Osmotic Demyelination Syndrome

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Abstract: The osmotic demyelination syndrome (ODS) has been a recognized complication of the rapid correction of hyponatremia for decades. However, in recent years, a variety of other medical conditions have been associated with the development of ODS, independent of changes in serum sodium. This finding suggests that the pathogenesis of ODS may be more complex and involve the inability of brain cells to respond to rapid changes in osmolality of the interstitial (extracellular) compartment of the brain, leading to dehydration of energy-depleted cells with subsequent axonal damage that occurs in characteristic areas. Features of the syndrome include quadriparesis and neurocognitive changes in the presence of characteristic lesions found on magnetic resonance imaging of the brain. Although slow correction of hyponatremia seems to be the best way to prevent development of the syndrome, there are new data that suggest reintroduction of hyponatremia in those patients who have undergone inadvertent rapid correction of the serum sodium and corticosteroids may play a role in prevention of ODS.

Key Indexing Terms: Hyponatremia; Osmotic demyelination syndrome **[Am J Med Sci 2010;339(6):561–567.]**

HISTORICAL PERSPECTIVES

Victor and Adams first described central pontine myelinolysis in 1959 in a series of 4 patients with the clinical findings of quadriparesis, pseudobulbar paralysis, and a characteristic pattern of myelin loss confined within the central pons.[1,2] At that time, this syndrome was felt to most likely be a sequela of alcoholism or malnutrition, and its relation to electrolyte disorders was not apparent because of the lack of routine measurement of serum electrolytes during the 1950s and 1960s.[3] It would be nearly 2 decades before a link was established in the mid-1970s between the rapid correction of hyponatremia and central pontine myelinolysis, which was later confirmed in a rat model of hyponatremia with rapid correction.[4–6]

A growing body of literature described extrapontine lesions in both rodent models of hyponatremia with rapid correction and in patients with findings of central pontine myelinolysis. Thus, the more general term osmotic demyelination syndrome (ODS) was introduced to better characterize the underlying process and highlight that demyelination may be a more generalized injury pattern in this setting. A pathological series of 58 cases revealed isolated pontine lesions in 50% of cases, with 30% of cases involving both pontine and extrapontine areas and 20% of cases solely involving extrapontine structures.[7] Pathologically, ODS is characterized by loss of the myelin sheath with relative sparing of axons and neurons in sharply demarcated lesions.[8] Notably, there is an absence of an inflammatory infiltrate in these lesions.[8] Although ODS has been most commonly reported in the context of rapid correction of hyponatremia, a number of other conditions have emerged over the last several decades, which have been associated with the development of ODS with or without a substantial change in serum sodium, suggesting that the finding of myelinolysis may be a more generalized injury pattern to changes in extracellular fluid osmolality.

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Pathogenesis of the ODS

Kleinschmidt-DeMasters and Norenberg[6] conclusively demonstrated a link between ODS and the rapid correction of hyponatremia in 1981, when they induced rapid correction of hyponatremia in rats and found demyelinating lesions in multiple areas throughout the brains on tissue examination. Further studies in rodent models of rapid hyponatremia correction have suggested that the underlying pathophysiology of ODS is linked to damage to the blood-brain barrier and changes in cellular volume that occur with rapid alterations in extracellular fluid osmolality.[9,10]

When hyponatremia/hypoosmolality ensues, extracellular water will move from an area of low solute content into cells with a higher solute content, leading to cellular edema and a risk of increased intracranial pressure. In the brain, the glial cells have an important role in brain water handling. Glial cells selectively swell after hypotonic stress and neurons do not, suggesting the existence of glia-specific water pores, which seem to consist of both aquaporin (AQP) 4 and AQP1.[11–13] The presence of AQP4 in the brain is important in the development of cerebral edema in response to hyponatremia, suggesting that these channels may have an important role not only in normal water regulation in the brain but also in the pathogenesis of hyponatremia-induced cerebral edema.[12] Over a period of about 24 to 48 hours, there is brain adaptation to cellular swelling in an effort to return cellular volume back to normal. In this regard, the glial cell rapidly expels solutes and water to restore cell volume. This response is an energy-dependent phenomenon and requires the Na-K-ATPase system (Figure 1). The enzyme Na-K-ATPase is ubiquitous and plays an essential role in cellular ion homeostasis through extrusion of intracellular sodium cations. Water obligatorily follows the extruded ions, reducing brain volume and protecting it from cerebral edema. In addition to inorganic osmolytes, organic osmolytes play an important role in brain cell volume regulation.[14,15] Animal studies have shown that osmolytes, including glycine, taurine, creatine, and myoinositol, efflux from cells during hyposmolar states and accumulate during hyperosmolar states.[16–20] This efflux occurs within 2 days of sustained hyponatremia.[20] As a consequence of both inorganic and organic solute removal, both the interstitium of the brain and cells within the brain are rendered hypoosmotic and cellular volume is returned toward normal. This process is critically important for the enclosed brain as cellular swelling in the confined space would rapidly lead to increased intracranial pressure and a risk for brainstem herniation (which can occur in acute hyponatremia). It should be noted that the brain's response to cellular edema is influenced by numerous factors including the following: estrogen (inhibits brain adaptation to edema through inhi-

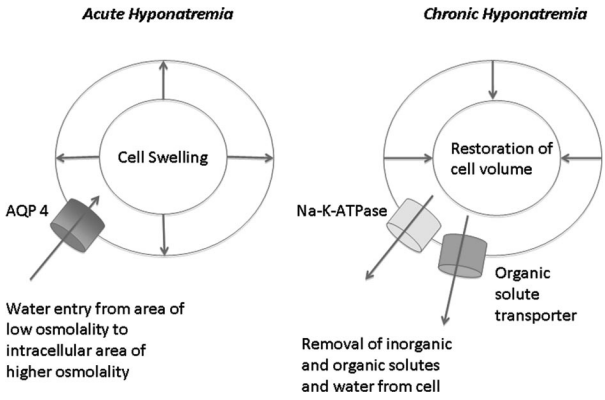

FIGURE 1. Defense of the intracellular volume in chronic hyponatremia. Initially, hyponatremia will lead to cellular swelling because of water entry from the hypotonic extracellular fluid into the relatively hypertonic cell. Over time (24–48 hours), adaptations that return cellular volume to normal occur. These include extrusion from the cell of osmotically active inorganic cations and organic molecules such as glycine, taurine, and myoinositol.

bition of the Na-K-ATPase), arginine vasopressin (leads to decreased cerebral perfusion and decrease ATP availability for ion exchange), and hypoxia (limits ATP availability).[19] In the acute setting, these modifying factors may increase the risk for acute hyponatremia encephalopathy because of impaired cellular volume regulation.

Problems can ensue if the chronic hypoosmolar state (hyponatremia) is rapidly corrected because brain cells have now adapted by decreasing their intracellular solute content (Figure 2). In the context of rapidly increasing serum osmolality (typically, as serum sodium is increased in an attempt to treat hyponatremia), brain cells will try to reverse the process described above and increase production of organic osmolytes and increase the intracellular inorganic ion content.[9] Again, these processes occur in an attempt to regulate cellular volume. However, the synthesis of organic osmolytes and the upregulation of ion pumps is a significant metabolic strain on glial cells leading to ATP depletion. In fact, there is evidence to suggest that the brain cells of alcoholic and malnourished

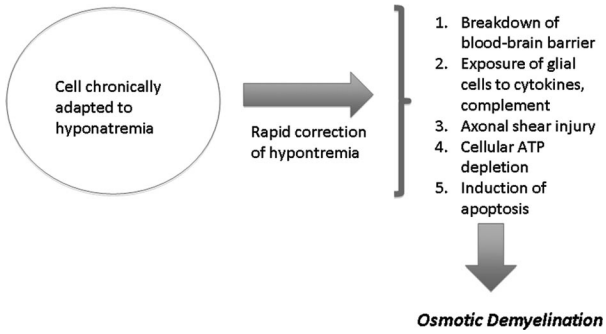

FIGURE 2. Pathogenesis of ODS. In the setting of rapid correction of hyponatremia, a series of processes occurs that leads to glial cell injury and demyelination. These include cellular ATP depletion, axonal shear injury, cellular injury and induction of apoptosis, and disruption of the blood-brain barrier with subsequent exposure of glial cells to complement and cytokines. ODS, osmotic demyelination syndrome.

patients are particularly vulnerable to energy deprivation in this setting, which renders these cells unable to respond to changes in extracellular osmolality and to regulate their cellular volume.[9] In this setting, during the correction of hyponatremia, as water shifts out of the cells to correct the imbalance between intracellular and extracellular osmolality, the resultant shrinkage of the glial cells may lead to axonal shear damage. In addition, the difference between intracellular and extracellular osmolality may lead to cellular damage and induction of apoptosis and disruption of tight junctions.[9,21] These processes result in damage and disruption to the blood-brain barrier.[21] The disruption of the blood-brain barrier in this setting may be critical, allowing serum complement, cytokines, and other inflammatory mediators to enter the central nervous system, and may directly lead to demyelination and damage to oligodendrocytes.[9,10,21]

It remains unclear why certain areas of the brain, such as the pons, are more vulnerable to developing lesions of ODS. However, a study involving a rat model of rapid correction of hyponatremia suggests that some of the areas of the brain frequently involved in ODS have delayed recovery of the loss of organic osmolytes that occur with chronic hyponatremia and, thus, cannot tolerate the rapid increases in serum osmolality.[22,23]

Potassium may also be a factor in the pathogenesis of ODS. Potassium is the principle intracellular electrolyte, and the concentration difference between extracellular and intracellular potassium is important in the modulation of cellular volume. However, adjustments of brain potassium stores occur more slowly than sodium stores. In the setting of hypokalemia, the difference between intracellular and extracellular osmolality within the brain may be potentiated during hyponatremia leading to increased water entry. There is significant evidence to show that the risk of ODS is potentiated by hypokalemia, although the mechanism of this is unclear.[5] One explanation is that hyponatremia may be more rapidly corrected with concomitant potassium administration because the Na-K-ATPase present on the cell membrane extrudes sodium as potassium is taken up into the cell to replenish depleted intracellular potassium stores. This leads to a more rapid increase in serum sodium then would be expected solely on the basis of sodium and water balance. An alternate possibility, demonstrated in rat models, is that hypokalemia leads to reduced potassium stores available to brain cells, with subsequent decrease in Na-K-ATPase activity.[24] As a result, the cell may be less able to respond to increasing osmolality in the setting of correction of hyponatremia and, thus, may be more susceptible to injury from shrinkage.

In direct contrast to the effects of hypokalemia is the protective effect of uremia against the development of ODS, noted in animal studies.[25] Brain myoinositol levels were demonstrated to increase much more quickly in azotemic rats than controls in the setting of rapid correction of hyponatremia. This ability to better regulate cellular volume led to lower rates of ODS in azotemic rats.[25] However, there is a case report of ODS in patients on dialysis who have undergone rapid correction of hyponatremia suggesting that this protective effect may be not complete.[26]

A growing body of reports of the ODS occurring in humans without any demonstrated change in serum sodium—such as patients postliver transplant, with dialysis disequilibrium syndrome, and after therapy for hyperammonemic diseases–suggests that a similar pathophysiology may occur in states where the levels of serum osmoles other than sodium change rapidly.[27–29] This suggests that any rapid change in serum

TABLE 1. Conditions associated with development of osmotic demyelination syndrome

Common
Rapid correction of hyponatremia
Alcoholism
Liver transplantation
Malnutrition
Uncommon
Cirrhosis
Severe burns
Hypokalemia
Hyperosmolar hyperglycemic state
AIDS
Postpituitary surgery
Posturological surgery
Psychogenic polydipsia
Beer potomania
Prolonged diuretic use
Hypophosphatemia
Folate deficiency
Alcohol withdrawal
Dialysis disequilibrium syndrome
Correction of hyperammonemia
Refeeding syndrome
Lithium toxicity
Hyperemesis gravidarum
Carbamate toxicity

TABLE 2. Signs and symptoms of osmotic demyelination syndrome[3,31]

Paresis (including paraparesis and quadriparesis)
Dysarthria
Dysphagia
Ataxia
Mutism
Agitated delirium
Catatonia
Parkinsonism
Dystonia
Encephalopathy
Tremor
"Locked-in" syndrome
Coma
Seizures
Impairment in short-term memory
Deficits in attention span

osmolality with resulting changes in brain cellular volume may lead to a stereotypical injury to myelin sheaths. It should also be pointed out that correction of hypernatremia and hyperglycemia have also been associated with the development of ODS.[30]

Incidence and Epidemiology

Although it is recognized that ODS is a rare disease, the frequency with which it occurs is not known. This is compounded by the frequency of asymptomatic cases, as the majority of pathologically diagnosed ODS cases are clinically asymptomatic.[5,7] The largest autopsy series have found a prevalence of 0.25% to 0.5% in a general population, of which the majority of cases were not diagnosed premortem.[5,7] Certain populations, such as alcoholics and liver transplant patients, have much higher rates of ODS on pathologic review; in particular, liver transplant patients have a postmortem rate of ODS of approximately 10%.[5,31] ODS has a peak incidence in adults aged 30 to 60 years and a male preponderance, possibly reflecting the incidence of alcoholism in this age group.[31,32] However, given the paucity of studies on the epidemiology of ODS, caution should be exercised in making any generalizations regarding the incidence of this condition.

Conditions Associated With Development of ODS

Many of the conditions predisposing to ODS are in some way related to risk factors for the development of/or rapid correction of chronic hyponatremia (Table 1). These include the syndrome of inappropriate antidiuretic hormone, burns, alcoholism, and psychogenic polydipsia.[31,32] However, conditions such as liver transplantation, dialysis disequilibrium syndrome, and congenital disorders causing hyperammonemia have been found in conjunction with the osmotic demyelination syndrome in recent years. These conditions share the common findings of disorders of solute metabolism and have a common link in that they are associated with alterations in cellular volume control.

In a review by Lampl and Yazdi in 2002, chronic alcoholism was found to be present in roughly 40% of patients with osmotic demyelination syndrome since 1986; this incidence was similar to that of cases before 1986.[5,31] Notably, they found that 17% of cases in recent decades were patients who underwent liver transplantation.

Liver transplantation is increasingly recognized as being frequently associated with ODS, both in the presence of and without rapid increase in serum sodium.[31,33] Preoperative serum sodium and the volume of blood products and crystalloid infused have been found to significantly affect the risk of development of ODS.[33,34] Both high model for end-stage liver disease-Na scores and low serum cholesterol (which has been associated with both poor liver function and malnutrition) were also found to increase the risk of development of ODS in patients undergoing liver transplant, suggesting that the cause of ODS in this group is not wholly dependent on fluctuations in serum sodium.[33]

Clinical Presentation

The classic presentation of ODS is that of mental status changes and rapidly progressive quadriparesis associated with dysphagia, dysarthria, and other pseudobulbar symptoms.[1,3] However, the clinical presentation can vary widely and is recognized to include ataxia and Parkinsonian symptoms in addition to the more common motor impairments (Table 2). Thus, a spectrum of neurological abnormalities ranging from mental status changes to full-blown quadriparesis may be encountered. The time course for development of symptoms is classically several days after the correction of hypoosmolality, although encephalopathy can occur within hours of the inciting event and symptoms may lag for up to 1 week after the inciting event.[5]

A large range of variation exists in the degree of recovery patients experience; symptoms may improve dramatically over time or not at all.[35] Serial neuropsychological examinations of patients with ODS have suggested that cognition is primarily impaired in the areas of memory retrieval and exec-

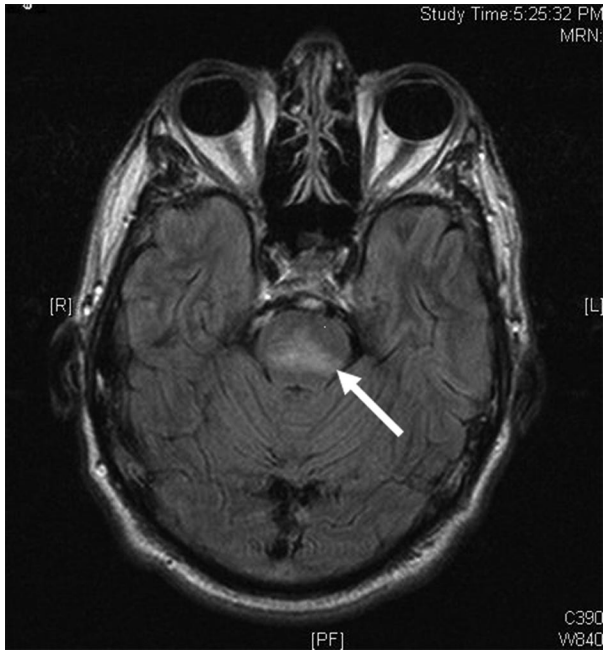

FIGURE 3. MRI of Brain. T2-weighted MRI of the brain demonstrating pontine demyelination (arrows). This patient had a history of alcoholism and cirrhosis and presented with initial serum sodium of 108 mEq/L. Treatment resulted in a rise of the serum sodium to 130 mEq/L in the first 12 hours. Subsequently, the patient developed quadriparesis and mental status changes 2 days later. There is predominant high intensity signal (T2-weighted) in the pons consistent with a demyelinating process. MRI, magnetic resonance imaging.

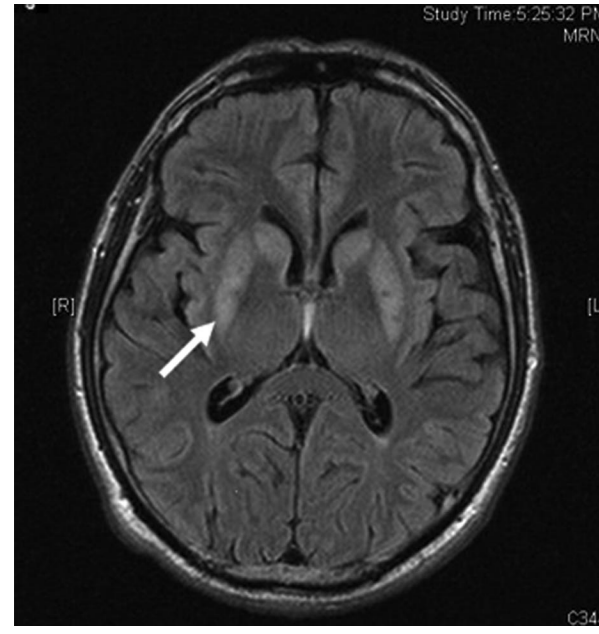

FIGURE 4. MRI of Brain. T2-weighted MRI of the brain demonstrating basal ganglia demyelination. This is the same patient described in Figure 3. MRI, magnetic resonance imaging.

utive function, with some reduction in the attention span and the speed of information processing.[5]

Findings from autopsy series suggest that asymptomatic or mildly symptomatic ODS may be significantly more common than suspected in at-risk populations such as alcoholics and postliver transplant patients.[7,32] Although the location of pontine and extrapontine myelinolysis may dictate the type of symptoms noted to a certain degree, the size of the lesions found on imaging and autopsy does not seem to predict the severity of clinical impairment.[35]

Diagnosis

Clinical suspicion for ODS should be high in any patient presenting with new-onset neurological symptoms with a recent rapid increase in serum sodium. In addition, the diagnosis should be entertained in patients postliver transplant and with any of the other risk factors listed in Table 1. Diagnosis is principally made through correlation of clinical findings with radiologic studies; there is no role for tissue examination in patients before confirmation at autopsy.

The imaging modality of choice is magnetic resonance imaging (MRI) of the brain, which has been demonstrated to be more sensitive than computed tomography.[36] Typical MRI lesions include hypointense T1-weighted lesions and hyperintense lesions demonstrated on T2-weighted, proton density-weighted, and FLAIR MRI (Figures 3 and 4).[36,37] These lesions often are present in a trident-shaped area in the central pons, with sparing of the ventrolateral pons and the corticospinal tracts, and do not enhance with contrast.[36,37] Modified MRI techniques may have a future role in predicting the long-term course in patients with ODS; one case report described improvements in diffusion-weighted MRI that were seen in a patient who had transient quadriparesis and dysarthria.[38] Typically, radiologic findings do not improve over time, even if the patient has made a complete or nearly complete clinical recovery.[35]

Prevention and Management

A recently convened panel of experts recommended that, based on the results of cohort studies and literature reviews, the optimal rate of sodium correction to avoid ODS is less than 10 to 12 mEq/L per 24 hours and less than 18 mEq/L in 48 hours.[39] However, they noted that patients with other risk factors for ODS may still be at risk for development of the syndrome at these rates of correction and may require slower rates.

The patient who presents with both risk factors for development of ODS and symptoms of hyponatremia necessitating an immediate rise in serum sodium, such as seizures or obtundation, presents a potentially difficult situation. Generally, most life-threatening manifestations of hyponatremia will abate with a 5% rise in serum sodium (for instance, a patient with a serum sodium of 105 mEq/L and seizing will usually respond with a rise in the serum sodium on the order of 5–7 mEq/L).[3] Subsequent correction of serum sodium should ideally be limited to a rise of no more than 8 to 12 mEq/L per 24 hours to limit the risk of developing ODS. As an additional caution, a prudent recommendation would be that patients with concomitant risk factors for development of ODS, such as alcoholism, malnutrition, or hypokalemia, should have their correction in serum sodium limited to no more than 8 mEq/L per 24 hours.

It is imperative to account for the effects of repleting potassium on serum sodium. As an example, consider a patient who presents with volume depletion and a history of diuretic use who has serum sodium of 120 mEq/L and serum potassium of 2.5 mEq/L. If this patient receives 1 L of 0.9% saline and 100 mEq of oral potassium chloride to correct both hyponatremia and hypo-

kalemia, the total amount of cations administered will be 254 mEq. As the volume of fluid infused is 1 L, in effect, this is equivalent to giving a hypertonic solution; the potassium ingested will serve to increase serum sodium concentration through the action of the Na-K-ATPase. Therefore, correction of hypokalemia should be undertaken with great care in patients at risk for ODS, especially those patients presenting with concomitant risk factors such as malnutrition and alcoholism.

Patients with hyponatremia who do not have an ongoing stimulus for vasopressin production, such as patients with hyponatremia caused by diuretics, beer potomania, psychogenic polydispia, or uncorrected adrenal insufficiency, represent a subset of patients who are likely to present with or develop a dilute urine concentration.[40] Correction of volume loss or repletion with corticosteroids can lead to a diuresis of urine with very little sodium, which may induce rapid correction of hyponatremia independently of ongoing sodium administration. Therefore, great care must be taken in monitoring serum sodium and urinary losses, and in some cases administration of desmopressin is necessary to prevent overly rapid "auto-correction" of hyponatremia by inducing a more concentrated urine.[41]

The introduction of selective vasopressin receptor antagonists (such as conivaptan and tolvaptan) allow for gradual correction of euvolemic or hypervolemic hyponatremia through induction of a dilute urine.[42,43] In clinical studies, the rates of serum sodium correction have been modest and within the goals suggested above.[44,45] There have been no reported instances of ODS with the use of these agents, but caution needs to exercised and close monitoring of serum sodium is required.[44–46]

Regardless of the steps taken to avoid a rapid increase in serum sodium while treating hyponatremia, patients will occasionally have overly rapid correction of their hyponatremia. Management in this setting is more uncertain than for prevention of rapid correction of serum sodium. Although the role of reinduction of hyponatremia to mitigate the effects of overly rapid correction of hyponatremia is controversial, there is growing evidence to support its use. Gankam Kengne et al[47] recently examined the effects of reinduction of chronic hyponatremia in rats who had roughly a 30-mEq/L change in serum sodium within 12 hours and found that reinducing mild hyponatremia reduced both neurological manifestations and mortality from 100% to 6%. Large studies in humans are lacking, but numerous case reports suggest that some level of protective effect can occur from reinduction of hyponatremia.[48,49] Similarly, there are cases that demonstrate improvement in neurologic symptoms after hyponatremia is reintroduced, suggesting that there may be some benefit to treating patients even after the onset of ODS.[48,49]

Corticosteroids have been used in anecdotal cases to mitigate the severity of ODS. One proposed mechanism of this effect is to stabilize the blood-brain barrier, which has been demonstrated in rodent studies.[47,50] Dexamethasone is the agent most commonly used in animal studies and has repeatedly demonstrated a modest benefit in reducing neurological symptoms.[47,50] However, these same studies suggest that it may be inferior to reintroduction of hyponatremia.[47] Although it remains unclear whether there is any conclusive benefit in humans, either as sole therapy or as an adjunct to reintroduction of hyponatremia, usage of corticosteroids may be a reasonable consideration in patients with overly rapid rise in serum sodium and associated conditions that raise the risk of ODS. However, the timing of corticosteroid administration is not well determined.

Administration of myoinositol, a naturally occurring osmolyte extruded by the brain in cases of severe hyponatremia, has also been shown to improve mortality in rodents with rapid correction of chronic hyponatremia.[23] The mechanism of protection is presumed to be restoration of intracellular organic osmotic particles and protection from cellular dehydration. Urea administration in animal studies of severe hyponatremia similarly increased brain organic osmolyte concentrations and reduced symptoms of ODS. Clinical experience is extant with this therapy, as oral and intravenous urea have been used in Belgium to correct hyponatremia for decades.[23,51]

Plasmapheresis appeared beneficial in a series of 4 patients with ODS; the putative mechanism was reduction in inflammatory mediators with potential preservation of the blood-brain barrier.[52] Further confirmatory studies are required regarding this therapeutic option.

After ODS is established, dopaminergic medications similar to those used in the treatment of Parkinson's disease are helpful in ameliorating symptoms.[5] As in other neurological disorders, a multidisciplinary approach involving physical therapy and other specialists in neurological rehabilitation is commonly used for patients with moderate to severe neurological impairment, although data for evidence of improvement are lacking.

Prognosis

The outcomes of patients with the ODS are often disappointing. Reviews from initial descriptions were dismal, and a mortality as high as 50% to 90% at 3 months from diagnosis was reported for decades.[35,53,54] A more recent review of 44 German patients with osmotic demyelination revealed only a 6% mortality during the study period, and 40% of patients recovered without any noticeable neurologic abnormalities.[35] Notably, 95% of the patients in this study population were chronic alcoholics. Tempering these data, however, is the persistence of at least 25% of patients cited in most studies who develop severe, incapacitating neurological disease requiring lifelong support ranging from persistent paralysis to severe ataxia.[35] It remains to be seen whether changing clinical practice and developing therapies for ODS will affect these outcomes.

CONCLUSION

The ODS is a devastating complication of rapid correction of hyponatremia and the result of a growing number of conditions that result in the same result independent of changes in serum electrolytes. Current models of the pathogenesis of the syndrome are able to characterize the effects of alterations in serum sodium on the blood-brain barrier and resultant axonal damage, but have not yet been able to explain how conditions such as postliver transplantation may result in ODS. In addition, pathologic studies suggest that the diagnosis of ODS is often clinically unapparent in many patients. Although therapies such as reintroduction of serum sodium, corticosteroids, myoinositol, and urea show benefit in animal models, clinical experience is limited, and no large multicenter clinical studies have been performed to demonstrate similar effects in humans. These studies are exceedingly difficult to perform given the heterogeneity of at-risk patients and the rarity of the condition. However, such studies are necessary to inform the judgment of clinicians. Until the time when this research is performed, the safest way to avoid the development of ODS is slow, judicious correction of hyponatremia with frequent laboratory monitoring.

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