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Hyponatraemic encephalopathy

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The most important clinical feature of hyponatraemia is its effect on the central nervous system. It is crucial to be familiar with the pathophysiological concepts of hypotonic stress and the various defence mechanisms against it. In many cases, the signs and symptoms associated with hyponatraemia are mild and will go undiscovered by both physician and patient. In some situations, however, the complications are severe and may lead to irreversible damage to the brain. The time course as well as the magnitude of the decline of sodium levels determine the severity of symptoms. Development of hyponatraemia within less than 48 h is called acute hyponatraemia and is associated with a more severe clinical picture while chronic hyponatraemia is often less dramatic. In this chapter, the acute and chronic changes and perturbations of the central nervous system in hyponatraemia as well as their clinical presentation – summarized as hyponatraemic encephalopathy – will be reviewed.

Historical introduction

The link between hyponatraemia and brain dysfunction can be traced back to the early 20th century. In 1921, Miller and Williams reported on the effect of the enteral administration of 5–10L of water in patients with hypertension. Some of these patients developed headache, dizziness and cramps as consequence of iatrogenic water intoxication [1]. After suppressing urinary output in patients suffering from diabetes insipidus using pituitary extract, Weir and colleagues found that, while the patients continued to ingest large amounts of water, they complained about headache, nausea and vomiting. Seeking further insight, the researchers induced water intoxication in animals and observed even more severe complications including seizures, coma, and death [2]. In subsequent animal studies in which large amounts of distilled water were rapidly administered to induce water overload, Rowntree discovered an increase of intracranial pressure secondary to the development of cerebral oedema [3]. The accompanying symptoms comprised restlessness, lethargy, polyuria, diarrhoea, salivation, nausea, retching, vomiting, muscle twitching, seizures, coma and death. For the first time, he was also able to show that intravenous administration of salt solutions cured the symptoms. Over the following years, it became clear that a marked decrease of serum chloride – assessment of sodium was technically not feasible at the time – was consistently found in all studies [4]. In 1938, a first report on a patient with severe water intoxication after receiving large amounts of tap water for proctolysis who was successfully rescued by infusion of hypertonic saline was published [5]. With an expanding

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research landscape and the advent of flame photometers that allowed for accurate measurement of serum sodium, the link between severe brain damage and hyponatraemia was soon confirmed, not only in water intoxication but also in other circumstances leading to extracellular hypoosmolality [6–12]. The main interest until the late 1970s remained to be on acute overhydration leading to severe and potentially detrimental neurological sequelae. However, one of the few phenotypic descriptions of less severe slow-developing hyponatraemia was already provided in 1936 by McCance et al. [13]. In a series of *heroic* experiments, the researchers induced hyponatraemia in themselves over a period of several days by applying heat baths, a low-salt diet and constant water loading. They experienced loss of taste, nausea, abdominal discomfort, fatigue, exhaustion and muscle cramping. Nightmares were reported and one participant noted profound mental slowing and apathy. In the seminal paper by Schwartz and Bartter introducing the syndrome of inappropriate antidiuresis (SIAD), two patients with bronchial carcinoma were characterized; one was described as grossly asymptomatic despite serum sodium between 103 and 114 mmol/L; the other showed unspecific and long-standing symptoms including anorexia, weakness, and fatigability with reported sodium levels between 105 and 116 [14]. Notwithstanding, until the 1970s, neurological descriptions in hyponatraemia were largely anecdotal and qualitative. Arieff and co-workers were among the first to systematically characterize the neurological consequences of patients with acute and chronic hyponatraemia. They examined 65 hospitalized patients with a serum sodium $\leq$ 128 mmol/L [12]. Fourteen of the patients experienced acute hyponatraemia, defined as a documented sodium drop from normal range-values within 12 h, the mean serum sodium in this group was 112 mmol/L. All patients were at least stuporous, five were comatose, and four had seizures. Treatment strategies included hypertonic saline, fluid restriction, and no active treatment. In total, seven patients died while those who survived were discharged without neurological sequelae. The remainder of the cohort was believed to suffer from chronic hyponatraemia (i.e. development in $>$ 3d). However, two distinct populations were identified: one consisting of 24 patients with mean serum sodium of 115 mmol/L that presented with symptoms and one consisting of 27 patients with mean serum sodium of 122 mmol/L that were asymptomatic. Notably, in the symptomatic group, two exhibited seizures, 11 were lethargic and 3 were comatose – confirming that severe symptoms may occur in chronic hyponatraemia, too. Given the higher overall incidence of chronic hyponatraemia (approximately 96 % according to a recent publication [15]) and the obviously more varied clinical presentation, the research focus shifted to this entity. The finding that cerebral oedema was reversed and brain volume restored with more gradual forms of hyponatraemia largely fostered the scientific activity in the field and led to a deeper understanding of the changes on a molecular level. The advent of standardized scales (e.g., Glasgow Coma Scale [GCS]), electroencephalographic (EEG) monitoring, and advanced imaging techniques initially helped to quantify severe encephalopathy but lacked sensitivity for subtle deficits. It was not until the 1990s that more refined assessments entered the stage and facilitated an accurate exploration of the extremely wide spectrum of signs and symptoms of chronic hyponatraemia.

Pathophysiology

In most instances, hyponatraemia indicates a state of true hypoosmolality. It is mainly (and probably exclusively) this decrease of extracellular osmolality that is responsible for the development of neurological manifestations in acute hyponatraemia. In a classic experiment, rats were rendered hyponatraemic by dilution with distilled water (hypotonic) or by dialysis using a mannitol solution (isotonic). While the rats with acute hypotonic hyponatraemia exhibited severe neurological symptoms including seizures and coma, the animals with isotonic hyponatraemia were only mildly lethargic or even asymptomatic [16]. Since extra- and intracellular osmolalities must be equal, hyponatraemia leads to a water influx into cells. This happens throughout the body, but the brain is exceptionally vulnerable to this process due to its confines within the skull [17]. In case of hyperacute development of hyponatraemia within less than approximately 12 h, the water influx will lead to cerebral oedema and ultimately fatal transtentorial or central herniation [17]. However, this process is not only a passive movement of water. Adaptive mechanisms in the brain are set in operation already minutes after onset of hyponatraemia modulating the brain's biochemical composition. Hence, the clinical presentation is determined by volume changes early in the development whereas, as time progresses, alterations in the brain content of mediators are predominantly responsible. This adaptation is believed to be fully in place after 2 days. Therefore, by convention, the borderline between acute and chronic hyponatraemia has been set to 48 h [18,19].

In contrast to the systemic capillary system, sodium cannot equilibrate freely with the interstitial fluid in the brain due to the blood-brain-barrier (BBB). The BBB consists of a specialized endothelial layer which is sealed by tight junctions, a basal membrane, pericytes, and an outer lining of astrocytic foot processes. Water movement across the BBB is facilitated through Aquaporin (AQP)4 channels in endothelial and astrocyte membranes [17]. Thus, hyponatraemia will initially lead to a water influx into the brain. In an AQP4-knockout mouse model, the extent of brain oedema was markedly reduced after acute water loading confirming that AQP4 represents the predominant route [20]. Following the entry of water into the brain, the drop of osmolality in the extracellular space will then lead to a water shift into the cells. In vitro, cerebral cell lines have been shown to increase in size by up to 40 % to even 100 % if challenged with a hypotonic surrounding [21,22]. Whether this degree of cellular swelling is likely to occur in vivo must be doubted. However, given that the brain can expand by only about 5 % within the rigid confines of the skull, these findings highlight the potentially fatal danger to which the brain is exposed. Hence, without prompt and highly-effective countermeasures, even small disturbances in water and solute homeostasis – let alone extreme pathological conditions like water intoxication – would be immediately detrimental.

The first defence line is thought to be loss of excess interstitial fluid into the cerebrospinal fluid (CSF) compartment and subsequently the systemic circulation driven by hydrostatic forces as the intracranial pressure rises [23,24]. This leads to an initial reduction in total brain volume but cannot prevent or reverse intracellular oedema. Cell volume control is a pivotal prerequisite for survival of any living creature and is orchestrated by evolutionary highly-conserved mechanisms [25]. The most obvious consequence

of cell swelling that must be prevented is rupturing of the cell membrane leading to cell death. Furthermore, the ensuing cytosolic hypoosmolality accompanied by volume increase has been shown to impair enzyme function, protein-folding, transport mechanisms etc. [26].

Neurons themselves have no or only few AQP4-channels which makes them more resistant to osmotic water shifts per se; instead, water influx can only occur by diffusion or non-aquaporin water channels at a much slower rate [27]. With the exception of a small population of osmosensitive neurons in the hypothalamus, neurons in vivo apparently do not change their volume when faced with osmotic challenges [27,28]. Instead, glia cells, mainly astrocytes, act as their bodyguards. By virtue of an abundance of AQP4-channels, they soak up all of the water. According to the Monro–Kellie doctrine which posits that the composite volume of intracerebral blood, CSF, and brain tissue must be constant [29], an increase in astrocyte volume (i.e., brain tissue) will inevitably lead to a reduction in blood volume and CSF volume which will compromise brain perfusion. In line with this notion, an invariable increase in brain water content was observed in a water intoxication dog model. Applying magnetic resonance imaging (MRI) techniques, the authors concluded that development of cerebral oedema is a two-phasic process; an early osmotic intracellular oedema is followed by an ischemic oedema secondary to a progressively decreasing perfusion pressure which heralds imminent herniation and death [30]. As the astrocytes swell and water is lost into the CSF, the extracellular compartment is reduced and the concentrations of extracellular components like potassium, glutamate, γ-aminobutyric acid (GABA) and other released transmitters are increased [31]. Intrinsic electrophysiological properties of neurons and glia cells are also altered. Together, this explains the markedly heightened excitability and the occurrence of seizures in acute hyponatraemia. This is supported by the finding that furosemide – by blocking chloride channels – inhibits reduction of extracellular space and effectively blocks epileptic activity [32]. Of note, essential cellular properties including resting membrane potential, action potential threshold and action potential duration are preserved in hypoosmolality [33].

Experimental work from the 1980s revealed that the increase of measured total brain water in animal models of acute hyponatraemia is only about 40 % of what would be expected if the cells behaved as perfect osmometers [34]. Hydrostatically driven fluid loss from the extracellular space alone, however, cannot solely account for this phenomenon since the volume fraction of the extracellular space is only approximately 20 % [35]. Hence, it became clear that other homeostatic mechanisms must be involved. Regulatory volume decrease (RVD) denominates a collection of several mechanisms immanent to osmosensitive cells that lead to effective water extrusion in order to restore normal cell volume. They all share the principle of water following osmotically active molecules that are expelled from the intracellular compartment. Almost instantly after commencement of cell swelling, astrocytes lose potassium through ion channels (mainly Kir4.1 [36] and TWIK-1, TREK-1 [37]) and chloride through so-called volume-regulated anion channels (VRAC) [16,38–40] as well as potassium-chloride co-transporters [41] together with osmotically obligated water. Subsequently, fluid (and solute) loss from the brain and, thus, reduction or at least limitation of cerebral oedema is achieved by removal either through capillary vessels or the CSF [34]. A significant total loss of brain potassium (from the intracellular compartment), sodium (from the extracellular compartment), and chloride (from both compartments) has been shown to occur over the first few hours after induction of severe acute hyponatraemia reaching a plateau after 3–6 h [16,34]. The net brain loss of all electrolytes is in the range of approximately 15 % (for potassium) to 25 % (for chloride) apparently irrespective of the degree of hyponatraemia [34,42,43]. Under physiological circumstances, tight control of extracellular potassium is instrumental in the context of cognitive processes like learning and building memory [44]. Moreover, progressive loss of potassium would inevitably impair resting membrane potential. This probably explains why the electrolyte depletion is limited. Therefore, once the capacity of brain electrolyte loss is exhausted, other osmotically active particles must become active. These organic osmolytes were soon identified as a heterogenic group consisting of amino acids (taurine [actually an amino sulfonic acid], glutamine, glutamate, N-acetyl-aspartate, aspartate, glycine), the amino acid derivatives betaine and creatine, polyalcohols (myo-inositol, sorbitol), glycerophosphorylcholine, GABA, and methylamines [45–49]. Animal models of chronic hyponatraemia have shown that both electrolyte and organic osmolyte brain loss is sustained until hyponatraemia itself abates. In recent years, it became evident that some if not most of the organic osmolytes, in particular amino acids and GABA, are shuttled out of the cell through VRACs – in parallel to chloride. To date, it is still incompletely understood how cell volume expansion is sensed and processed to induce the individual channels' activity. Lately, with-no-lysine-kinase 1 (WNK1) has been proposed as a major switch to control both, regulatory volume increase which is seen in hyperosmotic states and regulatory volume decrease [50]. Extrusion of organic osmolytes is slower than electrolyte mobilization, starts hours after the onset of hyponatraemia and takes about 24–48 h to be at full capacity [17,18,43,48,51,52]. Why and how the described mechanisms of immediate electrolyte efflux and delayed organic osmolyte efflux are orchestrated in this sequential manner remains elusive. Most likely, organic osmolytes or their precursors are primarily bound in membranes or are metabolically engaged and must be liberated, degraded or synthesised to provide sufficient supply for the extrusion machinery [53,54]. The individual contribution of loss of electrolytes and organic osmolytes has been estimated to be approximately 70 % and 30 %, respectively [48]. In particular, the efflux of taurine and myo-inositol seems to be constantly high even after the decrease of potassium and other organic osmolytes has settled [55,56].

While it is accepted that the most-severe symptoms (i.e., coma) in acute hyponatraemia are elicited by the high intracranial pressure, most of the less severe and often unspecific symptoms are most likely due to the disruption of the "milieu intérieur" depicted above. Extracellular increase in the concentration of transmitters like glutamate or potassium together with other changes in the electrical set-up of cells might also explain the hyperexcitability eventually eliciting epileptic seizures [31,33,57]. During adaptation, marked efflux of organic osmolytes might keep up the high concentration of extracellular transmitters despite the vanishing concentrating effect as brain cell volume is restored and despite a total loss from the brain. Together, these alterations can well explain the occurrence of seizures and other severe symptoms even in chronic hyponatraemia but may also provide an explanation for less severe symptoms: increased extracellular glutamate has been described in the hippocampus of rats with moderate

chronic hyponatraemia which display gait instability and memory deficits [58]. Furthermore, a significant role for taurine, glycine and potassium in cognitive performance and learning has been established, thus, their alteration might contribute to some of the clinical signs and symptoms observed in patients with chronic hyponatraemia [44,59].

Clinical picture of hyponatraemic encephalopathy

The effects of hyponatraemia on the central nervous system are collectively referred to as hyponatraemic encephalopathy (HNE). The clinical manifestations of HNE cover a wide clinical spectrum from subtle and barely noticeable changes in general health [60] to severe symptoms reflecting an increased intracranial pressure with potentially detrimental outcome. Failure to recognize or treat this condition in time is associated with high morbidity and mortality [61,62]. It must be taken into account that many underlying conditions that are responsible for the development of hyponatraemia can produce a clinical picture of encephalopathy themselves making it difficult to identify the genuine cause of the symptoms. Hepatic encephalopathy in liver cirrhosis, hypovolemia-associated cerebral hypoperfusion or brain tumours are only some examples in this respect. In general, acute hyponatraemia is associated with more severe symptoms (i.e., acute HNE) while chronic hyponatraemia usually presents with mild or moderate symptoms (i.e., chronic HNE). However, a considerable overlap exists and particularly in chronic hyponatraemia, severe symptoms can be observed. A summary of symptoms of hyponatraemia can be found in Table 1, information on prospective trials using assessment tools is gathered in Table 2.

Acute hyponatraemic encephalopathy

The European clinical Practice Guideline on diagnosis and treatment of Hyponatraemia (ECPG) [18] considers the following symptoms as severe: vomiting, abnormal and deep somnolence, seizures, GCS $\leq$ 8 and cardiorespiratory distress. Although the latter is not part of the spectrum of HNE in the narrow sense, it is induced by the increase of intracranial pressure in acute hyponatraemia leading to either a neurogenic pulmonary oedema and hypoxia or reduction of respiratory drive via brainstem affection leading to hypercapnia [63,64]. Not surprisingly, severe hyponatraemia is often accompanied by a pathological EEG [65,66]. Initial posterior slowing followed by diffuse delta activity are common but unspecific features [67–69] and certainly cannot inform about whether brain oedema or biochemical alterations are responsible. This information, however, is crucial to the treating physician because it might influence the therapeutic strategy. Urgent conduction of cerebral imaging studies after administration of a first bolus of hypertonic saline in the group of patients with the most dramatic clinical presentation seems therefore sensible. To this end, the widespread use of computed tomography (CT) scans has largely facilitated the confirmation of cerebral oedema [70–72]. Nonetheless, although there is ample evidence that cerebral oedema is the main cause of death in acute hyponatraemia, it must not be overlooked that death might ensue even without manifest oedema. Chen et al. undertook a literature review in 1995 detecting nine published cases of fatal water intoxication in which necropsy was performed - global cerebral oedema was found only in five of these patients [73].

Several predicting factors have been identified to be associated with more severe forms of HNE as well as mortality. *Rapidity of onset:* According to the pathophysiology depicted above, it stands to reason that severe symptoms occur when the decline in serum osmolality outpaces the brain's ability to adapt through electrolyte and osmolyte depletion. While this has been experimentally confirmed in various settings, clinical evidence comes mainly from case reports and small case series [61,74,75]. It is widely accepted that the rapidity of sodium decrease is the most important factor for the development of both severe symptoms and cerebral oedema [17–19] and in most cases, a development of hyponatraemia in less than 12(-24)h has been reported. Water intoxication by consuming large amounts of hypotonic liquid in a short period of time can exceed the excretory capacity of healthy kidneys leading to rapid development of hyponatraemia and represents the classical case of "hyperacute" hyponatraemia. Such conditions are observed in psychotic patients with primary polydipsia [76], after iatrogenic interventions (e.g., preparation for bowel examinations [77]), in the context of dares or water-drinking contests [78], or after drinking large amounts of water to compensate for previous losses. The latter mainly applies to endurance sports and has been well researched in marathon runners [79,80]. Acute and transient increase of vasopressin release - which can often be observed with physical stress (post-surgery, endurance sports, etc.) or as an adverse side effect of various drugs - further promotes development of acute hyponatraemia in the context of inappropriate water intake [81,82]. Also at risk are patients who consume synthetic phenethylamines like 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") for recreational use [83] – of note, recent work by Atila et al. suggest that increased oxytocin rather than vasopressin is the culprit in this circumstance [84]. By interfering with the kidney's capacity to excrete a diluted urine, thiazide diuretics have frequently been described as an underlying cause for dramatic acute hyponatremia [85]. *Severity (magnitude) of hyponatraemia:* The absolute decrement in serum sodium concentration is a key determinant of symptom severity. Clinical manifestations typically become evident when levels fall below 125 mmol/L [86], more severe features like seizures and coma have rarely been observed in patients with sodium above 125 mmol/L and will be more prominent with sodium well below 120 mmol/L [12]. In consequence, reports have been published showing that mortality rises in parallel with the degree of hyponatraemia, both among outpatients [87] and hospitalized patients [88.] However, some retrospective analyses suggest that mortality decreases with sodium levels falling below 120 mmol/L, most likely due to more aggressive treatment and increased awareness per se [89,90]. *Age:* Children and adolescents of both sexes are particularly vulnerable to severe forms of HNE [62]. Owing to the higher size ratio between the brain and cranial vault, the brain has a markedly reduced capacity to accommodate oedema. Even modest increases in cerebral water content therefore translate into a disproportionate rise in intracranial pressure compared with adults. A normal adult brain-skull-ratio is usually reached by the age of 16 years. In reverse, with higher age, cerebral involution occurs which might provide some protection from a too rapid rise of

Table 1
Selected symptoms of or related to hyponatraemic encephalopathy in observational reports on hyponatraemia (list not exhaustive).

Symptom	Population / setting	Acute HN	Chronic HN	not specified	Reference
		Serum sodium [mmol/L], median (IQR) ***or*** mean + /- SD ***or*** range xx - yy			
Weakness / generalized weakness / lethargy / apathy	Hospitalized patients with HN n = 65		122 + /- 4		Arieff [12]
	Postoperative HN with Na^+ ≤128 mmol/L in pre-menopausal women, n = 65	m: 110 + /- 2 f: 113 + /- 1, 91–128			Ayus [91]
	Chronic HN (Na^+ < 130 mmol/L) in post-menopausal women, n = 53		f:111 + /- 12		Ayus [109]
	Emergency admissions with Na^+ ≤120 mmol/L, n = 168			117 (114, 119) 97–120	Arampatzis [110]
	Emergency admissions with Na^+ < 125 mmol/L, n = 298			120 (116, 123)	Nigro [15]
	Emergency admissions with Na^+ < 125 mmol/L, n = 261			120 (116, 122)	Bokemeyer [111]
	Emergency admissions with Na^+ ≤125 mmol/L and primary polydipsia, n = 23			121 (114, 123)	Sailer [112]
Seizures	Hospitalized patients with HN n = 65	112 + /- 2	115 + /- 4		Arieff [12]
	Patients with TAH, n = 7			98–109	Ashraf [113]
	Postoperative HN with Na^+ ≤128 mmol/L in pre-menopausal women, n = 65	m: 110 + /- 2 f: 113 + /- 1, 91–128			Ayus [91]
	Na^+ ≤120 mmol/L on admission			115 + /- 5 94–120	Ellis [114]
	Chronic HN (Na^+ < 130 mmol/L) in post-menopausal women, n = 53		f:111 + /- 12		Ayus [109]
	Hospitalized patients with Na^+ < 125 mmol/L, n = 363			104–122	Halawa [115]
	Emergency admissions with Na^+ < 125 mmol/L, n = 298			120 (116, 123)	Nigro [15]
	Emergency admissions with Na^+ < 125 mmol/L, n = 261			120 (116, 122)	Bokemeyer [111]
	Emergency admissions with Na^+ ≤125 mmol/L and primary polydipsia, n = 23			121 (114, 123)	Sailer [112]
Nausea / vomiting	Postoperative HN with Na^+ ≤128 mmol/L in pre-menopausal women, n = 65	m: 110 + /- 2 f: 113 + /- 1, 91–128			Ayus [91]
	Post-Marathon, n = 7 all patients had brain oedema	121 + /- 3 117–127			Ayus [109]
	Emergency admissions with Na^+ ≤120 mmol/L, n = 168			117 (114, 119) 97–120	Arampatzis [110]
	Emergency admissions with Na^+ < 125 mmol/L, n = 298			120 (116, 123)	Nigro [15]
	Emergency admissions with Na^+ < 125 mmol/L, n = 261			120 (116, 122)	Bokemeyer [111]
	Emergency admissions with Na^+ ≤125 mmol/L and primary polydipsia, n = 23			121 (114, 123)	Sailer [112]
Gait disturbance / unsteadiness / ataxia Falls	Patients with chronic HN, Na^+ between 115 and 132 mmol/L, n = 122		126 + /- 5		Renneboog [60]
	Emergency admissions with Na^+ ≤120 mmol/L, n = 168			117 (114, 119) 97–120	Arampatzis [110]
	Emergency admissions with Na^+ < 125 mmol/L, n = 298			120 (116, 123)	Nigro [15]
	Emergency admissions with Na^+ < 125 mmol/L, n = 261			120 (116, 122)	Bokemeyer [111] Sailer [112]

(*continued on next page*)

Table 1 (*continued*)

Symptom	Population / setting	Acute HN	Chronic HN	not specified	Reference
	Emergency admissions with Na^+ ≤125 mmol/L and primary polydipsia, n = 23			121 (114, 123)	
	Patients with epilepsy taking carbamazepine or oxcarbazepine, n = 688			129 + /- 4	Berghuis [116]
Altered consciousness / obtundation / confusion / stupor	Hospitalized patients with HN, n = 65	112 + /- 2	115 + /- 4		Arieff [12]
	Patients with TAH, n = 7		103–116		Ashraf [113]
	Hospitalized patients with Na^+ < 125 mmol/L, n = 363			104–114	Halawa [115]
	Emergency admissions with Na^+ < 125 mmol/L, n = 261			120 (116, 122)	Bokemeyer [111]
Coma	Hospitalized patients with HN n = 65	112 + /- 2	115 + /- 4		Arieff [12]
	Patients with TAH, n = 7		98–104		Ashraf [113]
	Postoperative HN with Na^+ ≤128 mmol/L in pre-menopausal women, n = 65	m: 110 + /- 2 f: 113 + /- 1, 91–128			Ayus [91]
Headache / dizziness	Postoperative HN with Na^+ ≤128 mmol/L in pre-menopausal women, n = 65	m: 110 + /- 2 f: 113 + /- 1, 91–128			Ayus [91]
	Emergency admissions with Na^+ < 125 mmol/L, n = 261			120 (116, 122)	Bokemeyer [111]
	Emergency admissions with Na^+ ≤125 mmol/L and primary polydipsia, n = 23			121 (114, 123)	Sailer [112]
	Patients with epilepsy taking carbamazepine or oxcarbazepine, n = 688			129 + /- 4	Berghuis [116]
Behavioural change / agitation / irritability	Emergency admissions with Na^+ ≤120 mmol/L, n = 168			117 (114, 119) 97–120	Arampatzis [110]
	Emergency admissions with Na^+ < 125 mmol/L, n = 298			120 (116, 123)	Nigro [15]
	Patients with epilepsy taking carbamazepine or oxcarbazepine, n = 688			129 + /- 4	Berghuis [116]
Attention / cognitive deficits	Patients with epilepsy taking carbamazepine or oxcarbazepine, n = 688			129 + /- 4	Berghuis [116]
Respiratory arrest	Postoperative HN with Na^+ ≤128 mmol/L in pre-menopausal women, n = 65	m: 110 + /- 2 f: 113 + /- 1, 91–128			Ayus [91]
Non-cardiogenic pulmonary oedema	Postoperative patients with HNE, n = 40	114 + /- 7 100–127			Ayus [64]
	Post-Marathon, n = 7 all patients had brain oedema	121 + /- 3 117–127			Ayus [72]
Hypercapnic respiratory failure	Postoperative patients with HNE, n = 40	113 + /- 8			Ayus [64]

HN, Hyponatraemia; HNE, hyponatraemic encephalopathy; m, male; f, female
IQR, Interquartile range; SD, standard deviation

intracranial pressure. *Gender:* Female sex has consistently been identified as a major risk factor for the development of irreversible brain injury or death [91]. Women of reproductive age are particularly susceptible. Experimental studies suggest that oestrogen and possibly vasopressin contribute to this susceptibility by reducing cerebral blood flow [92]. Furthermore, cerebral adaptation to hyponatraemia is inhibited by oestrogen, whereas androgens enhance the adaptive response in animal models [93,94]. *Hypoxia:* Oxygen deficiency represents another risk factor for adverse outcomes in patients with HNE [95]. The precise mechanisms are not fully understood but experimental data indicate that hypoxia markedly reduces the brain's capacity to adapt to osmotic stress. In animal studies, cerebral blood flow was shown to decrease by more than 50 % under hypoxic conditions [96]. This combination of impaired adaptation and compromised perfusion likely explains the higher mortality associated with HNE in the presence of hypoxemia.

Table 2
Prospective studies on chronic asymptomatic/oligosymptomatic hyponatremia using standardized assessments, with or without controls (list not exhaustive).

Trial	Number of patients	Reference group	Baseline (mean or median) Serum Sodium [mmol/L]	Mean or median Serum Sodium after treatment [mmol/L]	Assessments		Results	
					Attention, Cognition, Mood	Motor performance/ Gait	Attention, Cognition, Mood	Motor performance/ Gait
Renneboog [60]	16	yes	128 + /- 3	138 + /- 2	Visual Vigilance, Working Memory or Digit Span, Go/No Go, Intermodal Comparison, Divided Attention (two tests), Phasic Alert (series 2–3, series 1–4)	Gait analysis with a calibrated platform: TTW after displacement of center of pressure (i.e., center of gravity)	Five of eight tests affected by hyponatraemia. Prolonged latency during hyponatraemia (mean response latency +58 ms)	Greater TTW during hyponatraemia (1336 +/- 320 mm vs. 1047 +/−172 mm)
SALT1 + SALT2 [101]	205 (SALT 1); 243 (SALT 2)	yes	SALT 1: 128.5 + / −4.5 SALT 2: 129 + /- 3.5	SALT 1: 135.7 + /−5.0 SALT 2: 135.9 + /- 5.9	Physical Component Summary and Mental Component Summary of the Medical Outcomes Study 12-item Short-Form (SF−12) General Health Survey	Not tested	SF−12 Mental Component: Improvement in the tolvaptan group in the combined analysis (P = 0.02) and in SALT−1 (P = 0.04), not in SALT−2 (P = 0.14). Higher Scores for the Mental Component Summary in the combined subgroup of patients with marked hyponatraemia (P = 0.04). SF−12 Physical Component: no significant changes	Not tested
Gosch [117]	129	yes	128 + /- 3.2	139.35 + /−2.5	ADL (Barthel), MMSE, CDT, Geriatric depression scale	TPOMA, TUG	Lower ADL and MMSE scores in hyponatraemic patients compared to reference group (69.26 +/- 20.52 vs. 87.56 +/- 13.08 [p < 0.001]; MMSE: 26.05 +/- 3.64 vs. 27.18 +/- 3.15 points; [p = 0.003]). Poorer results in CC in hyponatraemic patients (2.44 +/- 3.13, vs. 1.17 +/- 2.52 points in the reference group). GDS: Higher number of patients expressing Symptoms of depression in hyponatraemia group (34 vs. 15 [p = 0.003])	TPOMA score: 15.9 + /- 5.86 (hyponatraemia) vs. 19.2 + /- 4.23 (reference group [p < 0.001]); TUG: 53.73 + /- 43.15 s (hyponatraemia) vs. 21.3 + /- 7.99 s in the control group (p < 0.001)
Ahluwalia [118]	24	no	126 ± 2	132 ± 3	MMSE, HRQOL and CLDQ questionnaires, NCT (A/B), DST, BDT, LTT e/t, SDT, PHES, MRI (n = 14)	Not tested	Improvements after resolution of hyponatraemia: NCT-A: 64 ± 20–60 ± 14, NCT-B: 243 ± 123–194 ± 98, DST: 30 ± 10–41 ± 9, LTTt: 190 ± 31–179 ± 28, LTTe: 64 ± 59–55 ± 35, SDT: 133 ± 52–118 ± 60, ICT lures: 12 ± 6–11 ± 4, target %: 62 ± 24–85 ± 20; p < 0.05 for all but lures/NCT-A/LTTt. MRI (Tolvaptan group): Reduction in brain volumes (TBV and WMV)	Not tested

(*continued on next page*)

Table 2 (*continued*)

Trial	Number of patients	Reference group	Baseline (mean or median) Serum Sodium [mmol/L]	Mean or median Serum Sodium after treatment [mmol/L]	Assessments		Results	
					Attention, Cognition, Mood	Motor performance/ Gait	Attention, Cognition, Mood	Motor performance/ Gait
Vandergheynst [102]	11 (muscle strength, TUG) and 9 (nerve conduction	no	127.7 +/ 2.5 (muscle strength, TUG) and 121.9 + /- 2.4 (nerve conduction)	136.1 + /- 1.8 (muscle strength, TUG) and 135.5 + /- 3.4 (nerve conduction)	Not tested	GP, ICQ, TUG, NCV of peripheral nerves	Not tested	No changes in hand strength and ICQ; TUG: 14.9 + /- 5.1 s (hyponatraemia) vs. 12.5 + /- 4.7 s (normonatraemia)
Verbalis, INSIGHT-Trial[104]	57	yes	129.4 + /- 3.3	136 (SD not published)	CRT, DV, SRT, numeric working memory, RVP, word recognition, TMT A/B, Immediate/ delayed word recall	Romberg test, MTT, SWAY platform, TUG	No significant changes	MTT: significant improvement ($p = 0.02$) in Tolvaptan group
Refardt [103]	19	yes	128.8 + /- 3.9	133.5 + /- 3.5	Symptoms questionnaire, TAP	Standing exercise (sensor-platform): Romberg, Semi-Tandem stand, Tandem stand	Resolution of hyponatraemia: improvement in the "go/ no-go" evaluation ($p = 0.029$)	No positive effect on neuromuscular performance
Brinkkötter [105]	150	yes	127 (124, 129)	134 (131, 137)	ADL, MMSE, GDS, CDT	TPOMA, TUG, GT, ETS	Treatment of hyponatraemia: improvement of ADL (14.51 ± 18.08 vs. 9.73 ± 15.91 [$p = 0.014$]) and MMSE 1.67 ± 4.31 vs. 0.81 ± 2.17 [$p = 0.007$])	Treatment of hyponatraemia: significant improvement in TPOMA, TUG, GT
Suárez [106]	130	yes	122 (119, 126)	133 (130, 136)	MMSE, DemTect, TMT A/B, BDI	TUG	Treatment of hyponatraemia: amelioration of all test results (medium to large effect sizes [Cohen´s d])	
Suárez [107]	21	no	118.4 + /- 6.1	135.5 + /- 3.5	MMSE, DemTect, TMT A/B, BDI, MRI	TUG	MMSE, DemTect, TMT A/B and BDI: significantly better results after resolution of hyponatraemia (session 2). MRI: reduced GMV, WMV and whole brain volumes, as well as reduced neuronal activity in session 2	TUG: no significant improvement after resolution of hyponatraemia

Abbreviations: ADL: Activities of Daily Living; BDI: Beck's Depression Inventory; BDT: Block Design Test; CDT: Clock Drawing Test; CGA: Comprehensive Geriatric Assessment; CLDQ: Chronic Liver Disease Questionnaire; CRT: Choice Reaction Time; DST: Digit Symbol Test; DV: Digital Vigilance; ETS: Esslinger Transfer Scale; GCS: Glasgow Coma Scale; GDS: Geriatric Depression Scale; GMV: Grey Matter Volume; GT: Grip Test; HRQOL: Health-Related Quality of Life; ICQ: Isometric Contraction of the Quadriceps; ICT: Inhibitory Control Test; LTT e/t: Line Tracing Test errors/time; MMSE: Mini-Mental State Examination; MRI: Magnetic Resonance Imaging; MTT: Morse-Tapping Test; NCT (A/B): Number Connecting Test (A/B); NCV: Nerve Conduction Velocity; PHES: Psychometric Hepatic Encephalopathy Score; RVP: Rapid Visual Information Processing; SALT: Study of Ascending Levels of Tolvaptan in Hyponatremia; SDT: Serial Dotting Test; SRT: Simple Reaction Time; TAP: Test of Attentional Performance; TBV: Total Brain Volume; TMT A/B: Trail Making Test A/B; TPOMA: Tinetti's Performance-Oriented Mobility Assessment; TTW: Total Travelled Way; TUG: Timed Up & Go Test; WMV: White Matter Volume.

Chronic hyponatraemic encephalopathy

While acute hyponatraemia frequently elicits classical neurological symptoms that can be explained by an increased intracranial pressure, the clinical presentation of chronic hyponatraemia - which accounts for approximately 95 % of all cases [15,97] - is often unspecific. The ECPG lists the following symptoms as moderately severe: nausea without vomiting, confusion, and headache. Although these might be early signs of imminent brain oedema, they rarely are and rather represent features of chronic hyponatraemia. Any other symptom that might occur is considered as being of mild severity. The list of reported signs and symptoms is long; patients may complain of restlessness, lethargy, disorientation, dizziness, impaired memory, difficulty concentrating, confusion, mental slowing, agitation, muscle cramps, dysgeusia and many more [15,98–100]. Furthermore, many patients present without any apparent hyponatraemia-associated symptoms, especially in mildly and moderately decreased sodium levels. Beyond the mere reporting of symptoms, studies from the last 20 years have tried to systematically explore subtle alterations of cerebral function employing elaborated standardized assessment batteries, technical tools as well as imaging studies allowing a more objective characterization of the nature and severity of clinical manifestations associated with chronic non-severe hyponatraemia:

The SALT-trials were randomized controlled trials in the US and Europe that assessed efficacy of tolvaptan, a vasopressin V_2-receptor antagonist, in 448 patients with euvolemic or hypervolemic hyponatraemia (mean sodium 129 mmol/L). In a sub-analysis using the Medical Outcomes Study 12-item Short-Form General Health Survey, significant improvement in the score on the Mental Component was achieved after normalization of sodium at day 30 [101]. In a landmark trial, Renneboog et al. subjected 16 “asymptomatic” patients with chronic mild hyponatraemia (mean sodium 128 mmol/L) due to SIAD to eight attention tests. All patients had normal neurocognitive functioning as confirmed by a normal Mini-Mental State Examination (MMSE). Following correction of sodium, a significant improvement in response latencies was observed. Using a pressure-sensitive platform, the authors also investigated gait stability by measuring deviation of the pressure centre while patients performed standardized steps. Again, the balance performance of the 12 examined patients improved markedly after sodium normalization. The impairment observed in both, the reaction tests and the gait stability tests, was similar or even inferior to those found in healthy volunteers that had a blood alcohol level of 0.6 g/L [60]. These results might provide an explanation for the high incidence of falls frequently seen in patients with mild-to-moderate hyponatraemia. The same group later investigated whether muscle strength and nerve conduction velocity – two possible additional factors that might contribute to the propensity for falls – were impaired in chronic hyponatraemia, too. Notably, muscle strength was not altered but hyponatraemia indeed had a significant impact on conduction velocity of motor as well as sensory nerves suggesting that the peripheral nervous system is also affected [102]. Refardt and colleagues conducted a small prospective trial (n = 19) in patients with mild-to-moderate hyponatraemia of varied aetiologies. Although they were able to confirm that neurocognitive function tests yielded pathological results at baseline compared to healthy controls, a 14-day treatment did not clearly ameliorate these results. Notably, the outcome of various balance tests was not consistent, some even became worse with treatment [103]. In another placebo-controlled tolvaptan trial in 57 patients with chronic mild eu- or hypervolemic hyponatraemia, a broad test battery was used at baseline and at day 22. At baseline, the majority of test scores was significantly worse compared to the normative values from age-matched individuals. However, despite tendencies of improvement in all tested domains in line with the above-mentioned studies, a significant amelioration with sodium normalization was only detected in the domain of rapid motor movements [104]. In a larger study including 150 hospitalized geriatric patients (mean age 82 years) with moderate chronic hyponatraemia (median sodium: 127 mmol/L), our group compared the individual domains of a Comprehensive Geriatric Assessment (Barthel index of activities of daily living, Tinetti’s Performance Oriented Mobility Assessment, Timed Up and Go-Test (TuGT), MMSE, handgrip strength, Geriatric Depression Scale, Clock-drawing Test, and Esslinger Transfer Scale) on admission and before discharge. Correction of sodium by at least 5 mmol/L was associated with improvement in the Barthel index as well as MMSE with small-to-moderate effect sizes but no benefit with respect to the other domains [105]. A prospective trial conducted in two European centres prospectively assessed neurocognitive function, mood and motor performance in 130 patients with profound chronic euvolemic hyponatraemia (median sodium: 122 mmol/L). In contrast to the aforementioned trials that had looked at milder cases, most patients showed unspecific but detectable symptoms. When compared to a group-matched reference group (n = 50), all test scores were significantly worse and improved after treatment with medium to large effect sizes. There was a clear correlation between the magnitude of sodium decrease and the degree of deviation from normal values in most scores. The assessments with the largest between-group differences suggesting marked clinical importance were the DemTect test (dementia detection test), the Trail-making-test B (detects deficits in visuomotor processing, mental flexibility, and executive functions), the Beck Depression inventory and the TuGT (gait, balance, general motor skills) [106]. The incidences of impaired functional tests in this cohort were between 50 % and 90 % which might explain the discrepancies observed in the smaller studies above. To gain further insight, our group employed magnetic resonance imaging (MRI) studies including resting-state functional MRI combined with neurocognitive testing in patients with chronic profound hyponatraemia and after sodium normalization. Sodium control led to a reduction of total brain volume of about 2 %. Since the second MRI was performed with a considerable delay after completion of treatment in most patients, this suggests that there was still some cerebral oedema in chronic hyponatraemia despite adaptive RVD. Analysing specific predefined regions of interest, the volume changes were markedly more pronounced in the hippocampus (4 %) which might explain the susceptibility of hyponatraemic patients to memory deficits. Both, global neuronal activity and connectivity (i.e., synchronization of neuronal activity across the entire brain) were significantly enhanced during hyponatraemia and lower sodium was strongly correlated with a higher degree of synchronization of neuronal activity and an inferior outcome in neurocognitive testing [107]. Only few animal studies looking at chronic hyponatraemic encephalopathy have been published but are needed in order to eliminate the many confounding factors present in clinical populations. Miyazaki et al. described a significant memory impairment in rats with stable chronic hyponatraemia but observed no impact on motor function and gait [108]. In a well-designed experiment using rats

rendered chronically hyponatraemic by administering vasopressin and water, Fujisawa and co-workers confirmed the findings from clinical trials on cognitive function and gait, demonstrated that brain oedema was not causative, and showed that extracellular glutamate concentration was elevated in the hippocampus (possibly due to reduced uptake by astrocytes) leading to impaired long-term potentiation in the hippocampal CA3-CA1 synapses which is instrumental in memory building [58].

While there is now ample evidence that significant functional impairment does exist even in the absence of overt symptoms and that integrity can be restored by raising sodium levels, it remains elusive whether distinct treatment options are superior to others, whether auxiliary therapies (e.g., supplements) are supportive and which sodium level should be aimed for.

Summary

Hyponatraemic encephalopathy collectively describes pathological changes of cerebral functioning in acute as well as chronic hyponatraemia. Acute development of hyponatraemia in only a few hours inevitably leads to cerebral oedema and severe neurological symptoms reflecting increased intracranial pressure. This represents a true emergency and must be treated immediately by administering hypertonic saline. With time, adaptive mechanisms lead to restoration of near-normal brain volume eliminating the risk of imminent death. These mechanisms are incompletely understood but include bulk loss of electrolytes and organic osmolytes from the brain. At the same time, extracellular concentrations of transmitters (e.g., glutamate) might be increased. This transformation of biochemical properties is thought to be responsible for most of the non-fatal neurological sequelae. During the process, the clinical picture changes from classical neurological symptoms to unspecific features of varying severity to subtle changes that are often not detectable on individual examination. However, these subclinical alterations may greatly compromise quality of life, lead to an increased frequency of falls and fractures, cognitive impairment and mood instability. Effective correction of hyponatraemia has been shown to reverse some of the clinical and sub-clinical impairments. Areas of uncertainty include the precise molecular pathophysiology, the underlying reasons for the individual variability to develop symptoms, and the question whether a safe threshold for sodium exists.

Research Agenda:

- To decipher the role of glutamate and other organic osmolytes in the development of chronic HNE – more animal research is needed.
- To investigate optimal therapeutic strategies in terms of choice of treatment, rapidity of increase of sodium and sodium level to aim for.
- To better characterize the clinical features observed with chronic hyponatraemia (i.e., development in < 48 h) and long-standing hyponatraemia (i.e., hyponatraemia that exist over weeks, months and sometimes years.
- To explore why some patients are affected more by HNE than others.
- To identify methods that facilitate reliable detection of brain oedema in patients with severe symptoms.

Practice Points:

- Severe symptoms including coma and seizures are always suggestive of high intracranial pressure and must prompt emergency management.
- Adaptive mechanisms restoring normal brain volume are complete approximately 48 h after onset of hyponatraemia. Severe symptoms after this time period are less frequent and are associated with a much lower risk of dying.
- Changes of the biochemical integrity of the brain are believed to be the main reason for symptoms in chronic HNE.
- Even if overt symptoms are absent in chronic mild-to-moderate hyponatraemia, it is likely that sub-clinical alterations of attention, memory, cognition and balance exist. Treatment is therefore warranted in most instances.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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