

ORIGINAL ARTICLE

Severe hyponatraemia: investigation and management in a district general hospital

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Aims: To study the incidence, investigation, and management of severe hyponatraemia (serum sodium < 120 mmol/litre) over a period of six months in a district general hospital.

Methods: The laboratory computer was used to identify all inpatients who had a serum sodium concentration of less than 120 mmol/litre over a six month period. The records of these patients were reviewed for the relevant demographic, clinical, and laboratory data, in addition to diagnosis, treatment, and outcome of hospitalisation.

Results: Forty two patients were studied, with a female to male ratio of 2 : 1. Nine patients had central nervous system symptoms, and four of these patients died in hospital. Only 14 patients had their urinary electrolytes and/or osmolality checked. A diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was mentioned in eight patients, sometimes without checking their urinary electrolytes or osmolality. Twenty one patients died in hospital. The patients who died did not have lower serum sodium values or a higher rate of correction of hyponatraemia, but they all suffered from advanced medical conditions.

Conclusions: The possible cause of hyponatraemia should always be sought and that will require an accurate drug history, clinical examination, and assessment of fluid volume, plus the measurement of urinary electrolytes and osmolality in a spot urine sample. The diagnosis of SIADH should not be confirmed without the essential criteria being satisfied. The current or recent use of diuretics is a possible pitfall in the diagnosis of SIADH. The rate of serum sodium correction of less than 10 mmol/day is probably the safest option in most cases.

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Hyponatraemia, defined as serum sodium less than 135 mmol/litre, is the most common electrolyte abnormality in clinical practice.^{1,2} In most cases, hyponatraemia is mild and asymptomatic, but sometimes it is severe, with sodium concentrations less than 120 mmol/litre. Severe hyponatraemia is a serious medical condition, which is associated with substantial neurological complications and mortality.^{1,3} The correction of hyponatraemia has also been associated with the development of central pontine myelinolysis and extrapontine myelinolysis.^{4,5}

“Controversy still exists regarding the best way of managing severe hyponatraemia, with some advocating the rapid correction of symptomatic hyponatraemia, and others recommending a more conservative approach”

There are several causes of hyponatraemia and appropriate investigations and diagnosis are essential to obtaining the correct treatment. Controversy still exists regarding the best way of managing severe hyponatraemia, with some advocating the rapid correction of symptomatic hyponatraemia,⁶ and others recommending a more conservative approach.⁷

The purpose of our study was to determine the prevalence of severe hyponatraemia in a medium sized district general hospital and to look at how patients were investigated and managed. Our laboratory serves Queen Elizabeth Hospital with 500 beds and Bensham Hospital with 167 beds. The catchment population is 220 000.

METHODS

We used the laboratory computer to identify all inpatients who had a serum sodium concentration of less than 120 mmol/litre over a six month period. The records of these patients were

reviewed for the relevant demographic, clinical, and laboratory data, in addition to the diagnosis, treatment, and outcome of hospitalisation. Serum electrolytes were measured by an ion selective electrode system on an ILAB 900 analyser. Intrabatch and interbatch coefficients of variation were $\leq 0.5\%$ and $\leq 0.9\%$, respectively. A result of ≤ 125 mmol/litre is automatically checked by the machine. If there is a discrepancy in the results the serum sample is reassayed on the other ILAB 900 analyser.

Data were analysed by the computer software MEDCALC 5 (Medcalc Corp, Mariakerke, Belgium). Values are expressed as mean (SD). Significance was analysed by the Student's *t* test and *p* values < 0.05 were considered to be significant.

RESULTS

Over the six month period, 57 patients had serum sodium concentrations of ≤ 120 mmol/litre. These constituted 0.15% of the total requests for serum sodium during the study period. Fifteen sets of notes were excluded from the analysis or were not available and 42 sets of notes were studied. The mean patient age was 72.5 (SD, 12) years (range, 39–92). The female to male ratio was 2 : 1. However, this sex ratio in patients with severe hyponatraemia, and the sex ratio of all patients in the same age range (39–92 years) investigated in the hospital within the same period of the study (female : male ratio, 59 : 41) were not significantly different (χ^2 : *p* > 0.1). All cases in our study were chronic hyponatraemia, defined as hyponatraemia of more than 48 hours duration.⁸

Abbreviations: ADH, antidiuretic hormone; CNS, central nervous system; SIADH, syndrome of inappropriate secretion of antidiuretic hormone

Table 1 Medical conditions associated with severe hyponatraemia

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------------------------------|----|----|----|---|---|---|---|
| Use of diuretic (1) | 19 | 5 | 7 | 8 | 1 | 0 | 2 |
| Chest infection (2) | 5 | 15 | 3 | 2 | 0 | 0 | 5 |
| Renal impairment (3) | 7 | 3 | 12 | 3 | 3 | 0 | 1 |
| Cardiac failure (4) | 8 | 2 | 3 | 9 | 0 | 0 | 1 |
| Liver disease (5) | 1 | 0 | 3 | 0 | 5 | 0 | 1 |
| Serotonin reuptake inhibitor (6) | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| SIADH (7) | 2 | 5 | 1 | 1 | 1 | 0 | 8 |

This table shows the multifactorial nature of hyponatraemia in most cases.
SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Table 2 Diagnostic criteria for the syndrome of inappropriate secretion of antidiuretic hormone

Hyponatraemia and hypo-osmolality
Urine osmolality inappropriately concentrated in relation to plasma osmolality
High urinary sodium concentration (>30 mmol/l)
Clinically euvolaemic
Normal adrenal and renal function

The mean (SD) of the serum sodium concentration at presentation was 116.0 (8.1) mmol/litre (range, 106–120). The mean (SD) length of hospital stay was 22 (34) days (range, 1–153).

Table 1 details the underlying medical conditions associated with severe hyponatraemia.

Serum sodium was raised at a rate of 20 mmol/day in one patient, who survived. This correction rate of 20 mmol/day was excluded from the rest of the analysis. In the rest of the patients who received saline infusions (n = 37), the mean (SD) correction rate was 3.1 (1.8) mmol/day (range, 0.5–7). Normal saline was used in all 37 cases. In one case, 5% dextrose was given initially. Some of the patients suspected to have SIADH were given normal saline at some stage in their management.

Nine patients had symptoms and signs suggestive of cerebral oedema/cerebral cortical dysfunction. Of these, four died during their admission period and five were discharged from hospital. There was no significant difference between patients who developed central nervous system (CNS) symptoms (n = 9) and the rest of the group (n = 28) in serum sodium concentrations (mean (SD) 116.7 (4.3) v 116.8 (3.1) mmol/litre) or in the rate of correction of hyponatraemia (mean (SD) 3.8 (1.6) v 2.9 (1.8) mmol/day). Patients with CNS symptoms who died in hospital (n = 4) and patients with CNS symptoms who survived (n = 5) had similar

sodium values (mean (SD) 115.4 (5.6) v 118.2 (1.9) mmol/litre) and a similar rate of correction of hyponatraemia (mean (SD) 4.3 (2.2) v 3.3 (0.5) mmol/day). In most cases, the underlying diseases could have accounted for or contributed to the CNS symptoms. Hyponatraemia was possibly the main cause of neurological symptoms in three patients, two of whom survived. There was no evidence that hyponatraemia developed acutely (< 48 hours duration) in these three cases.

Urinary electrolytes were checked in only eight patients, whereas in another six patients only urinary osmolality was requested. Other biochemical investigations included: liver function tests (69%), random cortisol or short synacthen test (45%), and thyroid function tests (28.6%).

Only 17 patients had completed fluid balance charts.

A diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was mentioned in eight patients. The full criteria for the diagnosis of SIADH, as detailed in table 2, were not applied to these patients (table 3). Fluid restriction was used in three of these patients. On the other hand, fluid restriction was used in another three patients while they were still on diuretics or shortly after stopping diuretic intake.

Twenty one patients died in hospital, all of whom suffered from advanced medical conditions. There was no significant difference between the patients who died in hospital and those who survived in serum sodium concentrations (mean (SD) 116.7 (3.1) v 116.8 (3.4) mmol/litre) or in the rate of correction of hyponatraemia (mean (SD) 3.0 (1.3) (n = 18) v 3.2 (2.2) mmol/day (n = 19)).

DISCUSSION

Our study confirmed previously reported findings that severe hyponatraemia is likely to occur in the elderly.^{9–11} The higher number of women among the patients with severe hyponatraemia is probably because more women were investigated in the hospital during the study period. Therefore, our data do not indicate an increased incidence of severe hyponatraemia in the elderly female patients.

“The optimum rate of correction in severe hyponatraemia is still controversial because of the risk of developing central or extrapontine myelinolysis if rapid correction of serum sodium occurs”

The aetiology of severe hyponatraemia appears to be multifactorial, but the use of diuretics is an important cause. However, many of these patients suffered from conditions such as heart failure, chest infection, and liver failure, which could have contributed to their hyponatraemia (table 1).

We found no evidence to suggest that the evaluation of the patients, including assessment of extracellular fluid volume status, was carried out properly in most of the patients. This is supported by the fact that measurements of urinary electrolytes and osmolality were done only in a minority of patients. Similar suboptimal practice has been reported recently.¹²

Table 3 Application of diagnostic criteria for SIADH in eight patients suspected of having this condition

| Patient | Urine electrolytes and osmolality | TFT | Serum cortisol or synacthen test | Renal function | Diuretics |
|---------|-----------------------------------|-----|----------------------------------|----------------|-----------|
| 1 | Yes | No | Yes | Normal | Yes |
| 2 | No | No | No | Normal | No |
| 3 | No | No | Yes | Abnormal | No |
| 4 | No | No | Yes | Normal | Yes |
| 5 | Osmolality only | Yes | No | Normal | No |
| 6 | Osmolality only | No | Yes | Normal | No |
| 7 | Yes | No | No | Normal | No |
| 8 | Osmolality only | No | No | Normal | No |

SIADH, syndrome of inappropriate secretion of antidiuretic hormone; TFT, thyroid function tests.

In clinical practice, a diagnosis of SIADH rarely follows the classic criteria,¹³ and is often based on a limited number of features, such as hyponatraemia with inappropriately raised urine osmolality and natriuresis. Such a definition will include other causes of renal salt wasting, such as diuretic use, Addison's disease, or salt losing nephritis. Hypothyroidism is another cause of euvolaemic hyponatraemia. Diuretic use remains the main pitfall in the diagnosis of SIADH, particularly when patients drink enough water to correct their blood volume.¹⁴

The hyponatraemia in chronic SIADH is limited by the "escape from antidiuresis" phenomenon. The onset of this phenomenon is characterised by a rise in urine flow and a decrease in urine osmolality. The serum sodium concentration will tend to rise but remain in the hyponatraemic range.¹⁵ In the "reset osmostat" form of SIADH, antidiuretic hormone (ADH) is released at an abnormally low threshold for plasma osmolality. The lowering of plasma osmolality below this threshold leads to the abolition of ADH secretion and the development of diuresis, which also protects against severe hyponatraemia.¹⁶

A condition, which could possibly be misdiagnosed as SIADH, is the cerebral salt wasting syndrome.^{17, 18} This is a syndrome that is seen after cerebral insult and is characterised by hyponatraemia, diuresis, natriuresis, and hypovolaemia. It responds well to treatment by intravenous saline.¹⁹ The "sick cell syndrome" is a rare cause of hyponatraemia in seriously ill patients, which is associated with an increased plasma osmolality gap.²⁰ Plasma osmolality was not measured in most of our patients and it seems that practitioners rarely consider this syndrome.

ADH values are variable and not consistently raised in SIADH.¹⁶ They can also be raised in almost all categories of hyponatraemia.^{14, 21} Therefore, a single measurement of ADH is unlikely to be useful in the differential diagnosis of hyponatraemia.

"The aetiology of severe hyponatraemia appears to be multifactorial, but the use of diuretics is an important cause"

The treatment of hyponatraemia should be directed at the primary underlying disorder and this by itself may correct the hyponatraemia. Diuretics should be discontinued and glucocorticoid insufficiency and hypothyroidism should be treated by hormone replacement. Treatment should be guided by the outcome of the extracellular fluid volume assessment. In hypovolaemic hyponatraemia, blood volume would be restored with isotonic saline in most cases. In hypervolaemic hyponatraemia, as a result of heart failure or liver failure, a combination of fluid restriction and diuretics may reduce total body water. Fluid restriction is the first line treatment for SIADH but further treatment, such as demeclocycline, may be required. Saline infusion is an inappropriate treatment for patients with SIADH. This will promote the excessive urinary sodium loss characteristic of this condition, with little gain in plasma sodium. The underlying cause of SIADH should always be sought.^{2, 14, 22}

The optimum rate of correction in severe hyponatraemia is still controversial because of the risk of developing central or extrapontine myelinolysis if rapid correction of serum sodium occurs.²³ However, patients with acute symptomatic hyponatraemia are at high risk of cerebral oedema, cerebral herniation, and death, and they require rapid correction of hyponatraemia, using hypertonic saline (3% NaCl), preferably with a loop diuretic.^{2, 6, 22}

In chronic hyponatraemia, the brain adapts to the hypotonic extracellular milieu by losing intracellular potassium to begin with and later "idiogenic osmols", such as taurine or creatine, are lost. On rapid correction of chronic hypo-

Take home messages

- In this series, the appropriate tests were not always undertaken
- The possible causes of hyponatraemia should always be sought and this will require an accurate drug history, clinical examination, and assessment of fluid volume plus the measurement of urinary electrolytes and osmolality in a spot urine sample
- The diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) should not be confirmed without the essential criteria being satisfied
- The current or recent use of diuretics is a possible pitfall in the diagnosis of SIADH
- The rate of serum sodium correction of less than 10 mmol/day is probably the safest option in most cases

natraemia, the idiogenic osmols cannot be rapidly corrected and the extracellular compartment becomes hypertonic relative to the intracellular compartment. This results in dehydration and shrinkage of the oligodendrocyte, which cause demyelination.²⁴

The optimal correction rate for chronic symptomatic hyponatraemia has been advocated to be less than 10–12 mmol/litre in 24 hours,⁸ less than 25 mmol in the initial 48 hours,⁶ or an increase of serum sodium less than 0.5 mmol/litre/hour.²⁵

In our study, correction was done using normal saline, except for one patient who received 5% dextrose. Although 5% dextrose is normotonic when infused, it acts effectively as pure water because of the rapid clearance of dextrose. The practice of giving dextrose solutions to patients with severe hyponatraemia could therefore be detrimental.^{6, 26} Hypertonic saline was not used. Although we believe, like some others,⁸ that most cases of severe hyponatraemia are chronic in nature, there would be occasions when it is difficult to discriminate between chronic and acute hyponatraemia. In such patients, in whom an acute onset of hyponatraemia cannot be documented, a correction rate of less than 10 mmol/24 hours is probably the safest option.^{2, 12}

The patients who showed neurological signs in our study were not different from the rest of the group in their initial sodium concentration, or in the rate of correction of hyponatraemia. In such a retrospective study, it is difficult to determine whether these cerebral signs were the result of the underlying illness or whether they were caused by hyponatraemia. Most of these patients suffered from illnesses that might have caused or contributed to these neurological manifestations. Such patients with CNS symptoms, in whom an acute onset of hyponatraemia cannot be documented, should be corrected at a chronic rate (\approx 10 mmol/day) and not with hypertonic saline and frusemide. The patients who died did not have lower serum sodium values or a higher incidence of CNS symptoms compared with the survivors, as has been noted previously.⁷ However, most of them suffered from serious medical problems. At least in some of these cases, hyponatraemia appears to be a marker of severe underlying disease that carries a poor prognosis, rather than being the primary cause of death.^{11, 27}

CONCLUSIONS

The possible cause of hyponatraemia should always be sought and this will require an accurate drug history, clinical examination, and assessment of fluid volume, plus the measurement of urinary electrolytes and osmolality in a spot urine sample.

The diagnosis of SIADH should not be confirmed without the essential criteria being satisfied, including the assessment of glucocorticoid reserve. Fluid restriction should be practised cautiously and on the right patient; the current or recent use of diuretics is a possible pitfall in the diagnosis of SIADH.

If a diagnosis of SIADH is correctly made, possible causes should be sought including tumours.

The use of normal saline and slow sodium correction rate (≈ 10 mmol/day) will be appropriate for most patients.

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ECHO



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Mucin patterns may be worth watching in patients with ileoanal reservoirs

Changes in mucin gene expression may be a useful marker in surveillance for colorectal cancer in patients with a pelvic ileoanal reservoir (IAR), a molecular study has suggested. Biopsy specimens from IARs showed a mucin pattern similar to that in ulcerative colitis (UC): expression of membrane associated mucins MUC1 AND MUC3 was less than in ileal control specimens whereas expression of mRNA transcripts was unchanged. Conversely, no mRNA transcripts were detected for mucins MUC5AC, MUC5B, AND MUC6 associated with colorectal cancer, though MUC5AC protein occurred in five IARs and MUC6 protein in two. In one and two of these cases, respectively, this was in an ulcer associated cell lineage. None of the specimens showed histological evidence of cancer.

Specimens were taken from 40 patients undergoing yearly surveillance after an IAR constructed 1–10 years before for UC or familial adenomatous polyposis (FAP). These were taken at random from the back wall of the reservoir. Control ileal and colonic specimens were taken from other patients with neither UC nor FAP. Messenger RNA transcripts were detected by in situ hybridisation of thin sections with radiolabelled oligonucleotide probes. Mucins were detected by staining with antibody to peptide sequences of core protein.

Mucins form part of the mucosal defence of the gut. Their pattern changes in colorectal cancer, when MUC5AC and MUC6 are newly expressed. IARs show no evidence of cancerous change according to mucin glycosylation, but pattern of expression has not been looked at before. The risk of cancer after an IAR, although low, is still a concern.

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