MANAGEMENT OF HYPONATRAEMIA IN AN OUTPATIENT SETTING

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ABSTRACT

Hyponatraemia is a common blood abnormality encountered in an outpatient setting. With a suitable clinical approach and appropriate investigations, a cause can be found in most patients. The aim of this review is to provide a simple framework to achieve a diagnosis, and highlight certain situations in which a specialist referral is warranted.

Keywords: hyponatremia, water-electrolyte imbalance, inappropriate ADH syndrome

INTRODUCTION

With the popularity of health screening programs, abnormal blood results are being detected more frequently. The first point of contact for most people would be their family doctor, who has to decide whether the results are significant. Of these abnormalities, one of the most common is hyponatraemia. The aim of this review article is to enable family physicians to diagnose and treat easily reversible causes of hyponatraemia. In addition, certain situations are highlighted in which specialist referral may be more appropriate.

MATERIALS AND METHODS

A literature search was carried out on Medline and other relevant internet resources like *Endotext.com* and *eMedicine* to select articles which could contribute to the understanding of this subject. Only articles in English were selected, and priority was placed on those that dealt with management of hyponatraemia in an outpatient setting. The information obtained is presented in this paper as an educational review for family physicians.

RESULTS

Sodium and Osmolality

Sodium is the dominant extracellular cation and its concentration is maintained under tight control by homeostatic mechanisms involving thirst, pituitary secretion of anti-diuretic hormone (ADH), and renal sodium handling. Normal serum sodium is between 135-145 mmol/L. Hyponatraemia is defined as a serum sodium less than 135 mmol/L, and is considered severe when the concentration is less than 120 mmol/L[1].

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Generally, hyponatraemia is not symptomatic unless it causes an equivalent drop in serum osmolality. A hypo-osmolar state is defined as a serum osmolality less than 260 mOsm/kg, and always indicates an excess of total body water relative to body solutes. This can be caused by water retention, solute loss or a combination of both[2].

In the past, hyponatraemia has been erroneously diagnosed due to analytical interference from high levels of serum lipids or plasma proteins, especially in familial hyperlipidaemias and multiple myeloma. This is not an issue now as modern laboratories use ion-selective electrodes for sodium measurement[3], and recheck low values with a second method.

Neurological Manifestations

The symptoms of hyponatraemia are mostly neurological, reflecting vulnerability of neurons to osmotic change. If the onset of hyponatraemia is chronic (> 72 hours), neurons adapt by losing intracellular solute. Chronic hyponatraemia is asymptomatic or manifests only mild symptoms. It does not cause major problems by itself, and there is no evidence of brain swelling. On the other hand, if hyponatraemia is acute (< 48 hours), cerebral oedema can result in significant morbidity and death[4].

Volume Status and Aetiology

Hyponatraemia occurs in one of three settings: volume depletion, euvolaemia, and volume expansion.

Volume Depletion

Diarrhoea is a common cause of hyponatraemia due to volume depletion. When significant, it manifests clinically as orthostatic hypotension, tachycardia, decreased skin turgor, and dry mucous membranes. Fluid loss in itself does not cause hyponatraemia, as the lost fluid is usually isotonic or hypotonic relative to plasma. Rather, it is the physiological compensation to intravascular volume depletion that eventually results in a hyponatraemic state.

In response to volume depletion from any cause (diarrhoea, vomiting, diuretic use, blood loss), ADH is secreted by the posterior pituitary and acts via vasopressin V2 receptors on renal collecting ducts to cause migration of aquaporin-2 water channels to the apical membrane. This increases permeability of the collecting duct to water and promotes water reabsorption[5]. Simultaneously, reduced renal perfusion activates the renin-angiotensin cascade, causing the kidneys to avidly retain sodium. The net effect is an appropriate increase in sodium and water retention, with output of low-volume low-sodium (< 20 mmol/L) urine. The thirst mechanism in the hypothalamus is activated[6], causing the person to drink more

water or other low-solute liquid to restore fluid losses from diarrhoea. Hyponatraemia develops if fluid intake exceeds the capacity of the kidney to excrete free water.

Euvolaemia

The most common cause of euvolaemic hyponatraemia is the syndrome of inappropriate ADH secretion (SIADH). A diagnosis of SIADH can be made only when there is normal renal, adrenal, and thyroid function, and when hypotension and hypovolaemia have been excluded[7].

Many conditions can cause SIADH, and are broadly grouped into four categories: chest diseases, neurological diseases, neoplastic diseases and drugs. Increased urinary sodium loss is suggestive of SIADH, but its absence does not rule out the diagnosis. Significant urinary sodium loss (> 40 mmol/L) and hyponatraemia coexist in only a few conditions: SIADH, hypocortisolism, and diuretic use.

Another situation in which euvolaemic hyponatraemia occurs is when the osmotic threshold is reset. There is usually a linear relationship between serum osmolality and ADH, with a minimum osmotic threshold below which ADH secretion is negligible. A similar relationship also exists between serum osmolality and thirst. While there is significant variation of the osmotic threshold between individuals, this is remarkably constant within an individual over time[8]. In pregnant women and older people, this threshold is relatively low thus giving a tendency towards mild hyponatraemia (125-135 mmol/L). Typically these people are asymptomatic, and the sodium level remains stable for long periods.

Volume Expansion and Oedematous States

Oedema results when there is fluid movement from the intravascular space into the interstitium caused by an imbalance in Starling's forces across capillary walls.

Patients with advanced renal failure (glomerular filtration rate < 5 ml/min) have intravascular volume expansion and hyponatraemia resulting from excess water retention by the kidney in relation to sodium. The raised capillary hydrostatic pressure forces fluid into the interstitium causing tissue oedema. Oedema in congestive cardiac failure occurs through a similar mechanism where the raised capillary hydrostatic pressure is a result of venous congestion. Renal hypoperfusion from poor cardiac output causes hyponatraemia through the same processes as in advanced renal failure. This is compounded by intense diuretic therapy coupled with rigid sodium restriction.

In contrast, fluid movements out of the vascular compartment in other oedematous states like nephrotic syndrome and cirrhotic liver disease are caused by reduced capillary colloidosmotic pressure. This results in relative intravascular volume depletion, which causes hyponatraemia through the same compensatory changes as in true volume depletion.

Water Intoxication

In the absence of ADH, normal kidneys can excrete up to 20 litres of dilute urine (< 100 mOsm/kg) per day. Thus to induce hyponatraemia, an individual must consume more than 20 litres of water within a 24 hour period. Fluid intake of this magnitude is occasionally seen in the context of binge drinking of beer (beer potomania) and psychogenic polydipsia. If renal function is adequate, hyponatraemia from excessive water intake resolves rapidly on fluid restriction.

A Clinical Approach

Initial Assessment

The first step for the physician is to assess on an individual basis whether the patient's condition is serious enough to merit referral to a specialist centre. If symptoms of hyponatraemia are moderate or severe (Box 1), significant cerebral oedema is present and the patient should be admitted to hospital as soon as circumstances permit, regardless of the absolute sodium level. If the patient has only mild symptoms or is asymptomatic, but sodium is less than 130 mmol/L, then it is likely that hyponatraemia is chronic and well-adapted. In this case, rapid correction (> 12 mmol/L increase per 24 hours) should be avoided unless the patient is comatose or fitting, because of the risk of osmotic demyelination syndrome[4]. This can be managed with simple fluid restriction (500 ml/day), and referred early to an internal medicine specialist for evaluation.

If hyponatraemia is mild (serum sodium > 130 mmol/L) and the patient is asymptomatic, significant sequelae are unlikely[9] and this can be safely managed by the family physician.

History

A careful drug history is mandatory to identify commonly prescribed drugs that cause hyponatraemia (Box 3), and these should be discontinued if possible. Both thiazide diuretics and selective serotonin reuptake inhibitors (SSRIs) can cause significant hyponatraemia.

Thiazides inhibit sodium reabsorption in the distal tubule, resulting in salt wasting and impairing the kidney's diluting ability. Once volume depletion occurs, non-osmotic release of ADH causes further water retention through renal and thirst

Box 1: Manifestations of Hyponatraemia

- Asymptomatic
- Mild: headache, lethargy, dizziness
- Moderate: ataxia, mild confusion
- Severe: delirium, seizures, coma

Box 2: Diagnostic criteria for SIADH

- Low serum sodium and osmolality
- Urine osmolality > 100 mOsm/L
- Absence of volume contraction
- Low serum urea and creatinine
- Normal renal, adrenal and thyroid function

mechanisms. Thiazide-induced hyponatraemia may last for up to two weeks after stopping the drug. This responds well to simple fluid restriction (500 ml/day) until hyponatraemia resolves. Loop diuretics much less commonly cause hyponatraemia.

SSRIs cause hyponatraemia through direct stimulation of ADH release. Elderly patients are at particular risk of severe hyponatraemia[10] when both thiazides and SSRIs are co-prescribed, as they have a synergistic effect[11].

In the young, Ecstasy (3,4-methylenedioxymethamphetamine, a designer drug derived from amphetamine) abuse can cause rapidly progressive and potentially fatal hyponatraemia. Clubbers use it to stay awake and dance all night. Previous health warnings largely focused on the risk of hyperthermia due to temperature dysregulation and dehydration, and this led to the recommendation that users should drink large volumes of water. Evidence has emerged that Ecstasy and its metabolites are potent stimulators of ADH release from the posterior pituitary[12] and party-goers are especially prone to hyponatraemia due to a combination of excessive sweating, drug-induced SIADH, and drinking copious amounts of alcoholic beverages. Patients are generally young, and the onset of life-threatening cerebral oedema from acute hyponatraemia can be rapid, resulting in cerebellar tonsillar herniation and death[13].

Box 3: Drugs that can cause hyponatraemia

- Diuretics
- Anti-depressants
- Carbamazepine
- Opiates
- Sulphonylureas (esp. chlorpropamide)
- Haloperidol
- Ecstasy (3,4-MDMA)

Box 4: Threshold for referral

- Manage in clinic: asymptomatic, $Na^+ > 130$
- Refer to specialist clinic: mild symptoms or asymptomatic, $Na^+ < 130$
- Admit to hospital: moderate or severe symptoms regardless of Na^+ level, history of Ecstasy abuse

Box 5: Initial investigations

- Serum Na^+, osmolality
- Urine spot Na^+
- Thyroid function test
- 8 am cortisol
- Liver function tests & serum albumin
- Creatinine

Moreover, street Ecstasy is commonly adulterated with amphetamine, caffeine, and other pharmacoactive substances. Clinical evaluation is difficult as multiple drug effects may overlap. As such, the authors strongly recommend that all hyponatraemic patients with a recent history of Ecstasy or related drug use should be admitted to hospital for monitoring.

SIADH may be the first presentation of an occult pulmonary or non-pulmonary neoplasm. Hence a history of weight loss associated with hyponatraemia, especially in the elderly with other risk factors, should prompt a referral to an internal medicine specialist for further workup.

While hyponatraemia associated with diarrhoea and vomiting would commonly be attributed to gastroenteritis, adrenal insufficiency can present in a similar fashion. Hence, hyponatraemia associated with chronic diarrhoea and weight loss should lead one to consider the diagnosis of hypoadrenalism. The presence of hyperkalaemia further supports this, although it need not be present in all cases.

Physical Exam and Investigations

It is important to assess hydration and volume status (skin turgor, mucosal moisture, jugular venous pressure, postural blood pressure, peripheral and pulmonary oedema). Euvolaemic patients should be assessed for causes of SIADH. In contrast to oedematous states, the cause of euvolaemic hyponatraemia may not be immediately obvious, and initial investigations in Box 5 may be helpful.

Initial Management

Patients with fluid and electrolyte loss from gastroenteritis can be treated with oral rehydration salts. If unavailable, then one part of unsweetened pure fruit juice, lemonade or cola diluted with four parts of water can be given. These drinks should not be given undiluted as they may actually increase diarrhoea and dehydration through osmotic changes[14].

Follow-up Visit

The patient can be followed-up after a week to review results. Repeat serum sodium can be done on the clinic visit day, and if normal, nothing further needs to be done. If it has dropped below 130 mmol/L or symptoms have worsened, then the patient should be referred for specialist follow-up.

Hypothyroidism should be corrected, and serum sodium will normalise once thyroid function has improved. Hyponatraemia secondary to hypothyroidism is usually mild (130-135 mmol/L), but can be severe when it co-exists with hypoadrenalism in polyglandular autoimmunity[15].

Serum albumin, creatinine, and liver function tests, when correlated with clinical examination, allow for screening of oedema-causing states. Referral to a nephrologist, hepatologist, or cardiologist is appropriate once the diagnosis is made.

SIADH can be diagnosed according to the criteria in Box 2, and an 8 am cortisol less than 275 nmol/L suggests adrenal insufficiency. One should be especially cautious in the elderly as up to 20% with serum sodium less than 130 mmol/L have secondary hypoadrenalism from pituitary dysfunction[16]. Reset

Table 1. Volume Status and Aetiology of Hyponatraemia

	Volume Status	Volume depleted Euvolaemic	Volume expanded
Causes	diarrhoea, vomiting, excessive sweating, inadequate water intake, diuretic use, blood loss	SIADH, hypothyroidism, hypocortisolism, reset osmotic threshold	oedema-causing states (renal, hepatic and cardiac disease)
Serum Na^+ (mmol/L)	Low	Low	Low
Urine Na+ (mmol/L)	< 20*	> 40	< 20*
Urine appearance	concentrated	concentrated	concentrated
Clinical signs	Low jugular venous pressure Postural BP drop	Varies according to aetiology aetiology	Peripheral pitting oedema

** may be > 20 with concomitant diuretic use*
Table adapted from Yeates et al.[9]

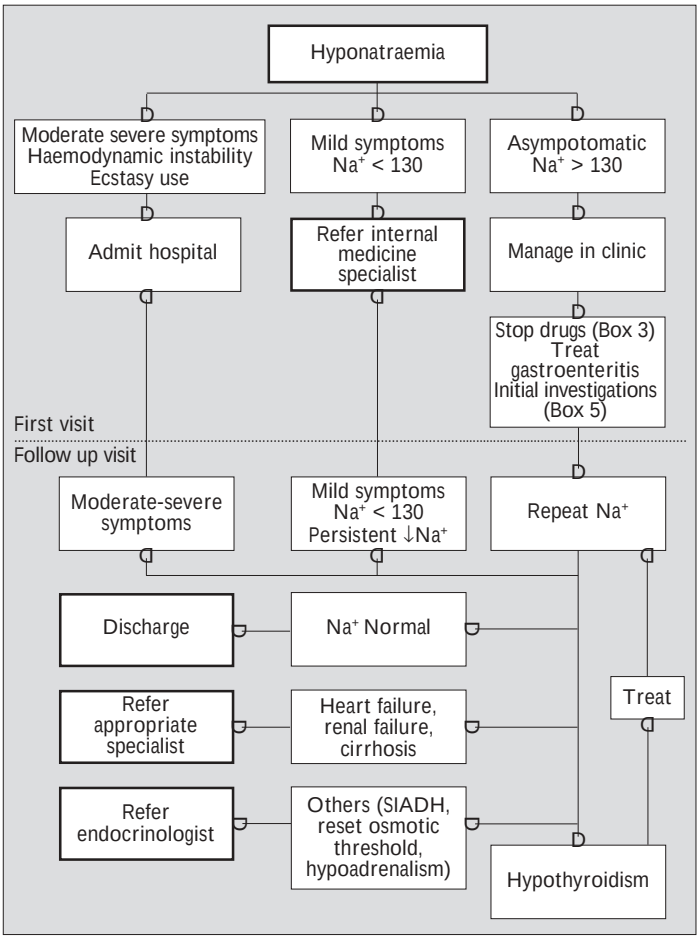

Fig 1. Algorithm for management of hyponatraemia in a clinic setting

osmotic threshold is a diagnosis of exclusion, and together with SIADH and hypoadrenalism, should be investigated further by an endocrinologist.

CONCLUSION

While there is no best way for management of hyponatraemia in a clinic setting, a suggested algorithm is given in Figure 1. It is hoped that this review will enable family doctors to manage this condition with some confidence, and recognise situations where referral to a specialist centre may be more appropriate.

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