ORIGINAL ARTICLE

Central diabetes insipidus is not a common and prognostically worse type of hypernatremia in neurointensive care

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Abstract

BACKGROUND: Hypernatremia is a common sodium dysbalance in neurointensive care which is associated with worse outcome. It can be caused by central diabetes insipidus (cDI) or by other mechanisms, more often from osmotherapy and furosemide. The aim of this study was to determine the incidence of cDI and to analyse outcome as compared with other causes of hypernatremias found in neurointesive care. **METHODS:** We analysed 75 hypernatremic (serum sodium, SNa^+ >150 mmol/l) patients (pts) with brain diseases admitted over a period of five years to Neurologic-Neurosurgical Intensive Care Unit (NNICU). Firstly we diagnosed cDI according to measured serum and urine osmolality, eletrolyte free water clearance (EWC) and response to desmopressin acetate. The remaining hypernatremias were categorised as "non cDI". We observed Glasgow Coma Scale (GCS) on onset of hypernatremia, incidence of cerebral complications, Glasgow Outcome Scale (GOS) upon discharge from NNICU and mortality in NNICU. **RESULTS:** We found cDI in 8 pts (mean SNa^+ 154.8 ± 5.4 mmol/l). Most pts (67) were classified as "non cDI" hypernatremias (mean SNa^+ 154.3 ± 3.6 mmol/l). There were no differences in serum sodium (p=0.682), serum osmolality (p=0.476) between the two groups, however patients with cDI indicated low urine osmolality (p=0.001) and positive EWC (p=0.049). We did not find any differences in GCS score on onset of hypernatremia (p=0.395), incidence of cerebral complications (p=0.705), GOS score upon discharge from NNICU (p=0.61) and mortality in NNICU (p=0.638). More patients in the "non cDI" group received antiedematic therapy (p=0.028) and diuretic furosemide (p=0.026). Multivariate logistic regression analysis showed that independent predictors of NNICU mortality was the highest level of serum sodium (Odds ratio, OR 1.13, per 1 mmol/l increase in maximal hypernatremia during NNICU stay, 95% confidence interval, CI 1.01–1.26, p=0.027), and GCS on admission of less than 9 (OR 2.61, 95% CI 1.41–5.44, p=0.003). **CONCLUSIONS:** Central diabetes insipidus is not a frequent type of hypernatremia in neurointensive care. Prognosis is connected with serum sodium level, not with type of hypernatremia.

Abbreviations:

ADH	- antidiuretic hormone
BpH	- blood pH
CCr	- creatinine clearance (ml/s)
CEl	- electrolyte clearance (ml/s)
CH_2O	- solute free water clearance (ml/s)
CNa^+	- sodium clearance (ml/s)
Cosm	- osmotically active substances clearance (ml/s)
cDI	- central diabetes insipidus
CI	- confidence interval
DDAVP	- desmopressine acetate
dUCr	- daily output of creatinine (mmol)
$dUNa^+$	- daily output of sodium (mmol)
EWC	- electrolyte free water clearance (ml/s)
FEH_2O	- fractional excretion of free water
$FENa^+$	- fractional excretion of sodium
FEOsm	- fractional excretion of osmotically active substances
GCS	- Glasgow Coma Scale
GOS	- Glasgow Outcome Scale
LISSTA	- Laboratory Information System Stapro
NNICU	- Neurologic-Neurosurgical Intensive Care Unit
OR	- Odds ratio
pts	- patients
SAlb	- serum albumin (g/l)
SCa^{2+}	- serum calcium (mmol/l)
SCl-	- serum chloride (mmol/l)
SCr	- serum creatinine (μmol/l)
SGlu	- serum glucose (mmol/l)
SK^+	- serum potassium (mmol/l)
SMg^{2+}	- serum magnesium (mmol/l)
SNa^+	- serum sodium (mmol/l)
SP	- serum phosphorus (mmol/l)
SOsm	- serum osmolality (mmol/kg)
SOsmC	- serum osmolality calculated (mmol/kg)
Sp gr	- specific gravity of urine
SUrea	- serum urea (mmol/l)
UpH	- urine pH
UOsm	- urine osmolality (mmol/kg)
V	- urine volume (litres)

INTRODUCTION

Hypernatremia is a prognostically serious complication in the neurointensive care unit (Ayus *et al.* 1996; Qureshi *et al.* 2002; Fisher *et al.* 2006). Levels above 160 mmol/l is one of the independent markers of rising mortality (Aiyagari *et al.* 2006).

Central diabetes insipidus (cDI) is a well known syndrome associated with brain disease (Singer *et al.* 1997). In the neurosurgical intensive care unit, however, it is not the most common type of hypernatremia. Reported incidence makes up only 3.7% of all hypernatremias, but mortality can be as high as 72.4% (Wong *et al.* 1998). Hypernatremia arises from water diuresis due to antidiuretic hormone (ADH) insufficiency in cDI. The resulting polyuria depends on the extent of the specific brain damage and may be temporary or permanent. In severe cases of polyuria, the patient's diuresis can reach more than 20 litres a day. Besides central etiology, there is another form known as nephrogenic diabetes insipidus (Morello & Bichet 2001; Sasaki 2004). The condition is characterised by the inability of kidneys to respond normally to ADH. It can be caused by acute or chronic disease of kidneys, ion dysbalances and other factors. Diagnosis of central diabetes insipidus is carried out by observing hourly diuresis, urine osmolality, specific gravity of urine, renal function parameter – electrolyte free water clearance (EWC) and response to desmopressine acetate (DDAVP). Therapy for cDI is causal via synthetic analogue – desmopressine acetate. Fluids are supplemented by using infusions according to serum sodium level.

In neurointensive care there are usually multifactorial causes of hypernatremia, most frequently connected with osmotherapy by hypertonic saline and mannitol. Renal failure is another possible cause of hypernatremia (Aiyagari *et al.* 2006).

Therapy of other types of hypernatremia is based upon the underlying mechanisms leading to these dysbalances. When there is no causal therapy hypotonic infusions and thiazides are used to correct sodium levels. Correction of serum levels depends on the speed of the hypernatremia's inception. The recommended decrease moves between 10–15 mmol/l/day and not more.

The purpose of our study was to determine the incidence of cDI and to analyse outcome as compared with other causes of hypernatremias found in neurointesive care.

METHODS

The study was conducted in the eight-bed neurological-neurosurgical intensive care unit (NNICU) of our Neurocenter. In the five-year observation period 1 422 patients with brain diseases were admitted. Laboratory data was collected using the database of Laboratory Information System Stapro (LISSTA) from the Department of Clinical Biochemistry. The criteria for patients' inclusion in the study were set as a serum sodium level above 150 mmol/l and measured serum osmolality increased above 295 mmol/kg.

Differential diagnosis of hypernatremia in all patients included tests for cDI. We used widely accepted criteria: hourly diuresis (>4 ml/kg/hour), measured serum osmolality (>295 mmol/kg), specific gravity of urine (<1 005 kg/m^3), and renal function parameter: eletrolyte free water clearance (EWC ≥0.005 ml/s) and response to DDAVP. Remaining hypernatremias were categorised as "non cDI".

We evaluated brain diagnosis, Glasgow Coma Scale (GCS) score, Glasgow outcome score (GOS) upon discharge from NNICU, mortality in NNICU, operation (type and time since operation), incidence of cerebral complications, pulmonary edema, relation to admission, onset of hypernatremia, length of dysnatremia, fluid intake (ml/day), fluid output (ml/day), and fluid balance (ml/day). We calculated all fluids given by mouth, tube and parentally into fluid intake. Fluid output included diuresis and drainage. Further therapy (diuretics and antidiuretics, antiedematic therapy with mannitol or hypertonic saline) and type of infusions were evaluated as well.

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The following biochemical parameters were examined: serum sodium (SNa^+), serum potassium (SK^+), serum calcium (SCa^{2+}), serum magnesium (SMg^{2+}), serum chloride (SCl^-), serum phosphorus (SP), serum osmolality (SOsm), urine osmolality (UOsm), serum albumin (SAlb), serum glucose (SGlu), serum urea (SUrea), serum creatinine (SCr), blood pH (BpH), urine pH (UpH), daily output of creatinine (dUCr) and sodium ($dUNa^+$), and specific gravity of urine (Sp gr, kg/m^3).

Sodium, potassium and chloride measurements in serum and urine were carried out on the COBAS Integra 800 system (Roche, Diagnostics, Switzerland) using selective ion electrodes. Creatinine in serum and urine, albumin in serum were also measured on this equipment, but photometrically. Osmolality was gauged on the cryoscopic osmometer Fiske 210 (Advanced Instruments, Inc, Norwood, Massachusetts). BpH was measured on the blood gas analyzer ABL 625 (Radiometer, Denmark). Assessment of urine pH (UpH) was made on Urisys 2400 equipment (Roche Diagnostics, Switzerland). Specific gravity of urine was measured on the urometer in the NNICU.

For the purpose of diagnosis, several parameters had to be calculated: calculated osmolality (SOsmC = 2 × Na^+ + glucose + urea), creatinine clearance (CCr), osmotically active substances clearance (COsm), electrolyte clearance (CEl), sodium clearance (CNa^+), solute free water clearance (CH_2O), eletrolyte free water clearance (EWC), fractional excretion of osmotically active substances (FEOsm), fractional excretion of sodium ($FENa^+$), fractional excretion of free water (FEH_2O). Clearance of creatinine was calculated with correction for the body's surface. Values of urine volume (V) are in litres and time in seconds. Biochemical parameters from urine were processed from 24 hours of urine collection. Calculations of the mentioned renal function parameters were conducted in a clinical biochemistry department.

The results were processed using the programme STATISTICA 9.0, StatSoft, Inc. The parametric t-tests or non-parametric M-W U tests were used for comparison of continuous variables. Comparison of categorical parameters was carried out with Fisher tests. Univariate logistic regression was used for identifying prognostic factors of mortality during NNICU stay. Factors from univarite analysis with level of significance defined as $p<0.1$ were used for multivarite regression analysis with forward stepwise method of final model building (p value for model enter was <0.1, p-value for remove from model was > 0.1). p-values of less than 0.05 were considered significant.

The study was conducted with the approval of the hospital ethical committee.

RESULTS

In the five-year observation period there were 75 (5%) hypernatremic patients. The mean age of the patients was 56.8 ± 14.8 years and there were 41 males and 34 females with the following diagnoses: stroke 43 pts (57%), tumour 20 pts (27 %), trauma 7 pts (9%), hydrocephalus 4 pts (5%) and epilepsy 1 pt (1%). The stroke group included 20 (46.5%) cases of subarachnoid hemorrhage, 17 (39.5%) cases of intracerebral hemorrhage and 6 (14.0%) patients with ischemic stroke. The mean stay in NNICU was 11.6 ± 9.6 days, the mean GCS score on onset of hypernatraemia was 12 ± 3, the mean GOS score upon discharge of NNICU was 3.3 ± 1.4. There were 62 (83%) patients who underwent an operation and the mean onset of hypernatremia since the operation was 3.7 ± 5.0 days.

We found cDI in 8 pts (mean SNa^+ 154.8 ± 5.4 mmol/l). There were 4 pts (50.0%) with stroke, 3 pts (37.5 %) with tumour and 1 pt (12.5%) with hydrocephalus. Further parameters are shown in table 1. The majority of pts (67) were classified as "non cDI"

Tab. 1. Characteristics of hypernatremic patients in neurointensive care.

Parameter	Unit	cDI	non cDI	p-value
Number of patients	pts	8	67	
Male	pts	6	35	0.281
Age	years	46.4 ± 13.3	58.0 ± 14.5	**0.034**
Stay in NNICU	day	15.8 ± 10.5	11.1 ± 9.5	0.197
Stroke	pts	4	39	0.717
Tumour	pts	3	17	0.433
Trauma	pts	0	7	1
Operation	pts	7	55	1
After operation	pts	6	51	1
Days after operation	day	3.8 ± 5.1	3.7 ± 5.0	0.939
Craniotomy	pts	6	42	0.703
Craniectomy	pts	0	4	1
GCS	1	11.0 ± 5.3	12.1 ± 3.1	0.395
Admission to NNICU	pts	3	10	0.136
Cerebral complications	pts	5	46	0.705
Focal	pts	2	32	0.280
Diffuse	pts	4	26	0.706
Pulmonary edema	pts	0	5	1
GOS	1	3.5 ± 1.7	3.2 ± 1.4	0.610
Mortality in NNICU	pts	2	12	0.638
Antiedematic therapy	pts	3	52	**0.028**
Furosemide	day	0	41	**0.026**

Neurologic-Neurosurgical Intensive Care Unit (NNICU), Glasgow Coma Scale (GCS) on onset of hypernatremia, Glasgow Outcome Scale (GOS) upon discharge from NNICU.

hypernatremias (mean SNa^+ 154.3 ± 3.6 mmol/l) with the following diagnoses: stroke 39 pts (58.2%), tumour 17 pts (25.4%), trauma 7 pts (10.5%), hydrocephalus 3 pts (4.5%) and epilepsy 1 pt (1.5%).

The characteristics of both cDI and "non cDI" groups of hypernatremic patients can be seen in Table 1. Biochemical parameters are presented in Table 2. Between the two groups there were no differences in serum sodium (p=0.682). No differences were found in serum osmolality (p=0.476, mean 323.3 ± 15.4 mmol/kg in cDI pts, mean 326.4 ± 16 mmol/kg in non cDI pts) either, but patients with cDI had lower urine osmolality (p=0.001). There were also no significant differences in sodium shift during 24 hours (p=0.14). The mean value in group patients with cDI was –5.0 ± 5.0 mmol/l and in the other group was –2.3 ± 5.6 mmol/l.

We did not find any differences in the mean GCS on onset of hypernatremia (mean 11.0 ± 5.3 in cDI, mean 12.1 ± 3.1 in "non cDI", p=0.395), in GOS score upon discharge of NNICU (mean 3.5 ± 1.7 in cDI,

Tab. 2. Biochemical parameters in hypernatremic patients.

Parameter	Unit	Reference range	cDI	non cDI	*p*-value
SNa^+	mmol/l	135–146	154.8 ± 5.4 (N=15)	154.3 ± 3.6 (N=176)	0.682
Length of dysnatraemia	day		5.3 ± 7.3	2.2 ± 1.5	0.625
Shift per 24 hours	mmol/l		–5.0 ± 5.0	–2.3 ± 5.6	0.14
SOsm	mmol/kg	275–295	323.3 ± 15.4	326.4 ± 16.0	0.476
SOsmC	mmol/kg	275–300	325.5 ± 13.4	326.2 ± 10.9	0.833
UOsm	mmol/kg	50–850	392.3 ± 221.9	578.8 ± 186.7	0.001
SK^+	mmol/l	3.8–5,5	4.0 ± 0.4	3.9 ± 0.6	0.561
SCa^{2+}	mmol/l	2–2.75	2.2 ± 0.1	2.1 ± 0.2	0.143
SMg^{2+}	mmol/l	0.7–1.1	1.0 ± 0.2	1.0 ± 0.2	0.637
SP	mmol/l	0.7–1.5	1.2 ± 0.4	1.0 ± 0.3	0.079
SCl^-	mmol/l	97–108	109.8 ± 5.8	113.5 ± 6.6	0.034
SAlb	g/l	32–53	37.8 ± 4.2	32.9 ± 6.4	0.107
SGlu	mmol/l	3.3–6.1	8.3 ± 2.0	7.5 ± 2.9	0.267
BpH		7.36–7.44	7.427 ± 0.041	7.424 ± 0.056	0.85
SUrea	mmol/l	2.8–7.5	7.0 ± 2.9	9.7 ± 5.3	0.083
SCr	µmol/l	35–115	96.3 ± 19.8	96.0 ± 37.3	0.972
CCr	ml/s	1.15–2	1.4 ± 0.4	1.7 ± 0.8	0.318
COsm	ml/s	0.03–0.05	0.056 ± 0.020	0.067 ± 0.031	0.32
CH_20	ml/s	–0.027– –0.007	0.010 ± 0.060	–0.026 ± 0.019	0.101
CNa^+	ml/s	0.008–0.016	0.021 ± 0.014	0.023 ± 0.018	0.692
CEl	ml/s	0.011–0.023	0.027 ± 0.015	0.031 ± 0.022	0.611
EWC	ml/s	–0.000 ± 0.006	0.038 ± 0.055	0.008 ± 0.016	0.049
$FENa^+$		0.004–0.012	0.017 ± 0.013	0.016 ± 0.015	0.885
FEOsm		0.01–0.035	0.040 ± 0.009	0.043 ± 0.022	0.719
FEH_20		0.01–0.02	0.049 ± 0.045	0.028 ± 0.019	0.284
Fluid intake	ml/day		4217 ± 1042	3798 ± 971	0.16
Infusion	ml/day		2379 ± 1442	2215 ± 934	0.478
Fluid output	ml/day		4137 ± 1900	3129 ± 1093	0.097
Diuresis	ml/day		4042 ± 1919	3000 ± 1165	0.086
Fluid balance – negative	day		3	18	0.372

Serum sodium (SNa^+), serum osmolality (SOsm), serum calculated osmolality (SOsmC), urine osmolality (UOsm), serum potassium (SK^+), serum calcium (SCa^{2+}), serum magnesium (SMg^{2+}), serum phosphorus (SP), serum chloride (SCl^-), serum albumin (SAlb), serum glucose (SGlu), blood pH (BpH), serum urea (SUrea), serum creatinine (SCr), creatinine clearance (CCr), osmotically active substances clearance (COsm), solute free water clearance (CH_2O), sodium clearance (CNa^+), electrolyte clearance (CEl), eletrolyte free water clearance (EWC), fractional excretion of sodium ($FENa^+$), fractional excretion of osmotically active substances (FEOsm), fractional excretion of free water (FEH_2O).

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mean 3.4 ± 1.4 in "non cDI", p=0.61) or in mortality in NNICU (p=0.638). No patients with cDI had a pulmonary edema, but there were 5 cases in "non cDI" group.

There were no differences in fluid intake (p=0.160) and amount of infusion (p=0.478) between the groups. More patients in the "non cDI" group received antiedematic therapy (p=0.028) and diuretic furosemide (p=0.026). Patients received predominantly Mannitol (96%) than hypertonic saline.

There were no differences in serum potassium (p=0.561), serum calcium (p=0.143), serum magnesium (p=0.637) or serum phosphorus (p=0.079). The levels of serum chloride (p=0.034) were significantly higher in "non cDI" patients. We did not find significant differences in serum urea (p=0.083) and serum creatinine (0.972). Creatinine clearance decresed below the reference range <1.15 ml/s in the "non cDI" group in 4 patients.

Univariate and subsequent multivariate logistic regression analysis was used for identifying significant predictors of mortality during NNICU stay. Studied factors were age, cDI, hypernatremia on admission, administration of steroids, antiedematic therapy, initial GCS, cerebral complications, diffuse or focal brain lesion, highest level of serum sodium during NNICU stay and time between admission and evolution of hypernatremia. Two significant independent predictors of NNICU mortality were identified – highest level of serum sodium during NNICU stay and initial GCS of less than 9. Results of multivariate regression analysis are summarized in Table 3.

Tab. 3. Results of multivariate regression analysis. OR for highest natremia is OR for unit increase in highest natremia encountered during whole NNICU stay.

Predictor	odds ratio	95% CI		p-value
GCS <9	2.77	1.41	5.44	0.003
Highest natremia	1.13	1.01	1.26	0.027

DISCUSSION

Hypernatremia is a common sodium dysbalance in acute brain diseases. In this retrospective study, hypernatremia above 150 mmol/l occurred in 5.3% of patients with brain disease admitted to our NNICU. Central diabetes insipidus is not a frequent cause of hypernatremia in neurointensive care and we diagnosed only 8 cases (0.56%) during a five-year period. Many more patients (67, 4.7%) were classified as "non cDI" hypernatremia. The most frequent brain disease in our population of hypernatremic patients was stroke (43, 57.3% pts), predominantly in subarachnoid hemorrhage (20 pts). We did not find cDI in traumatic brain injury patients, which was different from literature (Boughey *et al.* 2004; Agha *et al.* 2005; Hadjizacharia *et al.* 2008). All 7 cases with traumatic brain injury were in the "non cDI" group. Further comparison of parameters among hypernatremias did not show significant differences in the length of dysnatremia and its presence upon admission to the NNICU.

Diagnosis of cDI is not very difficult given proper monitoring. In our NNICU we use hourly diuresis, measured serum and urine osmolality, specific gravity of urine, renal function parameters and response to DDAVP. The most useful renal function parameter in cDI diagnosis is electrolyte free water clearance (EWC). Assessment of axis ADH-kidneys through this parameter was worked out by Shoker (Shoker 1994). EWC relates to effective osmolality, unlike solute free water clearance (CH_2O), which calculates with total osmolality including urea. This was seen in our study, we found significant changes in EWC, not in CH_2O, between the groups cDI and "non cDI". In therapy cDI has an advantage over other types of sodium dysbalances due to causal therapy with DDAVP. In our NNICU we prefer intravenous administration of DDAVP to nasal.

Multifactorial "non cDI" hypernatremia is reported to be the most frequent in neurointensive care. This was seen in our study. We found 67 pts. For the sake of simplicity and better orientation we did not further divide this category. We use the term "non cDI" also in clinical practice in the neuro-ICU with good experience. In our study we diagnosed only one patient with renal failure connected to "non cDI" hypernatremia, which is a much lower incidence than reported by Aiyagari (Aiyagari *et al.* 2006) . Subsequently we did not find any differences between the cDI and "non cDI" groups in values of serum creatinine and its clearance.

It seems that a frequent cause of the onset of "non cDI" hypernatremia lies in routine antidematic therapy. The other main reason for "non cDI" hypernatremias was the administration of furosemide. Loop diuretics lower reabsorbtions of iont in the Henle ascending loop and distal tubule, which disturbs the keeping of the osmotic gradient. Through this mechanism more water than sodium is lost, causing hypernatremia. The opposite effect can be achieved by administration of thiazide diuretics. More sodium than water is lost as a result of interrupting the dilution capabilities of the distal and collecting tubules. Hydrochlorothiazide is widely used drug of this group and we routinely use it in therapy of "non cDI" hypernatremias. Absence of the parenteral form of this drug means a rather significant limitation in therapy.

Hypernatremia is a prognostically serious complication in critically ill patients (Qureshi *et al.* 2002; Fisher *et al.* 2006; Hoorn *et al.* 2008; Stelfox *et al.* 2008) and therefore deserves great attention. In our study hypernatremia was confirmed as a significant independent prognostic factor of mortality during NNICU stay. It is important not only to accurately diagnose the dysbal-

ance but also to set precise target serum sodium values to be achieved. To avoid complications from quick correction we carefully followed our internal guideline not to exceed the safety range of sodium shift. In this study there were no differences in sodium shift between the two groups.

Comparing cDI and "non cDI" by outcome, there were no significant changes in mean value in GOS score upon discharge of NNICU (p=0.61), cerebral complications (p=0.705) and mortality in NNICU (p=0.638). The results suggest that bad outcome is closely connected with increasing the maximal level of serum sodium and initial GCS score below 9. The sodium level seems to be a more important factor than the type of hypernatremia. However, our results have the limitations of a retrospective study.

In conclusion, central diabetes insipidus (cDI) is not a frequent type of hypernatremia in neurointensive care. Most hypernatremias have multifactorial causes, mostly due to Mannitol and Furosemide medication. Prognosis is probably not connected with the diagnosis of cDI, but it seems to depend purely on serum sodium levels and initial GCS score. Meticulous ion-balance monitoring with early treatment prevents rapid onset of higher serum natrium values in cDI, thus reducing morbidity and mortality. Futher prospective cohort studies are needed to confirm these findings.

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