

Abnormal plasma sodium concentrations in patients treated with desmopressin for cranial diabetes insipidus: results of a long-term retrospective study

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Abstract

Context and objective: Patients with cranial diabetes insipidus (CDI) are at risk of developing both hypernatraemia and hyponatraemia, due to the condition itself or secondary to treatment with vasopressin-analogues or during administration of i.v. fluids. We aimed to assess the frequency and impact of dysnatraemias in the inpatient (INPT) and outpatient (OPT) setting in desmopressin-treated CDI, comparing those with normal thirst with those with abnormal thirst.

Design: The study included 192 patients with cranial diabetes, who were identified from the Beaumont Pituitary Database, a tertiary referral centre. Retrospective case note audit was performed and the clinical and biochemical information of 147 patients with CDI were available for analysis.

Results: A total of 4142 plasma sodium measurements for 137 patients with normal thirst, and 385 plasma sodium measurements for ten patients with abnormal thirst were analysed. In those with normal thirst, the most common OPT abnormality was mild hyponatraemia ($pNa^+ 131\text{--}134$ mmol/l) in 27%, while 14.6% had more significant hyponatraemia ($pNa^+ \leq 130$ mmol/l). Of those patients with normal thirst, 5.8% were admitted due to complications directly related to hyponatraemia. Compared with patients with normal thirst, those with abnormal thirst were more likely to develop significant OPT hypernatraemia (20% vs 1.4%, $P=0.02$) and significant INPT hyponatraemia (50% vs 11.1%, $P 0.02$).

Conclusion: OPT management of CDI is complicated by a significant incidence of hyponatraemia. In contrast, OPT hypernatraemia is almost exclusively a complication seen in adipsic CDI, who also had more frequent INPT hyponatraemia. CDI associated with thirst disorder requires increased physician attention and patient awareness of potential complications.

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Introduction

Central diabetes insipidus (CDI) describes the inability to concentrate urine due to deficiency of the antidiuretic hormone arginine vasopressin (AVP). Thirst sensation is almost always intact in patients with CDI (1), so that they maintain sufficient fluid intake to replace urinary free water losses. They are therefore usually able to maintain

normal plasma sodium concentrations, even before treatment with vasopressin analogues. However, if access to fluids is impaired or if vomiting prevents drinking, patients may not be able to adequately replace urinary water losses, and hypernatraemia can develop. Hypernatraemia is a more common problem in adipsic diabetes

insipidus (DI), where patients do not sense rising plasma osmolality and subsequently fail to respond with appropriate fluid intake (2).

Treatment of CDI with the vasopressin analogue desmopressin effectively abolishes the polyuria associated with vasopressin deficiency. In normal physiology, drinking fluids suppresses vasopressin secretion by non-osmotic mechanisms (3, 4), thus allowing an aquaresis, which prevents over-hydration. However, drinking cannot suppress antidiuresis in treated CDI, as the antidiuresis is secondary to exogenous long-acting desmopressin which results in failure to excrete water that is taken in excess of physiologic needs and contributes to dilutional hyponatraemia. Thus, there is no 'escape' mechanism in treated DI to protect against overhydration and excess water therefore accumulates, producing hyponatraemia, which is occasionally symptomatic and, rarely, life threatening.

Although hyponatraemia is a well-recognised side effect of CDI with desmopressin, the incidence of hyponatraemia is unknown in this group of patients (5). In addition, the incidence of dysnatraemia in patients with CDI admitted to hospital is not well described. We hypothesised that in the presence of normal thirst, hypernatraemia would be rare in the outpatient (OPT) setting, but that during emergency admissions to hospital, hypernatraemia would result from impaired water intake due to vomiting or diminished consciousness levels. Also, in our well-defined cohort of patients with adipsic DI, we hypothesised that hypernatraemia would be more common than in patients with normal thirst, in both the inpatient (INPT) and the OPT setting.

The aim of this study was therefore to document the frequency with which perturbations of plasma sodium concentrations occur in a large, unselected cohort of patients with CDI, in both OPT and INPT settings, and to identify any predictive factors which increase the likelihood of dysnatraemia. In addition, we wished to assess the relative vulnerability of a smaller cohort of patients with adipsic DI to the development of dysnatraemia.

Patients and methods

Retrospective case note analysis was carried out in all patients with cranial DI (CDI) identified from the Beaumont Hospital Pituitary Database. Beaumont Hospital is the site of the National Neurosurgery Centre in the Republic of Ireland, with a catchment population of four million. The patients were included in the study if they had biochemically confirmed CDI based on well-established biochemical and clinical criteria outlined

below ($n=192$). The patients were excluded if the follow-up was <1 year ($n=41$) or if there was incomplete clinical information available ($n=4$). Data were compiled regarding clinical and biochemical parameters. Information regarding plasma sodium measurements was recorded from all neurosurgical and non-neurosurgical INPT admissions and OPT visits to the institution. Our unit policy is to check serum electrolytes at each OPT visit. Patients with uncomplicated isolated CDI might only be seen annually, but in patients with pituitary tumours or craniopharyngiomas, the frequency of clinical visit was determined by the treatment of the underlying condition. The patients with adipsic DI are formally reviewed every 3 months, with interim monitoring with the primary care physician. The study was conducted with the approval of the Beaumont Hospital ethics committee.

Diagnosis and definition of abnormalities

Posterior pituitary function ► The diagnosis of DI was made by the water deprivation test (WDT) (6) or, in the neurosurgical setting, by the application of the criteria of Seckl & Dunger (7) in combination with clinical parameters. From 1998 onwards, thirst scores were recorded during the WDT using a validated and reproducible visual analogue scale (1, 8). If the diagnosis of adipsic DI was suggested clinically and by the results of thirst visual analogue scale applied to the WDT, the formal diagnosis of adipsic DI was confirmed by thirst and AVP responses to the i.v. infusion of hypertonic saline (855 nmol/l), as previously described by Smith *et al.* (9) in our centre.

Patient characteristics: investigation of salt water balance

Formal WDT data were available in 84/137 (61.3%). The remaining patients had CDI diagnosed on the basis of clinical symptoms and matched urine and plasma osmolalities following neurosurgical intervention (7), which responded to therapy with desmopressin. In all patients with CDI diagnosed following pituitary surgery, desmopressin therapy had been withdrawn within 3 months of surgery to confirm that CDI was persistent. In the WDT group, the median peak plasma osmolality was 305 mOsm/kg (inter-quartile range (IQR) 298–312) and the median peak urine osmolality was 329 mOsm/kg (IQR 158–515). In 124/137, the median total daily desmopressin dose was 300 µg (IQR 200–400), but accurate daily dose requirement data were not available for 13/137. All patients on desmopressin received oral replacement.

Analytical methods

Biochemical methodologies for measurement of electrolytes and osmolalities changed over the study period; however, the methodologies used were standard at their time of use. Plasma and urine osmolalities were measured by depression of the freezing point method (2400 osmometer, Fiske, Norwood, MA, USA). Plasma sodium was measured by the indirect ion-selective electrode method (Olympus 2700). Urea and creatinine were measured by standard laboratory methods (Olympus 2700). Plasma vasopressin concentrations were measured using a well validated two-step RIA (10). Intra-assay coefficient of variation (CV) was 12, 16 and 16% at plasma AVP concentrations of 3.82, 8.78 and 27.02 pmol/l respectively. Interassay CV was 8.7 and 10.1% at plasma AVP concentrations of 2.37 and 4.93 pmol/l respectively (11).

Assessment of plasma sodium during follow-up

For the purpose of analysis, plasma sodium concentrations were defined as follows:

1. Mild hyponatraemia – plasma sodium 131–134 mmol/l
2. Significant hyponatraemia – plasma sodium \leq 130 mmol/l.
3. Normonatraemia – plasma sodium 135–145 mmol/l.
4. Mild hypernatraemia – plasma sodium 146–149 mmol/l.
5. Significant hypernatraemia – plasma sodium \geq 150 mmol/l.

We selected these definitions based on previous research by our own group, in which we found that there was no difference in the rate of seizures or the length of hospital stay in those patients who developed hyponatraemia $<$ 125 mmol/l compared with those with hyponatraemia between 125 and 130 mmol/l, but there was a significant difference between these two groups and patients with sodium $>$ 130 mmol/l (12). Thus, we considered any sodium level $<$ 130 mmol/l to be clinically significant.

Statistical analyses

Data related to patient characteristics are presented as median and IQR unless otherwise stated. The Mann–Whitney *U* test, Fisher's exact test, Kruskal–Wallis and linear correlation tests were applied for comparison as appropriate. Results were deemed significant for a *P*-value $<$ 0.05. Data were analysed using GraphPad Prism version 5 (GraphPad Software Inc, San Diego, CA, USA).

Results

Full clinical information with more than 1-year follow-up was available on 147 of 192 patients identified with CDI, cared for by a single consultant endocrinologist (C J Thompson). Of those, ten patients had CDI in conjunction with a formally diagnosed thirst disorder and the remaining 137 patients had CDI with clinically normal thirst. There was no difference in the basic characteristics of patients between both groups (Table 1). Further results of the patients with normal and abnormal thirst will be presented separately.

CDI with normal thirst

In this group of 137 patients, a total of 4142 plasma sodium measurements were available for analysis, with a median of 20 per patient (IQR 13–34).

INPT dysnatraemias ► *Neurosurgical INPT sodium abnormalities* ► There were 119/137 patients (86.9%) who had neurosurgical intervention, 17 of them had surgery in another institution or had incomplete information. The remaining 102 patients had 152 admissions specifically for neurosurgical interventions. Eighty admissions were for the initial intervention, during which the diagnosis of CDI was made; those admissions were excluded from the analysis as the data would have included plasma sodium concentrations before the institution of treatment. There were 72 neurosurgical admissions in 48 patients where CDI was an established condition. Dysnatraemia was common in this setting, as 37/48 (77%) patients had abnormal plasma sodium concentrations recorded during any neurosurgical INPT admission, with the most common abnormality being mild hypernatraemia (Table 2).

Non-neurosurgical admissions ► Forty-five patients had 89 admissions for non-neurosurgical conditions, 37 (82%) of whom had 73 admissions for reasons unrelated to sodium abnormalities (Fig. 1). Of those, 27/45 (60%) patients developed dysnatraemia during hospitalisation. The most common abnormality was mild hyponatraemia in 53.3% patients, although significant hyponatraemia was not uncommon (44%) (Table 2). Hypernatraemia was less common, with nine (20%) developing mild hypernatraemia and five (11.1%) significant hypernatraemia. There were no admissions specifically for hypernatraemia in the group of 137 patients with normal thirst. There were 16 admissions in eight patients (5.8% all patients with normal thirst CDI) specifically for hyponatraemia or

Table 1 Characteristics of patients. Data expressed as median and interquartile range (IQR) unless stated otherwise. No statistical significance was found between the two groups in gender, age, follow-up, year of diagnosis or desmopressin dose.

Characteristic	Normal thirst CDI (n=137)	Abnormal thirst CDI (n=10)
Male (%)	49.6	40
Age at diagnosis (years)	38 (IQR 24–50)	33 (IQR 18–38)
Length of follow-up (years)	7 (IQR 3.5–12)	10 (IQR 3–14)
Diagnosis	Craniopharyngioma (n=40) Non-functioning adenoma (n=40) Secretory tumour (n=20) Idiopathic/autoimmune (n=12) Infiltrative (n=7) Other tumour (n=7) Vascular/TBI (n=6) Apoplexy (n=5)	Craniopharyngioma (n=5) Prolactinoma (n=1) Rathke's cyst (n=1) Hypothalamic syndrome (n=1) Infiltrative (n=1) Vascular (n=1)
Oral desmopressin dose (µg)	300 (IQR 200–400)	300 (IQR 200–600)

CDI, central diabetes insipidus; TBI, traumatic brain injury.

complications of hyponatraemia (Fig. 1). In these patients, the plasma sodium concentration upon admission ranged from 115 to 128 mmol/l. Notably two patients contributed 21 admissions and persistent non-compliance with prescribed medication, including hydrocortisone, and desmopressin was found to be a contributing factor. In these cases admissions appeared to be precipitated by refusal to take or increase appropriately their prescribed hydrocortisone, thyroid replacement and included intermittent or inappropriate use of desmopressin, which may have precipitated or exacerbated the concurrent complaints of gastrointestinal illness/sepsis/abdominal pain/anorexia that resulted in admission for observation, investigation to outrule concurrent illness and stabilisation.

Neurosurgical patients developed dysnatraemia more frequently than non-neurosurgical patients, predominantly due to an increase in rates of mild hypernatraemia (Table 2).

OPT dysnatraemias ▶ There were 1440 plasma sodium measurements carried out in 137 patients with a median of seven per patient (IQR 4–14), representing 1.1 estimations annually (IQR 0.7–1.75 checks/year per patient). Fifty-six patients (40.9%) had abnormal sodium as an OPT, with mild hyponatraemia being the most common abnormality in 27% of patients, while significant hypernatraemia was rare and occurred in 1.5% of patients (Table 2). The rates of hyponatraemia and hypernatraemia as an OPT are significantly lower than that reported in INPTs (Table 2).

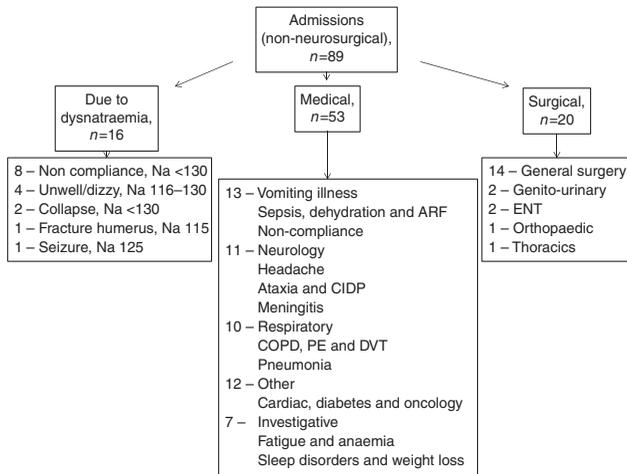
A total of five patients (3.6% of the cohort) contributed 40.4% of all abnormal OPT plasma sodium measurements, three of whom were also admitted for complications of hyponatraemia. These patients had a mean age of

56 years (+2 years) and included the one patient who was responsible for 50% of all non-neurosurgical admissions with hyponatraemia, a patient with cured Cushing's disease and recurrent issues with medication compliance as described previously. The other four patients in this group include two patients with non-functioning pituitary adenomas, one of whom had suspected issues with compliance, one craniopharyngioma and one with post-encephalitic DI. The median number of plasma sodium measurements carried out per year in the whole cohort as an OPT was 1.1 (range 0.15–9.7) and it is unlikely that the

Table 2 Plasma sodium measurements in the neurosurgical, non-neurosurgical inpatient and the outpatient settings, with cranial diabetes insipidus.

	Neuro-surgical inpatient admissions	Non-neuro-surgical admissions	Outpatient monitoring
Patients (n)	48	45	137
Admissions (n)	72	89	–
Total number of pNa ⁺ measurements (n)	1071	708	1440
Number of abnormal pNa ⁺ measurements (n, %)	355 (33%)	303 (42.8%)	178 (12.4%)
Patients with abnormal pNa ⁺ (n, %)	37 (77%)*	27 (60%) [†]	56 (40%) [‡]
Patients with			
pNa ⁺ 131–134 (n, %)	22 (45.8%)	24 (89%) [§]	37 (27%)
pNa ⁺ ≤ 130 (n, %)	13 (27.1%)	20 (74%)	20 (14.6%)
pNa ⁺ 146–149 (n, %)	26 (54.2%) ^a	9 (33%)	15 (11.6%) [‡]
pNa ⁺ ≥ 150 (n, %)	11 (22.9%)	5 (18.5%) [§]	2 (1.5%) [‡]

pNa⁺, plasma sodium, sodium concentrations (mmol/l). Individual patients may contribute to multiple categories. *P<0.001 vs non-neurosurgical, [†]P<0.05 vs outpatient, [‡]P<0.001 vs neurosurgical, [§]P<0.01 vs outpatient, ^{||}P<0.05 vs neurosurgical, ^aP<0.001 vs outpatient and ^bP<0.01 vs non-neurosurgical.

**Figure 1**

Reasons for non-neurosurgical admissions in patients with CDI and normal thirst. Na, plasma sodium in mmol/l; ENT, ear, nose and throat; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; ARF, acute renal failure; CIDP, chronic inflammatory demyelinating polyneuropathy; DVT, deep venous thrombosis.

five patients who contributed 40% of abnormal OPT measurements did so solely due to increased frequency of monitoring; they had a mean of 2.3 (+1.4) pNa measurements per year as OPT and 30 patients in total had more than two pNa measurements performed per year as an OPT.

Those who developed hyponatraemia as an OPT were older than those who did not develop hyponatraemia, (46.5 years, IQR 34–58 vs 33 years, IQR 21–46 respectively $P < 0.001$). Patients who developed hyponatraemia as an OPT were also at greater risk of developing hyponatraemia during INPT admission (31.8% vs 14%, $P = 0.02$) and developed more significant hyponatraemia ($pNa^+ \leq 130$ mmol/l in 27.3% vs 8.6%, $P = 0.008$) than patients who did not develop hyponatraemia as an OPT.

Urine osmolality at diagnosis and future risk of sodium abnormalities ▶ Patients with the lowest urine osmolalities on WDT (< 200 mOsm/kg) and the highest daily doses of desmopressin (400 μ g, IQR 240–400) had more admissions specifically for complications of hyponatraemia than patients with higher peak urine osmolality (> 400 mOsm/kg) at 15.4% compared with 2.7% respectively $P = 0.04$ (Table 3). A lower urine osmolality at diagnosis was associated with more common and more severe OPT hyponatraemia (Table 3). The rate of OPT hypernatraemia or INPT hypernatraemia was unrelated to severity of DI.

The interaction of anterior pituitary hormones with dysnatraemia ▶ There were 22 patients with isolated CDI and no anterior pituitary hormone deficit. In the isolated CDI group, during admissions, significant hyponatraemia was rare in 12 INPT, occurring on two occasions in one patient (4.5%) while mild hyponatraemia and mild hypernatraemia occurred in two (9%) and three (13.6%) patients respectively. When compared with patients with adrenocorticotrophin (ACTH) and/or thyrotrophin deficiency, there was no difference in the frequency of sodium abnormalities in OPT in the group with isolated CDI.

Thirst disorder group

There were ten patients in the thirst disorder group, whose characteristics are given in Table 1. Eight patients had documented adipsic DI on dynamic testing and two patients had hyperdipsia (one craniopharyngioma and one Rathke's cyst) in addition to vasopressin deficiency. Excluding neurosurgical admissions, these ten patients had 385 sodium measurements, of which 187 were as an INPT. This group had 22 hospital admissions, four of which were directly related to sodium abnormalities; two were for symptomatic hyponatraemia (hyperdipsic

Table 3 Analysis of the development of future sodium abnormality based on initial peak urine osmolality (uOsm) at diagnosis.

	uOsm < 200 (n=26)	uOsm 200–400 (n=22)	uOsm > 400 (n=36)	P value
UOsm (mOsm/kg)	131 (78–158)	285 (232–331)	528 (473–630)	
ddAVP dose (μ g)	400 (240–400)	400 (200–400)	200 (100–400)	< 0.02
Admission for hypoNa ⁺	4 (15.4%)	0	1 (2.7%)	0.04
Inpatient hypoNa ⁺	7 (26.9%)	4 (18.2%)	6 (16.7%)	NS
Inpatient hyperNa ⁺	3 (11.5%)	2 (9.1%)	1 (2.7%)	NS
OPT hypoNa ⁺	13 (50%)	4 (18.2%)	8 (22.2%)	0.02
OPT pNa ⁺ ≤ 130	7 (26.9%)	3 (13.6%)	1 (2.7%)	0.02
OPT pNa ⁺ 131–134	11 (42.3%)	2 (9.1%)	8 (22.2%)	0.03
OPT hyperNa ⁺	3 (11.5%)	0	4 (11.1%)	NS

uOsm, urine osmolality; OPT, outpatient; NS, non significant. P value relates to ANOVA. Sodium concentrations (mmol/l).

Table 4 Frequency of non-neurosurgical inpatient and outpatient sodium abnormalities compared between groups with abnormal and intact thirst. Data are expressed as number (*n* (%)).

	Adipsic/hyperdipsic CDI (<i>n</i> =10)	Normal thirst CDI (<i>n</i> =137)	P value
pNa ⁺ measurements ^a (<i>n</i>)	385	2148	–
Abnormal pNa ⁺ measurements	152 (39.5%)	587 (27.3%)	<0.001
Patients with abnormal pNa ⁺	9 (90%)	68 (49.6%)	0.02
INPT hypoNa ⁺	2/8 (25%)	27/45 (60%)	NS
pNa ⁺ 131–134	1/8 (12.5%)	24/45 (53.3%)	NS
pNa ⁺ ≤ 130	2/8 (25%)	20/45 (44.4%)	NS
INPT hyperNa ⁺	4/8 (50%)	9/45 (20%)	NS
pNa ⁺ 146–149	4/8 (50%)	9/45 (20%)	NS
pNa ⁺ ≥ 150	4/8 (50%)	5/45 (11.1%)	0.02
OPT hypoNa ⁺	4/10 (40%)	44/137 (32.1%)	NS
pNa ⁺ 131–134	3/10 (30%)	37/137 (27%)	NS
pNa ⁺ ≤ 130	3/10 (30%)	20/137 (14.6%)	NS
OPT hyperNa ⁺	4/10 (40%)	17/137 (12.4%)	0.04
pNa ⁺ 146–149	3/10 (30%)	15/137 (10.9%)	NS
pNa ⁺ ≥ 150	2/10 (20%)	2/137 (1.4%)	0.02

Sodium concentrations (mmol/l). INPT, inpatient; OPT, outpatient; pNa⁺, plasma sodium; hyperNa⁺, hypernatraemia; hypoNa⁺, hyponatraemia.
^aExcluding neurosurgical admissions.

patient) and two were for hypernatraemic dehydration (adipsic patient). The patients with adipsia were more likely to develop INPT and OPT hypernatraemia and less likely to develop INPT hyponatraemia than patients with CDI and intact thirst (Table 4).

Discussion

This paper documents for the first time the frequency of dysnatraemia in a large unselected cohort of CDI patients, treated with AVP analogues, in a single tertiary referral centre. We have divided the results into INPT and OPT care, as we feel that the two settings provide different challenges in the management of patients with CDI.

In the ambulatory care setting, hyponatraemia was relatively common, occurring in 32.1% patients with normal thirst, the majority being mild. Five patients (3.6%) contributed 40% of all abnormal OPT abnormalities, and one patient was responsible for 50% (8/16) of all admissions with hyponatraemia. The overall results are therefore skewed by a small number of patients in whom poor compliance with treatment led to frequent hyponatraemia. In most patients, hyponatraemia occurred as an isolated asymptomatic abnormality; however, as the rate of hyponatraemia in between routine testing is unknown, we are unable to speculate on the duration of hyponatraemia in our cohort. Prospective studies with frequent plasma monitoring would be required to address this question.

In contrast, in patients with intact thirst, hypernatraemia was rare in ambulatory care, with significant hypernatraemia (pNa⁺ ≥ 150 mmol/l) occurring in only

1.4% of patients. The pattern of dysnatraemias seen in the ambulatory care setting, with hyponatraemia relatively common and hypernatraemia rare, reflects the relevance of the intact thirst mechanism in CDI. As most patients with CDI have an intact thirst mechanism, they are able to respond to small rises in plasma sodium concentration with appropriate fluid intake, which prevents significant upward fluctuations in plasma sodium. In contrast, the relatively common occurrence of hyponatraemia reflects the inability to reverse antidiuresis produced by vasopressin analogues if fluid intake is excess to requirements. In physiological conditions, lowering of plasma sodium concentrations below the osmotic threshold for AVP secretion (13) switches off AVP secretion, thus allowing an aquaresis to occur. The half-life of AVP is very short, around 5–10 min, so that aquaresis occurs quickly, which prevents hyponatraemia in healthy individuals. The longer half-life of desmopressin, which has been modified by removal of the amino group (14), means that antidiuresis is not switched off and excess fluid intake is retained, with resultant dilutional hyponatraemia. Much of the fluid intake in humans is social and habitual, rather than thirst driven, which results in fluid intake in excess of physiological requirements which in subjects with treated CDI can easily lead to hyponatraemia. In clinical practice, we have found that omission (or even delay) of one dose of desmopressin per week allows an aquaresis to occur, which is sufficient to dramatically reduce the risk of hyponatraemia. However, the retrospective nature of this study makes it impossible for us to accurately assess the clinical effect of this change in policy in this paper.

The potential implication of chronic hyponatraemia due to over-treatment with desmopressin remains to be quantified. Recent publications have stressed the morbidity associated with chronic hyponatraemia, including gait instability and falls (15), fractures (16, 17), and osteoporosis (18), which suggests that even mild hyponatraemia may be detrimental to health. Further prospective studies are warranted to evaluate the nature of some of these morbidities, including defining whether they are an association or a direct result of hyponatraemia. In addition, hyponatraemia (plasma sodium 125–135 mmol/l) has been associated with increased mortality in almost every population studied, including community patients (19), hospitalised patients (20), patients with pneumonia (21) and patients in intensive care (22). For these reasons, even without data from intervention studies, it is prudent to try to maintain plasma sodium concentrations in the eunatraemic rather than the hyponatraemic range in CDI.

Although significant dysnatraemia was relatively uncommon in the ambulatory setting, it was, in contrast, very common during the context of acute hospital admission. Once patients were unable to maintain fluid intake, through drowsiness, cognitive dysfunction, excess gastrointestinal losses during vomiting, and particularly if vomiting prevented ingestion of desmopressin, then hypernatraemia became a significant problem. The importance of this development is clear, as hypernatraemia is associated in emergency care with excess morbidity and mortality (2). This highlights the need for active, well-monitored fluid balance in patients with CDI who are admitted with acute illness, with the almost certain need for i.v. fluid administration if they are unable to maintain adequate fluid intake.

We had hypothesised that patients treated for ACTH/cortisol deficiency with glucocorticoid therapy might be more vulnerable to hyponatraemia if steroid replacement was insufficient. However, only a small proportion of the acute admissions due to hyponatraemia were attributable to non-compliance with corticosteroids. In the ambulatory setting, hyponatraemia was not more common in patients treated with glucocorticoids than those who were not. We found that those patients with more severe DI, as defined by inability to concentrate urine during WDT, needed higher doses of desmopressin to control symptoms, and as a result were more likely to develop ambulatory hyponatraemia, and to be admitted due to significant hyponatraemia.

We have already published data on the high risk of hypothalamic complications and mortality in adipsic DI (2).

This paper also demonstrates the vulnerability of patients with adipsic CDI to ambulatory hypernatraemia, which contrasts markedly with the pattern of abnormalities in patients with CDI and intact thirst. The morbidity and mortality of mild ambulant hypernatraemia is less well defined than it is for hyponatraemia, but our view would be that eunatraemia should be the clinical aim in these patients. This needs extra efforts to encourage adequate fluid intake in adipsic DI, and our data emphasise that they remain a challenge, even in centres with experience in managing adipsic DI. These data also highlight the frequency of clinically serious hypernatraemia in patients with adipsic DI admitted with acute medical illnesses. Therefore, as our previous studies have shown, close physician supervision and regular electrolyte monitoring during INPT stay is essential. In response to our clinical observations on INPT hypernatraemia, and its association with thromboembolic events, including fatal pulmonary embolism, our unit has adopted a policy of formal prophylactic anticoagulation with low-molecular weight heparin, in patients admitted with hypernatraemic dehydration due to CDI, in addition to i.v. isotonic fluid replacement.

Conclusion

OPT management of CDI is complicated by a significant incidence of mild hyponatraemia; more serious hyponatraemia precipitating hospital admission occurs uncommonly, but is increased in patients with compliance issues. OPT hypernatraemia rarely occurs unless the patient has concurrent adipsia. Patients with CDI admitted to hospital with acute emergencies have very high rates of both hypernatraemia and hyponatraemia. The implications of these findings for clinical practice are as follows:

1. OPT care of CDI should be aimed at balancing control of polyuria with avoidance of desmopressin-induced hyponatraemia. Anecdotal evidence suggests this can be achieved by intermittent controlled omission of desmopressin. It has become our practice to recommend that all patients with normal thirst on desmopressin withhold, or delay one dose of desmopressin on 1 day of the week to allow diuresis. Generally, we advise our patients to do this on a day of the week that will be least disrupted by the subsequent diuresis. To date, clinically this appears to be sufficient; however, confirmation through formal monitoring is required.
2. Intercurrent illness precipitating acute admission in CDI is commonly associated with INPT hyponatraemia

and hypernatraemia; serious hypernatraemia is a particular feature of intercurrent illness in adipsic DI. Careful consideration should be extended to appropriate i.v. fluid replacement during acute admissions with patients with CDI, which will be guided by careful monitoring of fluid balance, including solute-free water and plasma sodium measurements.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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