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Invited Comment

The pathophysiology and treatment of hyponatraemic encephalopathy: an update

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Introduction

Hyponatraemia is a common disorder that occurs in both the out-patient and in-patient setting. Hyponatraemic encephalopathy can be difficult to recognize, as the most frequent symptoms are non-specific and can easily be incorrectly attributed to other causes. The patient usually presents with headache, nausea, vomiting and confusion, but can present with seizures, respiratory arrest and non-cardiogenic pulmonary oedema [1]. Over the past two decades, risk factors other than changes in the serum sodium level have been found to play a major role in the development of hyponatraemic encephalopathy, such as age, gender and hypoxia.

Pathogenesis of hyponatraemia

Hyponatraemia is defined as a serum sodium < 135 mEq/l. Under normal circumstances, the human body is able to maintain the plasma sodium within the normal range (135–145 mEq/l) despite wide fluctuations in fluid intake. The body's primary defence against developing hyponatraemia is the kidney's ability to generate a dilute urine and excrete free water. Hyponatraemia usually develops when there are underlying conditions that impair the kidney's ability to excrete free water. There are a few clinical settings where patients most often develop hyponatraemic encephalopathy.

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Hospital-acquired hyponatraemic encephalopathy

Hyponatraemic encephalopathy is most often encountered in hospitalized patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or in the post-operative state [2]. SIADH is caused by elevated ADH secretion in the absence of an osmotic or hypovolaemic stimulus [3]. SIADH can occur due to a variety of illnesses, but most often occurs due to central nervous system (CNS) disorders, pulmonary disorders, malignancies and medications. Among the latter, the chemotherapeutic drugs vincristine and cyclophosphamide, and the antiepileptic drug carbamazapine, are especially common.

Post-operative hyponatraemia is a common clinical problem occurring in ~1% of patients, with symptomatic hyponatraemia occurring in 20% of these patients [4–6]. Post-operative patients develop hyponatraemia due to a combination of non-osmotic stimuli for ADH release, such as subclinical volume depletion, pain, nausea, stress, oedema-forming conditions and administration of hypotonic fluids [6]. ADH levels are universally elevated post-operatively when compared with pre-operative values [7]. Premenopausal females are most at risk for developing hyponatraemic encephalopathy post-operatively [4], with post-operative ADH values in young females being 40 times higher than in young males [7].

Prophylaxis against hospital-acquired hyponatraemic encaphalopathy

The most important factor resulting in hospital-acquired hyponatraemia is the administration of hypotonic fluids to a patient who has a compromised ability to maintain water balance [4,5,8–10]. In adults, this will usually occur in the post-operative period. While a healthy male adult can excrete at least 15 l of fluid a day and maintain sodium homeostasis, it has been shown that in a women as few as 3–4 l of hypotonic

fluid over 2 days can result in fatal hyponatraemic encephalopathy in the post-operative setting [4,8]. Hyponatraemia can even develop if excessive near-isotonic saline is administered in the post-operative period [11]. Thus, the most important measure which can be taken to prevent hyponatraemic encephalopathy is to avoid using hypotonic fluids post-operatively and to administer isotonic saline unless otherwise clinically indicated. The serum sodium should be measured daily in any patient receiving continuous parenteral fluid.

Hospital-acquired hyponatraemia is of particular concern in children, as the standard care in paediatrics has been to administer hypotonic fluids containing 0.2–0.45% sodium chloride as maintenance fluids [12]. The safety of this approach has never been established. Hospitalized children have numerous non-osmotic stimuli for vasopressin production which place them at risk for developing hyponatraemia [13]. There are >50 reported cases of neurological morbidity and mortality in the past 10 years resulting from hospital-acquired hyponatraemia in children receiving hypotonic parenteral fluids [10]. Over half of these cases occurred in the post-operative setting in previously healthy children undergoing minor elective surgeries [14,15]. Hyponatraemia is especially dangerous in children with underlying CNS injury such as encephalitis, with mild hyponatraemia (sodium >130 mEq/l) resulting in cerebral herniation [16,17]. We have recently argued that isotonic saline should be the parenteral fluid of choice in paediatric patients unless there are ongoing free water losses or a free water deficit [10].

Hyponatraemic encephalopathy in the out-patient setting

Various conditions can result in hyponatraemic encephalopathy in the out-patient setting. It is usually due to either medications which impair the kidneys' ability to excrete free water, psychogenic polydypsia or water intoxication in infants. New and unusual presentations of hyponatraemic encephalopathy have been reported recently in the out-patient setting. Ayus *et al*. recently reported on hyponatraemic encephalopathy occurring in marathon runners, with a presenting symptom of non-cardiogenic pulmonary oedema [18]. All patients had been taking non-steroidal anti-inflammatory drugs (NSAIDs). Patients treated with hypertonic saline had prompt resolution of symptoms without neurological sequelae. Fatal hyponatraemic encephalopathy has also been reported following colonoscopy [19,20]. This appears to be due to a combination of large quantities of polyethylene glycol used for bowel preparation in conjunction with increased ADH levels from bowel manipulation. Hyponatramic encephalopathy has been reported to present with hip fractures in elderly women, resulting from an unexpected fall in the home [21]. Symptomatic hyponatraemia has also been reported with the recreational drug 3,4-methylenedioxymetamphetamine (Ecstasy) [22]. This results from increased vasopressin secretion and excess water ingestion. Symptomatic hyponatraemia can be particularly difficult to recognize in the out-patient setting, as the most common symptoms, namely headache, nausea, vomiting and confusion, can be attributed to other causes. Any patient with a risk factor for impaired urinary free water excretion should have his serum sodium measured if he is being evaluated for these symptoms.

Risk factors for developing hyponatraemic encephalopathy

The symptoms of hyponatraemic encephalopathy are largely caused by brain oedema from movement of water into the brain. The clinical sequence of hyponatraemic encephalopathy is shown in Table 1. The brain's adaptation to hyponatraemia initially involves a loss of blood and cerebrospinal fluid, followed by the extrusion of sodium, potassium and organic osmolytes in order to decrease the brain osmolality [23]. Various factors can interfere with successful brain adaptation and may play a more important role than the absolute change in serum sodium in predicting whether a patient will suffer hyponatraemic encephalopathy. The major factors that interfere with brain adaptation are physical factors related to age, hormonal factors related to gender, and hypoxaemia (Table 2) [24].

Age (Figure 1) [13]

Children under 16 years of age are at increased risk for developing hyponatraemic encephalopathy due to their relatively larger brain to intracranial volume ratio compared with adults [15,25]. A child's brain reaches adult size by 6 years of age, whereas the skull does not

Table 1. Anatomic and biochemical changes and clinical symptoms of hyponatraemic encephalopathy

Anatomical and biochemical changes	Clinical symptoms
Brain swelling	Headache Nausea Vomiting
Pressure on a rigid skull	Seizures
Excitatory amino acids	
Tentorial herniation	Respiratory arrest

Table 2. Risk factors for developing hyponatraemic encephalopathy

Risk factor	Pathophysiological mechanism
Children	Increase brain to intracranial volume ratio
Females	Sex steroids (oestrogens) inhibit brain adaptation
	Increase vasopressin levels
	Cerebral vasoconstriction
	Hypoperfusion of brain tissue
Hypoxaemia	Impaired brain adaptation

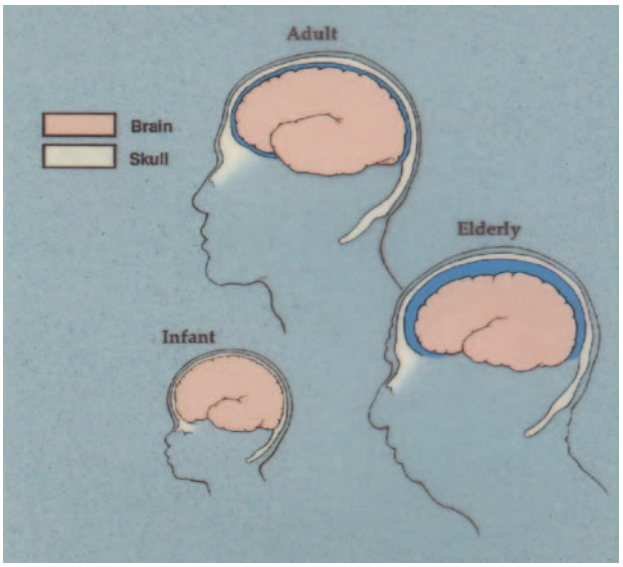

Fig. 1. Effects of physical factors on hyponatraemic encephalopathy.

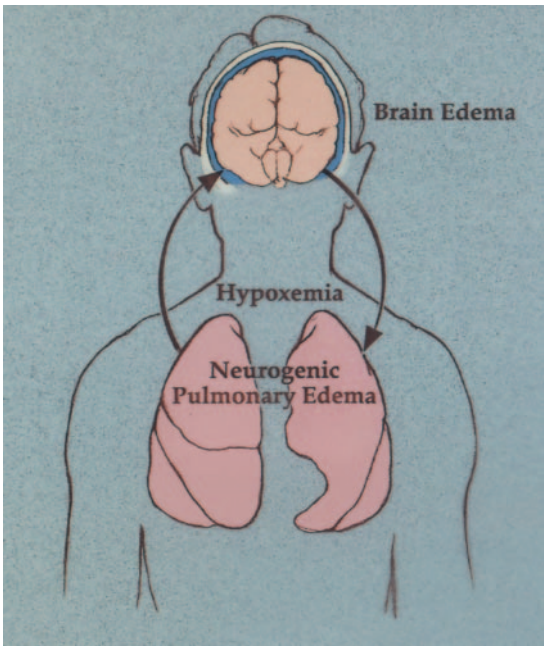

Fig. 2. Effects of hypoxaemia on hyponatraemic encephalopathy.

reach adult size until 16 years of age [26,27]. Consequently, children have less room available in their rigid skulls for brain expansion and are likely to develop brain herniation from hyponatraemia at higher serum sodium concentrations than adults. Children will have a high morbidity from symptomatic hyponatraemia unless appropriate therapy is instituted early [10,14–17]. After the third decade of life, the brain begins to atrophy, with the steepest reduction in brain volume occurring after 50 years of age [28,29]. The brain volume of an 80 year old is approximately 25% less than of a child. Consequently, the elderly are at the lowest risk of developing CNS manifestations of hyponatraemia.

Gender

Recent epidemiological data have clearly shown that menstruant women are at substantially higher risk for developing permanent neurological sequelae or death from hyponatraemic encephalopathy than men or postmenopausal females [4,5,8,21]. The relative risk of death or permanent neurological damage from hyponatraemic encephalopathy is ~30 times greater for women compared with men, and ~25 times greater for menstruant females than postmenopausal females [4]. Menstruant females can develop symptomatic hyponatraemia at serum sodium values as high as 128 mEq/l [8]. Hyponatraemic encephalopathy in menstruant females primarily occurs in healthy females following elective surgeries while receiving hypotonic fluids [4,8]. Premenopausal women are at high risk for developing hyponatraemic encephalopathy due to the inhibitory effects of sex hormones and the effects of vasopressin on the cerebral circulation, which in the female animal model as opposed to the male are characterized by cerebral vasoconstriction and hypoperfusion to brain tissue [25,30].

Hypoxia (Figure 2) [13]

Hypoxaemia is a major risk factor for developing hyponatraemic encephalopathy. The occurrence of a hypoxic event such as respiratory insufficiency is a major factor militating against survival without permanent brain damage in patients with hyponatraemia [8]. The combination of systemic hypoxaemia and hyponatraemia is more deleterious than is either factor alone because hypoxaemia impairs the ability of the brain to adapt to hyponatraemia, leading to a vicious cycle of worsening hyponatraemic encephalopathy [31]. Hyponatraemia leads to a decrement of both cerebral blood flow and arterial oxygen content [1]. Patients with symptomatic hyponatraemia can develop hypoxaemia by at least two different mechanisms: non-cardiogenic pulmonary oedema or hypercapnic respiratory failure [1]. Respiratory failure can be of very sudden onset in patients with symptomatic hyponatraemia [8,18]. The majority of neurological morbidity seen in patients with hyponatraemia has occurred in patients who have had a respiratory arrest as a feature of hyponatraemic encephalopathy [4,8,15,21,32]. Recent data have shown that hypoxia is the strongest predictor of mortality in patients with symptomatic hyponatraemia [33].

Does rapid correction of hyponatraemia lead to brain damage?

Cerebral demyelination is a rare complication which has been associated with symptomatic hyponatraemia [34]. Animal data have shown that correction of hyponatraemia by >20–25 mEq/l can result in cerebral demyelination [35]. This has resulted in a mistaken belief that a rapid rate of correction is likely to result in cerebral demyelination [36]. Recent data have now

shown that the rate of correction has little to do with development of cerebral demyelinating lesions, and that lesions seen in hyponatraemic patients are more closely associated with other co-morbid factors or extreme increases in serum sodium [32,33,37–40]. Animals studies have shown that azotaemia may decrease the risk of myelinolysis following the correction of hyponatraemia [41].

The lesions of cerebral demyelination can be pontine or extrapontine, and typically develop many days after the correction of hyponatraemia [34,42]. Cerebral demyelination can be asymptomatic or can manifest in confusion, quadriplegia, pseudobulbar palsy and a pseudocoma with a 'locked-in stare' [42]. The lesions of cerebral demyelination can be seen in the absence of any sodium abnormalities [40]. In fact, the primary cause of brain damage in patients with hyponatraemia is not cerebral demyelination, but cerebral oedema and herniation [4,8,15,21,32,40]. Most brain damage occurs in untreated patients and is not a consequence of therapy [21,33].

In one prospective study, it was observed that hyponatraemic patients who develop demyelinating lesions had either (i) been made hypernatraemic inadvertently; (ii) had their plasma sodium levels corrected by >25 mmol/l in 48 h; (iii) suffered a hypoxic event; or (iv) had severe liver disease (Table 3) [32]. Others have cautioned that cerebral demyelination could develop with elevations in serum sodium of 12–15 mEq/l/24 h [43]. A recent prospective study evaluating the development of demyelinating lesions in hyponatraemic patients found no association with a change in serum sodium [39]. The only factor associated with demyelination was hypoxaemia [39]. We retrospectively reviewed our experience with cerebral demyelination seen on autopsy specimens in children over a 15-year period [40]. There was no association between change in serum sodium and demyelination when compared with a matched control group. The only predisposing factors identified were underlying liver disease or CNS radiation in children with cancer.

Treatment of hyponatraemic encephalopathy

Despite the controversies surrounding the optimal treatment of hyponatraemic encephalopathy, there are two aspects generally accepted by experts in the field: (i) treatment should be directed based on the neurological involvement and not the absolute serum sodium; and (ii) hypertonic saline is not indicated in the asymptomatic patient who is neurologically intact, regardless of the serum sodium [13,32,44–49]. In general, correction with hypertonic saline is unnecessary and potentially harmful if there are no neurological manifestations of hyponatraemia. Symptomatic hyponatraemia, on the other hand, is a medical emergency. Once signs of encephalopathy are identified, prompt treatment is required in a monitored setting before imaging studies are performed. The airway should be secured, and endotrachial intubation and mechanical ventilation may be necessary. Fluid restriction alone has no place in the treatment of symptomatic hyponatraemia. If symptomatic hyponatraemia is recognized and treated promptly, prior to developing a hypoxic event, the neurological outcome is good [21,32,47,50].

Patients with symptomatic hyponatraemia should be treated with hypertonic saline (3%, 514 mEq/l) using an infusion pump (Table 4). The rate of infusion should continue until the patient is alert and seizure free. In patients who are actively seizing or with impending respiratory arrest, the serum sodium can be raised by as much as 8–10 mEq/l in the first 4 h, but the absolute change in serum sodium should not exceed 15–20 mEq/l in the first 48 h [5,24,32,46,47,49–52]. In general, the plasma sodium should not be corrected to >125–130 mEq/l. Assuming that total body water comprises 50% of total body weight, 1 ml/kg of 3% sodium chloride will raise the plasma sodium by $\sim$1 mEq/l. In some cases, furosemide can also be used to prevent pulmonary congestion and to increase the rate of serum sodium correction.

Table 3. Risk factors for developing cerebral demyelination in hyponatraemic patients

Risk factor
Development of hypernatraemia
Increase in serum sodium exceeding 25 mmol/l in 48 h
Hypoxaemia
Severe liver disease
Alcoholism
Cancer
Severe burns
Malnutrition
Hypokalaemia

Special problems in the treatment of hyponatraemia

A new equation has been proposed recently to aid in correcting the serum sodium in dysnatraemias [53]. This equation assumes that the body is a closed system and it does not account for renal water handling. This assumption is physiologically incorrect. It is important to recognize two groups of patients in which a closed-system equation that does not take into account urinary losses will result in a significant miscalculation. The first group is patients who will have a reverse urine osmolality or free water diuresis following volume expansion with hypertonic saline. Examples would be patients with psychogenic polydypsia, discontinuation of desmopressin (DDAVP), water intoxication in infants and diarrhoeal dehydration. These patients require special care, as hypertonic saline administration can result in a brisk free water diuresis and a consequent overcorrection of hyponatraemia, which leads to brain damage. If the serum sodium is overcorrected due to a free water diuresis, the serum sodium can be relowered by the administration of hypotonic fluids and DDAVP in order to prevent brain damage [54].

Table 4. Treatment of hyponatraemia

Most important step is prevention: avoidance of hypotonic fluid administration
Measure plasma osmolality to confirm hypoosmolality
Symptomatic hyponatraemia (headache, nausea, emesis, weakness)
Start treatment with hypertonic saline infusion (515 mM): use an infusion pump in an intensive care unit setting
Monitor serum sodium every 2 h until the patient is stable and symptom free
Stop hypertonic saline when the patient is symptom free or serum sodium is increased by 20 mmol/l in the initial 48 h of therapy
Avoid hyper- or normonatraemia during the initial 5 days of therapy, particularly in alcoholic or liver disease patients
Asymptomatic hyponatraemia
Fluid restriction
Therapy of underlying disorder

A recent study has reported on patients with symptomatic hyponatraemia from DDAVP administration, who suffered brain damage from overcorrection of hyponatraemia using this formula [55]. As an example, in a 70 kg patient with a total body water of 35 kg and a serum sodium of 110 mEq/l, a closed-system equation would predict that 1 l of 3% sodium chloride would increase the serum sodium by 11.2 mEq/l. In a patient with hyponatraemia as a complication of DDAVP, hypertonic saline administration in conjunction with discontinuation of DDAVP would result in a rise in serum sodium of 22 mEq/l if there was an estimated 3 l free water diuresis [55]. This is a significant overcorrection that could lead to brain damage. In order to prevent overcorrection of hyponatraemia in this situation, DDAVP should be reinstituted in order to curtail the free water diuresis, and hypotonic fluids should be administered [24,56].

The second group of patients where this equation will underestimate the change in serum sodium includes those with a natriuresis associated with volume expansion, such as SIADH or cerebral salt wasting. As an example, in a patient with SIADH with a fixed urine osmolality of 600 mOsm/kg, 1 l of 3% sodium chloride would probably result in an approximate rise in serum sodium of 7 mEq/l, assuming a 1 l urine output with a sodium plus potassium concentration of 250 mEq/l. This is much less than the 11 mEq/l rise predicted by a closed-system equation. In a patient with a fixed urine osmolality, as in the above case, administering isotonic saline will result in a fall in serum sodium, which would not be predicted by a closed-system equation. It must be emphasized that any formula that does not take into account the urinary response will be inaccurate and should not be used.

Future trends in the treatment of hyponatraemic encephalopathy

A new approach which holds great promise in aiding the treatment of hyponatraemic encephalopathy is the use of vasopressin 2 V2 receptor antagonists. Vasopressin V2 receptors are located in the distal nephron and increase free water permeability in response to vasopressin, while vasopressin V1 receptors are located in the blood vessels and brain. Pharmacological preparations of V2 antagonists are available for research purposes only, but have been used successfully in clinical trials in correcting hyponatraemia due to SIADH, cirrhosis and cardiac failure [57]. It is likely that in the future these agents will prove useful in treating symptomatic hyponatraemia due to SIADH or occurring postoperatively, as these conditions are associated with high vasopressin levels.

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