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DISTURBANCES OF EFFECTIVE OSMOLALITY IN ACUTE BRAIN DISEASES

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List of abbreviations

ACE	Angiotensin converting enzyme
ACoA	Arteria communicans anterior
ADH	Antidiuretic hormone, Vasopressin
ANP	Atrial natriuretic peptide
AQP	Aquaporin
BNP	B-typ natriuretic peptide
C_Cr	Creatinine clearance
C_El	Electrolyte clearance
C_H_2O	Solute free water clearance
C_K^+	Potassium clearance
C_Na^+	Sodium clearance
C_Osm	Osmotically active substances clearance
cAMP	3´, 5´-cyclic adenosine monophosphate
cDI	Central diabetes insipidus
CNP	C-type natriuretic peptide
CNS	Central nervous system
CPM	Central pontine myelinolysis
CSW	Cerebral salt wasting
CT	Computed tomography
CVP	Central venous pressure
DDAVP	Desmopressin, 1-desamino-8-D-arginine-vasopressin
DI	Diabetes insipidus
DNP	D-type natriuretic peptide
dU_K^+	Daily urine output of potassium
dU_Na^+	Daily urine output of sodium
ECF	Extracellular fluid
EPM	Extrapontine myelinolysis
EWC	Electrolyte free water clearance
FE_H_2O	Excretion fraction of free water
FE_K^+	Excretion fraction of potassium
FE_Na^+	Excretion fraction of sodium
FE_Osm	Excretion fraction of osmotically active substances
GCS	Glasgow Coma Scale
GFR	Glomerular filtration rate
GOS	Glasgow Outcome Scale
HCO3-	Hydrogencarbonate (bicarbonate)
ICF	Intracellular fluid
ICP	Intracranial pressure
ICH	Intracerebral haemorrhage
IS	Ischemic stroke
ISF	Interstitial fluid
IVF	Intravascular fluid
NNICU	Neurologic-neurosurgical intensive care unit
non cDI	Hypernatraemia non central diabetes insipidus
NP	Natriuretic peptide
NT-proBNP	N-terminal proB-type natriuretic peptide
NYHA	New York Heart Association
RAAS	Renin-angiotensin-aldosterone system
S_Alb	Serum albumin

S_Ca^{2+}	Serum calcium
S_Cl-	Serum chloride
S_Cr	Serum creatinine
S_Glu	Serum glucose
S_K^+	Serum potassium
S_Mg^{2+}	Serum magnesium
S_Na^+	Serum sodium
S_Osm	Serum osmolality
S_OsmE	Serum osmolality effective
S_OsmC	Serum osmolality calculated
SAH	Subarachnoid haemorrhage
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
Sp gr	Specific gravity of urine
TBI	Trauma brain injury
TBW	Total body water
U_Osm	Urine osmolality

Introduction

Dysbalances of effective osmolality are some of the most frequent and serious complications in neurointensive care. Their severity lies in brain oedema in hyponatraemia and dehydration of the brain in hypernatraemia [1-8]. In brain diseases there are three typical syndromes: Hyponatraemia involves two syndromes arising from different causes. The first is depletion hyponatraemia induced by natriuresis in cerebral salt wasting (CSW) syndrome, the second is dilutional hyponatraemia through water retention in syndrome of inappropriate secretion of antidiuretic hormone (SIADH), [3, 7, 9]. Hypernatraemia is brought about by water diuresis in central diabetes insipidus (cDI), [2, 8]. Due to the seriousness of dysnatraemia in acute brain diseases, timely and accurate diagnosis is necessary. Nowadays this is easily achieved through measuring and calculating renal function parameters [10-18].

Theory

Osmolality

Osmolality is given by the overall number of soluble particles in 1 kg of fluid regardless of their size or electrical charge. The most important soluble substances are ions, others include glucose, urea and proteins. The main part of water extent in the organism (total body water, TBW) is made up from intracellular fluid (ICF) and extracellular fluid (ECF), which is divided into intravasal (IVF) and interstitial fluids (ISF). Osmolality of these water extents is given by a different type of soluble particles. The differing distribution of ion concentration between ICF and ECF is the result of the presence of a semipermeable membrane between them, enabling the free flow of small ions and molecules according to Donan's balance as well as other activities of ion pumps in cell membranes. In ECF, overall osmolality is largely caused by sodium and its responding anions, less by glucose and urea and finally by plasma proteins. Ion composition in IVF and ISF is nearly the same. ISF is ultrafiltrate blood plasma with minimal proteins which leads to a difference in concentration of ions according to Gibbs and Donnan's balance, to maintain electronic neutrality. This means that in ISF there are more anions. In ICF the main osmotic particles are potassium and magnesium from cations, and protein and phosphates from anions.

Osmolality between individual spaces is kept in balance, meaning that whenever a change in osmolality occurs in a certain space, the newly arisen osmotic gradient is subsequently levelled. The principal is based on the permeability of the membranes between individual compartments of bodily fluids. Only water and urea can flow through them freely, other solutes are limited. Cell membranes separate ICF from ISF, while capillary walls separate ISF from IVF [12, 3, 19, 20].

Effective osmolality

Effective osmolality is caused by particles which do not flow freely but are distributed in some of the aforementioned bodily fluids. During their accumulation hypertonicity arises, and then water flows through the membrane and balances the osmotic gradient. It is therefore evident that only effective osmolality and not overall osmolality can induce the shift in water. Sodium and glucose participate in effective osmolality of ECF, whereas urea, which flows freely, does not. The main ion of ECF is sodium, thus its concentration has the biggest influence on effective osmolality of ECF. Hypernatraemia causes hypertonicity of ECF, and the following shift leads to dehydration of cells. On the other hand, hyponatraemia gives rise to cell oedema. In some cases, hyponatraemia is not connected to low effective osmolality, for example during osmotherapy by mannitol or hyperglycaemia (an increase of 5,5 mmol/l in glycemia lowers sodium by 1,5 mmol), [12, 13].

Regulation of osmolality

Plasma osmolality in the organism is maintained in the narrow range 275 – 295 mmol/kg [12]. Regulation is controlled from the brain by osmoreceptors in the hypotalamus, which make up the functional osmorceptor complex. Intake of fluids due to a feeling of thirst and the amount of diuresis due to antidiuretic hormone (ADH) are influenced by serum osmolality changes. During an increase in serum osmolality, thirst and ADH rise, while the opposite occurs during a decrease.

ADH is a nanopeptide, synthesised in neurons in the area of the nucleus supraopticus and paraventricularis in the hypothalamus. From here it is transported with neurofysin to storage granules in pars nervosa of the neurohypophysis. After stimulation, it is released into the blood stream [21]. Reference levels are up to 4 pg/ml, after stimulation they rise to 10 pg/ml. The maximum effective urine osmolality is at the level of 20 pg/ml. Its plasma half-life is very short, just 10 to 35 minutes [22].

ADH influences reabsorbtion of water in the kidneys through the V 2 receptors. This antidiuretic effect was described 10 years later than its vasopresoric effect, by Farini and von Velden in 1913. These tubular cells are relatively impermeable to water, so urine cannot concentrate in the absence of ADH. Water is transported through the membranes of epithelial cells by water channels – aquaporines (AQP). After connecting the hormone to specific V 2 receptors, intracellular 3',5'- cyclic adenosine monophosphate (cAMP) takes place, stimulating the insertion of aquaporine 2 (AQP 2) into the apical membrane and thus raising its water permeability [15, 21, 22].

ADH is not only released during raised serum osmolality, but also with other signals, i.e. nonosmolal stimulation. This occurs in hypovolemia (a 10 – 20 % volume decrease) and hypotension (a 10 % drop in blood pressure) induced by carotic and aortal baroreceptors and atrial volume receptors in the heart. Maximum secretion is reached during a 30 % fall in blood pressure. The vasoconstrictive effect of ADH is caused by the V 1 receptor in the cell wall, as described by Oliver and Schafer in 1895 before the antidiuretic effect was found, which is why its original name was vasopressin [20, 22]. Other stimuli include pain, nausea, hypoxia, pharyngeal stimulation and further endogenic and exogenic particles.

Measuring and calculating osmolality

Osmolality can be measured using the cryoscopic method on the osmometre. The point of a solution's solidification is proportionate to the amount of osmotically active particles. A unit is mmol/kg H_2O.

It is also possible to estimate osmolality by calculating the main osmotically active plasma components. There is a wide variety of formulae, but the most accessible and reliable is considered to be Kazda and Hendl's following equation, which was the result of comparing thirteen formulae with measured osmolality [23]:

$$P\_Osm_{calculated} = 2*P\_Na^{+} + P\_Glucose + P\_Urea$$

The difference between measured and calculated osmolality is known as the **osmolal gap**. Normal values are up to 10 mmol/kg, larger differences can be due to small molecular particles, which are not included in the formula [12, 15]. In neurointensive care the osmolal gap has a bearing on osmotherapy with mannitol [24].

Sodium

Sodium is the main extracellular cation, and therefore the most important in ECF osmolality. 50 % of the total amount of sodium in the body (approximately 4000 mmol) is found in ECF, 40 % in bone tissue and 10 % in ICF. Serum reference levels are between 135 – 143 mmol/l, with 120 – 240 mmol/day in urine. Around 22 400 mmol are filtered daily in the glomerules, 99 % of which is reabsorbed and only 1 % is excreted in urine [22]. Sodium excretion is regulated by several mechanisms in the kidneys.

Regulation of sodium in the organism

Sodium reabsorbtion in the tubules is influenced by the mineralocorticoid **aldosterone**, a steroid hormone from the adrenal cortex. Its production is controlled by renin from the juxtaglomerular apparatus of the kidneys. Renin secretion increases when blood pressure decreaeses, which leads to low pressure in the vasa afferent, and also during low concentration of sodium in the macula densa of the kidney. Renin turns angiotensinogen to angiotensin I, which goes on to become angiotensin II (through the angiotensin converting enzyme – ACE), and then III. This system is called renin-angiotensin-aldosterone (RAAS). Aldosterone raises sodium reabsorbtion and therefore water in the kidney's distal tubule. At the same time, it increases potassium excretion. The purpose of this regulation is to increase volume circulation and blood pressure through the vasoconstricter effect of angiotensin II. and III. This way of increasing aldosterone is known as secondary hyperaldosteronism, in contrast to primary hyperaldosteronism, which is caused by adenoma. In the urine there is a sodium-to-potassium concentration rate lower than 1. Hypoaldosteronism occurs during insufficiency in the adrenal gland. There is increased loss of sodium and reabsorbtion of potassium. In pharmacology, spiralactone is the antagonist of aldosterone, and fludrocortisone is a substance with mineral corticoid effect.

Further natriuretic regulation mechanism are **natriuretic peptides** (NP), which have the opposite effect to aldosterone. They cause diuresis and natriuresis, vasodilatation and inhibit the

RAAS. NP are a family of structurally similar peptides – Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP, brain natriuretic peptide), C-type natriuretic peptide (CNP) originating in the central nervous system and vascular tissues and D-type natriuretic peptide (DNP), which was isolated from the venom of the Green Mamba (Dendroaspis Angusticeps), [25-28].

The first NP to be described was ANP, which was seperated from atrium by de Bold in 1981 [29]. Later, in 1988, BNP was isolated from porcine brain tissue [30]. Even though it was first discovered in the brain, nowadays we know that it is mainly produced in the cardiac ventricular myocytes. The main stimulus for its synthesis and secretion is cardiac wall stretch [25, 27]. The natriuretic effect of ANP and BNP lies in increasing glomerular filtration, the direct effect in collecting tubule and suppression the RAAS [28]. Their synergy is assumed, BNP raises water and sodium to the collecting tubule, while ANP inhibits the reabsorbtion of sodium. Both hormones are synthesized in tissues from preprohormones (151-amino-acid pre-proANP, 132-amino-acid pre-proBNP), which are processed into prohormones (126-amino-acid proANP, 108-amino-acid proBNP). Shortly before release into circulation, C-terminal biologically active hormone ANP (28-amino-acid) and BNP (32-amino-acid), taking effect in the target tissues through specific receptors, are separated. The remaining parts also go into circulation and are known as N-terminal fragments. Both active hormones have a shorter half-life (ANP 3 minutes, BNP 21 minutes) than their N-terminal fragments. At present assessment of active and N-terminal parts is available. In clinical practice BNP and N-terminal pro B-type natriuretic peptide (NT-proBNP) are used. From the diagnostic point of view both methods are comparable, but in routine practice NT-proBNP is more suitable owing to its longer biological half-life [25, 27].

NT-proBNP is typically used in cardiology as a biochemical marker of heart failure due to left ventricular systolic dysfunction [31, 32]. However, elevated levels of ANP and BNP are also reported in hyponatraemia with natriuresis in acute brain diseases – Cerebral Salt Wasting (CSW) syndrome. This condition occurs very often in cases of subarachnoid haemorrhage (SAH), [33-36]. A relationship has been found between increased levels of BNP and symptomatic cerebral vasospasm [35]. Elevated BNP has also been found in intracranial hypertension [34]. Recently BNP assessment has been publicised in regard to further brain diseases: Sviri described increased levels in acute trauma brain injury [37] and Jensen has focused on observing NT-proBNP as a prognostic marker in acute ischemic stroke [38].

Further natriuretic regulation mechanisms are part of **Urodilatin**, produced in distal tubules, and a **Digitalis-like hormone** from the adrenal gland which causes natriuresis by inhibiting $Na^{+}K^{+}$-ATPase.

The influence of diuretics on serum sodium

Loop diuretics lower iont reabsorbtions in the Henle ascending loop and distal tubule, which leads to sodium secretion in tubule and currently they influence osmotic gradient. Through this mechanism more water than sodium is lost, causing hypernatraemia. Furosemide belongs to this group.

Thiazides diuretics, on the other hand, cause hyponatraemia, because more sodium than water is lost as a result of interrupting the dilution capabilities of the distal and collecting tubules. Hydrochlorothiazide is an example of this group.

Renal function parameters

Glomerular filtration rate

Primary urine from passing blood arises in the first functional part of the nephron, or glomerulus as it is known. Only low-molecular particles can filter through the glomerulus, larger molecules do not get into primary urine. Low-molecular particles, which freely filter through the glomerulus and do not turn into tubules (no secretion, reabsorbtion) are ideal for calculating glomelular filtration. Formula:

$GFR = U * V / P$

U – substance concentration in definite urine, V – volume of definite urine, P – substance concentration in plasma.

This substance is inulin, but is not used in practice due to its numerous disadvantages. Glomerular filtration is estimated according to clearance of endogenous creatinine. Although it is not ideal because creatinine is partly eliminated through tubular secretion, it is nonetheless very useful in clinical practice. The reference range is 1,3-2,8 ml/s (calculated to ideal body surface 1,73 m^2)

Tubular function

In the tubular part of the nephron, primary urine turns into definitive urine through reabsorbtion and secretion. Tubular reabsorbtion means the proportion from the original filtered amount in the glomerulus which is reabsorbed. Fraction excretion denotes the proportion from the original filtered amount in the glomerulus, which is eliminated into definitive urine. The formula for calculating substance fraction excretion:

$$FE\_X = U\_X / P\_X * P\_Cr / U\_Cr$$

For this formula concentration of the observed substance in urine (U_X) and plasma (P_X) and concentration of creatinine in plasma (P_Cr) are necessary. The advantage of this parameter is that urine collection is not needed. In clinical practice, the following are used: excretion fraction of free water (FE_H_2O), excretion fraction of osmotically active substances (FE_Osm), excretion fraction of sodium (FE_Na^+), excretion fraction of potassium (FE_K^+). The reference range for these individual parameters can be seen in table 1. During a decrease in glomerulus filtration the values of all four FE rise. This is the kidneys' compensatory mechanism, with the aim of maintaining sufficient diuresis even as glomerular filtration falls.

Table 1. Reference range of excretion fraction of: free water (FE_H2O), osmotically active substances (FE_Osm), sodium (FE_Na^+), potassium (FE_K^+).

Parameter	Reference range
FE_H_2O	0,01 – 0,02
FE_Osm	< 0,035
FE_Na^+	0,004 – 0,012
FE_K^+	0,04 – 0,19

Clearance of osmotically active substances, electrolyte, sodium, solute free water and electrolyte free water

Clearance informs us of the amount of plasma which is completely purified of a certain substance during blood-flow through the kidneys for a period of time. These calculation parameters enhance the observation of renal functions.

Clearance of osmotically active substances (C_Osm, ml/s) denotes the amount of plasma purified from all active osmotic substances.

$C\_Osm = V * U\_Osm / P\_Osm$

U_Osm – urine osmolality, P_Osm – plasma – serum osmolality, V – volume of definite urine (ml/s). This clearance is raised by hypercatabolic states with overproduction of urea, in diabetes mellitus or mannitol osmotherapy during overflow of osmotic diuresis.

Electrolyte clearance (C_El, ml/s) tells us of clearance of the main effective osmoles. There are different formulae according to calculated parameters. In the basic calculation there are only cation, sodium and potassium (1), more detailed formulae have their accompanying anions (2), while the most complex include glucose, mannitol and others (3).

1) $C\_El = V* (U\_Na^+ + U\_K^+) / (P\_ Na^+ + P\_K^+)$,

2) $C\_El = V* 2(U\_Na^+ + U\_K^+) / 2(P\_ Na^+ + P\_K^+)$,

3) $C\_El = V* [2(U\_Na^+ + U\_K^+) + U\_Other] / [2(P\_ Na^+ + P\_K^+) + P\_Other]$,

$U\_Na^+ + U\_K^+ + U\_Other$ – urine concentration of cations, sodium, potassium, others effective solutes, $P\_Na^+ + P\_K^+ + U\_Other$ – plasma sodium, potassium, others effective solutes, V – volume of definite urine (ml/s). Factor 2 includes accompanying anions. Formula 2 can be used when cation sodium and potassium along with their accompanying anions are the main extracellular effective solutes, meaning there is no hyperglycaemia with glycosuria and mannitol is not given.

Sodium clearance (C_Na^+, ml/s) relates to the main extracellular cation – sodium.

$$C\_Na^+ = V * U\_Na^+ / P\_Na^+$$

Solute free water clearance (C_H_2O, ml/s) informs us of the reabsorbtion of active particles in the distal part of nephron. It indicates in ml the amount of water which we would have to remove from hypertonic urine in order to adjust it to the level of plasma osmolality.

$C\_H_2O = V - C\_Osm$

$C\_H_2O = V - V * U\_Osm / P\_Osm$

The formula calculates all serum and urine osmolality. In low urine osmolality (hypotonic urine) its level is positive, whereas in high osmolality urine (hypertonic urine) it is negative.

Electrolyte free water clearance (EWC, ml/s) relates to effective osmolality. The EWC formula is derived from electrolyte clearance.

$$EWC = V - C\_El$$

$$EWC = V - V^* 2(U\_Na^+ + U\_K^+) / 2(P\_Na^+ + P\_K^+)$$

$$EWC = V - V^* [2(U\_Na^+ + U\_K^+) + U\_Other] / [2(P\_ Na^+ + P\_K^+) + P\_Other]$$

A raised level of EWC means that the kidneys are eliminating more water than effective osmotic solutes, which leads to hypertonicity ECF. A fall in EWC on the other hand results in lower elimination of water by the kidneys and a low concentration of effective solutes in ECF.

EWC and C_El are relatively new formulae, and are known as "second level" markers. They improve evaluation of effective osmolality dysbalances [18].

C_H_2O and EWC enable us to assess concentration efficiency of the kidneys. EWC relates to effective osmolality, unlike C_H_2O, which contains all osmolality including urea, so only EWC uses assessment of axis ADH-kidney disorders. Values of C_H_2O and EWC parameters are mostly parallel, although not in all situations, for example when kidneys eliminate more urea and save ions, C_H_2O will be negative and EWC positive. Table 2 shows the reference range for these clearances [11, 18].

During a drop in glomerular filtration C_Osm, C_El and C_Na^+ fall while C_H_2O rises. The dynamic for this change is due to alterations in glomerular filtration. This is in contrast to EWC, where practically the same values were discovered for moderately and steeply declining glomerular filtration (the only significant changes were from EWC to physiological GFR), [18].

Table 2. Reference range of clearance: osmotically active substances (C_Osm), electrolyte (C_El), sodium (C_Na^+), solute free water (C_H_2O) and electrolyte free water (EWC).

Parameter	Shoker 1994	Jabor 1997
C_Osm	0,066 ± 0,017	0,041 ± 0,012
C_El	0,018 ± 0,006	0,021 ± 0,007
C_Na^+	0,013 ± 0,004	0,018 ± 0,007
C_H_2O	-0,049 ± 0,017	-0,018 ± 0,011
EWC	-0,000 ± 0,006	0,002 ± 0,008

Evaluation of disorders of water and ion metabolisms due to renal function parameters

Assessment of axis ADH-kidneys through EWC parameters was worked out by Shoker in 1994 [11]. This is an evaluation of adequate secretion of ADH and kidney responses during serum osmolality changes. Shoker's evaluation of concentration efficiency:

Hypoosmolality, hypotonicity – serum osmolality < 280 mmol/kg
EWC > 0,116 ml/s (10 l/day).....normal response ADH-kidneys
EWC 0,006 – 0,116 ml/s.....impaired response ADH-kidneys
EWC < 0,006 ml/s (0,5 l/day).....abnormal response ADH-kidneys

Hyperosmolality, hypertonicity – serum osmolality > 295 mmol/kg
EWC < 0,005 ml/s (0,4 l/day).....normal response ADH-kidneys
EWC ≥ 0,005 ml/s.....abnormal response ADH-kidneys

Shoker used another parameter, C_Na^+. He did not include either a calculated sodium deposit (only a clinical estimate) or FE_Na^+.

These two parameters were added by Jabor in 1997. He used the Siggaard-Andersen model for extracellular and intracellular space for calculating sodium deposit. Extracellular space arises from serum sodium and an estimate of water volume of ECF. At the same time he inserted C_Na^+ and FE_Na^+ into the algorithm [16, 17].

Effective osmolality disorders in acute brain diseases

Dysnatraemia is one of the more frequent and serious dysbalances of effective osmolality in acute primary brain damage [1-8]. Hyponatraemia is more common than hypernatraemia, which is however prognostically worse [1].

Three typical syndromes are known in brain diseases (table 3 and 4). Two are in hyponatraemia, and one is in hypernatraemia. Antidiuretic hormone causes all types of dysnatraemia. During an abundance of ADH hyponatraemia arises from water retention in the kidney. When ADH is insufficient water diuresis occurs, leading to hypernatraemia and cDI.

Table 3. Typical syndromes of dysnatraemia in acute brain diseases.

	ADH	NP
Hyponatraemia	SIADH	CSW
Hypernatraemia	cDI	

Table 4. Differential diagnostics of CSW, SIADH and cDI.

Parameter		CSW	SIADH	cDI
S_Na^+	mmol/l	< 135		> 145
S_Osm	mmol/kg	< 280		> 295
Diuresis		N ↑	N ↓	↑
U_Na^+	mmol/l	> 25		< 25
dU_Na^+	mmol/day	> 150	100 – 150	≤ intake of Na^+
U_Osm/S_Osm		> 1		< 1
U_Osm/S_Osm		> 1		< 1
C_Cr	ml/s	N	↑	N
C_El	ml/s	↑	N	N
EWC	ml/s	N	↓	↑
FE_Na^+		↑	N ↓	N ↓
FE_H_2O		↑	N ↓	↑
ADH		N	↑	↓
NP		↑	N	N ↓
Renin,aldosterone		↑	N	N ↑

N – normal, ↓ – decreased, ↑ – increased. In SIADH it is necessary to dismiss: hypovolemia, hypotension, oedema, renal failure, hypothyreosis, hypocorticalism.

Hyponatraemia in acute brain diseases

Hyponatraemia is one of the more frequent dysbalances of effective osmolality in acute brain diseases [4, 5]. In subarachnoid haemorrhage it occurs in about 30 – 40% of patients [1, 7, 39, 40]. It can also be found in other brain diseases: tumours, especially in pituitary adenoma [41-43], brain abscess, bacterial meningitis (36 – 58 %), hydrocephalus and trauma brain injury (TBI), [3]. Hyponatraemia always means serious complications in neurointensive care. It is linked to higher morbity and mortality [44]. Its severity is due to the onset of brain oedema. Acute hyponatraemia leads to significantly higher volume in trauma contusions in animal models [45]. Unterberg et al [46] gave hyponatraemia as a cause of refractor intracranial hypertension in patients with TBI. Wijdicks [47] observed the relationship between hyponatraemia and the onset of ischemia in SAH. He found a significantly higher incidence in patients with hyponatraemia.

Hyponatraemia in acute brain disease was first described by Peters in 1950 [48]. Nowadays it is most often connected with two syndromes, which arise on the basis of entirely different causes. These are depletive hyponatraemia, brought about by loss of sodium through urine (natriuresis) **in cerebral salt wasting (CSW)** syndrome and dilution hyponatraemia, which arises during retention of free water in **syndrome of inappropriate secretion of antidiuretic hormone (SIADH)**. The first syndrome described in literature was CSW, by Peters (1950) and Cort (1954), [48, 49]. Later, in 1957, Schwartz [50] introduced SIADH. Differential diagnostics for these two syndromes is impossible by means of basic laboratory parameters, because they are the same [8]. However, this can be achieved by using renal function parameters, which were first evaluated for this purpose in the 1990s, [10, 11]. Lolin & Jackowski [10] used the first calculated indicators C_Osm, C_H_2O, FE_Na^+ and FE_H_2O in 1992. Later, the so-called "second row" indicators were added – C_El, EWC, C_Na^+. From these parameters, axis ADH-kidneys dysbalances can be better evaluated by EWC [18]. In CSW, when natriuresis is present, there is raised daily urine output of sodium (dU_Na^+), C_Osm, C_El, C_Na^+, FE_Na^+ and FE_H_2O. Negative EWC is characteristic for SIADH regarding retention of free water. Differential diagnostics of these syndromes is both simple and easily accessible in clinical practice using these parameters. This is in contrast to assessment of the hormones which induce these

syndromes, ADH in SIADH and NP in CWS, which is inaccessible in everyday clinical practice [8]. The significance of their measurement decreases with the development of compensatory mechanisms, which arise due to fluid volume changes and lead to secondary secretion of hormones. In SIADH, retention of free water causes volume expansion and further stimulation of NP. In CSW it is the other way round, primary elevation of NP leads to volume depletion and a secondary increase in levels of ADH [9, 51].

Adding renal function parameters to differential diagnostics of both syndromes contributes to their timely diagnosis. Results from further studies have shown that in patients with acute brain disease CSW is more common than SIADH. Incidence of CSW is linked to primary brain disease. The most common is found in SAH, but also occurs in other lesions, for example TBI, gliomas and meningitis [7, 52]. This is in contrast to SIADH, which is found not only in primary brain lesions but also in various illnesses, tumours, lung diseases, drugs and others [15].

Owing to the various mechanisms of the onset of hyponatraemia, entirely different therapy is needed. In SIADH, this means fluid restrictions and the application of loop diuretics. There are two antagonists of ADH in the kidney, demeclocycline and lithium. In CSW volume and sodium substitution is necessary (hypertonic saline), [3, 7, 53]. There are further published studies using hydrocortisone [54, 55] and fludrocortisone [56].

Hyponatraemia in acute brain diseases is usually associated with CSW or SIADH. However, there are more types of hyponatraemia that can be also found in neurointensive care (table 5), [57], the most common being hyponatraemia caused by incorrect therapy or inadequate fluid replacement.

Hyponatraemia is not always necessarily combined with a drop in serum osmolality. In some situations, there can be serum normoosmolality or even hyperosmolality, for example in hyperglycaemia, during mannitol osmotherapy or high serum levels of urea.

Clinical signs are given by neurological symptoms from brain oedema, which is dangerous because the brain is located in a closed cranium. If brain volume by oedema increases, compensatory mechanisms in cranial space can be exhausted, leading to a rise in intracranial pressure (ICP), so-called intracranial hypertension, [39]. According to the level of ICP, neurological symptoms are changed, beginning with headaches, nausea, vomitting, desorientation, agitation, apathy, and going as far as seizures, deep unconsciousness and brain death. Clinical symptoms depend on the speed of development of hyponatraemia and compensatory mechanisms in cranial space and in brain cells. The aim of adaptive changes in brain cells is to lower intracellular osmolality. This leads to a drop in potassium and sodium (early changes – up to 24 hours) as well as the contents of organic compounds (later – up to 48 hours). According to these adaptations hyponatraemia is divided into acute (up to 48 hours) and chronic (over 48 hours) stages. Neurological symptoms are often in acute hyponatraemia and steeper falls S_Na^+. The border of acute hyponatraemia is below 130 mmol/l and for chronic is 120 mmol/l.

Hyponatraemia therapy is determined by the mechanism of its origin. The correction of sodium levels depends on the speed of the inception of hyponatraemia and the presence of neurological symptoms.

Symptomatic hyponatraemia:

Acute (up to 48 hours): quick corrections 1-2 mmol/l/hour
Chronic (over 48 hours): slow corrections 0,5-0,6 mmol/l/hour

Asymptomatic hyponatraemia: 0,5 mmol/l/hour.

The basic aim in all extreme hyponatraemia is to achieve an increase in serum sodium of over 120 mmol/l and the disappearance of neurological symptoms. Correction should be about 12 mmol a day (from 10 to 15 mmol/l/day), [14].

During quick correction of hyponatraemia there is a risk of neurological symptoms from myelin damage (demyelinisation syndrom). There are **pontine and extrapontine myelinolysis** [58-63]. CMP was first described by Adams in 1949 in alcoholic patients. He named it according to the localisation of lesion and damage to myelin. Malnutrition and alcoholism are among the risk factors of this syndrome.

Hypernatraemia in acute brain diseases

Hypernatraemia is less frequent in acute brain disease than hyponatraemia, but it is prognostically more serious [1, 64, 65]. Levels above 160 mmol/l are one of the independent markers of rising mortality [6].

A typical, well-known syndrome associated with acute brain disease is **central diabetes insipidus** [66]. In the neurosurgical intensive care unit, however, it is not one of the more common types of hypernatraemia, making up a mere 3,7 % of all hypernatraemias, although it does have high mortality (72,4 %), [67]. It is most frequently found in SAH and TBI. In cDI hypernatraemia arises from water diuresis due to ADH insufficiency. There are three phases in its classic course. The initial diuretic period starts in 12 to 24 hours and lasts for 4 to 8 days. In the following antidiuretic phase, synthesised ADH from degenerating hypofysis is released. Finally, in the third stage, there is again polyuria, which depends on the extent of brain damage and may be temporary or permanent. During polyuria, there can be more than 20 litres of diuresis a day [8]. Diagnosis is carried out by observing hourly diuresis, urine osmolality, specific gravity of urine and renal function parametres (increased EWC), [19].

Central diabetes insipidus exists in two forms. Complete cDI occurs less frequently than partially incomplete cDI, in which water reabsorbtion is partially maintained in the case of large osmotic or hemodynamic stimuli. Diagnosis of the incomplete form of cDI can be carried out with the aid of responses to osmotic stimuli. Therapy for cDI is casual, and consists of the synthetic analogue desmopressin. In neurointensive care, parenteral treatment is preferred to nasal. Literature describes further medicine influencing ADH. Carbamazepine and chlorpropamide increase the ADH effect, clofibrate raises ADH secretion and thiazides are effective in the absence of ADH. Fluids are supplemented by using a different type of infusion according to serum sodium level, the speed of the decrease varies according to the recommendation for hypernatraemia.

Besides central diabetes insipidus, **nephrogenic diabetes insipidus** [68, 69] is also known, and arises due to the inability of the kidney to respond normally to ADH. It can be caused by acutely or chronically diseased kidneys, ion dysbalance and other factors.

In neurointensive care there are usually multifactorial causes of hypernatraemia, most frequently to be found in connection with osmotherapy by mannitol. Another cause is renal failure [6].

Clinical symptoms are neurological and connected to dehydration of the brain. During hypernatraemia, a compensatory mechanism takes effect in the brain cells, which is in contrast to hyponatraemia. Effective osmolality of cells increase through retention of intracellular effective solutes. In the next few days, up to one week, synthesis of organic osmotic of active compounds rises. Neurological symptoms during hypernatraemia develop from restlessness, confusion and apathy to seizures and unconsciousness. Symptoms depend on the degree of hypernatraemia and speed of its inception. Acute hypernatraemia has clinical symptoms during serum levels of above 150 mmol/l and chronic has sodium levels above 160 mmol/l.

Therapy of hypernatraemia is determined by the mechanism of these dysbalances. Correction of serum levels depends on the speed of hypernatraemia's inception.

Acute (up to 48 hours): quick corrections 1-2 mmol/l/hour
Chronic (over 48 hours): slow corrections 0,5-0,7 mmol/lhour

The decrease must not be more than 10 - 15 mmol/l/day. When there is no casual therapy we use hypotonic infusions and thiazides to correct sodium levels.

Table 5. Hyponatraemia and hypernatraemia.

	Hyponatraemia	Hypernatraemia
Serum sodium	**< 135 mmol/l**	**> 145 mmol/l**
Mechanism	decrease the amount of sodium in ECT with regards to water	increase the amount of sodium in ECT with regards to water.
1) Sodium	**Sodium loss**	**Sodium retention**
Gastrointestinal tract	vomiting, diarrhoea, drainage	use of salt
Kidney	hypoaldosteronism, hypocorticalism, natriuresis in CSW, thiazides, nephropathia	
Skin	sweating (inadequate fluid replacement), burns	
Others		infusion NaCl and $NaHCO_3$
2) Water	**Water retention**	**Water loss**
Gastrointestinal tract	polydypsia	diarrhoea
Kidney	SIADH, renal failure	central and nephrogenic diabetes insipidus, osmotic diuresis (glycosuria, urea, mannitol),
Skin	oedema	sweating (inadequate fluid replacement), burns
Others		lungs, ICT / shift from ECT to cells
Clinical signs	neurological symptoms from brain oedema	neurological symptoms from brain dehydration

The aims of the study

1. Establishing calculated renal function parameters as part of standard protocol when diagnosing and subsequently treating hyponatraemia and hypernatraemia in acute brain diseases.

2. Making a prospective diagnostic protocol on the basis of retrospective data processing.

3. Verification and evaluation of prospective standard protocol in diagnosing and monitoring therapy for hyponatraemia and hypernatraemia with the aim of assessing the clinical significance of established calculated renal function parameters.

4. Determining the significance of NT-proBNP in differential diagnostics of hyponatraemia.

Methods

Collection of patients

The study was carried out in an eight-bed neurological-neurosurgical intensive care unit (NNICU) in the Neurocentre of Regional Hospital Liberec. Here patients with various acute brain and spinal diseases, both neurological and neurosurgical, are admitted. The most frequent diseases include acute strokes and brain tumours, trauma brain injuries (TBI) are less common. The NNICU serves for adult patients, children from the age of 7 are admitted exceptionally. Since 2001 the NNICU has had a systematic computer database of patients.

Collections of patients and laboratory data were made from the database of Laboratory Information System Stapro (LISSTA) Pardubice in the department of clinical biochemistry in Regional Hospital Liberec with the aid of the programme LisBed. The retrospective study was worked out from this database alone. The prospective study was additionally compared with the NNICU database. The criteria for patients' inclusion in the study was acute brain disease and serum sodium below 135 mmol/l (hyponatraemia) and above 150 mmol/l (hypernatraemia). The basic characteristics of the patients can be seen in table 6 for the retrospective study and table 7 for the prospective study.

Table 6. Characteristics of the patients in the retrospective study.

Parameter	Dysnatraemia	Hypo-natraemia	Hyper-natraemia	p-value
Number of patients	326 (100,0%)	251 (100,0%)	75 (100,0%)	
1996	58 (17,8%)	52 (20,7%)	6 (8,0%)	0,007
1997	68 (20,9%)	59 (23,5%)	9 (12,%)	0,024
1998	62 (19,0%)	44 (17,5%)	18 (24,0%)	0,220
1999	67 (20,6%)	45 (17,9%)	22 (29,3%)	0,037
2000	71 (21,8%)	51 (20,4%)	20 (26,7%)	0,250
Male	201 (61,7%)	160 (63,7%)	41 (54,7%)	0,159
Age	54,6 years	53,9 years	56,8 years	0,268
Stay in NNICU	11,7 days	11,8 days	11,6 days	0,221
Focal brain lesion	203 (62,3%)	159 (63,3%)	44 (58,7%)	0,465
Diffuse brain lesion	123 (37,7%)	92 (36,7%)	31 (41,3%)	0,465
Diagnosis				
Stroke	144 (44,2%)	101 (40,2%)	43 (57,3%)	0,009
Tumour	100 (30,7%)	80 (31,9%)	20 (26,7%)	0,387
Trauma	40 (12,3%)	33 (13,1%)	7 (9,3%)	0,364
Epilepsy	13 (4,0%)	12 (4,8%)	1 (1,3%)	0,011
Infection	13 (4,0%)	13 (5,2%)	0 (0,0%)	0,008
Hydrocephalus	11 (3,4%)	7 (2,8%)	4 (5,3%)	0,309
Other	5 (1,5%)	5 (2,0%)	0 (0%)	0,104
Operation	250 (76,7%)	188 (74,9%)	62 (82,7%)	0,153

p-value – statistical significance between hyponatraemia and hypernatraemia, mean – in age and stay in NNICU.

Table 7. Characteristics of patients in the prospective study.

Parameter	Dysnatraemia	Hypo-natraemia	Hyper-natraemia	p-value
Number of patients	378 (100%)	245 (100%)	133 (100%)	0,009
2001	42 (11.1%)	27 (11,0%)	15 (11,3%)	1,000
2002	39 (10.3%)	17 (6,9%)	22 (16,5%)	0,005
2003	74 (19.6%)	42 (17,1%)	32 (24,1%)	0,135
2004	101 (26.7%)	72 (29,5%)	29 (21,8%)	0,116
2005	122 (32.3%)	87 (35,5%)	35 (26,3%)	0,084
Male	204 (54,0%)	132 (53,9%)	72 (54,1%)	1,000
Age (years)	58,4 ± 14,2	57,2 ± 14,1	60,6 ± 14,1	0,022
Weight (kg)	76,3 ± 15,0	76,0 ± 14,8	76,9 ± 15,3	0,561
Stay in NNICU (days)	11,1 ± 10,1	10,3 ± 9,8	12,6 ± 10,6	0,035
NYHA	1,4 ± 0,7	1,3 ± 0,6	1,5 ± 0,7	0,008
Focal brain lesion	202 (53,4%)	138 (56,3%)	64 (48,1%)	0,132
Diffuse brain lesion	176 (46,6%)	107 (43,7%)	69 (51,9%)	0,132
Diagnosis				
Stroke	198 (52,4%)	110 (44,9%)	88 (66,2%)	<0,001
Tumour	78 (20,6%)	59 (24,1%)	19 (14,3%)	0,024
Trauma	57 (15,1%)	38 (15,5%)	19 (14,3%)	0,880
Epilepsy	15 (4,0%)	14 (5,7%)	1 (0,8%)	0,024
Infection	14 (3,7%)	10 (4,1%)	4 (3,0%)	0,778
Hydrocephalus	10 (2,6%)	9 (3,7%)	1 (0,8%)	0,175
Other	6 (1,6%)	5 (2,0%)	1 (0,8%)	0,670
Operation	272 (72,0%)	161 (65,7%)	111 (83,5%)	<0,001
Type of operation				
Trepanation	33 (12,1%)	17 (10,6%)	16 (14,4%)	0,572
Craniectomy	45 (16,5%)	21 (13,0%)	24 (21,6%)	0,135
Craniotomy	150 (55,1%)	95 (59,0%)	55 (49,5%)	0,030

Mean ± standard deviation, p-value – statistical significance between hyponatraemia and hypernatraemia.

Observed clinical parameters

The parameters under observation in the retrospective and prospective parts of the study differed slightly. The prospective study was extended on the basis of processed data from the retrospective part. In both studies we observed the indicators related to:

the patient's prognosis: Glasgow Outcome Scale upon discharge from NNICU, mortality in NNICU, incidence of cerebral focal (haemorrhage, perifocal oedema) and diffuse complications (vasospasm, oedema, hydrocephalus), pulmonary oedema,

onset of dysnatraemia: brain diagnosis, time from brain damage, focal or diffuse brain damage, Glasgow Coma Scale (GCS), operation (type and time since operation), relation to hospitalisation, therapy (diuretics and antidiuretics, antioedematic theraphy with mannitol or hypertonic saline) and type of infusions,

length of dysnatraemia: time until normonatraemia, changes in natraemia in 24 hours and therapy of dysnatraemia,

fluid balance: fluid intake (ml/day), fluid output (ml/day), fluid balance (ml/day). We calculated all fluids given by mouth, tube and parentally into fluid intake. Fluid output in

the retrospective study was only from diuresis and drainage due to inaccurate documentation. In the prospective study we calculated the overall fluid output including loss caused by fever (200 ml per 1°C above 37°C) and skin loss (sweat). In neither study did we include metabolic water in fluid intake or immeasurable losses in fluid output.

The prospective study was extended to include New York Heart Association classification, central venous pressure measurements and sodium intake. The overall sodium intake was calculated from parenteral and enteral nutrition. We did not include sodium in food. We also followed changes in consciousness during the onset of this dysnatraemia, and when the patients had computed tomography (CT) of the brain, we compared these findings with the previous ones.

Observed biochemical parameters

1. Measured parameters

serum: sodium (S_Na^+), potassium (S_K^+), calcium (S_Ca^{2+}), magnesium (S_Mg^{2+}), chloride (S_Cl^-), phosphorus (S_P), osmolality (S_Osm), proteins (S_Prot), albumin (S_Alb), glucose (S_Glu), urea (S_Urea), creatinine (S_Cr), pH (B_pH).

urine: osmolality (U_Osm), daily output of sodium (dU_Na^+), potassium (dU_K^+), creatinine (dU_Cr), pH (U_pH), specific gravity of urine (Sp gr, the lowest and highest levels in 24 hours).

Sodium, potassium and chloride measurements in serum and urine were carried out on the COBAS Integra 800 (Roche, Diagnostics, Switzerland) machine by selective ion electrodes. Creatinine in serum and urine, magnesium, phorphorus, calcium, proteins and albumin in serum were also measured on this equipment, but by photometric method. Osmolality was gauged on the cryoscopic osmometre Fiske 210 (Advanced Instruments, Inc, Norwood, Massachusetts). B_pH was measured on the blood gas analyzer ABL 625 (Radiometer, Denmark). Assessment of urine pH (U_pH) was made on Urisys 2400 equipment (Roche Diagnostics, Switzerland). Specific gravity of urine was measured on the urometer in the NNICU.

2. Calculated parameters

Calculated osmolality (S_OsmC), calculated effective osmolality (S_OsmE), ratio urine and serum osmolality (U_Osm / S_Osm), ratio daily urine output of sodium and potassium (dU_Na^+ / dU_K^+), creatinine clearance (C_Cr), osmotically active substances clearance (C_Osm), electrolyte clearance (C_El), sodium clearance (C_Na^+), potassium clearance (C_K^+), solute free water clearance (C_H_2O), eletrolyte free water clearance (EWC), excretion fraction of osmotically active substances (FE_Osm), excretion fraction of sodium (FE_Na^+), excretion fraction of potassium (FE_K^+), excretion fraction of free water (FE_H_2O).

Formulae for calculated osmolality (S_osmC) and effective calculated osmolality (S_osmE):

$S\_OsmC = 2 \times Na^+ + glucose + urea;$

$S\_OsmE = 2 \times Na^+ + glucose.$

Formulae of renal function parameters:

1) $C\_Cr = (U\_Cr \times V) / (Time \times S\_Cr \times Surface)$
2) $C\_Osm = (U\_Osm \times V) / (Time \times S\_Osm)$
3) $C\_El = V \times [(U\_Na^+ + U\_K^+) + U\_Glu] / [(S\_Na^+ + S\_K^+) + S\_Glu] \times Time$
4) $C\_Na^+ = (U\_Na^+ \times V) / (Time \times S\_Na^+)$
5) $C\_K^+ = (U\_K^+ \times V) / (Time \times S\_K^+)$
6) $C\_H_2O = (V / Time) - C\_Osm$
7) $EWC = (C\_Osm + C\_H_2O) \times (1 - (U\_Na^+ + U\_K^+)) / (S\_Na^+ + S\_K^+)$
8) $FE\_Osm = (U\_Osm \times S\_Cr) / (S\_Osm \times U\_Cr \times 1000)$
9) $FE\_Na^+ = (U\_Na^+ \times S\_Cr) / (S\_Na^+ \times U\_Cr \times 1000)$
10) $FE\_K^+ = (U\_K^+ \times S\_Cr) / (S\_K^+ \times U\_Cr \times 1000)$
11) $FE\_H_2O = S\_Cr / (U\_Cr \times 1000)$

Clearance of creatinine (formula 1) was calculated according to general formulae for clearance with correction for the body's surface. Units of measured parameters in formulae are seen in table 8. Values of urine volume (V) are in litres and time in seconds. Biochemical parameters from urine were processed only from urine collected within 24 hours and with C_Cr above 1,15 ml/s. These renal function parameters became a component of the biochemical overview from the department of clinical biochemistry (formulae according "Encyclopaedia Laboratory Medicine", Jabor A, Zámečník J, Palička V).

Table 8. Overview of biochemical parameters observed in the retrospective and prospective study.

Parameter		Reference range	Retrospective study	Prospective study
S_Na^+	mmol/l	135 – 146	+	+
S_K^+	mmol/l	3,8 – 5,5	+	+
S_Ca^{2+}	mmol/l	2 – 2,75	+	+
S_Mg^{2+}	mmol/l	0,7 – 1,1	+	+
S_Cl^-	mmol/l	97 – 108	+	+
S_P	mmol/l	0,7 – 1,5	+	+
S_Osm	mmol/kg	275 – 295	+	+
S_OsmC	mmol/kg	275 – 300	+	+
S_OsmE	mmol/kg	272 – 290	+	+
S_Prot	g/l	65 – 80	+	+
S_Alb	g/l	32 – 53	+	+
S_Glu	mmol/l	3,3 – 6,1	+	+
S_Urea	mmol/l	2,8 – 7,5	+	+
S_Cr	umol/l	35 – 115	+	+
B_pH		7,36 – 7,44	+	+
U_Osm	mmol/kg	50 – 850	+	+
U_Osm / S_Osm			-	+
dU_Na^+	mmol/day	100 – 260	+	+
dU_K^+	mmol/day	40 – 90	+	+
dU_Na^+ / dU_K^+		100 – 260	-	+
C_Cr	ml/s	1,15 – 2	+	+
C_Osm	ml/s	0,03 – 0,05	+	+
C_El	ml/s	0,011 – 0,023	+	+
C_Na^+	ml/s	0,008 – 0,016	+	+
C_K^+	ml/s	0,083 – 0,250	-	+
C_H_2O	ml/s	-0,027 – -0,007	+	+
C_EWC	ml/s	-0,000 +/- 0,006	+	+
FE_Osm		0,01 – 0,035	+	+
FE_Na^+		0,004 – 0,012	+	+
FE_K^+		0,040 – 0,190	-	+
FE_H_2O		0,01 – 0,02	+	+
U_pH		5,0 – 6,0	-	+
Sp gr	kg/m^3	1015 – 1025	-	+

Study protocol

The study is composed of two parts. The first part consists of retrospective evaluation of data in the period from 1.1.1996 to 31.12.2000. In the second part there is data processed according to prospective protocol for diagnosis of hyponatraemia and hypernatraemia in the NNICU from 1.1.2001 to 31.12.2005. Both retrospective and prospective parts had the same five-year observation period. The prospective part was carried out at the same time as the NNICU database. In this period, from 2001 to 2005, 1546 patients with brain disease were admitted to the NNICU.

Retrospective study

The retrospective study was processed first, the hyponatraemia and hypernatraemia collections separately.

Hyponatraemia

In the first phase we divided them according to measured serum osmolality (normal values 275 - 295 mmol/kg) into three groups: 1) hyponatraemia with osmolality in the reference range, 2) hyponatraemia with hyperosmolality (S_osm > 295 mmol/kg) and 3) hyponatraemia with hypoosmolality (S_osm < 275 mmol/kg. In the next phase differential diagnostics were carried out by using measuring and calculating renal function parameters. CSW was evaluated separately, as were serum sodium values below 130 mmol/l.

Hypernatraemia

Firstly we diagnosed cDI according to hourly diuresis, urine osmolality, specific gravity of urine, renal function parameters and response to desmopressin. The remaining hypernatraemias were categorised "non cDI". We excluded patients without measured serum osmolality. Groups with serum sodium above 156 mmol/l a 160 mmol/l were processed seperately.

Prospective study

The prospective study took place according to standard protocol for diagnosing hyponatraemia and hypernatraemia (table 9).

In this prospective protocol, fluid balance was observed precisely, and in more serious cases hourly diuresis and CVP were measured. In patients with acute brain disease, serum sodium was measured daily. As soon as dysnatraemia occurred, monitoring and examination according to prospective protocol were immediately introduced. Target values for serum sodium after 24 hours were set according to recommendations for sodium correction to avoid pontine and extrapontine myelinolysis. When there was a larger sodium shift, sodium measurements were taken more frequently, for example at intervals of every one or three hours. Diagnosis of dysnatraemia was made using renal function parameters.

Hyponatraemia therapy in CSW consisted of continual administration of hypertonic saline and physiological solution. In polyuria, fludrocortisone was given. In cDI desmopressin was administered, mostly in parenteral form – intravenous bolus with an initial dose of 1 ug. Further doses were given according to the amount of diuresis. Therapy for other types of hypernatraemia consisted of administering thiazides diuretics. In all hypernatraemias different hypotonic infusions were applied according to serum sodium and recommendation for correction.

Data processing was carried out in accordance with the retrospective study.

Table 9. Standard protocol for diagnosis of hyponatraemia and hypernatraemia in NNICU.

PROTOCOL FOR SODIUM DYSBALANCES
In hyponatraemia (<135mmol/l) or hypernatraemia (> 150mmol/l). Abbreviation: Na protocol
Check test tubes!!! Do not mix them up!!! Check written slips before handing over to laboratory!!! Check ordained blood tests + written slips – night shift. All blood tests written into patient documentation.
Main times of blood tests: 6:00 – 12:00 – 18:00 – 24:00 hours
SAMPLES MUST NOT BE TAKEN FROM EXTREMITIES WHERE THERE IS AN INFUSION !!!
6:00 hours Biochemical tests from blood: glucose, Na, K, Cl, Ca, Mg, P, urea, creatinine, proteins, albumin, osmolality, blood gas. Blood count. Biochemical test from urine: osmolality, daily output (minerals, creatinine, urea), urinary casts, calculated renal function parameters.
12:00 hours Basic minerals – Na, K, Cl.
18:00 hours Basic minerals, serum and urine osmolality.
24:00 hours Basic minerals.

Assesment of N-terminal pro-B-type Natriuretic Peptide (NT-proBNP)

In the prospective study measurement of N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) was assessed in 40 patients with hyponatraemia and normal renal parameters. The basic characteristics of the patients can be seen in table 10. Statistical comparison between hypoosmolal and normoosmolal hyponatraemia was only carried out on patients categorised as NYHA I., (table 11). Further seperately group were patients with CSW and NYHA I. The control group was made up of patients with acute brain diseases according to the following criteria: 1) NYHA I. and 2) normal renal parameters. They were evaluated to the same clinical and biochemical parameters as in the hyponatraemia study.

NT-proBNP was assessed using the electrochemiluminscence immunoassay ECLIA on the Roche Elecsys 2010 and modular analytics E170 immunoassay analyzers utilizing the two-site sandwich principle. The cutoff of 125 pg/ml was taken from the manufacturer's package insert.

Table 10. Characteristics of patients with NT-proBNP.

Parameter	Hyponatraemia	Normonatraemia
Number of patients	40	20
Male	21 (52,5%)	12 (60%)
Age (years)	53,5 ± 14,4	51,7 ± 12,9
Weight (kg)	79,4 ± 15,7	77,6 ± 12,1
Stay in NNICU	18,0 ± 10,8	19,3 ± 13,4
NYHA	1,1 ± 0,4	1,0 ± 0,0
Operation	24 (60%)	16 (80%)
Stroke	21 (52,5%)	12 (60%)
Tumour	9 (22,5%)	3 (15%)
Trauma	4 (10%)	1 (5%)
Infection	1 (2,5%)	0 (0%)
Epilepsy	2 (5%)	1 (5%)
Hydrocephalus	3 (7,5%)	2 (10%)
Other	0 (0%)	1 (5%)

Mean ± standard deviation.

Table 11. Characteristics of patients with NT-proBNP in hypoosmolal and normoosmolal hyponatraemia.

Parameter		Hypoosmolal hyponatraemia	Normoosmolal hyponatraemia	p-value
Number of patients	pts	13	25	
Age	years	46,3 ± 16,2	54,9 ± 11,8	*0,069*
Weight (kg)	kg	70,8 ± 12,4	80,8 ± 14,2	0,038
Stay in NNICU	day	18,2 ± 13,0	20,7 ± 10,8	0,534
Operation	pts	9 (69%)	16 (64%)	
Time since operation	day	9,9 ± 11,5	10,6 ± 9,6	0,878
Stroke	pts	4 (31%)	14 (56%)	
Tumour	pts	4 (31%)	4 (16%)	
Trauma	pts	3 (23%)	3 (12%)	
Infection	pts	0 (0%)	1 (4%)	
Epilepsy	pts	1 (8%)	1 (4%)	
Hydrocephalus	pts	1 (8%)	2 (8%)	

Mean ± standard deviation, p-value – statistical significance between these groups.

The prospective study was carried out with the approval of the hospital ethical committee.

Statistical processing

The results were processed using the programme Statistica 7.0, StatSoft, Inc. (2004) STATISTICA (data analysis software system, version 7, USA). The parametric t-test (normality of data) or non-parametric M-W U test were used for differentiating connected variables. The ANOVA (normality of data) or non-parametric Kruskal-Wallis ANOVA test was used for differentiating between parameters in the three groups of patients. Comparison of categorical parameters was carried out with Fisher and M-L Chi-square tests. Correlation NT-proBNP with measured parameters was performed using Pearson (normality of data) or Spearman rank correlation.

Results

Retrospective study

In the five-year observation period there were 326 (100 %) patients (pts) with serum sodium dysbalances. The majority had hyponatraemia (251 pts, 77 %). Hypernatraemia was less frequent, in 75 (23 %) pts (table 12). Overall there were 928 (100 %) days of dysnatraemia, usually hyponatraemia (736 days, 79 %), less often hypernatraemia (192 days, 21 %), (table 12).

Table 12. Characteristics of the retrospective study.

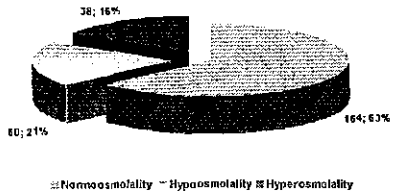
Parameter		Dysnatraemia	Hypo-natraemia	Hyper-natraemia	p-value
Number of patients	pts	326 (100,0%)	251 (100,0%)	75 (100,0%)	
Operation	pts	218 (66,9%)	161 (64,1%)	57 (76,0%)	0,056
After operation	pts	107 (32,8%)	89 (35,5%)	18 (24,0%)	0,056
Time since operation	day	5,5 ± 6,5	6,2 ± 6,5	3,7 ± 5,0	0,002
Cerebral complications	pts	166 (50,9%)	115 (25,8%)	51 (68,0%)	0,001
Focal	pts	103 (62,0%)	69 (60,0%)	34 (66,7%)	0,344
Diffuse	pts	98 (59,0%)	68 (59,1%)	30 (58,8%)	0,970
No pulmonary oedema	pts	317 (97,3%)	247 (98,4%)	70 (93,3%)	0,480
GOS		3,7 ± 1,2	3,9 ± 1,1	3,3 ± 1,4	0,002
Mortality in NNICU	pts	20 (6,1%)	6 (2,4%)	14 (18,4%)	0,001
Days of dysnatraemia	day	928 (100,0%)	736 (100,0%)	192 (100,0%)	
Lenght of dysnatraemia	day	2,8 ± 3,6	2,9 ± 3,8	2,6 ± 2,8	0,713
GCS		13,2 ± 2,6	13,6 ± 2,2	12,0 ± 3,4	0,001
Time since brain damage	day	14,4 ± 18,8	14,4 ± 17,7	14,2 ± 22,1	0,359
At admisson in NNICU	pts	87 (26,7%)	74 (29,5%)	13 (17,3%)	0,030
Osmotherapy	pts	156 (47,9%)	101 (40,2%)	55 (72,4%)	0,001
Mannitol	pts	152 (97,4%)	99 (98,0%)	53 (96,4%)	0,541
Diuretics	pts	31 (9,5%)	20 (8,0%)	11 (14,5%)	0,099
Furosemid	pts	27 (87,1%)	16 (80,0%)	11 (100,0%)	0,050
Fluid intake	ml/day		4000,9 ± 1504,0	3836,3 ± 980,9	0,240
Infusion	ml/day		2020,3 ± 1334,1	2229,9 ± 984,8	0,097
Fluid output	ml/day		3693,2±1856,3	3210,6±1199,8	0,018
Diuresis	ml/day		3550,9 ± 1849,3	3082,9 ± 1262,2	0,016

Mean ± standard deviation, p-value – statistical significance between hyponatraemia and hypernatraemia, GCS – on onset of dysnatraemia, GOS – Glasgow Outcome Scale upon discharge from NNICU.

Hyponatraemia

Hyponatraemia was most often linked with serum normooosmolality (154 pts, 297 days) and sometimes with hyperosmolality (38 pts, 41 days), while a mere 50 patients (169 days) had hypoosmolality (figure 1, table 13). The others were without measured serum osmolality.

Figure 1. Numbers of patients with hyponatraemia in relation to measured serum osmolality.



Hypoosmolal hyponatraemia

Over a five-year period hypoosmolal hyponatraemia was found in 50 pts. Renal function parameters were examined in 29 pts (58%), of whom 25 pts had CSW (table 14), the remaining 4 pts suffered from hyponatraemia as a result of incorrectly prescribed desmopressin and nobody had SIADH. No patients had central pontine myelinolysis.

Cerebral Salt Wasting

CSW was found in 25 patients, 19 men and 6 women with the mean age 48,6 ± 17,9 years. The mean stay in the NNICU lasted 20,4 ± 14,5 days. There were altogether 75 days of hyponatraemia, with an average duration of 4,9 ± 5,1 days. Mean GCS upon onset of hyponatraemia was 13,0 ± 2,5. The most frequent diagnosis in these patients was stroke (9 pts), second was TBI (8 pts). Cerebral complications appeared in 19 patients (76 %), two of whom died in the NNICU. The mean GOS was 3,8 ± 1,2. No patient had a pulmonary oedema. 22 patients were treated with hypertonic saline, 7 of whom also received fludrocortisone.

Table 13. Characteristics of hyponatraemia in the retrospective study.

Parameter		Hypoosmolal	Hyperosmolal	Normoosmolal	p-value
Number of patients	pts	50 (100,0%)	38 (100,0%)	154 (100,0%)	
1996	pts	10 (20,0%)	6 (15,8%)	24 (15,6%)	0,767
1997	pts	10 (20,0%)	10 (26,3%)	40 (26,0%)	0,668
1998	pts	8 (16,0%)	7 (18,4%)	35 (22,7%)	0,544
1999	pts	11 (22,0%)	6 (15,8%)	30 (19,5%)	0,762
2000	pts	11 (22,0%)	9 (23,7%)	25 (16,2%)	0,458
Male	pts	37 (74,0%)	22 (57,9%)	105 (68,2%)	0,278
Age	years	48,5 ± 18,9	53,9 ± 14,4	55,2 ± 15,2	0,089
Stay in NNICU	day	18,7 ± 12,7	9,8 ± 10,4	13,7 ± 11,2	0,001
Focal brain damage	pts	28 (56,0%)	28 (73,7%)	98 (63,6%)	0,226
Diffuse brain damage	pts	22 (44,0%)	10 (26,3%)	56 (36,4%)	0,226
Stroke	pts	17 (34,0%)	13 (34,2%)	65 (42,2%)	0,458
Trauma	pts	13 (26,0%)	4 (10,5%)	19 (12,3%)	0,061
Tumour	pts	9 (18,0%)	18 (47,4%)	52 (33,8%)	0,010
Epilepsy	pts	1 (2,0%)	1 (2,6%)	4 (2,6%)	0,969
Infection	pts	4 (8,0%)	2 (5,3%)	6 (3,9%)	0,538
Hydrocephalus	pts	5 (10,0%)	0 (0,0%)	5 (3,2%)	0,035
Others	pts	1 (2,0%)	0 (0,0%)	3 (1,9%)	0,502
Operation	pts	43 (86,0%)	30 (78,9%)	127 (82,5%)	0,683
Days after operation	day	11,4 ± 9,0	4,2 ± 3,7	7,5 ± 7,8	0,002
Cerebral complications	pts	35 (70,0%)	16 (42,1%)	79 (51,3%)	0,019
Focal	pts	22 (62,9%)	9 (56,3%)	45 (57,0%)	0,824
Diffuse	pts	22 (62,9%)	13 (81,3%)	51 (64,6%)	0,358
No pulmonary oedema	pts	49 (98,0%)	37 (97,4%)	150 (97,4%)	0,969
GOS		3,8 ± 1,2	3,8 ± 1,2	3,8 ± 1,1	0,956
Mortality in NNICU	pts	3 (6,0%)	2 (5,3%)	5 (3,2%)	0,660
S_Na^+	mmol/l	129,6 ± 4,0	132,3 ± 2,6	132,5 ± 1,7	0,001
S_Na^+ 130 -134	day	104 (61,5%)	36 (87,8%)	278 (93,6%)	
S_Na^+ <130	day	65 (38,5%)	5 (12,2%)	19 (0,3%)	
Shift (+) S_Na^+ in 24 h	mmol/l	4,9 ± 3,8	4,2 ± 3,8	4,0 ± 3,1	0,173
Days of dysnatraemia	day	169 (33%)	41 (8%)	297 (59%)	
Length of dysnatraemia	day	3,4 ± 4,0	1,1 ± 0,2	1,9 ± 1,7	0,001
GCS	day	13,1± 2,3	13,5 ± 2,5	13,5 ± 2,3	0,001
Since brain damage	day	18,0 ± 18,6	10,5 ± 22	18,7 ± 20	0,001
Admission in NNICU	pts	11 (22,0%)	15 (39,5%)	30 (19,4%)	0,043
Antioedematic therapy	pts	11 (22,0%)	22 (57,9%)	60 (38,7%)	0,002
Mannitol	pts	11 (100,0%)	22 (100,0%)	58 (96,7%)	0,406
Fluid intake	ml/day	4153,9 ± 1221,9	3339,2 ± 856,5	3957,5 ± 1695,2	0,001
Infusion	ml/day	2038,5 ± 1108,2	1983,2 ± 772,7	2007,6 ± 1506,0	0,994
Fluid output	ml/day	3930,4 ± 1675,9	2600,0± 1012,6	3619,5 ±1997,1	0,001
Diuresis	ml/day	3799,5 ± 1670,3	2418,8 ± 1018,4	3479,7 ± 1983,8	0,001
Fluid balance - negative	day	50 (29,6%)	1 (2,4%)	65 (21,9%)	0,001
S_Osm	mmol/kg	267,3 ± 6,4	303,9 ± 7,9	283,0 ± 5,4	0,001
S_OsmC	mmol/kg	269,2 ± 8,6	284,4 ± 9,0	277,8 ± 4,9	0,001
S_OsmE	mmol/kg	265,4 ± 8,0	274,2 ± 5,5	272,0 ± 4,1	0,001
U_Osm	mmol/kg	509,5 ± 178,9	571,1 ± 205,5	575,8 ± 190,7	0,003
S_K^+	mmol/l	4,1 ± 0,5	4,5 ± 0,7	4,2 ± 0,6	0,006
S_Alb	g/l	36,7 ± 4,8	37,4 ± 6,0	37,4 ± 4,7	0,733
S_Glu	mmol/l	6,1 ± 1,3	9,8 ± 5,2	7,0 ± 2,4	0,001
S_Urea	mmol/l	3,9 ± 1,6	9,9 ± 6,9	5,8 ± 2,7	0,001
S_Cr	umol/l	67,8 ± 15,0	118,9 ± 129,8	78,0 ± 53,1	0,001
B_PH		7,438 ± 0,045	7,421 ± 0,057	7,436 ± 0,042	0,237

Mean ± standard deviation, p-value –statistical significance between these groups, GCS – on onset of dysnatraemia, admission to NNICU – dysnatraemia present on admission.

Table 14. Characteristics of patients with CSW.

Parameter		Mean	SD	Median	p-value
S_Na^+	mmol/l	129,5	3,4	130,0	<0,001
S_Na^+ 130 -134	mmol/l	131,9 (N42)	1,5	132,0	<0,001
S_Na^+ <130	mmol/l	126,5 (N33)	2,6	127,0	<0,001
Shift (+) S_Na^+ in 24 h	mmol/l	5,5	3,7	5,0	<0,001
S_Osm	mmol/kg	267,5	5,8	269,0	<0,001
S_OsmC	mmol/kg	268,8	7,5	269,0	<0,001
S_OsmE	mmol/kg	265,3	7,0	265,0	<0,001
U_Osm	mmol/kg	537,6	171,3	528,5	<0,001
S_K^+	mmol/l	4,1	0,5	4,1	
S_Alb	g/l	37,4	4,8	37,7	
S_Glu	mmol/l	5,9	1,1	5,7	
S_Urea	mmol/l	3,6	1,6	3,4	
S_Cr	umol/l	66,4	13,9	65,0	
B_PH		7,429	0,041	7,429	
dU_Na^+	ml/day	546,6	383,7	507,0	<0,001
dU_K^+	ml/day	66,3	38,5	60,1	<0,001
C_Cr	ml/s	2,2	0,6	2,1	0,053
C_Osm	ml/s	0,092	0,042	0,084	<0,001
C_EI	ml/s	0,065	0,036	0,057	<0,001
C_Na^+	ml/s	0,061	0,036	0,052	<0,001
C_H_2O	ml/s	-0,042	0,034	-0,044	<0,001
EWC	ml/s	-0,015	0,032	-0,013	<0,001
FE_Osm		0,045	0,021	0,039	0,001
FE_Na^+		0,029	0,016	0,025	<0,001
Fluid intake	ml/day	4464,1	1464,4	4200,0	
Infusion	ml/day	2239,4	1229,3	1950,0	
Fluid output	ml/day	4270,4	1856,1	3925,0	
Diuresis	ml/day	4175,8	1869,6	3900,0	
Fluid balance - negative	ml/day	890,7 (N=29)	661,1	800,0	
Fluid balance - positive	ml/day	1113,4	1378,1	800,0	

SD – standard deviation, p-value – statistical significance with respect to the reference range, N – all days.

Hyponatraemia with serum sodium below 130 mmol/l

From 251 patients with hyponatraemia, only 51 (21 %) were recorded with serum sodium below 130 mmol/l. Altogether there were 106 days, the majority of which were with serum hypoosmolality (65 days), fewer with normoosmolality (19 days) and the fewest with hyperosmolality (5 days), (table 15). The remainder were without measured serum osmolality.

Table 15. Characteristics of hyponatraemia with serum sodium below 130 mmol/l.

Parameter		S_Na^+ < 130 mmol/l	S_Na^+ 130 – 134 mol/l	p-value
Stay in NNICU	day	16,7 ± 12,8	10,5 ± 9,5	<0,001
Cerebral complications	pts	37 (72,6%)	78 (39,4%)	<0,001
Focal	pts	23 (62,2%)	46 (59,0%)	0,744
Diffuse	pts	23 (62,2%)	45 (57,7%)	0,648
GCS		13,0 ± 2,3	13,8 ± 2,1	0,018
GOS		3,7 ± 1,1	3,9 ± 1,1	0,152
Mortality in NNICU	pts	3 (5,9%)	3 (1,5%)	0,103
Days of dysnatraemia	day	6,3 ± 6,6	2,1 ± 1,4	<0,001
Length of dysnatraemia	day	106 (100,0%)	630 (100,0%)	
Antioedematic therapy	pts	21 (41,2%)	80 (40,4%)	0,920
Mannitol	pts	21 (100,0%)	78 (97,5%)	0,332
Fluid intake	ml/day	4122,6 ± 1261,8	3975,2 ± 1550,9	0,457
Infusion	ml/day	1972,1 ± 985,8	2030,5 ± 1397,5	0,740
Fluid output	ml/day	3887,8 ± 1574,9	3651,1 ± 1911,4	0,348
Diuresis	ml/day	3717,4 ± 1593,1	3514,8 ± 1900,6	0,413

Mean ± standard deviation, p-value –statistical significance between these groups, GCS – on onset of dysnatraemia, GOS – Glasgow Outcome Scale in discharge of NNICU, admission to NNICU – dysnatraemia present upon admission.

Hypernatraemia

Of the 75 patients with hypernatraemia, cDI was found in only 8 of them (15 days). We classified 59 patients as "non-cDI" (163 days), (table 16). The remaining patients were not evaluated because they had no serum osmolality measurements.

Hypernatraemia with serum sodium above 156 mmol and 160 mmol

From the 75 hypernatraemic patients, 25 had (33 %) S_Na^+ above 156 mmol/l and 12 (16 %) had S_Na^+ above 160 mmol/l. In a comparison of both extreme groups with all hypernatraemias we found significantly longer durations of hypernatraemia (for both groups $p < 0,001$) and higher mortality in the NNICU (S_Na^+ above 156 mmol/l $p = 0,041$, S_Na^+ above 160 mmol/l $p = 0,040$). However, we did not found any significant changes between these extreme groups (table 17).

Table 16. Characteristics of hypernatraemia in the retrospective study.

Parameter		cDI	non cDI	p-value
Number of patients	*pts*	8 (100,0%)	59 (100,0%)	
1996	pts	0 (0,0%)	2 (3,4%)	0,767
1997	pts	2 (25,0%)	6 (10,2%)	0,668
1998	pts	3 (37,5%)	16 (27,1%)	0,544
1999	pts	2 (25,0%)	20 (33,9%)	0,762
2000	pts	1 (12,5%)	15 (25,4%)	0,458
Male	pts	2 (25,0%)	30 (50,8%)	0,278
Age	years	46,4 ± 13,3	58,3 ± 15,3	0,089
Stay in NNICU	day	15,8 ± 10,5	11,9 ± 10,3	0,001
Focal brain lesion	pts	4 (50,0%)	36 (61,0%)	0,226
Diffuse brain lesion	pts	4 (50,0%)	23 (39,0%)	0,226
Stroke	pts	4 (50,0%)	30 (50,8%)	0,507
Tumour	pts	3 (37,5%)	17 (28,8%)	0,789
Trauma	pts	0 (0,0%)	7 (11,9%)	0,222
Operation	pts	7	52	0,767
After operation	pts	6	48	0,444
Days after operation	day	3,8 ± 5,1	3,0 ± 4,0	0,352
Cerebral complications	pts	5 (62,5%)	39 (66,1%)	1,000
Focal	pts	2 (40,0%)	29 (74,4%)	0,283
Diffuse	pts	4 (80,0%)	21 (53,8%)	0,380
No pulmonary oedema	pts	8 (100,0%)	54 (91,5%)	0,307
GOS		3,5 ± 1,7	3,4 ± 1,3	0,857
Mortality in NNICU	pts	2 (25,0%)	7 (11,9%)	0,210
S_Na^+	mmol/l	155,0 ± 5,5 (N=15)	154,5 ± 3,7 (N=149)	0,736
S_Na^+ 151 - 155	mmol/l	152,4 ± 1,2 (N=11)	152,6 ± 1,3 (N=104)	0,638
S_Na^+ 156 - 160	mmol/l	157,5 ± 0,7 (N=2)	157,4 ± 1,2 (N=32)	0,770
S_Na^+ >160	mmol/l	167 ± 5,7 (N=2)	163,3 ± 3,2 (N=13)	0,234
Shift (-) S_Na^+ in 24 h	mmol/l	6,7 ± 4,7	6,1 ± 4,1	0,757
Length of dysnatraemia	*day*	5,3 ± 7,3	2,8 ± 3,0	0,706
GCS		11,0 ± 5,3	12,6 ± 2,6	0,631
Since brain damage	day	14,0 ± 15,0	14,4 ± 24,3	0,370
Admission to NNICU	pts	3 (37,5%)	10 (16,9%)	0,319
Antioedematic therapy	pts	3 (37,5%)	48 (81,4%)	0,013
Mannitol	pts	3 (100,0%)	47 (97,9%)	0,772
Diuretics	day	2 (13,3%)	63 (42,3%)	0,019
Furosemid	day	0 (0,0%)	40 (63,5%)	0,048
Fluid intake	ml/day	4036,4 ± 874,4	3803,0 ± 985,3	0,450
Infusion	ml/day	2368,2 ± 1511,7	2203,0 ± 944,0	0,281
Fluid output	ml/day	3876,7 ± 1815,8	3139,2 ± 1115,8	0,074
Diuresis	ml/day	3771,1 ± 1821,3	3008,7 ± 1188,9	0,079
Fluid balance - negative	day	2 (13,3%)	18 (12,1%)	0,889
S_Osm	mmol/kg	323,3 ± 15,4	326,4 ± 16,0	0,476
S_OsmC	mmol/kg	325,6 ± 13,4	326,1 ± 10,9	0,558
S_OsmE	mmol/kg	318,3 ± 11,3	316,5 ± 8,5	0,555
U_Osm	mmol/kg	392,3 ± 221,9	578,8 ± 186,7	0,001
S_K^+	mmol/l	4,0 ± 0,4	3,9 ± 0,5	0,656
S_Glu	mmol/l	8,4 ± 2,0	7,4 ± 2,9	0,010
S_Urea	mmol/l	7,0 ± 2,9	9,6 ± 5,3	0,075
S_Cr	umol/l	96,3 ± 19,7	95,1 ± 37,0	0,387
B_PH		7,422 ± 0,033	7,429 ± 0,051	0,679

Table 17. Comparison of hypernatraemia with serum sodium above 156 mmol/l and 160 mmol/l.

Parameter		S_Na > 156 mmol/l	S_Na⁺ > 160 mmol/l	p-value
Number of patients	pts	25 (100,0%)	12 (100,0%)	
Stay in NNICU	day	12,6 ± 10,9	15,5 ± 13,6	0,490
Length of dysnatraemia	day	4,2 ± 4,2	5,3 ± 5,7	0,721
GCS		11,2 ± 4,2	10,0 ± 4,6	0,355
GOS		2,8 ± 1,6	2,5 ± 1,6	0,592
Mortality in NNICU	pts	8 (32,0%)	5 (41,7%)	0,567

Mean ± standard deviation, p-value – statistical significance between these groups.

Prospective study

In the five-year observation period, serum sodium dysbalances occurred in 24 % patients with acute brain diseases admitted to our NNICU. There were 378 (100 %) patients, the majority had hyponatraemia (245 pts, 65 %). Hypernatraemia was less frequent, in 133 (35 %) pts (table 18). Overall there were 1089 (100 %) days of dysnatraemia, usually hyponatraemia (661 days, 61 %), less often hypernatraemia (428 days, 39 %), (table 18).

Hyponatraemia

Hyponatraemia occurred in 245 pts. Overall there were 661 days of dysnatraemia, which was most often linked with serum normooosmolality (429 days) and sometimes with hyperosmolality (52 days), while a mere 50 patients (105 days) had hypoosmolality (figure 2, table 19). The others were without measured serum osmolality.

Figure 2. Days of hyponatraemia in relation to measured serum osmolality.

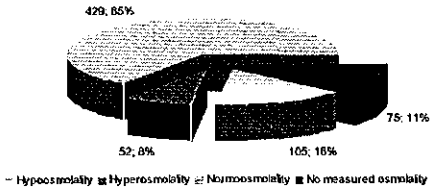


Table 18. Characteristics of the prospective study.

Parameter		Dysnatraemia	Hypo-natraemia	Hyper-natraemia	p-value
Number of patients	pts	378 (100%)	245 (100%)	133 (100%)	0,009
Operation	pts	272 (72,0%)	161 (65,7%)	111 (83,5%)	<0,001
After operation	pts	222 (58,7%)	115 (46,9%)	107 (80,5%)	<0,001
Time since operation	day	6,1 ± 8,6	7,4 ± 8,9	4,8 ± 8,1	0,020
Cerebral complications	pts	210 (55,6%)	105 (42,9%)	105 (78,9%)	<0,001
Focal	pts	146 (69,5%)	72 (68,6%)	74 (70,5%)	0,881
Diffuse	pts	142 (67,6%)	66 (62,9%)	76 (72,4%)	0,184
Oedema	pts	64 (45,1%)	20 (30,3%)	44 (57,9%)	0,001
Vasospasms	pts	39 (27,5%)	20 (30,3%)	19 (25,0%)	0,572
Hydrocephalus	pts	32 (22,5%)	18 (27,3%)	14 (18,4%)	0,232
Pulmonary oedema	pts	22 (5,8%)	9 (3,7%)	13 (9,8%)	0,021
GOS		3,3 ± 1,3	3,8 ± 1,1	2,4 ± 1,2	<0,001
Mortality in NNICU	pts	58 (15,3%)	15 (6,1%)	43 (32,3%)	0,003
Days of dysnatraemia	day	1089 (100%)	661 (100%)	428 (100%)	
Length of dysnatraemia	day	2,9 ± 2,6	2,7 ± 2,8	3,2 ± 2,2	0,059
On admisson to NNICU	pts	143 (37,8%)	134 (54,7%)	9 (6,8%)	<0,001
GCS		11,7 ± 4,1	13,3 ± 3,0	9,4 ± 4,3	<0,001
Consciousness	pts				<0,001
Regression	pts	13 (3,4%)	6 (2,4%)	7 (5,3%)	0,235
Without change	pts	204 (54%)	156 (63,7%)	48 (36,1%)	<0,001
Progression	pts	97 (25,7%)	20 (8,2%)	77 (57,9%)	<0,001
CT of brain	pts				<0,001
Regression	pts	21 (5,6%)	9 (3,7%)	12 (9,0%)	0,036
Without change	pts	15 (4,0%)	11 (4,5%)	4 (3,0%)	0,589
Progression	pts	56 (14,8%)	11 (4,5%)	45 (33,8%)	<0,001
Time from brain damage	day	9,9 ± 9,2	11,8 ± 9,1	7,6 ± 8,7	<0,001
Acute onset	pts	285 (75,4%)	154 (62,9%)	131 (98,5%)	<0,001
Impossible - admission	pts	84 (22,2%)	83 (33,9%)	1 (0,8%)	<0,001
Osmotherapy	pts	208 (55%)	95 (38,8%)	113 (85,0%)	<0,001
Mannitol	pts	94 (45,2%)	49 (51,6%)	45 (39,8%)	0,212
NaCl 10%	pts	164 (78,8%)	63 (66,3%)	101 (89,4%)	<0,001
Diuretics	pts	90 (23,8%)	32 (13,1%)	58 (43,6%)	<0,001
Furosemid	pts	68 (75,6%)	13 (40,6%)	55 (94,8%)	<0,001
CVP	torr	5,5 ± 3,8	5,8 ± 3,1	5,5 ± 4,0	0,684
Fluid intake	*ml/day*	*3613,2 ± 748,9*	*3535,1 ± 711,0*	*3710,6 ± 783,7*	*<0,001*
Sodium intake	mmol/day	415,5 ± 187,6	408,9 ± 188,6	423,8 ± 186,3	0,262
Fluid output	ml/day	3169,5 ± 1135,8	3287,5 ± 1038,3	3022,3 ± 1232,5	0,001
Diuresis	ml/day	3030,3 ± 1156,1	3213,7 ± 1037,7	2802,8 ± 1252,7	<0,001
dU_Na^+	mmol/day		558,8 ± 211,9	374,6 ± 185,3	<0,001
dU_Na^+/dU_K^+			7,9 ± 4,8	3,7 ± 2,3	<0,001
C_Cr	ml/s		1,8 ± 0,5	1,7 ± 0,4	0,011
C_Osm	ml/s		0,074 ± 0,022	0,060 ± 0,018	<0,001
C_El	ml/s		0,054 ± 0,020	0,035 ± 0,015	<0,001
C_Na^+	ml/s		0,049 ± 0,019	0,028 ± 0,014	<0,001
C_H_2O	ml/s		-0,037 ± 0,018	-0,027 ± 0,013	<0,001
EWC	ml/s		-0,017 ± 0,016	-0,002 ± 0,012	<0,001
FE_Osm			0,040 ± 0,012	0,035 ± 0,009	<0,001
FE_Na^+			0,026 ± 0,011	0,016 ± 0,008	<0,001
FE_H_2O			0,021 ± 0,008	0,020 ± 0,008	0,160

Mean ± standard deviation, p-value – statistical significance between hyponatraemia and hypernatraemia, GCS – on onset of dysnatraemia, GOS – Glasgow Outcome Scale upon discharge of NNICU, impossible - admission – founded on admisson.

Table 19. Characteristics of hyponatraemia in the prospective study.

Parameter		Hypoosmolal	Hyperosmolal	Normoosmolal	p-value
Number of patients	pts	55 (100,0%)	45 (100,0%)	184 (100,0%)	
Male	pts	28 (50,0%)	20 (40,0%)	84 (50,0%)	0,756
Age	years	73,5 ± 12,5	77,8 ± 17,1	57,1 ± 13,9	0,224
Stay in NNICU	day	14,5 ± 11,1	8,0 ± 9,1	11,8 ± 10,4	0,001
Stroke	pts	27 (49,1%)	15 (33,3%)	87 (47,3%)	0,194
Trauma	pts	10 (18,2%)	6 (13,3%)	27 (14,7%)	0,769
Tumour	pts	9 (16,4%)	20 (44,4%)	39 (21,2%)	0,003
Operation	pts	35 (63,6%)	32 (71,1%)	120 (65,2%)	0,697
Days after operation	day	13,9 ± 15,5	2,7 ± 3,7	8,5 ± 7,6	<0,001
Cerebral complications	pts	31 (56,4%)	13 (28,9%)	88 (47,8%)	0,017
Pulmonary oedema	pts	1 (1,8%)	4 (8,9%)	7 (3,8%)	0,231
GOS		3,8 ± 1,2	3,8 ±1,0	3,7 ± 1,1	0,856
S_Na+	mmol/l	129,2 ± 4,5	132,8 ± 2,1	132,8 ± 1,4	<0,001
S_Na+ 130 -134	day	60 (57,1%)	49 (94,2%)	415 (96,7%)	<0,001
S_Na+ <130	day	45 (42,9%)	3 (5,8%)	14 (3,3%)	<0,001
Shift (+) S_Na+ in 24 h	mmol/l	5,5 ± 4,7	4,6 ± 2,8	3,5 ± 2,6	<0,001
Days of dysnatraemia	day	105 (100,0%)	52 (100,0%)	429 (100,0%)	
Length of dysnatraemia	day	1,9 ± 1,2	1,2 ± 0,5	2,3 ± 2,4	<0,001
GCS		13,0 ± 3,3	13,1 ± 3,7	13,2 ± 3,1	0,666
Since brain damage	day	15,5 ± 14,4	11,1 ± 9,1	11,9 ± 9,5	0,406
Acute onset	pts	36 (65,5%)	26 (57,8%)	135 (73,4%)	0,105
Impossible - admission	pts	17 (30,9%)	18 (40%)	44 (23,9%)	0,091
Osmotherapy	day	59 (56,2%)	45 (86,5%)	293 (68,3%)	<0,001
Manitol	day	12 (20,3%)	30 (66,7%)	64 (21,8%)	<0,001
Diuretics	day	11 (10,5%)	9 (17,3%)	67 (15,6%)	0,337
Fluid intake	ml/day	3855,6 ± 867,8	3058,1 ± 394,6	3476,9 ± 678,1	<0,001
Infusion	ml/day	2143,5 ± 877,0	1601,9 ± 560,1	1952,1 ± 683,4	0,040
Sodium intake	mmol/day	462,8 ± 223,3	347,8 ± 109,3	410,1 ± 188,7	0,135
Sodium intake	mmol/kg/ day	6,5 ± 3,2	5,0 ± 1,6	5,5 ± 2,7	0,068
Fluid output	ml/day	3595,1±1152,2	2636,2 ± 606,4	3242,7 ± 998,5	0,003
Diuresis	ml/day	3502,4 ± 1135,9	2555 ± 561,8	3174,9 ± 1007,9	0,003
Fluid balance - negative	day	25 (23,8%)	5 (9,6%)	114 (26,6%)	0,979
S_Osm	mmol/kg	267,4 ± 7,8	302,3 ± 6,0	283,6 ± 5,3	<0,001
S_OsmC	mmol/kg	267,7 ± 9,0	283,3 ± 8,3	277,2 ± 4,0	<0,001
U_Osm	mmol/kg	525,1 ± 177,5	644,5 ± 178,4	612,7 ± 168,8	<0,001
U_Osm/S_Osm		2,0 ± 0,7	2,1 ± 0,6	2,2 ± 0,6	0,018
S_K+	mmol/l	4,0 ± 0,5	4,4 ± 0,5	4,1 ± 0,5	<0,001
S_Glu	mmol/l	5,8 ± 1,4	9,0 ± 4,0	6,4 ± 1,8	<0,001
S_Urea	mmol/l	3,9 ± 1,4	8,6 ± 5,2	5,2 ± 2,2	<0,001
S_Cr	umol/l	69,2 ± 14,9	94,3 ± 47,9	71,2 ± 19,1	<0,001
B_PH		7,4 ± 0,0	10,1± 18,3	7,4 ± 0,0	<0,001
dU_Na+	mmol/day	638,8 ± 232,2	510,1 ± 105,1	544,8 ± 209,9	0,040
dU_Na+ /dU_K+		8,2 ± 5,1	11,4 ± 2,8	7,6 ± 4,7	0,002
C_Cr	ml/s	2,1 ± 0,5	1,6 ± 0,5	1,8 ± 0,4	<0,001
C_Osm	ml/s	0,083 ± 0,025	0,064 ± 0,010	0,073 ± 0,022	0,030
C_El	ml/s	0,062 ± 0,021	0,045 ± 0,008	0,053 ± 0,019	0,016
C_Na+	ml/s	0,057 ± 0,021	0,044 ± 0,009	0,047 ± 0,018	0,017
C_H2O	ml/s	-0,042 ± 0,020	-0,034 ± 0,008	-0,036 ± 0,018	0,137
EWC	ml/s	-0,022 ± 0,018	-0,015 ± 0,006	-0,016 ± 0,015	0,100
FE_Osm		0,041 ± 0,014	0,041 ± 0,010	0,040 ± 0,012	0,908
FE_Na-		0,028 ± 0,012	0,028 ± 0,009	0,026 ± 0,010	0,399
FE_H2O		0,020 ± 0,008	0,019 ± 0,006	0,022 ± 0,008	0,435

Hypoosmolal hyponatraemia

Over a five-year period hypoosmolal hyponatraemia was found in 55 pts. CSW was diagnosed in 26 pts (table 20). In two cases the cause of hyponatraemia was incorrectly administered therapy, in one instance desmopressin and in the second an unsuitable dose of hypotonic solutions. No patient had SIADH.

For the remaining patients (27), it was impossible to carry out differential diagnostics because the renal function parameters were missing. Eighteen of them had one-day hypoosmolal hyponatraemia, which was in 12 cases discovered upon admittance to the NNICU. A further 6 patients had two-day hyponatraemia. Renal function parameters were not taken for the others, even though they had hyponatraemia for three or four days.

43 patients were given NaCl (10 %) concentrated solution, while 22 patients received fludrocortizon.

No patients had central pontine myelinolysis.

Cerebral Salt Wasting

CSW was found in 26 patients, 15 men and 11 women with the mean age 50,4 ± 15,3 years. The mean stay in the NNICU lasted 18,2 ± 11,3 days. There were altogether 100 days of hyponatraemia, with an average duration of 6,5 ± 4,0 days. Mean GCS upon onset of hyponatraemia was 12,8 ± 3,3. The most frequent diagnosis in these patients was stroke (12 pts), then tumour (6 pts) and TBI (5 pts). Cerebral complications appeared in 17 patients (65,4 %), two of whom died in the NNICU. The mean GCS was 3,8 ± 1,2. No patient had a pulmonary oedema. 22 patients were treated with hypertonic saline, 7 of whom also received fludrocortisone. Further parameters are shown in table 20.

Hyponatraemia with serum sodium below 130 mmol/l

From 245 patients with hyponatraemia, only 46 (19%) were recorded with serum sodium below 130 mmol/l. Altogether there were 66 days, the majority of which were with serum hypoosmolality (45 days), fewer with normoosmolality (14 days) and the fewest with hyperosmolality (4 days), (table 21). The remainder were without measured serum osmolality.

Table 20. Parameters in patiensts with CSW in the prospective study.

Parameter		Mean	SD	Median	p-value
S_Na^+	mmol/l	130,9	3,8	133,0	<0,001
S_Na^+ 130 -134	mmol/l	132,8 (N=74)	1,2	133,0	<0,001
S_Na^+ <130	mmol/l	125,6 (N=26)	3,5	127,0	<0,001
Shift (+) S_Na^+ in 24 h	mmol/l	3,9	3,3	3,0	<0,001
S_Osm	mmol/kg	273,7	9,0	273,0	<0,001
S_OsmC	mmol/kg	270,5	8,8	273,0	<0,001
S_OsmE	mmol/kg	267,5	8,4	271,0	<0,001
U_Osm	mmol/kg	591,9	157,1	591,0	<0,001
U_Osm/S_Osm		2,2	0,6	2,2	
S_Glu	mmol/l	6,2	2,5	5,3	
S_Urea	mmol/l	3,7	1,3	3,5	
S_Cr	umol/l	64,8	12,9	64,0	
B_PH		7,4	0,0	7,4	
dU_Na^+	mmol/day	654,2	212,9	619,5	<0,001
dU_K^+	mmol/day	90,4	34,1	85,3	0,936
dU_Na^+/dU_K^+		8,2	4,4	7,6	
C_Cr	ml/s	2,0	0,5	2,0	
C_Osm	ml/s	0,082	0,022	0,081	<0,001
C_El	ml/s	0,064	0,020	0,064	<0,001
C_Na^+	ml/s	0,058	0,019	0,055	<0,001
C_H_2O	ml/s	-0,041	0,018	-0,040	<0,001
EWC	ml/s	-0,023	0,017	-0,02	<0,001
FE_Osm		0,041	0,012	0,038	<0,001
FE_Na^-		0,029	0,011	0,029	<0,001
FE_K^+		0,129	0,061	0,113	<0,001
FE_H_2O		0,021	0,008	0,021	0,164
CVP	torr	6,9	2,9	8	
Fluid intake	ml/day	3743,2	899,7	3710,0	
Infusion	ml/day	2147,0	821,4	2100,0	
Sodium intake	mmol/day	515,9	225,5	486,0	
Sodium intake	mmol/kg/ day	7,3	3,4	6,1	
Fluid output	ml/day	3737,3	1156,2	3620,0	
Diuresis	ml/day	3676,5	1125,7	3580,0	
Fluid balance - negative	ml/day	639,1 (N=42)	503,6	502,5	
Fluid balance - positive	ml/day	607,4 (N=45)	530,7	440,0	

SD – standard deviation, p-value – statistical significance with respect to the reference range, N – all days.

Table 21. Characteristics of hyponatraemia with serum sodium below 130 mmol/l.

Parameter		S_Na^+ < 130 mmol/l	S_Na^+ 130 – 134 mol/l	p-value
Stay in NNICU	day	13,4 ± 10,1	9,5 ± 9,6	0,003
Cerebral complications	pts	26 (56,5%)	79 (39,7%)	0,039
Focal	pts	15 (57,7%)	57 (72,2%)	0,175
Diffuse	pts	17 (65,4%)	49 (62,0%)	0,758
GCS		13,4 ± 2,4	13,3 ± 3,1	0,649
GOS		3,8 ± 1,1	3,8 ± 1,1	0,725
Mortality in NNICU	pts	3 (6,5%)	12 (6,0%)	0,901
Days of dysnatraemia	day	5,0 ± 2,8	2,2 ±2,2	<0,001
Osmotherapy	pts	5 (10,9%)	90 (45,2%)	<0,001
Mannitol	pts	4 (80,0%)	45 (50,0%)	0,176
Fluid intake	ml/day	3501,1 ± 668	3537,4 ± 714,5	0,824
Infusion	ml/day	1859,3 ± 611,2	1977,9 ± 711,8	0,540
Sodium intake	mmol/day	373,1 ± 184,7	411,3 ± 188,9	0,269
Fluid output	ml/day	3144,1 ± 1163,4	3297,2 ± 1030,2	0,404
Diuresis	ml/day	3125,4 ± 1177,7	3219,6 ± 1028,9	0,612

Mean ± standard deviation, p-value –statistical significance between these groups.

Hypernatraemia

From 133 patients with hypernatraemia, cDI was found in 16 patients (27 days). We classified 118 patients as "non-cDI" (349 days), (table 22). Five patients had both types of hypernatraemia. The remaining patients were not evaluated because they had no serum osmolality measurements.

Hypernatraemia with serum sodium above 156 mmol and 160 mmol

Of the 133 patients with hypernatraemia, 61 (46%) had serum sodium above 156 and 34 had serum sodium above 160. Significant differences were found in duration of hypernatraemia, GCS upon onset of the dysbalance and GOS between these extreme groups and other hypernatraemias. However, no significant differences were found between the two extreme groups (table 23).

Table 22. Characteristics of hypernatraemia in the prospective study.

Parameter		cDI	non cDI	p-value
Number of patients	pts	16 (100,0%)	118 (100,0%)	
Male	pts	4 (25,0%)	56 (47,5%)	0,166
Age	years	48,9 ± 17,8	61,6 ± 13,6	0,009
Stay in NNICU	day	7,9 ± 6,9	13,3 ± 10,8	0,014
NYHA		1,3 ± 0,6	1,5 ± 0,7	0,527
Stroke	pts	10 (62,5%)	79 (66,9%)	0,809
Tumour	pts	3 (18,8%)	15 (12,7%)	0,247
Trauma	pts	2 (12,5%)	18 (15,3%)	0,572
Operation	pts	11 (68,8%)	101 (85,6%)	0,085
Days after operation	day	2,5 ± 2,3	5,1 ± 8,4	0,145
Cerebral complications	pts	14 (87,5%)	94 (79,7%)	0,809
Pulmonary oedema	pts	0 (0,0%)	13 (11,0%)	0,110
GOS		1,6 ± 1,3	2,5 ± 1,2	0,079
Mortality in NNICU	pts	12 (75,0%)	34 (28,8%)	0,012
Days of dysnatraemia	day	27 (100,0%)	349 (100,0%)	
S_Na^+	mmol/l	160,1 ± 8,4	154,4 ± 3,4	<0,001
S_Na^+ 151 - 155	mmol/l	153,0±1,2(N=11)	152,5±1,3(N=249)	0,246
S_Na^+ 156 - 160	mmol/l	157,0±1,4(N=4)	157,6±1,3(N=71)	0,405
S_Na^+ >160	mmol/l	167,6±7,1(N=12)	162,3±1,7(N=29)	0,001
Lenght of dysnatraemia	day	3,3 ± 2,1	3,4 ± 2,3	0,139
GCS		6,8 ± 5,1	9,6 ± 4,1	0,192
Admission in NNICU	pts	2 (12,5%)	6 (5,1%)	0,158
Osmotherapy	pts	13 (81,3%)	102 (86,4%)	0,221
Mannitol	pts	5 (38,5%)	40 (39,2%)	0,925
NaCl 10%	pts	11 (84,6%)	93 (91,2%)	0,219
Diuretics	pts	5 (18,5%)	179 (51,3%)	0,001
Furosemid	pts	4 (80,0%)	154 (86%)	0,716
CVP	torr	6,2 ± 2,8	5,2 ± 4,1	0,441
Fluid intake	ml/day	4306,7 ± 1251,6	3683,5 ± 741,9	<0,001
Infusion	ml/day	3634,8 ± 1291,8	2435,1 ± 950,0	<0,001
Sodium intake	mmol/day	462,7 ± 215,2	422,4 ± 187,7	0,327
Sodium intake	mmol/kg/day	6,0 ± 3,0	5,7 ± 2,8	0,663
Fluid output	ml/day	5030,7 ± 2198,7	2872,8 ± 971,1	<0,001
Diuresis	ml/day	5195,9 ± 2134,2	2624,9 ± 929,0	<0,001
Fluid balance - negative	day	17 (63,0%)	47 (13,5%)	<0,001
S_Osm	mmol/kg	329,3 ± 16,2	322,3 ± 13,3	0,027
S_OsmC	mmol/kg	333,8 ± 17,7	325,8 ± 9,9)	0,043
U_Osm	mmol/kg	436 ± 256,9	608,5 ± 174,6	<0,001
S_K^+	mmol/l	4,0 ± 0,4	3,9 ± 0,5	0,229
S_Glu	mmol/l	6,8 ± 1,7	6,1 ± 1,6	0,029
S_Urea	mmol/l	6,0 ± 3,5	10,7 ± 6,7	<0,001
S_Cr	umol/l	99,9 ± 26,9	117,8 ± 88,5	0,614
dU_Na^+	mmol/day	437,4 ± 181,5	369,7 ± 185,9	0,198
dU_Na^+/dU_K^+		4,1± 1,7	3,7 ± 2,3	0,412
C_Cr	ml/s	1,7 ± 0,4	1,7 ± 0,4	0,472
C_Osm	ml/s	0,061 ± 0,019	0,060 ± 0,017	0,823
C_El	ml/s	0,039 ± 0,014	0,035 ± 0,015	0,311
C_Na^+	ml/s	0,031 ± 0,013	0,028 ± 0,014	0,340
C_H_2O	ml/s	-0,007 ± 0,016	-0,028 ± 0,012	<0,001
EWC	ml/s	0,016 ± 0,014	-0,003 ± 0,010	<0,001
FE_Osm		0,036 ± 0,008	0,035 ± 0,009	0,637
FE_Na^+		0,019 ± 0,006	0,016 ± 0,008	0,212
FE_H_2O		0,034 ± 0,009	0,019 ± 0,006	<0,001

Mean ± standard deviation, p-value –statistical significance between these groups, N – all days, p-value is without 5 pts, who had both DI and non cDI.

Table 23. Comparison of hypernatraemia with serum sodium above 156 mmol/l and 160 mmol/l.

Parameter		S_Na^+ > 156 mmol/l	S_Na^+ > 160 mmol/l	p-value
Number of patients	pts	61 (100,0%)	34 (100,0%)	
Stay in NNICU	day	12,5 ± 11,3	11,6 ± 9,9	0,825
Length of dysnatraemia	day	4,3 ± 2,4	4,4 ± 2,6	0,853
GCS		8,1 ± 4,4	7,8 ± 4,4	0,743
GOS		2,0 ± 1,2	1,9 ± 1,2	0,718
Mortality in NNICU	pts	28 (45,9%)	18 (52,9%)	0,510

Mean ± standard deviation, p-value –statistical significance between these groups.

Significantly higher mean serum values of NT-proBNP were found in patients with hyponatraemia (379,3 ± 490,2 pg/ml) compared to the given reference level (125 pg/ml, p < 0,001).

However, significantly higher values were also found in the control group (268,3 ± 203,9 pg/ml, p = 0,005), i.e. in patients with acute brain disease, normonatraemia, normoosmolality and who were classified NYHA I.

There were no significant differences found either while comparing hypoosmolal and normoosmolal hyponatraemias in patients with NYHA I (p = 0,933), or comparing hypoosmolal and normoosmolal hyponatraemias with the control group (p = 0,776).

In patients with CSW and NYHA I. serum sodium values were significantly higher than those of the control group (p < 0,001), (table 24). The mean value was 430,4 ± 706,4 pg/ml (p = 0,001). The relationship between NT-proBNP and the measured parameters in patients with CSW and normonatraemia can be seen in table 25. No patient with CSW had pulmonary oedema during the course of their hospitalisation.

Table 24. Comparison of serum NT-proBNP and other parameters in CSW and in patients with normonatraemia in acute brain diseases and NYHA I.

Parameter		CSW NYHA I.	Normonatraemia NYHA I.	p-value
NT-proBNP	pg/ml	430,4 ± 706,4	268,3 ± 203,9	<0,001
Number of patients	pts	19 (100,0%)	20 (100,0%)	
Age	years	44,9 ± 16,3	51,7 ± 12,9	0,267
S_Na^+	mmol/l	129,3 ± 3,6	139,7 ± 3,6	0,292
S_Osm	mmol/kg	271,6 ± 9,7	287,3 ± 4,0	<0,001
S_OsmC	mmol/kg	268,4 ± 8,9	289,2 ± 7,0	0,295
U_Osm	mmol/kg	663,0 ± 169,2	667,5 ± 177,1	0,000
U_Osm/S_Osm		2,4 ± 0,6	2,3 ± 0,6	0,938
C_Cr		2,2 ± 0,4	2,1 ± 0,6	0,681
dU_Na^+	mmol/day	682,4 ± 216	548,0 ± 163,9	0,036
dU_K^+	mmol/day	95,6 ± 41,1	78,7 ± 29,4	0,150
dU_Na^+/dU_K^+		8,7 ± 6,4	7,9 ± 3,9	0,930
C_Osm	ml/s	0,087 ± 0,023	0,079 ± 0,032	0,373
C_El	ml/s	0,070 ± 0,021	0,050 ± 0,013	0,001
C_Na^+	ml/s	0,061 ± 0,019	0,045 ± 0,014	0,007
C_H_2O	ml/s	-0,047 ± 0,019	-0,042 ± 0,023	0,503
EWC	ml/s	-0,030 ± 0,018	-0,013 ± 0,009	0,001
FE_Osm		0,040 ± 0,008	0,038 ± 0,015	0,566
FE_Na^+		0,029 ± 0,01	0,022 ± 0,010	0,059
FE_H_2O		0,019 ± 0,005	0,018 ± 0,006	0,713
Fluid intake	ml/day	3606,5 ± 821,8	3453,0 ± 567,7	0,440
Sodium intake	mmol/day	589,4 ± 258,4	433,5 ± 133,4	0,508
Sodium intake	mmol/kg/ day	8,4 ± 4,1	5,8 ± 2,1	0,024
Fluid output	ml/day	3627,6 ± 1132,1	3222,4 ± 959,7	0,317
Diuresis	ml/day	3538,2 ± 1052,8	3199,0 ± 976,8	0,019

Mean ± standard deviation, p-value –statistical significance between these groups.

Table 25. The relationship between NT-proBNP and the observed parameters in patients with CSW and normonatraemia in acute brain disease and NYHA I.

Parameter	Correlation with NT-pro BNP – Rs (p-value)	
	CSW (N=19)	Normonatraemia (N=20)
GCS	-0,207 (p=0,394)	-0,240 (p=0,308
S_Na^+	-0,521 (p=0,022)	0,300 (p=0,199)
S_Osm	-0,259 (p=0,284)	0,339 (p=0,144)
S_OsmC	-0,317 (p=0,186)	0,298 (p=0,202)
U_Osm	-0,004 (p=0,989)	-0,159 (p=0,515)
U_Osm/S_Osm	-0,030 (p=0,906)	-0,179 (p=0,464)
S_Uren	-0,323 (p=0,177)	-0,204 (p=0,394)
S_Cr	-0,067 (p=0,784)	-0,130 (p=0,582)
dU_Na^+	-0,462 (p=0,054)	-0,063 (p=0,792)
dU_Na^+/dU_K^+	-0,011 (p=0,964)	-0,231 (p=0,327)
C_Osm	-0,510 (p=0,031)	-0,248 (p=0,292)
C_El	-0,474 (p=0,047)	-0,119 (p=0,621)
C_Na^+	-0,453 (p=0,059)	-0,089 (p=0,708)
C_H_2O	0,466 (p=0,051)	0,227 (p=0,335)
C_EWC	0,389 (p=0,111)	-0,091 (p=0,702)
FE_Osm	-0,332 (p=0,178)	0,129 (p=0,587)
FE_Na^+	-0,230 (p=0,359)	0,293 (p=0,211)
FE_H_2O	0,100 (p=0,694)	0,332 (p=0,179)
Fluid intake	-0,488 (p=0,047)	-0,090 (p=0,707)
Sodium intake (mmol/day)	-0,243 (p=0,348)	-0,001 (p=0,995)
Sodium intake (mmol/day/kg)	-0,147 (p=0,573)	0,058 (p=0,809)
Fluid output	-0,201 (p=0,439)	-0,193 (p=0,414)
Diuresis	-0,216 (p=0,406)	-0,202 (p=0,392)

Discussion

The results of our study showed that dysnatraemia is a frequent dysbalance of effective osmolality in acute brain diseases [1-8]. In the prospective study, which was carried out along with the systematic database NNICU, acute dysnatraemia occurred in 24% of patients admitted to our NNICU. These results show that it is necessary to pay attention to and actively search for sodium dysbalances in neurointensive care. The daily monitoring of serum sodium should be a matter of course in all acute brain diseases.

The overall incidence of dysbalances in the prospective study slightly increased, from 326 to 378 patients. This rise was in hypernatraemia (1,7 x), which was connected with the introduction of two beds with a ventilation facility in 2003, which led to the admittance of patients with serious brain diseases. The mean value of GCS upon onset of hypernatraemia was $12 \pm 3,4$, compared to the prospective study, where it was $9,4 \pm 4,3$. The new equipment also led to a rise in hyponatraemia, which had been stable in previous years.

The most frequent diagnosis in both groups in our study was stroke, then brain tumours and trauma. This is because our NNICU focuses more on strokes and tumours than trauma. The majority of patients in our study had operations, which is also in keeping with the character of our NNICU, which admits more neurosurgical than neurological patients. No differences were found between the onset of dysnatraemia and brain damage in the retrospective study, in contrast to the prospective study, where hypernatraemia arose significantly earlier ($p < 0,001$).

In accordance with literature [1], in both the retrospective (77 %) and the prospective (65 %) study the majority of patients had hyponatraemia, but hypernatraemia was prognostically more serious. Hypernatraemia was connected with more cerebral complications, worse GOS, and higher mortality in the NNICU, but it arose with significantly lower GCS. Meanwhile, the incidence of these dysbalances was not different for focal and diffuse brain lesions. These findings were the same in the retrospective and prospective studies. In the prospective study, where we observed change of consciousness during the onset of dysnatraemia, hypernatraemia was related to worsening consciousness ($p < 0,001$), in hyponatraemia consciousness did not change ($p < 0,001$), and in neither group did consciousness improve ($p = 0,235$). Similar changes were found in brain CT, progress was observed in hypernatraemia, as was regression, but only 110 of the patients had this examination. No changes were found in either of the dysbalances. In the prospective study, not only did we evaluate the the overall incidence of difuse complications but their individual components too. We did not find differences between dysnatraemias in incidence of vasospasms ($p = 0,572$) and hydrocephalus ($p = 0,232$) but difuse brain oedema was significantly higher in hypernatraemia ($p = 0,001$). Our results therefore support the theory of the onset of hypernatraemia and severity of brain disease within the framework of compensatory regulation in the organism.

During the observation of further parameters among dysnatraemias, significant differences were not found in the length of dysnatraemia, but in its presence upon admission to the NNICU. Hyponatraemia was more common, and was found more often in the prospective study (134, 54,7 %) than in the retrospective (101, 40,2 %). The reason for this was hyperglycaemia, mannitol and increased urea, and less frequently the use of diuretics.

In acute brain disease, acute dysnatraemias prevail. The prospective study showed that hypernatraemia was acute in 98,5 % of patients. We found that hyponatraemia was acute in about 62,9 % of patients, but we did not evaluate the onset in all cases because in 33,9 % of patients the dysbalance was discovered in the admission blood test. Six of these patients received mannitol.

In literature, it is known that antioedematic therapy leads to dysnatraemia [6, 70]. In both our retrospective ($p = 0,001$) and prospective ($p < 0,001$) study antioedematic therapy most often led to hypernatraemia. Regarding use of hypertonic saline, there were no differences between

these dysbalances in sodium intake. Diuretics were more frequent in hypernatraemia, but only in the prospective study ($p < 0,001$). In 94,8 % of case, furosemide was given.

These dysbalances had no influence on CVP ($p = 0,684$). This parameter, however, was measured only in the prospective study. In the period of retrospective study, especially at the beginning, it was not a routine monitoring method in our NNICU.

In our experience it is possible to carry out differential diagnostics of hyponatraemia only when measured and calculated renal function parameters are available, in contrast to hypernatraemia, where complete cDI can be diagnosed without these parameters.

Hyponatraemia

Hyponatraemia is a serious complication in the NNICU when it is connected to low effective osmolality, i.e. with serum hypoosmolality [7]. Therefore, in the first phase of our study we divided hyponatraemias into three groups according to measured serum osmolality. The results of both parts of our study showed that hyponatraemia with hypoosmolality is not a frequent type of hyponatraemia. In the retrospective study, there were 50 (20 %) cases and in the prospective (22 %) study there were 55. Regarding the total number of hyponatraemias, there was an almost equal incidence of this dysbalance. Even though serum osmolality was not measured in all hyponatraemias, more were found in the retrospective study. Measured osmolality was mostly missing in hyponatraemia lasting one day. Due to the amount of mannitol use, we did not apply calculated serum osmolality for dividing the hyponatraemias.

The majority of hyponatraemias had measured serum osmolality within the reference ranges. Fewer hyponatraemias occurred with serum hyperosmolality. These hyperosmolal hyponatraemias did not last long: their mean duration in the retrospective study was $1,1 \pm 0,2$ days, in the prospective $1,2 \pm 0,5$ days. The reason for normoosmolal and hyperosmolal hyponatraemia can be seen first of all in hyperglycaemia, high levels of urea or mannitol osmotherapy. The highest mean values of glycaemia and urea in serum were found in hyperosmolal hyponatraemia, followed by normoosmolal, and finally hypoosmolal hyponatraemia. These differences were significant in both the retrospective and prospective studies.

Regarding the possibility of a brain oedema arising, it is necessary to pay special attention to hypoosmolal hyponatraemia. Timely and accurate diagnosis is essential. We consider measured and calculated renal function parameters to be a relatively simple method, with the further advantage of being accessible in daily clinical practice.

In neurointensive care hypoosmolal hyponatraemia is connected to two different syndromes – the more frequent CSW and less common SIADH [34], as was also seen in our study. We did not have one case of SIADH in either the retrospective or the prospective study. Diagnostics were not carried out in all patients with hypoosmolal hyponatraemia, due to not having renal function parameters for these patients. There were 21 patients in the retrospective study and 27 in the prospective study. This is a relatively high count in the prospective study, but 18 of them had one-day hyposmolal hyponatraemia, which was discovered upon entry to the NNICU in 12 cases. The other 6 patients had hyponatraemia lasting two days.

During evaluation of renal function parameters in diagnosis of dysnatraemia it is important in every case to distinguish its cause from the organism's compensatory response, which means correctly identifying the ADH-kidney axis [16]. In the case of normonatraemia with polyuria with low specific urine weight and positive EWC, if we prescribe desmopressin then hyponatraemia can arise due to free water retention. This situation came about in 4 patients in the retrospective study and one in the prospective study. There was no hyponatraemia caused

by hypotonic solution in the retrospective study, and one case in the prospective study. From our results it can be seen that the prevalent hypoosmolal hyponatraemia in acute brain disease is CSW. We had 51 such patients in our 10 year retrospective study. We found this figure surprisingly low and we incline towards Singh's opinion (2002) that CSW probably occurs less frequently than is supposed in literature [51]. Even though differential diagnosis was not carried out in all hypoosmolal hyponatraemias, in our experience CSW is not seen in hyponatraemia lasting only one- or two-days.

The assessment of the hormones which participate in the cause of these two syndromes is not beneficial with regards to the compensatory changes to the fluid volume [8]. In SIADH, free water retention leads to volume expansion and following stimulation of natriuretic peptides. In CSW it is the other way around, the primary rise in NP leads to content depletion and a secondary increase in ADH levels. Furthermore, only NP assessment is accessible in practice, especially NT-proBNP.

Differential diagnosis is essential because different mechanisms require different therapies [39]. In CSW [7, 53] sodium and fluids are substituted, in SIADH [51] fluids are restricted and diuretics applied. In SAH with vasospasms it is even dangerous to carry out fluid restriction [47]. Renal function parameters therefore are of benefit in diagnosing hyponatraemia [8]. According to basic laboratory parameters (serum sodium, measured serum osmolality and ratio urine and serum osmolality) it is impossible to carry out diagnosis, because CSW and SIADH are the same. Assessment of renal function parameters has even led to the re-evaluating the original diagnosis of SIADH as CSW [10].

During comparisons of individual groups according to measured serum osmolality it was found that there were significantly more cerebral complications in hypoosmolal hyponatraemia, but without any influence on the outcome of these patients. These findings were in both parts of the study. Neither did we discover significant changes of consciousness and brain CT. When we compared sodium intake in these three groups, we also did not find any differences.

During hyponatraemia therapy, we must always bear in mind the rule of sodium correction. In a fast rise there is a risk of pontine and extrapontine myelinolysis [58-63]. First, we need to find out whether the hyponatraemia is acute or chronic [63]. Next, we have to set the target value of sodium in 24 hours. To prevent this complication, it is important to take at least four serum sodium samples per day (6 hours interval), which was why we included this rule in our prospective protocol. However, in some cases we had to take more samples. In our 10-year study we did not have this complication, even though three patients exceeded the safety range of sodium shift, with 16, 20 and 22 mmol/24 hours. The mean increase in serum sodium was 4,9 ± 3,8 mmol/l, in the retrospective study and 5,5 ± 4,7 mmol/l in the prospective study. To prevent late discovery of hyponatraemia, we carry out serum sodium testing every day on patients with acute brain diseases.

If we do not find the typical syndromes accompanying acute brain disease, CSW and SIADH, we need to look for other causes of hyponatraemia [57]. Hypocorticalism, hypoaldosteronism, polydypsia in chronic alcoholism or iatrogenic, and especially unindicated administration of desmopressin all appeared in our study. In these cases we also find renal function parameters useful, especially EWC [16].

Patient numbers with extreme hyponatraemia with serum sodium levels below 130 mmol/l were almost the same in the retrospective (21 %) and prospective (19 %) studies. There were, however, differences in the duration of the dysbalance (106 days in the retrospective study and 66 days in the prospective study. In comparison with this extreme group, other hyponatraemias lasted significantly longer and had more cerebral complications, although with no negative influence on the outcomes of the patients. These results were the same in both studies.

Hypernatraemia

Hypernatraemia occurs less frequently in acute brain disease than hyponatraemia, but is prognostically more serious [1]. It is therefore necessary to pay it greater attention. With regards to its seriousness, it is important not only to timely and accurately diagnose the dysbalance but also precisely set target serum sodium values to be achieved. All hypernatraemias with hyperosmolality cause hypertonicity ECT to shift water from the brain cells to ECT, thereby leading a decrease of intracranial pressure.

Typical hypernatraemia connected to acute brain disease is known as central diabetes insipidus [66]. Nowadays, however, it is not a frequent hypernatraemia in neurointensive care [6]. In our 10-year study we only had 24 patients with cDI, 8 of whom were in the retrospective study. More were in the prospective study, also with higher mortality (75% to 25%), which was related to the introduction of two beds with ventilation in our NNICU in 2003.

In none of our patients did we observe the illness' three-phase process as described in literature [8], in our view because of precise doses of desmopressin according to hourly diuresis, specific gravity of urine and osmolality of urine, and especially due to EWC. The antidiuretic phase, following the diuretic phase, is less down to release of previously synthesized ADH as to degenerating hypofysis, casused by continuing regular desmopressin therapy.

Central diabetes insipidus generally arises from pressure built up around the hypofysis and hypothalamus. It can be in local lesions, for example adenoms, base skull fractures etc, or in diffuse brain lesions with intracranial hypertension which are so large that they cause pressure in this area [8]. Antioedematic therapy is used to lower intracranial pressure in patients with severly worsening brain damage. In these cases, when we prescribe hypertonic saline, daily sodium intake persists during the onset of cDI, then EWC is diagnostically beneficial. In our evaluation, renal function parameters differed significantly between cDI and "non cDI" groups in EWC ($p < 0,001$), C_H_2O ($p < 0,001$) a FE_H_2O ($p < 0,001$).

This dysnatraemia has one advantage compared to others, in that casual desmopressin therapy is available. In neurointensive care we prefer intravenous administration to nasal, as it is more exact. Nowadays Octostim is only available by extraordinary import.

In neurointensive care the most frequently occurring hypernatraemia is not cDI but that with multifactorial causes [6]. For simplification and better orientation in this field we have termed these hypernatraemias "non cDI." This name has also been accepted in daily clinical practice. There were 59 patients in this group in the retrospective study, and 118 patients in the prospective study, a considerably higher number. Five patients had both types of hypernatraemia.

Aiyagari Venkatesh [6] wrote of the higher incidence of renal failure in hypernatraemia in his studies. In our study, there was one patient in the retrospective study and 20 in the prospective study with this illness.

Antioedematic therapy is a frequent cause of the onset of "non cDI" hypernatraemia. During the 10-year study, this therapy changed considerably. In the retrospective study, mannitol was ususally given (81 % pts), whereas in the prospective study only 39 % of patients received it. In this period we started using hypertonic saline. This change had an influence, in that there was no difference in daily intake of sodium between cDI and "non cDI" groups.

Comparing cDI and "non cDI" by outcome, there were no significant changes in mean value in GOS ($p = 0,079$), but NNICU mortality was higher in cDI ($p = 0,012$).

Hypernatraemias with serum sodim above 156 mmol/l and 160 mmol/l were more serious in both parts of the study. These extreme hypernatraemias, in comparison with others, had significantly lower GOS and higher NNICU mortality, but differences between the two extreme groups were not found.

Natriuretic peptides are mostly used in cardiology, where their usefulness as biochemical markers of heart failure [31] and prognostic significance [32] are well known. Assesment of these NP in neurointensive care lags behind cardiologists, although studies have been published on the relationship between natriuretic peptides and acute brain diseases [33-36], especially in hyponatraemia with natriuresis in CSW [33, 34].

The cause of raised natriuretic peptide levels in brain disease is still unclear, but both cerebral and cardiac ethiology are under consideration. It is thought that the origin could be related to the heart because the expression of these peptides is far higher in the myocardium than the brain [35] and because the concentration of natriuretic peptides is higher in serum than in cerebrospinal fluid.

The possible influence of hypervolaemia or a neurogennic lung oedema in SAH has also been considered. When intracranial pressure is raised, the patient's ANP and BNP serum levels also rise, which leads to the logical assumption that raising natriuretic peptides constitutes an adaptational response to raised intracranial pressure and brain oedema [35].

In our collection, we found patients with CSW to have significantly higher NT-proBNP levels compared not only to the reference range ($p = 0,001$), but also to the control group ($p < 0,001$). There were no differences in fluid intake ($p = 0,440$) between the two groups, but there were in sodium intake per kg body weight ($p = 0,024$) and diuresis ($p = 0,019$). Patients with CSW had high daily sodium output ($p = 0,036$), C_El ($p = 0,001$) and C_Na^+ ($p = 0,007$). Our results showed that natriuresis with hypoosmolal hyponatraemia in CSW was related to high serum levels of NT-proBNP. Further analysis of the control group did not show any relationship between NT-proBNP and measured parameters, in contrast to CSW, where we found a negative relation between NT-proBNP and serum sodium, C_Osm, C_El and fluid intake. Only patients with NYHA I. and physiological renal parameters were assessed in our study in order to preclude possible influence by high levels of NT-proBNP. We tried to obtain precise NYHA classification evaluations. We made use of results from cardiological, medical and anaesthesiological examinations. No patient with CSW had pulmonary oedema.

However, significantly high serum levels of NT-proBNP compared to the reference value were found in normoosmolal hyponatraemia and also in the control group, i.e. in patients with acute brain disease, normonatraemia, serum normoosmolality and without heart disease with NYHA I. From these results we can deduce that the spectrum of causes of NP is much more complex. On the basis of studies published until now and regarding the presence of BNP in the brain [30], we suppose that acute brain disease could be another field of its use. In this way neurointensive care can become another possible area for research of NT-proBNP as a prognostic marker and thereby broaden the perspectives of its function.

1. Dysbalances of effective osmolality are some of the most frequent and serious complications in neurointensive care. It is necessary to pay attention to and actively search for them. Daily monitoring of serum sodium should be part of the daily care of every patient with acute brain disease.

2. Hyponatraemia is more common than hypernatraemia, but hypernatraemia is prognostically worse.

3. Hyponatraemia with low effective osmolality is not a frequent type of hyponatraemia in neurointensive care. The prevalent hyponatraemia had serum osmolality within the reference range.

4. Typical hypoosmolal hyponatraemia in acute brain disease is cerebral salt wasting (CSW) syndrome, in contrast to syndrome of inappropriate secretion of antidiuretic hormone (SIADH), which was not found in our ten-year study. Hypoosmolal hyponatraemia can also arise from other reasons, for example due to iatrogenic causes.

5. In neurointensive care central diabetes insipidus (cDI) is not the most common type of hypernatraemia. Most hypernatraemias have multifactorial causes (due to antieoedematic therapy, renal failure). In daily clinical practice the term "non cDI' is useful to describe these hypernatraemias remaining after separating cDI.

6. Timely and accurate diagnosis of dysnatraemia in acute brain diseases is due to the seriousness essential. Nowadays this is easily achieved through measuring and calculating renal function parameters, which had the further advantage of being accessible in daily clinical practice. The most important parameter is electrolyte free water clearance (EWC).

7. In our experience it is possible to carry out differential diagnostics of hyponatraemia only when measured and calculated renal function parameters are available, in contrast to hypernatraemia, where complete cDI can be diagnosed without these parameters.

8. Implementation of renal function parameters in clinical practice ought to be carried out in all places where patients with acute brain diseases are treated.

9. In order to prevent the onset of pontine and extrapontine myelinolysis, the recommendations for the proper correction of natraemia must be kept, i.e. do not exceed the planned target levels of serum sodium. We consider 6 hours to be the minimal interval for checking the serum sodium levels.

10. Natriuresis with hypoosmolal hyponatraemia in CSW was related to high serum levels of NT-proBNP.

11. The assessment of NT-proBNP in the brain and the finding of raised NT-proBNP values in patients with acute brain disease and normonatraemia in neurointensive care could be the subject for further research.

Summary

Introduction: Dysbalances of effective osmolality are some of the most frequent and serious complications in neurointensive care. Their severity lies in brain oedema in hyponatraemia and dehydration of the brain in hypernatraemia. Due to the seriousness of dysnatraemia in acute brain diseases, timely and accurate diagnosis is necessary. Nowadays this is easily achieved through measuring and calculating renal function parameters.
The aims of this study were 1) evaluation of hyponatraemia and hypernatraemia in acute brain diseases after establishing these renal parameters into clinical practice in our NNICU and 2) determining the significance of NT-proBNP in differential diagnostics of hyponatraemia.

Methods: Over a ten-year period, in a retrospective (1.1.1996 – 31.12.2000) and a prospective study (1.1.2001 – 31.12.2005) we evaluated all patients hospitalised in our NNICU with acute brain diseases, who had serum sodium below 135 mmol/l (collection hyponatraemia) or above 150 mmol/l (collection hypernatraemia). The prospective part took place according to standard protocol for diagnosing hyponatraemia and hypernatraemia in the NNICU, which includes the measuring and calculating of renal function parameters. In the prospective study, assesment of NT-proBNP was carried out on 40 patients with hyponatraemia. The control group consisted of 20 patients with acute brain disease and normonatraemia.

Results:

Table 1. Overview of dysnatraemias in patients with acute brain diseases.

		Retrospective study	Prospective study
Dysnatraemia	pts	326 (100,0%)	378 (100%)
Hyponatraemia	pts	251 (77%)	245 (65%)
Hypernatraemia	pts	75 (23%)	133 (35%)
Hyponatraemia	pts		
Hypoosmolal	pts	50	55
Normoosmolal	pts	154	184
Hyperosmolal	pts	38	45
CSW	pts	25	26
SIADH	pts	0	0
cDI	pts	8	16
Non cDI	pts	59	118

CSW - cerebral salt wasting, SIADH - syndrome of inappropriate secretion of antidiuretic hormone, cDI - central diabetes insipidus, non cDI - hypernatraemia non central diabetes insipidus, NB. Not all natraemias had measured serum osmolality, and some patients had more types of dysnatraemia during stay in NNICU.

Table 2. Serum levels of NT-proBNP in CSW and normonatraemia in patients with acute brain diseases and NYHA I.

Parameter		CSW	Normonatraemia	p-value
NT-proBNP	pg/ml	430,4 ± 706,4	268,3 ± 203,9	< 0,001

Mean ± standard deviation.

Conclusion: Measured and calculated renal function parameters represent an easy and accessible method in differential diagnostics of hyponatraemia and hypernatraemia in patients in neurointensive care. Differential diagnostics of hyponatraemia cannot be carried out without them, whereas in hypernatraemia where there is complete cDI it is possible. Due to the seriousness of dysnatraemia in acute brain diseases, their implementation in clinical practice ought to be a matter of course in all places where patients with acute brain diseases are treated. Natriuresis with hypoosmolal hyponatraemia in CSW was related to high serum levels of NT-proBNP.

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