Severe hyponatraemia in medical in-patients: aetiology, assessment and outcome

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Summary

Background: Hyponatraemia is the most commonly identified electrolyte abnormality. Published data on severe hyponatraemia in general medical in-patients is lacking.

Aim: To determine the aetiology, adequacy of assessment, and outcome of severe hyponatraemia in general medical in-patients.

Design: Retrospective case-note review.

Methods: All general medical in-patients \( n = 108 \) with serum sodium \( < 125 \text{ mmol/l} \) were identified from the clinical chemistry database, over a six-month period. A full review of notes and computer records was undertaken at the index date and a pre-determined follow-up date.

Results: Follow-up data were available in 105 patients. There was a wide range of aetiologies: diuretic therapy (loop and thiazide), congestive cardiac failure and liver disease were the most common, and 75.3% of patients had multiple causes. None of the 48% of patients whose history suggested a possible diagnosis of the syndrome of inappropriate anti-diuretic hormone (SIADH) met the generally accepted diagnostic criteria. Overall mortality was 20% during the index admission and 44.6% at follow-up, vs. 7.1% and 22%, respectively, for other patients admitted to the same directorate over the same time period \(( p < 0.001)\). Mortality was linked to aetiology, but not to reduced absolute serum sodium concentration at admission.

Discussion: Severe hyponatraemia in general medical patients is associated with a complex, multifactoral aetiology and a very poor prognosis. Outlook is governed principally by aetiology, and not by serum sodium level. Assessment of patients with hyponatraemia requires a practical clinical algorithm for diagnosing SIADH.

Introduction

Hyponatraemia is the most commonly observed electrolyte imbalance in hospitalized patients, occurring in up to 6%.\(^1\)\(^-\)\(^3\) In the vast majority of cases, it is due to hypotonic hyponatraemia. This arises when there is an excess of water in relation to sodium stores, and is traditionally divided according to the fluid status of the patient.\(^4\)\(^,\)\(^5\)

Mild hyponatraemia is generally asymptomatic, but where the decrease in serum sodium is marked \((\leq 125 \text{ mmol/l})\) or acute (occurring over <48 h), serious neurological complications can ensue as a result of cerebral oedema.\(^4\)\(^-\)\(^6\) Early symptoms of headache, muscular weakness, nausea, lethargy, ataxia and confusion can progress to seizures,
irreversible neurological damage, coma and death, if unrecognized and untreated. In chronic hyponatraemia, cerebral wasting of intracellular potassium followed by organic osmolytes reduces cerebral swelling, delaying the onset of symptoms. The correction of hyponatraemia should be carefully managed, because of its association with the osmotic demyelination syndrome (central pontine myelinolysis). Patients with chronic hyponatraemia appear to be particularly vulnerable to this complication.2,4,5,7

Severe hyponatraemia has a high mortality. In order to instigate correct treatment, an accurate clinical assessment must be made, focusing on fluid status, chronicity and potential aetiology, along with appropriate investigations. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the commonest causes of severe hyponatraemia.8,9 Accurate diagnosis of SIADH requires clinical and biochemical criteria (based on Bartter’s original description10) to be met.2,5 However, the application of these diagnostic criteria is reportedly poor.11 We undertook a retrospective case-note review study to determine the aetiology and outcome of unselected general medical in-patients with severe hyponatraemia in a busy university hospital. We also reviewed the clinical and biochemical assessment made of these patients to establish whether the diagnostic criteria for SIADH were met.

Methods

Patients

Queen’s Medical Centre serves a catchment population of 630,000, and has 470 acute medical beds. Patients admitted to the departments of general internal medicine (GIM) and healthcare of the elderly (HCE) departments over a six-month period (August 2002 to January 2003) with a sodium concentration ≤125 mmol/l were identified using clinical chemistry computerized records. Both patients who were hyponatraemic on admission, and those who developed hyponatraemia during admission, were included in the study. The case notes, prescription charts and electronic records were reviewed at the time of hospital admission and at the end of follow-up (defined prospectively as 1 August 2004). Relevant demographic and clinical details including presentation, past medical history, drug history and examination findings were collected, along with the results of the biochemical and radiological investigations requested by the physicians responsible for the patients’ care.

This information was used by two of the authors (JAC and IRL) to determine all of the potential causes of hyponatraemia relevant to each case. Volaemic status was determined by the physical examination findings of the admitting physician. Re-admissions and mortality data were collected at the end of follow-up. The study was registered with the hospital audit department, which contributed data on overall mortality for all general medical and health care of the elderly admissions over the same time period.

Biochemistry

Serum sodium concentrations were measured on the VITROS 950 dry-slide chemistry analyser in the department of clinical chemistry. This apparatus contains an ion-selective electrode, ensuring identification of true hyponatraemia. The normal range for the laboratory is 135–145 mmol/l.

Statistical analysis

The χ² test was used for comparisons of outcome. Survival analysis used Kaplan-Meier survival curves. Both were performed using SPSS v. 11. Cox regression models were used to calculate the effects of admission sodium and aetiology on mortality at the end of follow-up, allowing for the potential confounding effects of age and gender. These analyses were performed using Stata 7.

Results

Over the six-month period, 108 in-patients were identified with a serum sodium concentration of ≤125 mmol/l at or during admission. The medical records of 105 (97%) were available at follow-up. Their median age was 75 years (range 28–95); 42 (40%) were male and 102 (98%) were Caucasian.

At admission, serum sodium concentrations ranged from 101 to 144 mmol/l; 16 (15.2%) had a sodium concentration within the normal range and in 62 (59.0%) it was <125 mmol/l. Thirty-eight (36.2%) had neurological symptoms attributable to the hyponatraemia at presentation. These included seizures (n=9), reduced consciousness level (n=5), confusion (n=14) and unsteadiness and falls (n=10).

Aetiology and assessment

In four patients (3.8%) no obvious cause for the hyponatraemia was identified. Twenty-two (20.9%) had a single aetiology, while in 79 (75.3%) the
aetiology was multifactorial (Figure 1). Table 1 provides a comprehensive breakdown of the specific observed causes. All patients had detailed clinical details including a complete drug history. An assessment of volume status was documented in 97 (92.4%). Investigations of relevance ordered by the responsible medical team during the patients admission with hyponatraemia were as follows: laboratory glucose 73 (69.5%); serum osmolality 64 (61.0%); urine osmolality 49 (46.7%); urine sodium concentration 42 (40%); liver function tests 96 (91.4%); thyroid function tests 51 (48.6%); random cortisol or short synacthen test 16 (15.2%); chest radiograph 89 (84%); and computed tomography scan of the head 25 (23.8%).

A number of the established aetiologies suggest SIADH as a possible underlying mechanism for the hyponatraemia; these aetiologies are indicated by an asterisk in the left-hand column of Table 1. Fifty (47.6%) of the study patients had one or more aetiologies suggesting SIADH. We went on to determine whether the clinical assessment and biochemical investigations performed met the generally accepted diagnostic criteria for SIADH (Figure 2a).²,⁵,¹⁰ None of the 50 patients fulfilled the diagnostic criteria. The flow chart (Figure 2b) shows the points at which the patients failed to meet these criteria when applied in a clinically relevant order.

**Outcomes**

Twenty-one patients (20.0%) with severe hyponatraemia died during their index admission, and by the end of follow-up, in total 47 (44.8%) had died, giving a mortality rate of 41 deaths per 100 person-years. Over the recruiting period, 9622 patients were admitted under general medicine and health care of the elderly. Of these, 685 (7.1%) died during

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**Table 1** Observed aetiology of hyponatraemia in general medical in-patients

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Single cause</th>
<th>Multifactorial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretic</td>
<td>0</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>11</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>0</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Liver disease</td>
<td>4</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Lower respiratory tract infection*</td>
<td>1</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>CNS lesion/stroke*</td>
<td>2</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor (SSRI)*</td>
<td>0</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Intravenous fluid replacement</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Lung carcinoma*</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Carbamazepine*</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Unclear*</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Other drug*</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hypopituitarism/Addison’s disease</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Post-operative*</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*Potential cause of SIADH.

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![Figure 1. Number of aetiologies contributing to hyponatraemia.](image-url)
admission, and by August 2004, the figure reached 2,119 (22.0%). Thus mortality was significantly higher in the patients with severe hyponatraemia both during admission ($p < 0.001$) and at follow-up ($p < 0.001$).

Mortality according to the aetiology of hyponatraemia is summarized in Table 2. Of the most common aetiologies, annual mortality was highest in patients in whom aetiology included

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**Table 2** Mortality according to aetiology of hyponatraemia

<table>
<thead>
<tr>
<th>Aetiology of hyponatraemia</th>
<th>n</th>
<th>Dead at discharge (%)</th>
<th>Dead at follow-up (%)</th>
<th>Deaths per 100 person-years</th>
<th>Odds ratio for death at follow-up (95% CI)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>105</td>
<td>21 (20.0)</td>
<td>47 (44.7)</td>
<td>41</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>34</td>
<td>10 (29.4)</td>
<td>20 (58.8)</td>
<td>69</td>
<td>1.91 (0.80 – 4.56)</td>
<td>0.143</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>29</td>
<td>2 (6.9)</td>
<td>8 (27.6)</td>
<td>19</td>
<td>0.32 (0.12 – 0.82)</td>
<td>0.019</td>
</tr>
<tr>
<td>CCF</td>
<td>27</td>
<td>8 (29.6)</td>
<td>18 (66.6)</td>
<td>90</td>
<td>2.70 (1.02 – 7.15)</td>
<td>0.046</td>
</tr>
<tr>
<td>Liver disease</td>
<td>21</td>
<td>5 (23.8)</td>
<td>13 (61.9)</td>
<td>77</td>
<td>10.61 (2.36 – 47.79)</td>
<td>0.002</td>
</tr>
<tr>
<td>Dehydration</td>
<td>20</td>
<td>6 (30.0)</td>
<td>9 (45.0)</td>
<td>42</td>
<td>0.82 (0.30 – 2.28)</td>
<td>0.710</td>
</tr>
</tbody>
</table>

Odds ratios for death at follow-up were generated using Cox regression models, allowing for the confounding effects of age and gender. CCF, congestive cardiac failure.
congestive cardiac failure and liver disease, and lowest in those on a thiazide diuretic. Figure 3 shows the Kaplan-Meier survival curves for all hyponatraemic patients and the subgroups on a thiazide or a loop diuretic; all patients on a loop diuretic had at least one other aetiology (in the majority, congestive cardiac failure), whereas thiazide treatment was often the sole cause of the low sodium.

Patients with a higher sodium concentration at admission who subsequently became hyponatraemic had a significantly higher mortality (Table 3). This may reflect the underlying aetiology: the majority of patients (24/29) with thiazide-induced hyponatraemia had a sodium concentration <125 mmol/l at admission, whereas many of those with congestive cardiac failure or liver disease had a normal sodium concentration on admission, which subsequently dropped. Patients with a multifactorial aetiology had higher mortality. Compared to those with a single identified aetiology patients with two aetiologies had significantly greater

Table 3  Mortality by sodium concentration at admission to hospital

<table>
<thead>
<tr>
<th>Admission Na (mmol/l)</th>
<th>n</th>
<th>Dead at discharge n (%)</th>
<th>Dead at follow-up n (%)</th>
<th>Odds ratio for death at follow-up (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>135–145</td>
<td>16</td>
<td>7 (43.8)</td>
<td>11 (68.8)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>125–134</td>
<td>27</td>
<td>8 (29.6)</td>
<td>15 (55.6)</td>
<td>0.52 (0.14 – 1.98)</td>
<td>0.339</td>
</tr>
<tr>
<td>115–124</td>
<td>47</td>
<td>5 (10.6)</td>
<td>19 (40.4)</td>
<td>0.33 (0.10 – 1.14)</td>
<td>0.079</td>
</tr>
<tr>
<td>&lt;115</td>
<td>15</td>
<td>1 (6.7)</td>
<td>2 (13.3)</td>
<td>0.08 (0.01 – 0.50)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Odds ratios for death at follow-up were generated using Cox regression models, allowing for the confounding effects of age and gender. All patients developed a sodium concentration <125 mmol/l during the course of their hospital admission, as a condition of entry into the study.
mortality (OR 6.78, 95% CI 1.39–33.04; p = 0.018) and those with three or more causes even more so (OR 15.91, 95% CI 3.02–84.00; p = 0.001).

Median length of in-patient stay was 16 days (range 1–121). Of the 84 patients alive at discharge, 52 (61.9%) were readmitted on at least one occasion during follow-up, and over half had multiple readmissions. Of these, 65.4% were hyponatraemic (<135 mmol/l) on readmission.

**Discussion**

This study demonstrates both the poor outcome associated with severe hyponatraemia in general medical in-patients, and the difficulties in assessing this common problem that frequently occurs in an elderly population with multiple co-morbidities. Hyponatraemia had a complex and multifactorial aetiology in the majority of our patients.

This study focuses on general medical in-patients, and thus more accurately represents the range of aetiologies seen in this group. The most common aetiologies were loop and thiazide diuretics, congestive cardiac failure, liver disease, and of interest, we found that selective serotonin reuptake inhibitors (SSRIs) are now a frequent iatrogenic cause. Thiazide diuretic therapy was the most common cause of hyponatraemia in those with a single aetiology. Thiazide diuretics are a common cause of severe hyponatraemia. Up to a third of elderly patients taking a thiazide at hospital admission are hyponatraemic, and 14% of patients prescribed a thiazide diuretic in primary care have a sodium below the normal range. Severe hyponatraemia occurs almost exclusively with thiazide rather than loop diuretics.

Our hyponatraemic patients taking a loop diuretic all had at least one other cause for the hyponatraemia: loop diuretics are frequently used to treat conditions such as congestive cardiac failure and cirrhosis in which hyponatraemia occurs.

The in-patient mortality of patients with a serum sodium concentration \(\leq 125 \text{ mmol/l}\) during the course of their hospital admission was three times higher than that for all general medical patients, and their mortality remained significantly elevated at follow up. Hyponatraemia in hospitalized patients has a high mortality rate. Our in-patient mortality rate was very similar to that described by Nzereu et al., although their study was not confined to medical patients and studied more severe hyponatraemia. Our breakdown of mortality by aetiology supports previously published data suggesting that hyponatraemia is an independent risk factor for mortality in specific conditions including congestive cardiac failure and liver disease.

Patients with a multifactorial cause for their hyponatraemia had significantly higher mortality. This observation most likely reflects increased disease severity and comorbidity, and could be examined in more detail in future studies by inclusion of disease severity scores.

Outcome was least favourable in those patients who were normonatraemic at admission and became hyponatraemic during the course of their admission. We believe that this unexpected finding results from a combination of factors. Firstly, a higher proportion of those with very low sodium were taking thiazide diuretics. This was often the sole aetiology, is easily recognizable and easily rectified. Secondly, a higher proportion of patients with congestive cardiac failure and liver disease had a normal sodium concentration on admission and became hyponatraemic due to a combination of disease decompensation and therapeutic intervention, reflecting the severity of their underlying disease. Our data suggest that the aetiology of the hyponatraemia was a more important prognostic indicator than the absolute level of serum sodium in medical patients, which is consistent with previous reports. Our study design did not allow for the collection of complete data on chronicity, or the rate of correction of hyponatraemia, and we recognize that future research prospectively investigating the association of aetiology and outcome in hyponatraemia should control for these potential confounders.

Given the poor outcome of severe hyponatraemia and the complexity of its aetiology in medical in-patients, it is essential that physicians make an accurate clinical assessment and appropriate biochemical evaluation, as this determines subsequent management. It is surprising, within a purely medical service, that none of our patients met the generally accepted criteria for diagnosis of SIADH. Although many of the listed aetiologies were accurately diagnosed on the basis of history, examination and first-line investigations, the diagnosis of SIADH was often presumptive, and practising clinicians did not observe all of the stringent criteria required to make a definitive diagnosis.

The implications of misdiagnosis include inappropriate management, with potentially dangerous fluid restriction, and the risk of missing a diagnosis of adrenal insufficiency. The majority of patients failed to meet the diagnostic criteria for SIADH because they were taking diuretics. There are two important messages from this. Firstly, when a patient is taking diuretics, measurements of urine osmolality and urinary sodium to try and establish an diagnosis of SIADH
are uninterpretable, and thus waste resources. Secondly, some hyponatraemic patients taking diuretics will probably also have SIADH, and there is currently no guidance on the appropriate ‘washout’ period for diuretics before appropriate biochemical investigations can be performed. In the majority of patients, there was an accurate clinical assessment including drug history and fluid status, but failure to interpret the biochemistry in the context of this information led to misdiagnosis. An assessment of adrenal reserve was not performed in the majority of patients. These findings are in keeping with frequent references in the literature to the relatively poor investigation of hyponatraemia.\textsuperscript{11,16,17}

Hoorn et al have recently illustrated the pitfalls of many of the existing clinical diagnostic algorithms for diagnosing hyponatraemia, and they have suggested a physiology-based approach which takes into account the chronicity and the pathophysiology of the hyponatraemia using a combination of history, laboratory findings and mechanism.\textsuperscript{23} Hyponatraemia is a very common clinical problem, and the application of simple clinical principles and diagnostic algorithms can hopefully improve the assessment and management of these patients. In order to avoid the pitfalls of diagnosing SIADH, we suggest that the existing diagnostic criteria are used in a clinically applicable order, such as that illustrated in Figure 2b.

In conclusion, severe hyponatraemia (\(\leq 125\) mmol/l) is a commonly encountered clinical problem in general medical patients, and is associated with a poor prognosis. Our data suggest that outcome in severe hyponatraemia is governed by aetiology, and not by the serum sodium level. Correct diagnosis of the aetiology of hyponatraemia in this patient group is critical, both to determine correct management and prognosis. In practice, interpretation of clinical and biochemical findings was poor, due to a combination of the complex, multifactorial aetiology encountered frequently in this elderly population group, and the lack of a clinically applicable diagnostic algorithm to define SIADH with accuracy.

References

23. Hoorn EJ, Halperin ML, Zietse R. Diagnostic approach to a problem in general medical patients, and is associated with a poor prognosis. Our data suggest that outcome in severe hyponatraemia is governed by aetiology, and not by the serum sodium level. Correct diagnosis of the aetiology of hyponatraemia in this patient group is critical, both to determine correct management and prognosis. In practice, interpretation of clinical and biochemical findings was poor, due to a combination of the complex, multifactorial aetiology encountered frequently in this elderly population group, and the lack of a clinically applicable diagnostic algorithm to define SIADH with accuracy.