with abnormal liver function tests resulted in an FDA warning for its use to be avoided in patients with known liver disease, and to be limited to no more than 30 days. It is sensible to monitor liver function in all patients receiving these medications and check them more urgently in the event of relevant symptomatology. Overall, inpatient initiation is recommended, but some newer studies have reported that outpatient initiation of tolvaptan at a dose of 7.5 mg can also be safe, provided the appropriate infrastructure and protocols are in place.[26]

For more acute hyponatremia (development within past 48 hours) and or severe (associated with neurological complications, such as reduced level of consciousness, seizures and coma, often with sodium <120–125 mmoL/L), hypertonic (3%) saline is recommended. The use of hypertonic saline has regained ground in recent years, as reflected in the recent guidelines.[2] Dose-wise, 150 mL can be infused over 20 min, after which the serum sodium should be re-checked, and while waiting for the results, a repeat infusion of 150 mL of 3% hypertonic saline should be given over 20 min; this regime could be repeated until the symptomatology resolves or until a target of 5 mmoL/L initial rise in serum sodium levels is achieved.[2] Complex equations are available for calculating the rate of infusion in such circumstances, such as the Adrogue-Madias formula.[27]

Finally, in cases of over-rapid correction of hyponatremia, such as with a serum sodium increase of >10 mmoL/L in the first 24 hours or >8 mmoL/L in any 24 hours thereafter, the recommendation is for re-lowering the serum sodium.[1] This can be achieved by infusion of 10 mL/kg body weight of electrolyte-free fluid (e.g., dextrose) over 1 hour under close monitoring of fluid balance,[1] ideally in the intensive care setting; the use of IV desmopressin 2 μg may be considered in such instances,[1] under specialist supervision.

6. CONCLUSIONS

Hyponatremia is not merely an incidental finding, but an independent risk factor for morbidity, including neurocognitive defects, falls, osteoporosis and fractures, and for mortality. A structured approach by a specialist team is paramount to the assessment of hyponatremia, including the diagnosis of SIADH. There is no "one way fits all" approach to its management, which depends on the underlying cause(s), and on the local availability of, and experience with, the various medications.

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ΠΕΡΙΛΗΨΗ

Υπονατριαιμία και σύνδρομο απρόσφορης έκκρισης αντιδιουρητικής ορμόνης: Παλαιά θέματα και νέες προοπτικές

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Παρά το γεγονός ότι η υπονατριαιμία είναι ένα κοινό θέμα και ενδιαφέρει τους γενικούς ιατρούς, τους παθολόγους και τους χειρουργούς, συχνά αντιμετωπίζεται ανεπαρκώς λόγω της έλλειψης συστηματικής προσέγγισης, ολοκληρωμένης επεξεργασίας και θεραπείας. Νέα δεδομένα για την επίδραση της χρόνιας υπονατριαιμίας είναι τώρα διαθέσιμα. Για παράδειγμα, φαίνεται να συσχετίζεται με ήπια νευρολογική δυσλειτουργία, πτώσεις/κακώσεις, οστεοπόρωση, οστεοπορωτικά κατάγματα και με αυξημένη θνητότητα. Περίπου οι μισές από τις χρόνιες περιπτώσεις υπονατριαιμίας οφείλονται στο σύνδρομο απρόσφορης έκκρισης αντιδιουρητικής ορμόνης (SIADH). Είναι απολύτως σημαντικό να λαμβάνεται υπ' όψη μια τέτοια διάγνωση και να ακολουθείται αυστηρά ένας διαγνωστικός αλγόριθμος πριν από την έναρξη της θεραπείας για υπονατριαιμία. Αυτό οφείλεται στο γεγονός ότι η θεραπευτική προσέγγιση για το SIADH διαφέρει από άλλες υπονατριαιμίες. Επί πλέον, μόλις αρχίσει η θεραπεία, γίνεται δύσκολη η κατανόηση ορισμένων από τις δοκιμασίες που χρησιμοποιούνται συνήθως για τη διάγνωση του SIADH. Οι ανταγωνιστές του υποδοχέα V_2 έχουν φέρει επανάσταση στη θεραπεία του SIADH και υπάρχει πλέον η εμπειρία σχετικά με τη χρήση των εν λόγω παραγόντων. Παρ' όλα αυτά, η συγκεκριμένη φαρμακευτική αγωγή δεν ενδείκνυται για την πλειονότητα των περιπτώσεων υπονατριαιμίας, αλλά η χρήση τους πρέπει να περιορίζεται σε έναν επιλεγμένο πληθυσμό με επιβεβαιωμένο SIADH.

Λέξεις ευρετηρίου: ΑΕΑΔΟ, Διάγνωση, Διαχείριση, Επιπλοκές, Σύνδρομο απρόσφορης έκκρισης αντιδιουρητικής ορμόνης, Υπονατριαιμία

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