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Neurological Counterparts of Hyponatremia: Pathological Mechanisms and Clinical Manifestations

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Abstract Hyponatremia, defined as a serum sodium concentration <135 mEq/L, represents the most frequent electrolyte disorder in older hospitalized patients. Early recognition of hyponatremia is mandatory, since it represents an independent risk factor that increases hospital mortality by 40 %. Delayed correction of hyponatremia may worsen brain edema, resulting in different degrees of neural damage. However, an overly rapid correction of serum sodium levels can lead to osmotic demyelination syndrome (ODS), a dreadful neurological picture. In recent years, hyponatremia and ODS have received growing attention both in terms of clinical management and pathophysiology, leading to the discovery of new drugs and treatment algorithms. In this review, we recapitulate the pathogenetic background, clinical manifestations, and treatment guidelines of hyponatremia, focusing on the neurological alterations. Neurological symptoms may be neglected when they manifest as early signs of mild hyponatremia, while brain damage can irremediably affect patients' conditions in the context of ODS.

Keywords Hyponatremia · Osmotic demyelination syndrome · Central nervous system · Pathogenesis · Therapy

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Introduction

The extracellular fluid osmolarity ranges from 280 to 295 mOsm/L, assuring the normal distribution of water between intra- and extracellular compartments. In physiological conditions, serum sodium (Na^+) and glucose are the most relevant solutes regulating extracellular osmolarity. Moreover, blood Na^+ concentration is tightly connected to the effective extracellular volume, since serum water content is the most relevant determinant of serum Na^+ concentration.

The total amount of serum Na^+ is maintained constant despite large variations in the salt-water intake by the activity of many neurohormonal agents that include the renin-angiotensin-aldosterone axis, atrial natiuretic peptide, brain natriuretic peptides, and sympathetic nervous system. Water metabolism is regulated by arginine-vasopressine (AVP), whose synthesis is activated by osmoreceptors of the anterior hypothalamus when extracellular osmolarity rises. Another stimulus for AVP secretion derives from aortic arch and carotid bodies baroreceptors stimulation in systemic hypovolemia. AVP increases thirst and water retention by reducing diuresis and free water clearance.

Hyponatremia, defined as a serum Na^+ concentration <135 mEq/L, represents the most frequent electrolyte disorder in older hospitalized patients. Epidemiological data report that

the overall incidence of hyponatremia in hospitalized patients is ranging from 1 to 2 % [1]. A Na^+ concentration <130 mmol/L has been described in 4 % of surgical patients, which raises to about 30 % in critically ill patients admitted to ICU [2]. In this setting, the early recognition of hyponatremia is mandatory, since this disorder is an independent risk factor increasing hospital mortality by 40 % [3]. In the present review, we recapitulate the pathogenetic background, clinical manifestations, and recent treatment guidelines of hyponatremia, with a particular focus on neurological manifestations and complications.

Acute and Chronic Hyponatremia

Brain Adaptation to Hyponatremia: Pathophysiology of Acute and Chronic Injury

Severe acute hyposmolarity and hyponatremia promote interstitial and intracellular water entry with a rate that is dependent on both the degree and rapidity of the electrolytic imbalance. The brain is separated from the systemic circulation by the blood-brain barrier (BBB), whose impermeability is granted by tight junctions at the endothelial level and by astrocyte foot processes surrounding the capillary walls [4] (Fig. 1). Astrocytes play a central role in water handling during hyponatremia. These glial cells selectively swell under hypo-osmotic stress, and volume change depends on their closeness to brain blood vessels [5]. By contrast, neurons seem to be relatively unaffected, in terms of volume changes, by hyposmolarity [6, 7]. This may be explained by the difference in membrane permeability to water of these cell types. In addition to direct crossing of the lipid layer, water flow through astrocyte membranes is granted by aquaporins (AQP), small integral membrane proteins through which water permeates by concentration gradient. AQP4 is the most abundant isoform found in brain tissues and it is highly expressed on astrocyte foot processes forming the BBB [8]. There is solid evidence that AQP4 plays a major role in acute hyponatremic swelling: the selective removal of perivascular AQP4 or its complete deletion in animal models delayed and partially prevented brain edema formation and astrocyte swelling in the setting of water intoxication [9, 10].

Several changes occur in the brain after astrocyte swelling, most of which are compensatory mechanisms aimed at reducing edema formation both on the intracellular and extracellular compartment. Loss of water, Na^+, and Cl^- by shunting of liquid from the interstitium to the cerebrospinal fluid (CSF) is the first response that takes place [11, 12]. Recent data showed that the permeability to water and electrolytes of the blood-CSF barrier, the interface between choroid plexus epithelial cells and fenestrated blood capillaries, is increased after 6 h in a mouse model of acute hyponatremia. This is due to the increased expression of AQP1 and NKCC1 (Na^+-K^+-$2Cl^-$ cotransporter 1) on the apical membrane of choroid plexus epithelial cells [13]. Consequently, the excess cerebrospinal fluid flows back into the systemic circulation [14].

Astrocytes respond to swelling by increasing osmotic compounds secretion via different mechanisms: first, by increasing Na^+ secretion through the activation of the Na^+-K^+ ATPase system, which is followed by water passive extrusion [4, 6]. This is an energy-dependent phenomenon that can be influenced by a large number of factors, such as hypoxia, estrogens, and vasopressin [4]. Another adaptive reaction is represented by extrusion of

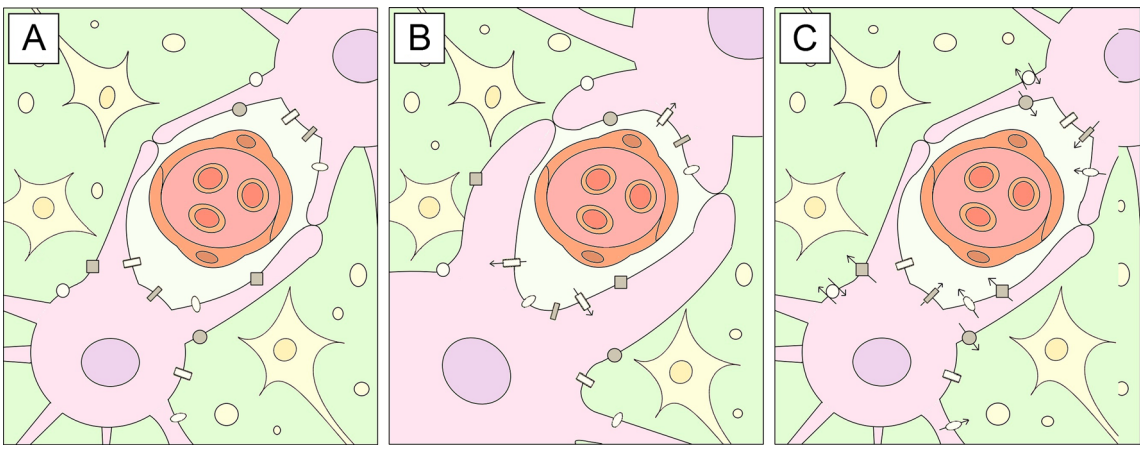

Fig. 1 Consequences of hyponatremia on the BBB. **a** Normal structure of the BBB: endothelial cells (*red*) with tight junctions surrounded by astrocyte foot processes (*pink*), separating them from neurons (*yellow*). Transporters: *white circle*, Na^+/K^+ ATPase; *grey circle*, Cl^- channel; *grey square*, organic solute transporter; *white rectangle*, AQP4; *grey rectangle*, Na^+-K^+-$2Cl^-$ co-transporter; *white oval*, K^+ channel. **b** Hyponatremia causes passive water entry into astrocytes mainly by AQP4, inducing cellular swelling. **c** Activation of protective mechanisms at cellular level (solute transporters) that lead to recovery of the baseline cellular volume

intracellular K^+ and Cl^- by passive transport through volume-sensitive channels, which open in response to astrocyte swelling [15, 16].

After these initial losses of inorganic solutes, the electrolyte content of the brain does not drop any further, but the water content keeps decreasing [17]. Electrolytes are the major determinants of total brain osmolarity (62–70 %), but organic osmolytes also play a pivotal role in the response to hyponatremia [14]. Within 48 h from the onset of hyponatremia, organic osmolytes such as myoinositol, creatine, and amino acids efflux from astrocytes [4, 18].

As a consequence of solutes removal, intracellular and interstitial osmolarity progressively drop to the serum value, resetting the brain volume to the normal set-point. However, when serum osmolarity drops too abruptly, the mechanisms employed by the brain to buffer the intracranial rise in volume are overcome: since the skull is a rigid compartment, edema results in a markedly increased intracranial pressure. This process leads to compression of vascular and neuronal structures, generating ischemia, neuronal death and, in severe cases, caudal herniation of the brain through the foramen magnum [12, 14].

Volume and pressure increase also lead to a dramatic rise of extracellular glutamate levels. Cellular swelling causes the release of glutamate by astrocytic volume-sensitive anion channels [19] and also inhibits astrocytic glutamine synthetase activity, disrupting glutamate recycle [20•]. This may explain, at least in part, the increased susceptibility to seizure observed in hyponatremia: excess glutamate mediates excitotoxicity by over-activation of glutamate receptors such as the Ca^{2+} permeable NMDA receptor on oligodendrocytes. The calcium influx leads to increased oxidative stress and apoptosis [21, 22].

Recent experimental data suggests that hyponatremia effects on the brain, especially in chronic forms, may be due to mechanisms that extend beyond osmotic changes. Benvenuti et al. found a significant decline in cellular adhesion and viability of both neuroblastic and stromal neuroblastoma cellular lines when these were exposed to low Na^+ concentrations. Interestingly, these results were largely independent of the medium osmolarity [23•]. The same authors found a reduced expression of anti-apoptotic genes such as Bcl2 and DHCR24 in cells exposed to hyponatremic environment, along with an enhanced expression of the protein HMOX1, which acts as a general marker of oxidative stress. These findings may explain the clinical manifestations of chronic hyponatremia, which persist despite the absence of the osmotic stress buffered by adaptative mechanisms and argues in favor of chronic mild hyponatremia correction using available strategies.

Neurological Manifestations of Mild Hyponatremia

Hyponatremia is usually classified according to plasma sodium level as mild (130–135 mmol/L), moderate (125–129 mmol/L), and profound (<125 mmol/L) [24••]. Mild hyponatremia has been often considered asymptomatic. In the last years, however, a bulk of evidence has underlined the risk of neglecting this finding. Several series have proved that mild hyponatremia is associated to worse outcomes. Sahadieh et al. examined the role of mild hyponatremia in a cohort of 671 community subjects with no history of cardiovascular disease, stroke, or cancer with a median follow-up of 6.3 years. The authors found that patients with baseline sodium level ≤134 meq/L had significant worse outcomes compared to controls when data were corrected for age, sex, diabetes, smoking, heart rate variability, and C-reactive protein levels. Of note, even when the authors chose a more conservative serum sodium level as cut-off (≤137 mEq/L), the hazard ratio was significant [25]. This may mean that even lower normal-range sodium levels can be dangerous. Moreover, worse outcomes for mild degrees of hyponatremia have been documented in morbid conditions in an independent fashion from the already known risk factors [26]. Elderly patients are particularly susceptible to the detrimental effects of mild hyponatremia. In geriatric population, hyponatremia is related to impaired cognition and falls [27]. In a case-control study, patients who arrived to the emergency department in a 3-year period with chronic and stable hyponatremia had a dramatic increased incidence of falls compared to well-matched controls, independently of other risk factors. In the same study, the authors submitted 16 chronic "asymptomatic" patients with hyponatremia due to SIADH to gait and attention tests before and after sodium correction with water restriction or urea administration. Hyponatremic patients, after sodium correction, had comparable results to controls. However, performances declined significantly while they were hyponatremic, suggesting that hyponatremia impairs attention and gait control. To compensate for eventual learning biases, the authors studied half patients with normal sodium level at baseline and after treatment discontinuation when hyponatremia had been present for at least 3 days. Curiously, performances of hyponatremic patients were significantly worse than another control group of 10 volunteers who consumed 0.55 g of alcohol per kilogram of body weight and had a mean blood alcohol content of 0.6±0.2 g/L [28]. This unsteadiness may account for the increased frequency of falls observed in frail patients and claim for increased awareness of physicians to the detrimental effects of this often neglected disorder.

Neurological Manifestations of Severe Hyponatremia

Acute hyponatremia comprises a wide array of different neurological signs and symptoms, ranging from headache,

agitation, and cramps to consciousness alterations, respiratory distress, seizures, and death [12, 29].

Several risk factors have been associated with worse outcomes in hyponatremic encephalopathy. Most of them are non-modifiable risk factors, which nevertheless need to be considered when dealing with severe forms. Sex and age are a paradigmatic example: since estrogens impair brain adaptation to hyponatremia through inhibition of the Na^+/K^+ ATPase, it is not surprising that fertile women are at increased risk of worse outcomes [30]. Other risk factors include high levels of vasopressin and discrepancy between skull size and brain size. Hypoxemia is a modifiable risk factor that has been shown to worsen the primary damage of hyponatremia through the impairment of ATP-dependent mechanisms of volume homeostasis in astrocytes. Hypoxemia may result from either central respiratory depression as a consequence of brain edema or from neurogenic pulmonary edema that follows the rise of intracranial pressure [4].

In a clinical setting, it is crucial but often difficult to discriminate between acute and chronic hyponatremia. Spasovski et al. decided to consider every doubtful case as a chronic disorder, since this form is more common and needs more caution when treated. It should also be considered that extremely low values of Na^+ concentration seem to hold some significance: symptoms become more common and severe below the threshold of 125 mEq/L [24]. Even though profound hyponatremia was shown to double the mortality risk in a hospital setting, Na^+ concentration and mortality are not related in a linear fashion [3, 31]. Thus, a valuable approach to classify hyponatremia as severe relies on patient's symptoms. Nausea, confusion, and headache are considered as moderately severe, while vomiting, cardiorespiratory distress, abnormal and deep somnolence, seizures, and a Glasgow Coma Scale score <8 define severe hyponatremia. Even though patients experiencing moderately severe symptoms have a lower risk of death, it should be remembered that their condition may rapidly deteriorate. However, this classification allows a better risk stratification and a more appropriate treatment choice [24].

Osmotic Demyelination Syndrome

Pathogenesis

Osmotic demyelination syndrome (ODS) is a neurologic condition featured by acute paralysis and neurocognitive problems related to damage of the myelin sheath. ODS is a demyelinating pathology involving especially the central basis pontis (pontine myelinolysis) but also other brain regions such as thalamus, internal capsule, and deep cerebral cortex (extrapontine myelinolysis) [32, 33••]. Pathological hallmarks include loss of oligodendrocytes, presence of apoptotic cells, reactive micro- and macrogliosis, macrophagic infiltration, and the relative sparing of neurons and axons [34].

ODS is usually caused by overly rapid correction of serum sodium levels in patients affected by chronic (usually more than 1 week) severe hyponatremia, with the majority of cases occurring when rates of correction exceeded 0.5 mEq/L per hour or 12 mEq/L per day. Other conditions considered as risk factors for developing ODS include liver diseases, malnutrition, SIADH, hypokalemia, and sepsis [35].

Modifications of intracellular osmolarity due to a chronic state of hyponatremia comprehend a depletion of both electrolytes (principally Na^+, K^+, and Cl^-) and organic components such as carbohydrates (myoinositol) and amino acids (glutamine, taurine, glutamate, alanine) [35]. When rapid correction of sodium levels occurs, cells are able to replace efficiently intracellular electrolytes (usually within minutes) followed by osmotically drived water, while the reintegration of organic compounds requires more time (about 4–5 days) and metabolic efforts [36].

Organic osmolites play a crucial role in preserving cell protein structure and function in contrast to high concentrations of inorganic ions, which can affect proper protein turnover by directly binding proteins and leading to their aberrant misfolding [37]. Accordingly, the re-integration of organic osmolites occurs at different rates within different brain regions and the severity of demyelination lesions inversely correlates with the local efficiency in reintegrating organic osmolites [12]. Exogenous myoinositol administration has been shown to increase survival and reduce demyelination in ODS animal models [12].

Moreover, the attempt to equilibrate the increase of extracellular osmolarity results in a great energetic effort and ATP waste by glial cells. The process is especially evident in cachectic or alcohol-addicted patients whose cells are more vulnerable to the deprivation of metabolic energy [32]. As a result, water migrates from glial cells to the interstitium causing their shrinkage which impact on adjacent axons [6].

Several studies have pointed out the crucial role of astrocytes both in maintaining brain osmolar homeostasis and myelin integrity [33••]. Astrocytes and oligodendrocytes share several connections through structured connexin-based gap junctions forming a complex network, which is essential in the maintenance of myelin turnover and can be highly affected by rapid correction of chronic hyponatremia [38–40].

In addition, the damage provoked by the imbalance between intracellular and extracellular osmolarity might cause endothelial cell dehydration and stress which, in association with other mechanisms such as the osmotic injury itself and the local release of nitric oxide, lead to alteration of tight junctions and leaking of the BBB [35]. Disruption of BBB can be assessed by immunostaining for immunoglobulin G (IgG) which does not transpass BBB in physiological conditions. A positive staining for IgG is considered as a reliable

marker of local BBB disruption [40]. The presence of IgG has been detected in the same area of the demyelinating lesions, thus suggesting a causative connection between BBB leakage and myelin damage [40]. Accumulating evidence suggests that BBB impairment is crucial in the context of ODS since it causes the passage of inflammatory serum components, which can further contribute to oligodendrocytes apoptosis and myelin damage [41]. Complement enrichment seems to be detrimental to oligodendrocytes and myelin in culture and such mechanism could be involved in ODS: C3d complement staining nicely correlated with neurological outcome in ODS experimental models [41].

In experimental models of ODS, an enhanced microglia activation has been observed following BBB damage and oligodendrocyte stress [42•]. Cytokines produced by activated glia could further contribute to BBB disruption maintaining active the early pathogenetic cascade [42•]. Indeed, chemical compounds able to reduce BBB permeability have been shown to reduce demyelination in the animal model [40, 43].

To summarize, different pathological mechanisms have been considered causative in ODS: BBB alteration, microglia activation, direct osmotic insult, oligodendrocytes apoptosis, and astrocytes alterations appear to be involved in determining the neurological phenotype. Further studies are necessary to elucidate the key pathogenetic events which need to be targeted in order to develop effective therapies for ODS.

Clinical Manifestations

ODS is considered as a rare disease with a higher incidence observed in individuals with alcohol dependence and among liver transplant patients [6]. The typical clinical presentation of central pontine myelinolysis (CPM) consists of dysarthria, dysphagia, and flaccid quadriparesis that later becomes spastic. These symptoms represent the involvement of the corticobulbar and corticospinal tracts [32, 44]. Pupillary and oculomotor disturbances may occur if the lesion reaches the tegmentum of the pons. Also, various degrees of mental status alterations, as stupor and coma, have been described. The locked-in syndrome was observed occasionally and represented the result of a large lesion of the basis pontis [36, 44].

Typical symptoms of extrapontine involvement (EPM) are mutism, parkinsonism, dystonia, and catatonia. The fact that CPM and EPM may occur isolated or simultaneously explains why the clinical presentation can vary widely from mental status changes to motor impairments [6, 44].

ODS is now also recognized as a neurobehavioral disorder characterized by the involvement of both pons and supratentorial structures. Neurobehavioral symptoms include emotional lability, apathy, agitation, insomnia, paranoia, rage, and disinhibition [45–48]. In general, the clinical presentation of ODS resembles a white matter dementia [36].

The pathogenesis of the neurobehavioral symptoms is still not clear but seems to be related to the involvement of the frontal system and ascending reticular activating system. The latter determines a reduction in the supply of serotonin, acetylcholine, and norepinephrine to the thalamus and cortex and, subsequently, an inhibition of the arousal system [36, 45].

Although the role of the frontal systems impairment remains prominent, myelinolysis within the pons may be associated with both cognitive and behavioral dysfunction [47]. Van Zandvoort et al. found that isolated pons lesions produced symptoms similar to supratentorial white matter lacunar infarcts [49]. EPM seems to contribute to frontal systems dysfunction, even though its role has not been fully elucidated.

Neuropsychological tests performed in few ODS cases showed that IQ is mildly modified, memory retrieval and executive function are impaired, and attention span and information processing speed are reduced, whereas language is relatively spared [47, 50]. The recovery from cognitive disorders may be incomplete [50]. A solid estimate of ODS prognosis is still not possible. This is due to the low incidence of the disease and to the fact that the possibility of a timely diagnosis exists only since the introduction of CT and MRI. The time required to recover and the degree of the recovery from ODS are variable [6, 44, 51].

ODS must be considered whenever new neurological symptoms arise in the setting of a rapidly corrected hyponatremia, or in case of a condition previously mentioned. The diagnosis is now simple and is made by correlating clinical findings with the lesions observed at MRI [6]. Typical findings on MRI are hypointense T1-weighted and hyperintense T2-weighted lesions, not enhancing after gadolinium administration [52].

Treatment and Management

Optimal treatment strategies for hyponatremia have not been well defined [53]. Since an overly rapid correction of hyponatremia via inappropriate therapy may result in worse damage than the disorder itself, physicians need to be aware of the risk of delayed diagnosis and inappropriate management.

The presence and/or severity of symptoms determine the urgency and goals of therapy [54]. Spasovski et al. reported that in patients with severe or moderately severe symptoms, urgent treatment is needed to reduce the rate of complications in both an acute and chronic setting, since the risk of brain oedema is much higher than that of ODS (Table 1) [24]. Thus, correction should be rapid in patients with presenting symptoms that range from headache, nausea, vomiting, and seizures. Delayed correction of hyponatremia may worsen brain edema, resulting in different degrees of neural damage and cellular death. This is especially true in the setting of acute hyponatremia, in which the mechanisms employed by the

Table 1 Management of hyponatremia with severe symptoms as indicated by Spasovski et al. [24••]

Hyponatremia with severe symptoms	
Either acute or chronic hyponatremia	Improvement of symptoms after a 5 mmol/L increase in serum Na^+ in the first hour
Start with infusion of 150 mL 3 % hypertonic over 20 min	Stop the infusion of hypertonic saline
Check the serum sodium concentration after 20 min while repeating an infusion of 150 mL 3 % hypertonic saline for the next 20 min	Keep the i.v. line open by infusing the smallest feasible volume of 0.9 % saline until cause-specific treatment is started
Repeat therapeutic recommendations twice or until a target of 5 mmol/L increase in serum sodium concentration is achieved	Start a diagnosis-specific treatment if available, aiming at least to stabilize sodium concentration
Manage patients with severely symptomatic hyponatremia in an environment where close biochemical and clinical monitoring can be provided	Limit the increase in serum sodium concentration to *a total of 10 mmol/L during the first 24*h and an additional *8 mmol/L during every 24 h* thereafter until the serum sodium concentration reaches 130 mmol/L

brain to buffer the osmotic water movement are overcome [55]. In these circumstances, prompt intravenous infusion of 150 mL 3 % hypertonic saline over 20 min needs to be considered a life-saving procedure. It is generally accepted that a 5-mmol/L increase in serum sodium concentration is usually enough to attain symptoms improvement and to prevent brain stem herniation. However, owing to the risk of ODS development, it has been suggested to avoid an increase in serum sodium concentration of 10 mmol/L during the first 24 h and 8 mmol/L during every 24 h thereafter. If the symptoms do not improve, other explanations should be explored [56]. On the other hand, if an overly rapid correction has occurred, the recommendation is to re-lower serum sodium concentration. It is appropriate to consult an expert before starting the re-lowering of serum sodium concentration for the lack of evidences regarding benefits and harms. Infusion of electrolyte-free water (e.g., 5 % glucose solutions 10 mL/kg over 1 h) and/or injections of desmopressin (2 μg i.v. not more frequently than every 8 h) are the main choices [24].

Another critical point to consider when treating hyponatremia is that even with correct estimates by different available formulas, the response to therapy can be highly unpredictable. For this reason, frequent monitoring of plasma Na^+ concentration during corrective therapy is essential [57].

When hyponatremia develops over more than 48 h, it usually bears milder symptoms and brain stem herniation is unlikely. In patients with chronic mild hyponatremia, there is still no solid evidence that correcting hyponatremia itself improves outcomes, so interventions with the sole aim of increasing the serum sodium concentration are not justified [58]. In patients with moderate or even profound hyponatremia, there is little or no evidence to support the treatment. However, in the same studies, treatment is considered for prevention of a sudden, further deterioration of the patient leading to severe or moderately severe symptoms (Table 2).

As already described, in chronic hyponatremia the risk of ODS is consistently higher. Apart from prevention, different strategies to ameliorate the prognosis and the sequelae of ODS have been explored. Two studies on rat models investigated the possible role of minocycline, a second generation tetracycline, in the reduction of mortality and severity of neurologic symptoms in ODS [43, 59]. In the study by Gankam et al. [43] such results were obtained when minocycline was administered 12 h before the correction of hyponatremia. On the other hand, among rats treated 18 h after correction, all symptomatic animals died while the asymptomatic ones survived: these findings and the fact that usually patients are asymptomatic within the first 24 h of a rapid correction of hyponatremia, confirmed a potential utility of minocycline in clinical practice. Also, in the study by Suzuki et al. [59], an improvement in survival and severity of symptoms was observed. However in both studies emerged that, although minocycline reduces activation of glia and inflammatory cytokines release, rats developed the typical demyelinating lesions. Gankam et al. also demonstrated in another study that better results on survival can be obtained combining the administration of minocycline with the re-lowering of serum sodium level [60]. More recently, Takagi et al. showed that minocycline is able to prevent demyelination induced by rapid correction of hyponatremia through the use of vaptans in a rat model [61•].

Sugimura et al. [62] demonstrated a comparable improvement of symptoms and survival with dexamethasone administration simultaneously with the correction of hyponatremia or after 6 h. They also observed a reduction in demyelinative changes, supporting the hypothesis that glucocorticoids can regulate the BBB permeability and prevent its disruption [40, 62].

The management of neurobehavioral deficits consists of rehabilitation and treatment of the underlying diseases that can exacerbate the encephalopathy. In case of acute

Table 2 Management of chronic hyponatremia as indicated by Spasovski et al. [24••]

Chronic hyponatremia			
General management	Management of patient with expanded extracellular fluid	Management of patients with SIADH	Management of patients with reduced circulating volume
Stop non-essential fluids, medications, and other factors that can contribute to or provoke hyponatremia	Avoid treatment with the sole aim of increasing the serum sodium concentration in mild or moderate hyponatremia	In moderate or profound hyponatremia, restrict fluid intake as first-line treatment	Restore extracellular volume with i.v. infusion of 0.9 % saline or a balanced crystalloid solution at 0.5–1.0 mL/kg per hour
Cause specific treatment is recommended	Fluid restriction is suggested to prevent further fluid overload	In moderate or profound hyponatremia increase solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral NaCl	Manage patients with hemodynamic instability in an environment where close biochemical and clinical monitoring can be provided
In mild hyponatremia, avoid treatment with the sole aim of increasing the serum sodium concentration	Do not use vasopressin receptor antagonists	In moderate or profound hyponatremia do not use lithium or demeclocycline	In case of hemodynamic instability, the need for rapid fluid resuscitation overrides the risk of an overly rapid increase in serum sodium concentration
In moderate or profound hyponatremia, avoid an increase in serum sodium concentration of 10 mmol/L during the first 24 h and 8 mmol/L during every 24	Do not use demeclocycline	In moderate hyponatremia do not use vasopressin receptor antagonists	
In moderate or profound hyponatremia, check the serum sodium concentration every 6 h until the serum sodium concentration has stabilized under stable treatment		In profound hyponatremia do not use vasopressin receptor antagonists	
In case of unresolved hyponatremia, reconsider the diagnostic algorithm and ask for expert advice			

confusional state, there is not a standardized therapy but a treatment with low doses of antipsychotic may be helpful [36]. A case report described the improvement of motor, cognitive, emotional, and behavioral dysfunctions in a woman affected by ODS treated with methylphenidate, a psycostimulant drug used for attention deficit hyperactivity disorder (ADHD) and narcolepsy [63]. This report enhances the necessity to better investigate the role of the ascending reticular activating system in ODS.

Conclusions

Hyponatremia is a common finding in community-based studies and hospitalized patients. This electrolyte imbalance and its overly rapid correction lead to protean neurological manifestations that bear a high impact on mortality and morbidity depending on the severity of the disorder. Since manifestations are frequently subtle and clinical conditions may worsen abruptly, serum sodium concentration should be closely monitored in patients at risk and in hospitalized patients. In recent years, hyponatremia and ODS have received growing attention both in terms of clinical management and pathophysiology, leading to the discovery of new drugs and to more appropriate treatment algorithms. Further work will be needed to better assess the impact of hyponatremia on neural damage and to reduce complications of both this disorder and its correction to a minimum.

Compliance with Ethics Guidelines

Conflict of Interest Manuel Alfredo Podestà, Irene Faravelli, David Cucchiari, Francesco Reggiani, Silvia Oldani, Carlo Fedeli, and Giorgio Graziani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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