PERSONAL PRACTICE

Management of hyponatraemia in patients with acute cerebral insults

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Abstract

Hyponatraemia is a common finding in patients with acute cerebral insults. The main differential diagnosis is between syndrome of inappropriate ADH secretion and cerebral salt wasting. Our aim is to review the topic of hyponatraemia in patients with acute cerebral insults and suggest a clinical approach to diagnosis and management.

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Hyponatraemia is a common finding in patients with acute cerebral insults, especially after neurosurgical procedures for hypothalamic-pituitary tumours. It can be associated with the syndrome of inappropriate ADH secretion (SIADH), cerebral salt wasting (CSW), treatment of transient/permanent diabetes insipidus (DI), and excessive fluid administration in patients with adipsia. These conditions may occur in isolation or may coexist. For instance, after neurosurgical procedures involving the hypothalamic-pituitary area, an initial transient DI phase can be followed by transient remission or excessive SIADH and then followed by permanent DI. The initial treatment of DI with desmopressin (vasopressin analogue) can be challenging and hyponatraemia may occur either following an excessive dose of desmopressin or during an SIADH phase.

Impairment of thirst can arise following the destruction of hypothalamic osmoreceptors, and its coexistence with DI makes the fluid management extremely complex. In these circumstances avoidance of wide swings in serum sodium concentration can be challenging, even when high expertise among medical and nursing staff is available. CSW is another cause of hyponatraemia, which can be difficult to differentiate from SIADH. It has been proposed that CSW represents the commonest cause of hyponatraemia in neurosurgical patients.^{1 2} It can also coexist with DI and in this case the excessive polyuria secondary to natriuresis can be easily misinterpreted as poor control of DI. An increase in desmopressin dose will only cause a further deterioration in the degree of hyponatraemia. Overall, a clear

understanding of the underlying cause of hyponatraemia is required so that the appropriate therapeutic approach can be taken.

The aim of this review is to clarify the different pathogenic mechanisms responsible for hyponatraemia in patients with cerebral insults, in particular after neurosurgical procedures involving the hypothalamic area, to raise the level of awareness of CSW and to suggest a practical approach to the diagnosis and treatment of hyponatraemia in this cohort of patients. Finally, we describe an adipsic child with a hypothalamic brain tumour who developed DI and intermittent CSW to illustrate the practical difficulties encountered in the management of hyponatraemia and fluid balance.

Background

DIABETES INSIPIDUS

Central DI³ is caused by a deficiency of antidiuretic hormone (ADH), caused by destruction or degeneration of the neurones that originate in the supraoptic and paraventricular nuclei of the hypothalamus. Hypothalamic tumours (craniopharyngioma and germinoma) represent the commonest causes of DI in childhood, followed by Langerhans' cell histiocytosis or other infiltrative processes such as leukaemia, lymphoma, and sarcoidosis. DI is caused by the destructive lesion, or more often the neurosurgery for removal of the hypothalamic-pituitary tumour. Postsurgery a triple response is also described and it is characterised by initial DI followed, after 4–8 days, by a transient remission or excessive release of ADH lasting 1–14 days and then reoccurrence of often permanent DI. Cerebral insults resulting from head trauma or hypoxic brain injury involving the hypothalamic-pituitary area are also well known causes of transient/permanent DI. Cerebral malformation and familial cases of ADH deficiency are less common causes of DI. An idiopathic form of DI is rare and always requires regular neuroimaging to rule out an evolving organic lesion.

ADH deficiency normally leads to polyuria with excessive urine free water loss that in the presence of intact thirst sensation will be compensated by an excessive drinking: plasma osmolality should be maintained if adequate replacement of fluid losses occurs. Fluid restriction, inadequate intravenous fluid replacement, impaired thirst sensation, and

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inability to obtain water because of young age will all result in hypernatraemic hypovolaemia. The laboratory findings of ADH deficiency will be an inappropriate low urine osmolality compared to the high plasma osmolality (urine to plasma osmolality ratio < 1.5). Coexistence of ACTH and partial ADH deficiency may clinically mask polyuria as cortisol is required for free water excretion and following corticosteroid treatment (for instance high dose dexamethasone used for cerebral oedema), partial DI may clinically become manifest. To confirm the diagnosis of partial forms of DI a water deprivation test with urinary ADH measurements⁴ may be required; if cortisol deficiency is suspected, the patient should be given cortisol replacement.

SYNDROME OF INAPPROPRIATE ADH SECRETION

Many conditions affecting the brain (postneurosurgery, head injury, haemorrhage, infections, etc) can cause SIADH. The syndrome may also occur as a result of the interaction/enhancement of ADH action induced by anti-convulsant drugs, especially carbamazepine and lamotrigine.^{5,6} An excess of ADH, exogenous or endogenous, acts on the distal renal tubules and causes free water retention. This is often associated with stimulation of thirst. The excess free water is evenly distributed throughout the body, leading to hypo-osmolar expansion of extracellular fluids and consequent swelling of cells without clinical signs of peripheral oedema.

The counteractive mechanism to volume expansion is urine sodium loss via an increased glomerular filtration and decreased proximal tubular sodium reabsorption. Plasma renin activity is always low, even though aldosterone might not be suppressed. Natriuresis will progress until a new steady state is reached when, in the presence of low plasma sodium, the urine sodium loss may decrease. Furthermore, water retention will reach a plateau and the urine will then be less concentrated. Plasma ADH concentration is usually within the normal range but at an inappropriately high concentration for the low plasma osmolality. The biochemical characteristics will be: low plasma osmolality with inappropriate high urine osmolality (urine to plasma osmolality ratio > 1), hyponatraemia with urine sodium loss more than 20 mmol/l, suppressed plasma renin activity, low haematocrit, and low plasma urea and uric acid. Clinical manifestations such as anorexia, confusion, headache, weakness and muscular cramps, followed by nausea, vomiting, and progressive neurological abnormalities may develop. They will depend on the rate of development of intracellular hypo-osmolality as cells can compensate by decreasing the intracellular solute concentration and thus correct

the primary swelling. In the most severe cases a rapid decline in plasma sodium can precipitate seizures, lethargy, coma, and death.

CEREBRAL SALT WASTING

CSW was initially described⁷ in patients with cerebral diseases in 1950. It has been reported in cases with subarachnoid haemorrhage,⁸ infections,⁷ head injury,⁹ brain tumours,¹⁰ trans-sphenoidal pituitary surgery,¹¹ and neurosurgery.¹² It is characterised by extracellular fluid depletion and hyponatraemia caused by progressive natriuresis with concomitant diuresis. It has been hypothesised that one or more salt losing factors, such as atrial natriuretic peptide¹³ or hypothalamic secretion of ouabain like factors,¹⁴ can cause CSW. Current evidence¹⁵⁻²⁰ suggests that even though atrial natriuretic peptide and brain ouabain like factors might have a role in CSW, several other factors can also be implicated.

The main biochemical findings of CSW will be low plasma osmolality with inappropriate high urine osmolality (urine to plasma osmolality ratio > 1), hyponatraemia with urine sodium loss more than 20 mmol/l, normal/high haematocrit, and plasma urea. Plasma renin activity can be raised or in the high normal range; occasionally it may be depressed or in the normal range.²¹ The clinical presentation of hyponatraemia will depend on the rate of development of hyponatraemia.

Differential diagnosis

Identical acute cerebral insults may cause either SIADH or CSW. The clinical and biochemical manifestation of both conditions can be virtually identical and the only discriminative feature is the status of extracellular volume: it tends to be expanded in SIADH and low in CSW. Clinical and biochemical findings helpful to differentiate CSW from SIADH include fluid intake and urine output monitoring, daily body weight, blood urea, creatinine clearance, and plasma renin activity (table 1). However, none of these are pathognomonic for either condition. At presentation, changes in extracellular volume can be subtle and neither clinical or biochemical estimations are able to ascertain them with consistent accuracy. For this reason, in any hyponatraemic patient with deteriorating clinical status, in the absence of clinical signs of hypovolaemia such as hypotension, a practical approach (fig 1) would be to perform a formal measurement of blood volume using either central venous pressure or radioisotope dilution techniques (labelled red blood cell studies) to differentiate between SIADH and CSW.^{1,2} An echocardiogram may also be required²² to rule out cardiac compromise which might cause discrepancy between central venous pressure and volume status. Other causes of hypo-osmolar hypovolaemia secondary to non-renal losses, renal tubulopathy, mineralcorticoid deficiency, cardiac or liver failure, and use of diuretics should be excluded at the onset of hyponatraemia.

Hyponatraemia in a patient with DI (fig 2) can be caused by water intoxication secondary to excessive desmopressin replacement, to

Table 1 Biochemical and clinical findings helpful in differentiating CSW from SIADH

	SIADH	CSW
Creatinine clearance	Normal or increased	Normal or decreased
Blood urea	Normal or decreased	Normal or increased
Plasma renin	Suppressed	Normal or raised, or occasionally suppressed
Urine volume	Normal or decreased	Normal or increased
Body weight	Stable or increased	Stable or decreased

Figure 1 Algorithm for the differential diagnosis between CSW and SIADH in hyponatraemic patients with acute cerebral insult.

coexistent CSW, to concurrent untreated or undertreated cortisol deficiency,²³ anticonvulsant treatment,⁶ or to a different source of sodium loss. In the case of excessive desmopressin replacement, the diagnosis will be confirmed by documented improvement of the hyponatraemia following desmopressin withholding. The presence of hyponatraemia and natriuresis in urine samples collected while the

patient develops polyuria (prior to desmopressin dose) will point towards a coexistence of CSW and DI.

In hyponatraemic patients with brain tumours receiving nephrotoxic chemotherapeutic agents, it can be very difficult to differentiate CSW from renal tubulopathy. The excessive degree of natriuresis compared to the degree of altered renal tubular threshold for phosphate,

Figure 2 Algorithm for evaluation of hyponatraemia in patients with cerebral insult and DI.

Figure 3 Algorithm for therapeutic approach to hyponatraemia in CSW and SIADH.

hypokalaemia, and tubular protein leak should suggest CSW.

Therapeutic approach

In SIADH, therapeutic interventions should include water intake restriction; only in advanced SIADH with total body sodium depletion, should the sodium be replaced. In severe hyponatraemia, treatment with diuretics can be attempted. Severe symptomatic hyponatraemia (associated with seizures and/or coma) should be partially corrected by infusion of hyperosmolar sodium solution—that is, infusion of 3% saline (500 mmol/l) at 1–2 ml/kg/h (0.5–1 mmol/kg/h) for two to three hours, followed by conservative measurements to limit the rate of correction to less than 12 mmol/l per day. Rapid correction of hyponatraemia can be associated with pontine myelinolysis.

In CSW, therapeutic intervention will include replacement of both sodium and extracellular volume deficit, avoiding rapid corrections. High dose fludrocortisone (0.2–0.4 mg/day) has been found to be beneficial in some patients with CSW,^{24–27} but its use requires close monitoring of plasma potassium concentrations as notable hypokalaemia may occur, especially in childhood.

In situations where any hyponatraemic patient with acute cerebral insults/postneurosurgery and inappropriate urinary sodium loss is clinically euvoemic, a practical approach² is to administer sodium supplement and maintain normal fluid intake first. If no improvement or further deterioration occurs within 72 hours, the volume status should be formally assessed (central venous pressure

monitoring and/or dilutional studies) to confirm the diagnosis and institute appropriate fluid treatment. Figure 3 illustrates the suggested therapeutic approach for patients with hyponatraemia.

Postneurosurgery patients with suprasellar tumours require close monitoring of fluid and electrolyte balance. The onset of polyuria (urine output > 5 ml/kg/h) in the presence of urine/plasma osmolality ratio < 1.5 is suggestive of DI, and desmopressin should be administered. Low doses should initially be used and according to the clinical response, dose adjustments made. Initially, desmopressin should be given as required (waiting for the onset of polyuria before giving a further dose of desmopressin), as prediction of desmopressin requirement is impossible because of the evolving nature of DI in these patients. An alternative regimen in the acute onset of DI is to use intravenous vasopressin infusion titrated against plasma and urine biochemistry and urine output. It requires frequent blood and urine electrolyte monitoring, and urethral catheterisation, which is not always feasible in children. As soon as a pattern of desmopressin requirement becomes clear, regular desmopressin should be prescribed. The aim is to achieve an appropriate 24 hour urine output for the child's weight and to allow urine breakthrough once a day prior to desmopressin dose, to avoid the risk of water intoxication. When DI becomes stable and regular treatment is required, desmopressin is the drug of choice because of the longer duration of action and lack of vasoconstriction. In hypodyspic patients, fixed daily fluid intake appropriate for weight and target

weight, at which the patient is known to be eunatraemic and euvoalaemic, should be established, and desmopressin dose adjusted accordingly.

In patients with coexistent DI and CSW, it should be considered that natriuresis contributes to the increased urine output and is not an index of poor controlled DI. An increase in desmopressin dose will be inappropriate because it will lead to an increase in renal free water reabsorption and therefore to a further deterioration of hyponatraemia. Therapeutic intervention should include sodium and fluid replacement, and administration of desmopressin, with close monitoring of plasma electrolytes and osmolality. If the patient deteriorates clinically, central venous pressure monitoring is mandatory to guide fluid replacement.

Case history

A 2.5 year old girl underwent partial surgical resection of a suprasellar ependymoma. She presented with symptoms of severe hypernatraemia, secondary to DI and acute obstructive hydrocephalus while holidaying abroad. Her fluid/electrolytes balance proved to be very difficult to manage. Initially she was on free water replacement to correct the hypernatraemic dehydration secondary to DI. She subsequently developed symptomatic water intoxication with a seizure following commencement of vasopressin infusion. Postsurgery, CSW was suspected because of inappropriate urine sodium loss despite hyponatraemia. Her urine output was very high (6–16 ml/kg/h), as was her urine Na concentration which varied between 130 and 300 mmol/l; serum Na ranged between 130 and 180 mmol/l and vasopressin requirement was 0.05–2.0 mU/kg/h. In addition to DI, she had panhypopituitarism and was treated with replacement thyroxine and glucocorticosteroids. She was subsequently transferred to London. On admission the major problems encountered were:

- Poor response to intravenous infusion of vasopressin, with persistent high urine volume output
- Fluctuating excessive natriuresis, resulting in hyponatraemia
- Excessive fluid intake as, to avoid dehydration, urine losses had to be replaced intravenously when exceeding the fixed oral maintenance
- Difficulties with fluid replacement, because of the coexistence of adipsia and polyuria (secondary to excessive fluid intake, under treated DI, and natriuresis).

Our management plans included:

- Exclusion of other causes of excessive urine sodium losses, such as inappropriate cortisol replacement or renal tubulopathy
- Exclusion of other causes of exacerbating CSW, such as CNS infection or reoccurrence of obstructive hydrocephalus. The latter was documented on repeat brain imaging and a ventricular-peritoneal shunt was inserted. This was followed by an improvement in natriuresis and polyuria

Key messages

- Careful adjustment of dose of desmopressin, cortisol, and some anticonvulsants, as all three interact
- Provided that fluid replacement is maintained, DI is not life threatening
- Excessive administration of desmopressin can result in hyponatraemia with fatal fluid overload and may require dialysis
- The only biochemical difference between CSW and SIADH is the extracellular volume, decreased in the former and increased in the latter
- In euvoalaemic and hyponatraemic patients with cerebral insults: give sodium supplement and maintenance fluid intake first. If no improvement or deterioration, assess volume state with central venous pressure monitoring
- Limit the rate of correction of plasma sodium to less than 12 mmol/l/day

- Keeping accurate fluid/sodium balance charts, with daily body weight and paired urine/plasma osmolality and electrolytes, taken before administering desmopressin
- Slowly reducing excessive urine output by tackling the different exacerbating factors:
 - Undertreated DI: changing from parenteral to oral desmopressin, but given as required, allowing urine breakthrough (increase in urine output to more than 5 ml/kg/h for two consecutive hours) before repeat administration, to avoid water overload
 - Excessive fluid intake: slow reduction in urine loss replacement, aiming to give fixed oral maintenance appropriate for body weight, age, and insensible losses
 - Fluctuating plasma sodium concentrations: prompt recognition of incoming natriuresis and treatment with saline replacement, avoiding rapid changes in plasma sodium and osmolality.

With the above regimen a progressive improvement occurred in the fluid/electrolyte management but, unfortunately, in view of her neurological impairment and a rapid growth in the hypothalamic tumour, palliative care was instigated. She died nine months after initial diagnosis but her DI was easily controlled with small doses of oral desmopressin, and her electrolytes remained normal.

Conclusions

Hyponatraemia in patients with cerebral disorders is a common finding. Close monitoring of body weight and both fluid and sodium balance with paired urine and plasma electrolytes and osmolality is required. The initial differential diagnosis should include both CSW and SIADH when other causes of hyponatraemia—that is, hypo-osmolar dehydration secondary to non-renal losses, renal tubulopathy, mineralocorticoid deficiency, cardiac or liver failure, anticonvulsants, and use of diuretics, have been excluded. The coexistence of DI and CSW

should be considered in hyponatraemic patients who undergo hypothalamic neurosurgery. When both coexist, and high sodium intravenous infusion rates are required, great care is necessary with vasopressin/desmopressin treatment in order to avoid exaggerated plasma sodium fluctuation which can easily produce cerebral damage. Of course there is an interaction between cortisol and ADH and allowance in the dose of the latter must be made for changes in the former. When it is clinically not possible to differentiate between CSW and SIADH, monitoring of central venous pressure or isotope dilution techniques are required to be able to define the degree of volume expansion and undertake the correct treatment.

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