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Review

Adaptation of the brain to hyponatremia and its clinical implications.

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Abstract: Hyponatremia is the commonest electrolyte disorders which can occurs in up to 25% of hospitalized patients. Hypo-osmotic hyponatremia when severe and left untreated invariably results in cell swelling which could lead to fatal consequences especially in the central nervous system. The brain is particularly vulnerable to consequences of a decrease extracellular osmolarity because of being encased into the rigid skull, it cannot withstand persistent swelling. Moreover, serum sodium is the major determinant of extracellular ionic balance which in turn governs crucial brain function such as excitability of neurons. For these reasons, the human brain has developed specific ways to adapt to hyponatremia and prevent brain edema. On the other hand, it is well known that rapid correction of chronic and severe hyponatremia can lead to brain demyelination, a condition known as osmotic demyelination syndrome. In this paper, we will discuss the mechanisms of brain adaptation to acute and chronic hyponatremia and the neurological symptoms of these conditions as well as the pathophysiology and prevention of osmotic demyelination syndrome.

Keywords: Keywords: Hyponatremia; osmolarity; osmotic demyelination; brain; astrocytes

Introduction

In cell physiology, a semi permeable membrane describes a membrane separating two compartments that is permeable only to certain substances and non-permeable to others.

Osmosis describes a phenomenon in which when two compartments are filled with a solvent and are separated by a semi permeable membrane, the movement of the solvent across the membrane is driven by the concentration of the solute (osmotic concentration or osmolarity) in the respective compartment. The solvent will move across the membrane from the compartment with the osmolarity to the compartment with the highest osmolarity. The driving forces that makes this movement possible is called the osmotic pressures which depends mainly on the concentration of solutes across the membrane and the compartment with the highest osmolarity will have a higher osmotic pressure while the compartment with the lowest osmolarity will have the lowest osmotic pressure. Water will then move from the compartment with the highest osmotic pressure to the compartment with the lowest osmotic pressure until the osmotic pressure in both compartments is the same. ~~For review, see~~ [1]

Another important phenomenon takes underlies movements across a semi permeable membrane is the Gibbs - Donnan effect. It describes the movement of charged particles across the semi permeable membrane in order to maintain electroneutrality across the membrane or if not to reach an equilibrium called Gibbs - Donnan equilibrium at which no movement of charged particles is seen.

The cell membrane which separates the inside of the cell (intracellular compartment) from the outside of the cell (extracellular compartment) is ~~a~~ made of a phospholipid

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bilayer which from a physiological standpoint serves as a semi permeable membrane. This means that the cell membrane is only selectively permeable to some solutes. For review see [2, 3]

Both intra and the extra cellular compartment are filled with solutes of different nature, many of them being charged particles such as ions and proteins. Movement of solutes across the cell membrane can occurs through various mechanisms, including passive diffusion, active transport or passive transport. As of movement of water across the cell membrane, it occurs mainly through water channel called aquaporins. [4]

The intracellular compartment is selectively enriched with large anionic molecules (mostly proteins), the cell membrane is impermeable to these molecules and therefore other small diffusible charged molecules need to be to attained the Gibbs-Donnan equilibrium. This process will invariably modify the osmotic pressure across the membrane and drive water movement.

Movement of the water across the cell will affect the global water content of the cell. In extreme cases, when there is too much water inside the cell, the cell will burst and conversely, when the is too little water inside the cells, they will shrink. Early application of these principles was provided by the work of Hewson on hemolysis where, when RBC where submitted to an hypoosmotic solution exploded (a phenomenon called hemolysis) and likewise, they shrunk when immersed into an hyperosmotic solution. [5]

Serum sodium concentration is the main determinant of the extracellular osmolarity. Serum sodium concentration is determined in turn by the Edelman equation by the sum of total exchangeable body sodium and potassium over the total body water volume.[6]

Brain adaptation to acute hyponatremia

It is expected that a drop in the serum sodium concentration will result in a proportional drop in the extracellular osmolarity. In that case, water will flow from the extracellular compartment to the inside of the cell. This will cause dilution of the intracellular compartment. In extreme cases as discussed before, cellular edema and cell rupture may ensue.

The brain is particular in the regard that after the adult brain is encased into a rigid structure that limits the expansion of the brain volume. If the brain volume increases too much, herniation of the brain will occur through anatomical defined areas.

Brain cells have developed significant mechanisms to prevent cell volume increase during hyponatremia. These mechanisms are collectively called mechanism of regulatory volume decrease as they counter regulated the increase of cell volume imposed by hypoosmolarty induced cell increase in the cell volume. [7] [8]

These mechanisms occur in a time defined fashion (for full review, see [9]). The first being is the release of intracellular potassium and chloride which will decrease intracellular ionic content and induce an osmotic shift of the water from the inside of the cell to the outside, in order to prevent further cell volume increase. This is seen within minutes of hypoosmotic cell swelling and is maximal after 3 hours.[10-12]

Another mechanism that occurs after the first one involves extrusion of non-ionic osmotically actives substances from the inside of the cell. They are mostly organic osmolyte which of diverse nature including betaine, taurine, myoinisitol for the most important.[13-15] This phenomenon might be mediated by active transport involving an increase in the activity and/or an increase in the number of such transporter.[16, 17]

Experimental studies as well as clinical observation have shown that despite these adaptive mechanisms, hyponatremia might still induce symptoms attributed to cell swelling[18]. This suggest that the buffering capacity of the brain cell is unfortunately not perfect. In other terms there is a threshold at which the RVD mechanism are insufficient to prevent cell swelling. This depends on both the amplitude and the acuteness of hyponatremia as the mechanisms of RVD are sequential. Indeed in acute and profound hyponatremia the content of intracellular ions (K, Na, and Cl) will be insufficient to

counterbalance the water influx inside the cell especially if hyponatremia developed at a rate that prevented the proper installation of organic osmolytes extrusion.[18-21] Likewise the buffering capacity of organic osmolyte is also limited and if the cause of hyponatremia persists after maximal extrusion of organic osmolytes, cell swelling can still occurs as evidenced by symptoms seen in acute on chronic hyponatremia.[19]

Symptoms of acute hyponatremia.

Acute hyponatremia can induce a myriad of neurological symptoms depending on the severity.[18, 21-23] Previous studies have suggested that the symptoms could range from mild cognitive impairment, seizures and even brain herniation and death (see table 1).

Table 1. Manifestations of hyponatremic encephalopathy.

Acute hyponatremia	Chronic hyponatremia
Nausea and vomiting	
Headaches	Nausea
Seizures	Fatigue
Coma	Gait and attention deficit
Death	Falls and Bone fractures
Respiratory arrest	
Non cardiogenic pulmonary edema	

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It is however very difficult to put a threshold on what is considered acute hyponatremia in terms of time of installation. Most experts agree that acute hyponatremia develops within 48 hours. This practical definition was adopted because it is considered that the secondary mechanisms of RVD (organic osmolyte extrusion) are fully in place after 48 hrs. Still, in a clinical setting when facing a patient in ER or in a ward with hyponatremia, in many instances serum sodium value in the preceding hours might be lacking. For these reasons it is our opinion that a symptomatic hyponatremia should be considered acute or acute on chronic until proven otherwise.

Treatment of acute hyponatremia.

The main goal of treatment for acute hyponatremia is to prevent further cell swelling which will cause brain herniation. To achieve this goal, extracellular (plasma) osmolarity should be increased until the symptoms stops. Several algorithms have been proposed to achieved such goal. Based on neurosurgery studies it has been determined that in most cases, an increase in the serum sodium of 5-6mEq/l will be enough to decrease brain volume to prevent brain herniation. [24, 25]Such increase can be obtained through serial boluses of hypertonic saline and some authors have suggest that enteral urea could be useful in decreasing intracranial pressure in hyponatremic brain injury patients.[26]

In any cases, serum sodium should be increased enough to stop the symptoms.

Table 2 is a proposaed treatment approach for severe hyponatremia and Fig 1 displa a proposed algorithm, adapted from a consensus by European expert for treatment o acute symptomatic hyponatremia. [27]

Table 2. Proposed approach for the treatment of severe hyponatremia.

Tratment of severe hyponatremia	
Signs or symptoms of brain edema ICU admission Hypertonic saline boluses (100 ml NaCl 3%) Repeat if symptoms persist Measure serum sodium q 1-2hrs Stop when symptoms abate Stop when Na increment is 6mEq/L Keep checking serum sodium q3-4 hrs	**No signs or symptoms of brain edema** Etiologic evaluation Determine chronicity (> 48hrs) Assess for risk factors for ODS (chronic hyponatremia hypokalemia, liver disease, alcoholism) Treatment of the cause and avoid hypertonic saline. If risk factors for ODS are present Q6-12hr serum sodium check Limit increment of Na < 6 mEq/l/24* If no risk factors for ODS Limit increment of Na to < 8 mEq/l/24 hrs*. Additional measures: If SIADH, use of urea is better.** Relower the serum sodium if increment of > 12 mEq/l/day DDAVP + D5W

ODS: osmotic demyelination syndrome, SIADH: syndrome of inappropriate antidiuretic secretion, D5W: dextrose 5% in water.

Brain adaptation to chronic hyponatremia.

When hyponatremia develops over days and at a slow pace, brain cells have enough time to put in motion more sustained mechanisms of adaptation. It has been shown that brain water content in chronic hyponatremic animal is roughly the same as in normonatremic animals.[20, 28, 29] Considering that the maximal outflow of ions in the brain is achieved within few hours of hyponatremia installation, these evidence suggest that other mechanisms must have taken place to maintain normal water balance in the brain. As discussed above, these mechanisms involve the extrusion of several organic osmolytes from the intracellular compartment. The most studied brain organic osmolytes are betaine, taurine, glutamate and myoniositol. Several studies have confirmed that the brain content of these substance in hyponatremic animals and humans is strikingly decreased.[13, 14, 30] It is still unclear which if the kinetic of brain depletion of organic osmolyte is uniform in terms of anatomical distribution and some studies have shown that there are some areas of the brain that are more prone to organic osmolyte loss. [31, 32] Likewise, it is unknown if these organic osmolyte are interchangeable in their osmotic brain buffering capacity.

One might think that since the brain volume in chronic hyponatremia remains stable, then chronic hyponatremia should not induce any significant clinical consequence. That is not true as several experimental and clinical studies have now showed that chronic hyponatremia is associated with displays significant neurological impairment although less striking and dramatic than in acute hyponatremia.

Symptoms and treatment of chronic hyponatremia.

A particularly well conducted animal study has shown that chronic hyponatremia in rats induces significant gait disturbance, memory impairment and mechanistically, it was hypothesized that chronic hyponatremia induces significant changes in synaptic plasticity, partly because of deletion of brain glutamate content[33]. Prior to this experimental observation it was already well established that chronic hyponatremia in humans could induces gait disturbances and significant attention deficit which were corrected upon normalization of serum sodium. [34]

Other well described neurologic manifestation of chronic hyponatremic encephalopathy are less dramatic than in acute hyponatremic encephalopathy and those include malaise, nausea, gait deficit, attention disturbances, mild confusion. [14, 34, 35]

Fall and bone fractures are also more frequently seen in patients with chronic hyponatremic encephalopathy.[34, 36] Brain imaging is usually normal with no signs of brain edema.

Table 1 compares and contrast neurological manifestation of acute and chronic hyponatremia.

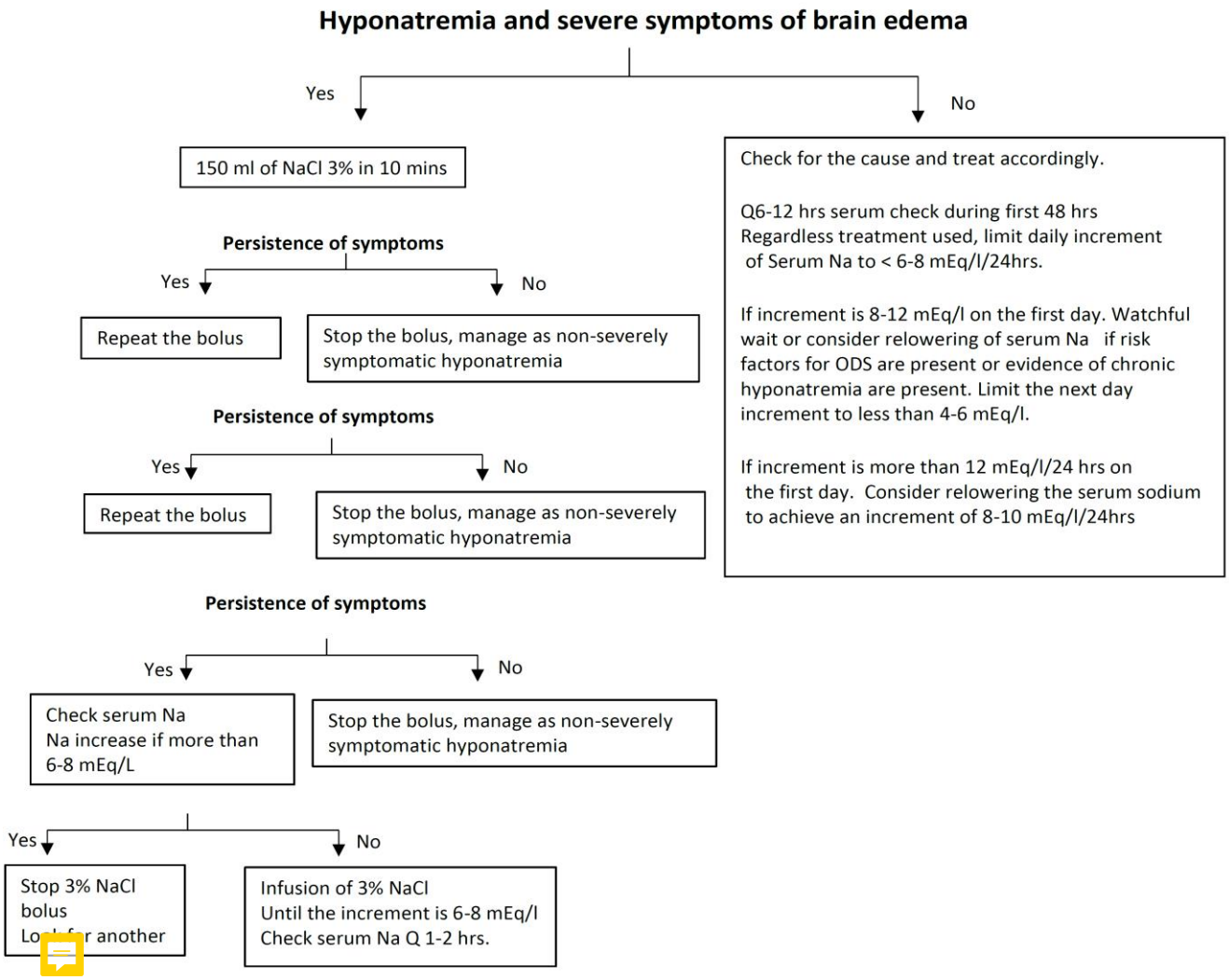
The treatment of chronic hyponatremia usually involves treating the cause. In the absence of acute neurological manifestation specifically seizures or severely altered mental state, treatment of chronic hyponatremia should be undertaken with much caution and over several days as rapid correction of chronic hyponatremia could lead to osmotic demyelination syndrome (ODS).

An important parameter to consider when treating chronic hyponatremia is the duration of hyponatremia. Usually, patients with fully adapted chronic hyponatremia will have no symptoms of brain edema and those patients should be corrected very slowly in the appropriate setting with readily available serial serum sodium measurements when the chronic hyponatremia is severe.

Although there is abundant evidence that associate poor clinical outcomes with even mild clinical hyponatremia, It remains unclear if meaningful clinical benefit could be derived from the treatment of mild chronic hyponatremia (S_{Na} > 132 mEq/l). From a neurological standpoint, patients with a SNa of > 128-130 are at a lower risk of brain complication during correction of hyponatremia.

Figure 1 provides treatment scheme for chronic hyponatremia.

Figure 1. Proposed algorithm for management of hyponatremia with regards to brain complications.



The most important parameter in determining the need of urgent treatment should be the presence of neurological symptoms attributable to hyponatremia and not the chronicity of hyponatremia or the magnitude of hyponatremia. Chronic hyponatremia with no neurological symptoms is a risk factor for ODS and dictates very slow correction of serum sodium regardless the correction method selected. Acute hyponatremia with no neurological symptoms should not be corrected rapidly as there some many caveats in the evaluation of the duration of hyponatremia and little is known about the duration that poses a risk for ODS.

*These limits are based on the current state of the literature, but unpublished evidence suggests that the lower increment is the better.

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Several agents have been shown to be effective in the treatment of chronic hyponatremia depending on the cause. These include urea (for SIADH), vaptans, fluid restriction or salt tablets etc… This topic is discussed elsewhere in this issue.

Osmotic demyelination syndrome (ODS).

When chronic and severe hyponatremia is corrected rapidly in humans, it has been shown in some cases, brain damage can ensue. [37-39] Experimental studies have confirmed that chronicity of hyponatremia as well as the magnitude and the speed of correction are the most important risk factors for development of myelinolysis during correction of serum sodium[40-44]. Brain imaging, when obtained after 2-3 days following correction of the hyponatremia will usually show radiological signs of myelin loss in various areas of the brain including but not limited to the pons.[45-47] In fact extrapontine lesions are at least as common as pontine lesion which are rarely isolated[48]. This syndrome is called osmotic demyelination syndrome and sometimes the terms central pontine myelinolysis is used as historically as it was believed that only the central pontine region was affected.

Physiopathology of ODS.

The study of an animal (rat) model of osmotic demyelination syndrome has allowed us to gain much insight into the mechanisms leading to demyelination after rapid correction of chronic hyponatremia.

From the most recent studies it is now clear that demyelination is only the final part of a complex pathological process.

Several factors play a role into the pathophysiology of the disease.

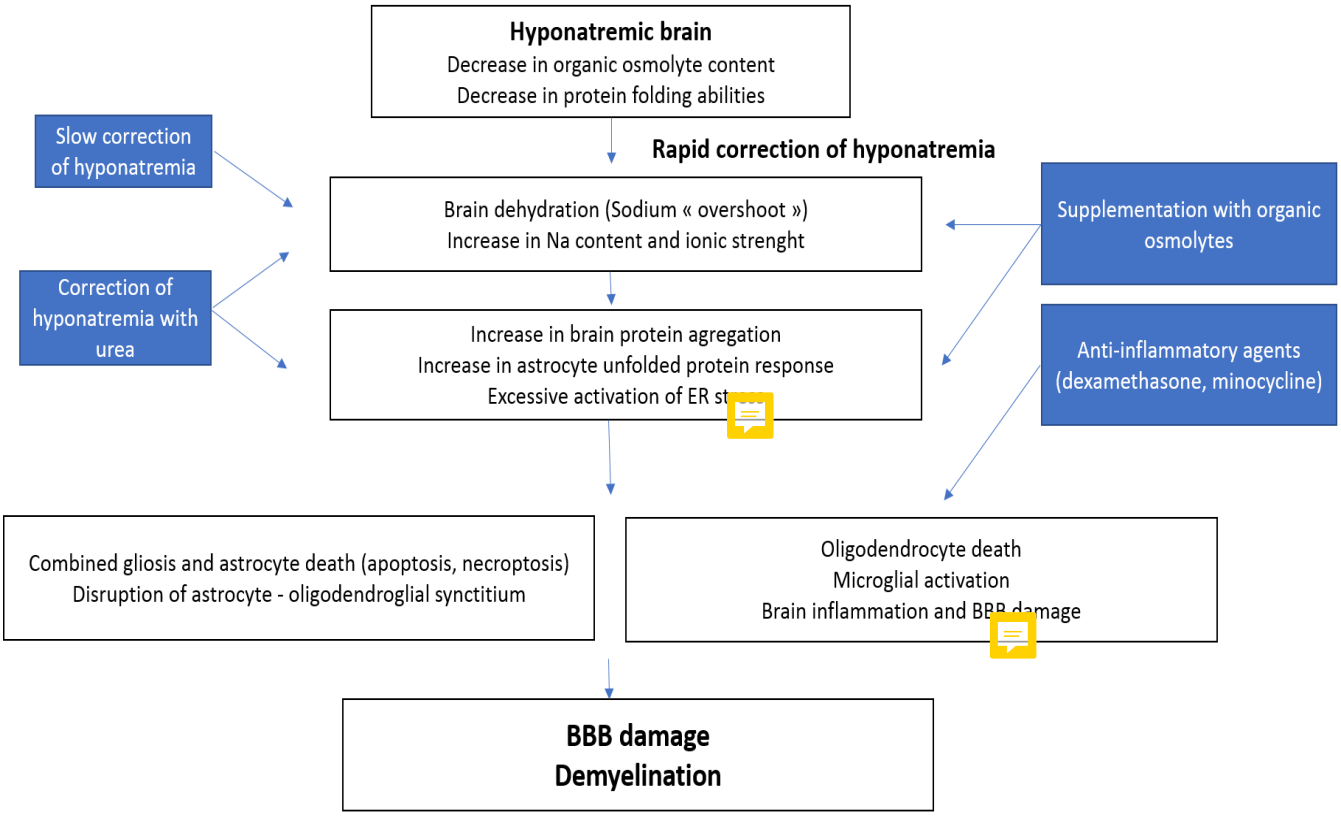
Historically, the rupture of the blood brain barrier was believed to be the main culprit allowing myelino-toxic substance such as complement factors to exert deleterious effects on the brain [49, 50]. Subsequent studies have shown that despite a nearly intact BBB permeability, demyelination lesions can still ensue. This has clarified that the opening of the BBB is probably a two steps phenomenon with one brief osmotic opening and a second more lasting inflammatory disruption which occurs in consequence of the demyelination itself[51, 52].

Likewise, microglial activation was previously thought to be ordinal in the mechanisms leading to demyelination but now it is admitted that earlier and more significant events take place before microglial activation[53].

Astrocyte are known recognized to play a significant part into the pathophysiological process with both astrocyte hypertrophy and gliosis as well as astrocyte death[51, 54, 55]. In fact, astrocyte death was shown to occur very early in regions that will later be demyelinated whereas astrogliosis actually occurs later around the demyelinating regions[53, 56]. A later study suggested that rapid correction of chronic hyponatremia induces an increase in the amount of misfolded and insoluble proteins that overload the processing capacity of the astrocyte leading to cell death. [54] It is believed that organic osmolytes which are depleted during chronic hyponatremia and not fully replenished during its correction could help to prevent osmotic and ionic buffering abilities of the cells and decrease the unfolded protein response and endoplasmic reticulum stress in astrocytes[54]. See Figure 2

Of interest rapid correction of hyponatremia with urea or in uremic animals rarely results into osmotic demyelination [57, 58]and it has been hypothesized that urea can act as an organic osmolyte Likewise, administration of exogenous myoinositol was able to prevent osmotic demyelination after rapid correction of chronic hyponatremia.

Figure 2. Proposed model for the physiopathology of osmotic demyelination syndrome.



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Clinical course and prognosis of osmotic demyelination.

The clinical course of ODS is variable, some cases of osmotic demyelination follow a biphasic course where there is an initial improvement of the clinical status of the patients as chronic severe hyponatremia is corrected, followed by a rapid deterioration when demyelination actually sets in which is usually 2-3 days after the initial correction. Other case evolves directly into severe neurological impairment without the initial improvements.

Once believed to be invariably fatal, recent reports have shown that the prognosis is actually very variable with as many as half of the patients experiencing significant recovery[59-61]

Treatment of osmotic demyelination.

Several experimental approaches have been suggested for the treatment of osmotic demyelination including administration of steroids, plasmapheresis, minocycline. However, to date the best approach relies on prevention of too rapid correction of chronic hyponatremia and if inevitable relowering of serum sodium has been shown to be helpful both experimentally and clinically when undertaken in the 24 to 48 hours following the initial overcorrection.[62-64]. Such approach involves administration of desmopressin along with either saline or dextrose infusion and should be undertaken with caution under expert guidance.

Conclusion and perspectives.

Brain as an organ has developed extraordinary adaptation mechanisms to counterbalance the effect of hyponatremia and hyposomolarity. However, these mechanisms are

clinically challenged in the daily clinical practice. Indeed, neurological consequences of hyponatremia and its correction still carries a significant toll in terms of mortality and morbidity.

Tremendous amount of work ~~that~~ has been accomplished regarding the understanding the physiopathology of hyponatremia encephalopathy either ~~chronic~~ or chronic and the mechanisms of osmotic demyelination syndrome.

There are some simple rules and protocols that can be followed to minimize deleterious consequences of hyponatremia or its correction on the brain and every clinician should be familiar with them. Although, there are still many research questions ~~remains~~ unsolved regarding the neurological complications of hyponatremia and its treatment, careful understanding of the physiological basis of brain response to hypoosmolarity can certainly lead to a better prevention of these deleterious neurological consequences.

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