SciMedCentral

JSM Brain Science

Review Article

Prevention and Treatment of the Osmotic Demyelination Syndrome: A Review

Mohamed Osama Hegazi* and Abdallah Nawara

Department of Internal Medicine, Al Adan Hospital, Kuwait

***Corresponding author**

Mohamed Osama Hegazi, Department of Internal Medicine, Al Adan Hospital, PO Box 262, Hadeya, 52853, Kuwait, Telephone: 965-97403085; Fax: 965-23941836; Email: drosama02@gmail.com

Submitted: 26 September 2016

Accepted: 28 November 2016

Published: 01 December 2016

Copyright

© 2016 Hegazi et al.

OPEN ACCESS

Keywords

- Demyelination
- Osmotic
- Prevention
- Sodium
- Treatment

Abstract

The osmotic demyelination syndrome (ODS) is a central nervous system disorder that results from neuronal damage related to abrupt fluctuations of osmolality. In spite of the possibility of full or partial recovery in a considerable proportion of cases, ODS is still categorized as a disorder with poor prognosis that may lead to severe permanent disability or death. Efforts towards the better understanding of the nature of the disorder and the development of effective modes of prevention and treatment continued since Adams, et al., in 1959, first identified the syndrome. Prevention of the ODS that is related to hyponatremia overcorrection starts from the differentiation between chronic and acute hyponatremia, goes through defining a target and method for serum sodium elevation, and ends with re-lowering the unpredicted overly rapid rise of serum sodium. Treatment of the ODS with re-lowering the serum sodium has been evaluated in an animal study and human case reports. Treatment with plasmapheresis and/or intravenous immunoglobulin has been also reported. In the absence of controlled human studies, treatment options for the ODS remain devoid of certainty and validity. Patients who have already developed the syndrome may require long-term intensive supportive therapy looking for a possible complete or partial recovery.

INTRODUCTION

The osmotic demyelination syndrome (ODS) is a central nervous system disorder that results from neuronal damage related to abrupt fluctuations of osmolality. ODS is mainly described in relation to the rapid correction of hyponatremia [1-4]. The increased awareness of the disorder together with the rapidly rising utilization of magnetic resonance imaging (MRI) helped to improve the detection and evaluation of the ODS. Efforts towards the better understanding of the nature of the disorder and the development of effective modes of prevention and treatment continued since Adams, et al., in 1959, first identified the syndrome [5]. ODS is reported not only due to the rapid correction of hyponatremia, but also in relation to a number of other insults including, hypernatremia [3,6,7], hemodialysis [8-10], hyperglycemia or its treatment [11-17], alcohol abuse [5,18-20] and liver transplantation [21-23]. Pathologically, ODS is characterized by the development of demyelinating brain lesions that classically occur in the basis pontis (central pontine myelinolysis); in addition to a number of often bilateral extrapontine sites including the cerebellum, basal ganglia, lateral geniculate bodies, thalamus and cerebral cortex (extrapontine myelinolysis) [5, 24]. Histopathologic findings include non-inflammatory injury or death of oligodendrocytes as well as astrocytes; and loss of myelin with relative axonal sparing [3,5,25,26]. Pathophysiologically, ODS mainly occurs with the rapid correction of chronic (≥ 48 h or unknown duration) hyponatremia [3,4]. The brain adapts to hyponatremia by losing extracellular water into the cerebrospinal fluid and by extruding sodium, potassium and certain organic solutes (osmolytes) out of the brain cells [6]. Both mechanisms result in lowering the brain volume towards normal, thus avoiding brain edema. Organic osmolytes move and re-accumulate slowly compared to inorganic ions [2,3,26,27]. In the setting of chronic hyponatremia, the overly rapid correction of serum sodium concentration without sufficient time for osmolytes to re-accumulate into the brain cells may result in an undesired brain cell injury (osmotic demyelination) [2,3,6,26]. The clinical manifestations of ODS mainly include dysarthria, dysphagia, quadriparesis, movement disorders, behavioral disturbances, seizures, lethargy and coma [2,3,7,19]. Although ODS may cause permanent disability or death, many patients can have a full or satisfactory spontaneous functional recovery [19,28]. However, recovery with the help of supportive care is unpredictable i.e. unrelated to the severity of the initial presentation [7,28].

Etiology of the ODS

As mentioned above, ODS is mainly described with the rapid correction of chronic hyponatremia. The disorder is more likely to occur after correction of the severe chronic hyponatremia with serum sodium concentrations below 120 mmol/L [3]. The

magnitude of rise in serum sodium represents the absolute value of increase in sodium in an identified period i.e. the extent of rise in mmol/l in 12 hours, 24 hours or 48 hours. Some studies in rats showed a stronger correlation of ODS with the rate of correction [29] while others showed that the magnitude of correction is a more important factor for the development of ODS [30]. Some authors believe that both the magnitude and rate of increase in serum sodium concentration during treatment are critical [31,32]. The majority of ODS cases occurred after a rate of correction that exceeds an arbitrary cut off of 0.5 mmol/L/h [33,34]. In a review of 56 cases with severe hyponatremia (serum sodium ≤ 105 mmol/L) no neurologic sequelae were observed among patients in whom the rate of correction was ≤ .55 mmol/L/hour [35]. Nevertheless, ODS has been reported in relation to slower rates of correction [36-38], and rarely, with the correction of milder degrees of hyponatremia [39]. A rapid controlled increment in serum sodium is observed to be well tolerated in both animals [30] and humans [4], provided the 24-hour limit is not exceeded. Owing to this observation, researchers nowadays consider the magnitude of rise as the crucial factor in determining overcorrection. In a review of 54 cases of ODS, the sodium concentration increased by ≥ 12 mmol/L during the first 24 hours or ≥ 20 mmol/L during the first 48 hours [40]. However, in risky patients e.g. those with alcohol abuse, ODS may develop with a smaller magnitude of sodium rise [40]. Experts now consider a rise of ≥ 10 mmol/24 hours or ≥ 18 mmol/48 hours as overcorrection that may carry the risk of the development of the ODS [41].

The overly rise in serum sodium with consequent ODS was not only related to the use of 3% saline, but also to normal (0.9%) saline [35,42,43]. In addition to the amount and rate of infused saline, the potentially disastrous superfluous rise of serum sodium could be related to one or more other additional factors that include:

a) A decrease in antidiuretic hormone (ADH) release due to correction of hypovolemia, drug modifications, stabilization of the patient's initial condition, and/or glucocorticoid use [44],

b) The progress to a water diuresis phase with excretion of large amounts of dilute urine [41]

c) The employment of other therapeutic measures to treat the hyponatremia such as water restriction and diuretic cessation.

Certain conditions make the patient with rapid sodium rise vulnerable to develop the ODS. These include a very low sodium level (serum sodium of 105 or less) before attempting correction [41], concomitant hypokalemia [45], alcohol abuse [5,41], liver disease [39,41] and malnutrition [5,39,41].

As mentioned in the introduction, ODS has been also reported in relation to a number of conditions other than the rapid correction of hyponatremia, including severe hypernatremia [3] or hyperosmolality [7], hemodialysis [10], marked hyperglycemia and its treatment [14], alcohol abuse [18] and liver transplantation [22]. The pathophysiology of the ODS in relation to these disorders is more obscure [7,22].

Pathogenesis the ODS

The exact etiopathophysiology of the ODS is not fully understood. Sever hyponatremia may result in brain edema with its consequences in the form of headache, vomiting, disturbed level of sensorium, and convulsions. The increase in intracranial pressure carries the risk of brain herniation and death. However, the detrimental consequences of brain edema are more likely to occur with the acute severe hyponatremia rather than with the chronic one. The brain adapts to hyponatremia by losing extracellular water into the cerebrospinal fluid and by extruding sodium, potassium and certain organic solutes (osmolytes) out of the brain cells [46]. Both mechanisms result in diminution of the brain volume toward the normal thus reversing or minimizing brain edema [46]. Organic osmolytes move and re-accumulate slowly compared to inorganic ions [26,27]. Therefore, in the setting of chronic hyponatremia the overly rapid correction of serum sodium before giving time for osmolytes to re-accumulate may further shift the water from the brain cells resulting in more shrinkage of the brain volume [46]. That further shrinkage is believed to induce neuronal cell injury resulting in osmotic myelinolysis. Interestingly, regional differences in organic osmolytere accumulation have been associated with particular patterns of demyelination in ODS, but the mechanisms connecting impaired osmolytere accumulation, myelin loss, and the cells involved in this process remain elusive [26]. Previously, it was believed that oligodendrocytes that constitute the sheaths are particularly sensitive to osmotic changes and that the distribution of ODS lesions parallels that of oligodendroglial cells as also supported by the pathologic findings of loss of myelin sheaths with relative axonal preservation [47]. Researchers are recently shedding the light on the role of astrocytes in the process of osmotic demyelination [26]. The foot processes of astrocytes, which encircle both brain capillaries and neurons, express aquaporins (such as aquaporin-4) that allow water to cross the blood-brain barrier [3]. Astrocytes protect neurons from osmotic stress; in response to hypotonicity allowing neurons to lose water and maintain their volume while astrocytes swell. Within 24 to 48 hours after this transfer, astrocytes restore their volume through loss of organic osmolytes, but this makes them vulnerable to injury from rapid normalization of the plasma sodium concentration. Recapture of lost brain osmolytes may take a week or longer. Therefore, rapid correction of hyponatremia is a hypertonic stress to astrocytes that are depleted of osmolytes, triggering astrocyte apoptosis, and, eventually, brain demyelination [3]. Additionally, microglial activation with release of pro-inflammatory mediators and disruption of the blood brain barrier contribute to the process of osmotic demyelination [26].

Prevention of the ODS

Differentiation of acute from chronic hyponatremia: Trials to avoid the development of the osmotic demyelination syndrome started after shedding the light on its relation to the rapid correction of hyponatremia [1]. First step in prevention is to differentiate chronic from acute hyponatremia. Patients with severe hyponatremia of less than 48 hours duration (acute hyponatremia) usually present with neurological symptoms due to brain edema and are prone to fatal brain herniation if untreated [31,48]. Nonetheless, they respond to a bolus or more of hypertonic (3%) saline that are capable of producing rapid controlled rises of their serum sodium. However, they tolerate the controlled rapid rises of serum sodium and their risk of

developing ODS is significantly low [4,31,49]. The typical forms of acute hyponatremia include acute hyponatremia in Marathon runners, ecstasy abusers and some cases of self water intoxication in psychotic patients. On the other hand, patients with chronic hyponatremia (hyponatremia of ≥ 48 hours or uncertain duration) are presumed to have already developed the process of adaptation with extrusion of water, electrolytes as well as organic osmolytes out of the brain cells. Therefore they are candidates to develop the post-therapeutic neurological deterioration termed the ODS [46]. Caution should be taken while attempting to raise the serum sodium of chronic hyponatremia patients. Whenever uncertainty exists about the duration of hyponatremia, it is prudent to consider it chronic.

The method used to raise serum sodium: Next would come the method used to raise the serum sodium in chronic hyponatremia patients. In all patients, conservative measures should be initiated with withdrawing an offending medication such as a diuretic or a drug that may produce inappropriate antidiuretic hormone release. In cases with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), water restriction should be employed. In a review of 185 patients with symptomatic hyponatremia, none of the 27 patients who were treated with water restriction and the 35 who were treated with diuretic cessation developed ODS [50]. Hypertonic saline is usually reserved for patients with severe chronic hyponatremia with severe neurological symptoms; particularly convulsions and coma. Additionally, it may be used with caution in patients with moderate neurological symptoms that are persistent or progressive in spite of the conservative measures with failure to reach a satisfactory initial rise of serum sodium of 6mmol/L in the first 24 hours [1]. Isotonic saline (0.9% saline) infusion is usually indicated for the treatment of hypovolemic hyponatremia [4]. However, it should be kept in mind that isotonic saline infusion may indeed cause an overly rapid correction of plasma sodium with ODS as a possible consequence. Treating chronic hyponatremia patients with isotonic saline should be associated with as much caution as with hypertonic saline.

Target and rate of serum sodium rise: It is very difficult, if not impossible, to set 'safe' rate limits for correcting hyponatremia [40]. The risk of developing the ODS seems to depend not only on the rate of increase in serum sodium concentration but also on associated underlying risk factors, such as a history of alcohol abuse, liver disease, use of thiazides or antidepressant medications and the original biochemical degree and duration of hyponatremia [40].

In patients with chronic hyponatremia and severe neurological symptoms (active convulsions or coma), a rapid correction of hyponatremia is required to control the severe symptoms. An increase in serum sodium of 2-4 mmol/L in 2-4 hours may be beneficial with low risk of ODS; provided it is followed by caution not to exceed the total of 6-8 mmol/L in 24 hours [4]. This rapid controlled rise is usually achieved with a bolus or two of 100 ml of 3% saline.

Systematic review of the cases of ODS published during the past 15 years generally supports restricting increases in serum sodium concentration to < 10 mmol/L in the first 24 h and < 18 mmol/L in the first 48 h [40]. Hence, in the management of chronic hyponatremia without severe symptoms, it is advocated to adopt a cautious approach and limit the correction to 6-8 mmol/L in the first 24 hours, 12-14 mmol/L in the first 48 hours [41].

Extra caution with high risk patients: Patients at high risk of developing the ODS include those with alcohol abuse, concomitant hypokalemia, malnutrition and liver disease. A thoughtful balanced approach that takes into account the presence or absence of significant hyponatremia symptoms, the chronicity of the process, and the susceptibility of the patient to develop the complications of the hyponatremia itself as well as its overcorrection should be adopted [49]. Whenever possible, in these cases, the conservative measures such as water restriction and stopping the offending drug should be given the chance before implementation of more active measures, especially in absence of severe symptoms. Moreover, a controlled correction of hyponatremia with desmopressin prophylaxis may be considered [51]. In cases of concomitant hypokalemia, the administration of potassium may raise the serum sodium and osmolality in the hyponatremic patient. Therefore, the impact of the given potassium on hyponatremia correction should be taken into account. Additionally, whenever hypokalemia and severe hyponatremia present simultaneously, a more gentle approach in correction of the hyponatremia is necessary. Generally, in all high-risk patients, slower rates of correction and lower targets of serum sodium should be considered in the presence of vigilant monitoring. Weighing the risk of developing the ODS versus the benefit of correcting the severe hyponatremia is always crucial.

Monitoring: There no way to precisely predict the rise in serum sodium in response to a given rate of infusion of isotonic or hypertonic saline. Even treatment with salt tablets was reported to produce an overshoot of serum sodium [52]. Hence, monitoring is of utmost importance. Monitoring helps to anticipate or early-detect the inadvertent rise in serum sodium and guides the physician to stop active hyponatremia treatment measures and to consider remedies that reverse the rapid serum sodium rise.

Monitoring of serum sodium should be carried out every 2-4 hours. Some experts advocate vigilance whenever the rate of sodium rise exceeds 0.5 mmol/L/hour while others prefer to record it in terms of increments per a specified period (12 or 24 hours) [4].

Monitoring of urine output and urine osmolality is also as important as monitoring of serum sodium; however, it is not always feasible. The water diuresis phase is characterized by a remarkably rapid excretion of dilute urine and is observed in a significant proportion of sodium overcorrectors [4,41,53]. In one of the recorded cases, the urine output reached 1950 ml in 7 hours with urine osmolality of 90 mOsm/kg [53]. Perianayagam et al., studied reversal of hyponatremia overcorrection and recorded the urine output in most of the overcorrectors [54]. The range of urine output was 93-425 ml/hour in 13 overcorrected cases with a calculated average of 292 ml/hour before attempting reversal [54]. Some experts define the water diuresis phase by a urine osmolality of 80 mOsm/kg [55]. Generally speaking, a rise in urine output of 100 ml/hour or more in the context of hyponatremia active treatment signals increased risk of overly rapid rise in

serum sodium concentration and warrants measuring urine osmolality [40].

Prophylaxis against overcorrection: Prophylaxis against inadvertent serum sodium rise may be contemplated in patients with high risk of developing the ODS, or in hypovolemic patients who are liable to serum sodium overshoot after volume resuscitation. Desmopressin (DDAVP) given in conjunction with the hypertonic saline might result in a more controlled rate of correction of hyponatremia, avoiding the unanticipated emergence of water diuresis in patients at high risk for overcorrection (e.g., patients with inappropriate antidiuretic hormone secretion as a result of antidepressants; hyponatremia caused by hypovolemia, low dietary solute intake, cortisol deficiency, or thiazide diuretics) [54]. Sood et al., reported a series of 24 patients admitted with sodium <120 mmol/L treated with a combination of DDAVP and hypertonic saline infusion [56]. The authors were targeting a rise of sodium of <6 mmol/L within the first 24 hours, and achieved an average increase of 5.8 mmol/L [56]. None of the patients had excessive correction [56]. Additionally DDAVP may be given to prevent the inadvertent sodium rise once the water diuresis phase is detected [54,57].

However, DDAVP may be avoided "or used with extreme caution" in patients who cannot control their fluid intake (e.g. psychogenic polydipsia patients) [54]. It is also considered ineffective in hypervolemic hyponatremia patients [58]. DDAVP is typically prescribed for central diabetes insipidus, von Willebrands disease and for enuresis. DDAVP-associated hyponatremia is a known complication of DDAVP therapy. Achinger et al., reported a series of ODS cases following the discontinuation of DDAVP with or without hypertonic or isotonic saline infusion to treat the DDAVP-related symptomatic hyponatremia [59].

Another approach to minimize the risk of ODS is to infuse 5% dextrose (D5W) that matches the urine output whenever the sodium is observed to rise too rapidly or once the water diuresis phase ensues [60].

It has been observed that patients with azotemia have low liability to develop ODS on rapid correction of hyponatremia by hemodialysis [61]. The reasons why ODS is uncommon in patients treated with hemodialysis are not completely understood; however, one mechanism may be that the rise in serum osmolality induced by the rise in serum sodium during dialysis may be counterbalanced by a fall in serum osmolality induced by the removal of urea [62]. Urea (given orally or enterally) is an option to treat the chronic hyponatremia in euvolemic patients with SIADH [63]. In a study in rats, overcorrection of severe hyponatremia with urea resulted in significantly lower mortality and neurological impairment than the overcorrection caused by lixivaptan or hypertonic saline [64]. Thus in the future, urea therapy may represent an option to prevent ODS in cases of hyponatremia overcorrection.

Re-lowering of the serum sodium after inadvertent overcorrection: Overcorrection of hyponatremia should be viewed as a medical emergency [55]. Relowering the serum sodium may be considered in patients on treatment for chronic severe hyponatremia with rate of correction having exceeded the recommended limit (8 mmol/L in any 24-hour period), particularly if they are prone to develop the ODS (starting serum sodium of ≤105 mmol/L, alcoholism, liver disease, malnutrition, hypokalemia). The concurrent administration of desmopressin and 5% dextrose (D5W) in water can be given to cautiously re-lower the serum sodium concentration when therapeutic limits have been exceeded [55]. Re-lowering serum sodium using DDAVP and D5W was described in 22 patients reported in two retrospective studies [54,65]. The serum sodium was re-lowered by 2 to 9 mmol/L below the peak level at rates ranging from 0.09 to 1.6 mmol/L per hour. No adverse effects were observed.

The ODS in situations other than hyponatremia overtreatment: The pathophysiology of ODS in relation to hypernatremia or hyperosmolality, liver transplantation, hemodialysis, marked hyperglycemia or its treatment, and alcohol abuse is not clearly understood. Hence there is no way to prevent the ODS whenever it occurs with any of these conditions without sodium changes. A careful look at the serum sodium and its changes may reveal minor fluctuations that may be responsible for the complication in these susceptible patients. Additionally, care while prescribing I.V. fluids to these patients is advocated with close monitoring of the changes in serum sodium, serum osmolality may be helpful. Frequent monitoring may lead to better understanding of the nature of ODS with these conditions. We encourage researchers who report the ODS with hyperglycemia, hypernatremia or hyperosmolality to frequently record and document the changes in glucose, sodium, and measured osmolality. Moreover calculation of the corrected sodium may be of help in the setting of ODS with the hyperosmolar hyperglycemic state or with severe hyperglycemia.

Treatment of ODS

Generally, there is no specific treatment of certain benefit for the ODS [43,47,57]. Patients who have already developed the syndrome may require long-term intensive supportive therapy looking for a possible complete or partial recovery [28]. Since patients with severe ODS frequently develop aspiration pneumonia and respiratory failure, endotracheal intubation and ventilator support are often required [28]. The decision to withhold life-supporting therapies should not be taken unless the probability of a delayed favorable outcome has been seriously considered. The initial severity of the illness is not predictive of the long-term prognosis [28].

To date, all the ODS suggested modes of treatment are considered experimental and are published in animal studies, single case reports or small case series. The pathophysiology of CPM is related to a relative dehydration of the brain during the correction of hyponatremia, resulting in cell death and demyelination, therefore relowering serum sodium may theoretically produce gentle rehydration that is not an unreasonable approach to attempt reversal of the myelinolysis process [66]. The potential benefit of re-lowering of serum sodium after the development of ODS symptoms was shown in an animal study [67] and human case reports [66,68-70]. Soupart et al., studied reinduction of hyponatremia in rats with myelinolysis-related symptoms [68]. Survival was significantly better among rats treated with relowering serum sodium with hypotonic fluids. Moreover, the rats that were treated four hours

after symptom onset had better outcomes than those that were treated 8 to 10 hours after symptom onset; indicating a beneficial role of early intervention . Early manifestations of osmotic demyelination following excessive correction of hyponatremia have been reversed in individual case reports by re-lowering of the serum sodium concentration. The published human case reports showed improvement in neurological manifestations of the ODS after relowering serum sodium with D5W [69] or D5W and DDAVP [68,70]. There is no defined target for lowering the sodium level. However re-lowering sodium to a level that is just below the maximal target value at 48 hours (< 18 mmol/L above the initial serum sodium) appears to be reasonable [70].

Plasmapheresis (PP) and/or intravenous immunoglobulin (IVIG) have been suggested as possible options for the management of ODS [71-74]. The mechanism of action of PP and IVIG in the management of ODS is unknown [71]. One proposed theory is that myelinotoxic products are released after the osmotic stress insult and the burden may be reduced by PP [72]. One other proposed theory is ODS may be a result of immunologic process, and thus IVIG treatment may help improve the outcome [71]. In most of the reported ODS cases successfully treated with IVIG and PP together, or either alone, treatment was initiated within the first week of symptom onset. Atchaneeyasakul et al., reviewed most of the published case reports of ODS cases receiving IVIG or/and PP. Studied cases showed neurological improvement, however a proportion of them were left with residual deficits. In most of the reported ODS cases successfully treated with PP/IVIG, treatment was initiated within the first week of symptom onset [71]. In the case when the treatment started after a much longer delay, neurological improvement was less satisfactory [71]. This observation may emphasize an “as early as possible” concept also with regards to PP/IVIG treatment of the ODS [75]. Intriguing is the observation that in a few of these cases, the ODS was due to hypernatremia rather than hyponatremia rapid overcorrection [76-78]. These cases of ODS are more poorly understood and will not benefit from the option of sodium re-lowering [75]. So far, and until additional studies with larger numbers of patients show up, PP &/or IVIG remain to be experimental in the ODS treatment.

CONCLUSION

ODS is a central nervous disorder that is related to fluctuations or abrupt changes in osmolality; with the rapid correction of chronic hyponatremia being the main etiological factor. The syndrome is also reported in relation to a number of other conditions that include severe hypernatremia or hyperosmolality, hemodialysis, hyperglycemia, alcohol abuse and liver transplantation. In the setting of overly rapid correction of hyponatremia, certain factors make the patient more prone to develop the ODS. These include concomitant hypokalemia, very low serum sodium before correction, malnutrition, alcohol abuse and liver disease. Prevention of the ODS starts with evaluation of every hyponatremia case concerning the urgency in raising serum sodium and the patient’s risk of developing myelinolysis. The extent of serum sodium elevation should be limited to 4-6 mmol/L in the first 24 hours and 12-14 mmol/L in the first 48 hours. Frequent periodic monitoring of serum sodium, urine output, and urine osmolality is mandatory especially with the fact that hyponatremia overcorrection is often unpredictable. Prophylaxis against overcorrection D5W or with DDAVP may be employed in risky patients. Re-lowering the serum sodium after the inadvertent rise with D5W and DDAVP may be effective in preventing the ODS. There no way described so far to prevent the ODS in relation to conditions other than hyponatremia correction. Currently, there is no standard therapy for ODS other than supportive therapy. Re-lowering serum sodium with D5W and/or DDAVP is a treatment option that may be effective in reversing early manifestations of ODS following excessive correction of hyponatremia, however evidence came only from case reports and animal studies. Treatment with PP and/or IVIG showed some benefit only in human case reports, however improvement was observed in a few cases of hypernatremia-related ODS without hyponatremia overcorrection. With the paucity of evidence concerning the ODS treatment, we believe an ounce of prevention is worth a pound of cure.

REFERENCES

1. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med. 1986; 314: 1535-1542.
2. Sterns RH, Thomas DJ, Herndon RM. Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. Kidney Int. 1989; 35: 69-75.
3. Sterns RH. Disorders of plasma sodium--causes, consequences, and correction. N Engl J Med. 2015; 372: 55-65.
4. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013; 126: 1-42.
5. Adams RD, Victor M, Mancall EL. Central pontine myelinolysis: a hitherto undescribed disease occurring in alcoholic and malnourished patients. AMA Arch Neurol Psychiatry. 1959; 81: 154-172.
6. McKee AC, Winkelman MD, Banker BQ. Central pontine myelinolysis in severely burned patients: relationship to serum hyperosmolality. Neurology. 1988; 38: 1211-1217.
7. Hegazi MO, Mashankar A. Central pontine myelinolysis in the hyperosmolar hyperglycaemic state. Med Princ Pract. 2013; 22: 96-99.
8. Tarhan NC, Agildere AM, Benli US, Ozdemir FN, Aytekin C, Can U. Osmotic demyelination syndrome in end-stage renal disease after recent hemodialysis: MRI of the brain. AJR Am J Roentgenol. 2004; 182: 809-816.
9. Jha AA, Behera V, Jairam A, Baliga KV. Osmotic demyelination syndrome in a normonatremic patient of chronic kidney disease. Indian J Crit Care Med. 2014; 18: 609-611.
10. Kim J, Song T, Park S, Choi IS. Cerebellar peduncular myelinolysis in a patient receiving hemodialysis. J Neurol Sci. 2007; 253: 66-68.
11. Esforzado N, Poch E, Cases A, Cardenal C, López-Pedret J, Revert L. Central pontine myelinolysis secondary to frequent and rapid shifts in plasma glucose in a diabetic haemodialysis patient. Nephrol Dial Transplant. 1993; 8: 644-646.
12. Burns JD, Kosa SC, Wijdicks EF. Central pontine myelinolysis in a patient with hyperosmolar hyperglycemia and consistently normal serum sodium. Neurocrit Care. 2009; 11: 251-254.
13. Guerrero WR, Dababneh H, Nadeau SE. Hemiparesis, encephalopathy, and extrapontine osmotic myelinolysis in the setting of hyperosmolar hyperglycemia. J Clin Neurosci. 2013; 20: 894-896.

14. Donnelly H, Connor S, Quirk J. Central pontine myelinolysis secondary to hyperglycaemia. Pract Neurol. 2016.

15. Saini M, Mamauag MJ, Singh R. Central pontine myelinolysis: a rare presentation secondary to hyperglycaemia. Singapore Med J. 2015; 56: 71-73.

16. O'Malley G, Moran C, Draman MS, King T, Smith D, Thompson CJ, et al. Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state. Ann Clin Biochem. 2008; 45: 440-443.

17. Chang YM. Central Pontine Myelinolysis Associated with Diabetic Hyperglycemia. JSM Clin Case Rep. 2014; 2: 1059.

18. McNamara PH, Williams J, McCabe DJ, Walsh RA. Striking Central Pontine Myelinolysis in a Patient with Alcohol Dependence Syndrome Without Hyponatremia. JAMA Neurol. 2016; 73: 234-235.

19. Musana AK, Yale SH. Central pontine myelinolysis: case series and review. WMJ. 2005; 104: 56-60.

20. Bernsen HJ, Prick MJ. Improvement of central pontine myelinolysis as demonstrated by repeated magnetic resonance imaging in a patient without evidence of hyponatremia. Acta Neurol Belg. 1999; 99: 189-193.

21. Boon AP, Carey MP, Adams DH, Buckels J, McMaster P. Central pontine myelinolysis in liver transplantation. J Clin Pathol. 1991; 44: 909-914.

22. deMorais BS, Carneiro FS, deMorais Araújo R, Araújo GF, de Oliveira RB. Central pontine myelinolysis after liver transplantation: is sodium the only villain? Case report. Rev Bras Anestesiol. 2009; 59: 344-349.

23. Estol CJ, Faris AA, Martinez AJ, Ahdab-Barmada M. Central pontine myelinolysis after liver transplantation. Neurology. 1989; 39: 493-498.

24. Gocht A, Colmant HJ. Central pontine and extrapontine myelinolysis: a report of 58 cases. Clin Neuropathol. 1987; 6: 262-270.

25. Popescu BF, Bunyan RF, Guo Y, Parisi JE, Lennon VA, Lucchinetti CF. Evidence of aquaporin involvement in human central pontine myelinolysis. Acta Neuropathol Commun. 2013; 1: 40.

26. Gankam Kengne F, Nicaise C, Soupart A, Boom A, Schiettecatte J, Pochet R, et al. Astrocytes are an early target in osmotic demyelination syndrome. J Am Soc Nephrol. 2011; 22: 1834-1845.

27. Burg MB, Ferraris JD. Intracellular organic osmolytes: function and regulation. J Biol Chem. 2008; 283: 7309-7313.

28. Louis G, Megarbane B, Lavoué S, Lassalle V, Argaud L, Poussel JF, et al. Long-term outcome of patients hospitalized in intensive care units with central or extrapontine myelinolysis. Crit Care Med. 2012; 40: 970-972.

29. Verbalis JG, Martinez AJ. Neurological and neuropathological sequelae of correction of chronic hyponatremia. Kidney Int. 1991; 39: 1274-1282.

30. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G. Treatment of chronic hyponatremia in rats by intravenous saline: comparison of rate versus magnitude of correction. Kidney Int. 1992; 41: 1662-1667.

31. Tzamaloukas AH, Malhotra D, Rosen BH, Raj DS, Murata GH, Shapiro JI. Principles of management of severe hyponatremia. J Am Heart Assoc. 2013; 2: 005199.

32. Gross P, Reimann D, Henschkowski J, Damian M. Treatment of severe hyponatremia: conventional and novel aspects. J Am Soc Nephrol. 2001; 17: 10-14.

33. Al-Salman J, Kemp D, Randall D. Hyponatremia. West J Med. 2002; 176: 173-176.

34. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases. Ann Intern Med. 1987; 107: 656-664.

35. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. J Am Soc Nephrol. 1994; 4: 1522-1530.

36. Omari A, Kormas N, Field M. Delayed onset of central pontine myelinolysis despite appropriate correction of hyponatraemia. Intern Med J. 2002; 32: 273-274.

37. Leens C, Mukendi R, Forêt F, Hacourt A, Devuyst O, Colin IM. Central and extrapontine myelinolysis in a patient in spite of a careful correction of hyponatremia. Clin Nephrol. 2001; 55: 248-253.

38. Ashrafian H, Davey P. A review of the causes of central pontine myelinosis: yet another apoptotic illness? Eur J Neurol. 2001; 8: 103-109.

39. Ruiz-Sandoval JL, Chiquete E, Alvarez-Palazuelos LE, Andrade-Ramos MA, Rodríguez-Rubio LR. Atypical forms of the osmotic demyelination syndrome. Acta Neurol Belg. 2013; 113: 19-23.

40. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol. 2014; 170: 1-47.

41. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. Semin Nephrol. 2009; 29: 282-299.

42. Tavare AN, Murray D. IMAGES IN CLINICAL MEDICINE. Central Pontine Myelinolysis. N Engl J Med. 2016; 374: 8.

43. Abbott R, Silber E, Felber J, Ekpo E. Osmotic demyelination syndrome. BMJ. 2005; 331: 829-830.

44. Lin SH, Hsu YJ, Chiu JS, Chu SJ, Davids MR, Halperin ML. Osmotic demyelination syndrome: a potentially avoidable disaster. QJM. 2003; 96: 935-947.

45. Osama Hegazi M. Effect of hypokalemia on the clinical impact of hyponatremia. J Clin Hypertens (Greenwich). 2012; 14: 656.

46. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000; 342: 1581-1589.

47. Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. J Neurol Neurosurg Psychiatry. 2004; 75: 22-28.

48. Chawla A, Sterns RH, Nigwekar SU, Cappuccio JD. Mortality and serum sodium: do patients die from or with hyponatremia. Clin J Am Soc Nephrol. 2011; 6: 960-965.

49. Berl T. Treating hyponatremia: damned if we do and damned if we don't. Kidney Int. 1990; 37: 1006-1018.

50. Harris CP, Townsend JJ, Baringer JR. Symptomatic hyponatraemia: can myelinolysis be prevented by treatment? J Neurol Neurosurg Psychiatry. 1993; 56: 626-632.

51. Sterns RH, Hix JK, Silver S. Treating profound hyponatremia: a strategy for controlled correction. Am J Kidney Dis. 2010; 56: 774-779.

52. Kerns E, Patel S, Cohen DM. Hourly oral sodium chloride for the rapid and predictable treatment of hyponatremia. Clin Nephrol. 2014; 82: 397-401.

53. Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH. Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. Clin J Am Soc Nephrol. 2007; 2: 1110-1117.

54. Perianayagam A, Sterns RH, Silver SM, Grieff M, Mayo R, Hix J, et al. DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. Clin J Am Soc Nephrol. 2008; 3: 331-336.

55. Sterns RH, Hix JK. Overcorrection of hyponatremia is a medical emergency. Kidney Int. 2009; 76: 587-589.

56. Sood L, Sterns RH, Hix JK, Silver SM, Chen L. Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. Am J Kidney Dis. 2013; 61: 571-578.

57. Kamel KS, Halperin ML. Managing overly rapid correction of chronic hyponatremia: an ounce of prevention or a pound of cure. J Am Soc Nephrol. 2010; 21: 2015-2016.

58. Tzamaloukas AH, Shapiro JI, Raj DS, Murata GH, Glew RH, Malhotra D. Management of severe hyponatremia: infusion of hypertonic saline and desmopressin or infusion of vasopressin inhibitors? Am J Med Sci. 2014; 348: 432-439.

59. Achinger SG, Arieff AI, Kalantar-Zadeh K, Ayus JC. Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series. Nephrol Dial Transplant. 2014; 29: 2310-2315.

60. Sterns RH, Hix JK, Silver SM. Management of hyponatremia in the ICU. Chest. 2013; 144: 672-679.

61. Dhrolia MF, Akhtar SF, Ahmed E, Naqvi A, Rizvi A. Azotemia protects the brain from osmotic demyelination on rapid correction of hyponatremia. Saudi J Kidney Dis Transpl. 2014; 25: 558-566.

62. Soupart A, Penninckx R, Stenuit A, Decaux G. Azotemia (48 h) decreases the risk of brain damage in rats after correction of chronic hyponatremia. Brain Res. 2000; 852: 167-172.

63. Decaux G, Andres C, Gankam Kengne F, Soupart A. Treatment of euvolemic hyponatremia in the intensive care unit by urea. Crit Care. 2010; 14: 184.

64. GankamKengne F, Couturier BS, Soupart A, Decaux G. Urea minimizes brain complications following rapid correction of chronic hyponatremia compared with vasopressin antagonist or hypertonic saline. Kidney Int. 2015; 87: 323-331.

65. Rafat C, Schortgen F, Gaudry S, Bertrand F, Miguel-Montanes R, Labbé V, et al. Use of desmopressin acetate in severe hyponatremia in the intensive care unit. Clin J Am Soc Nephrol. 2014; 9: 229-237.

66. Yamada H, Takano K, Ayuzawa N, Seki G, Fujita T. Relowering of serum na for osmotic demyelinating syndrome. Case Rep Neurol Med. 2012; 2012: 704639.

67. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G. Reinduction of hyponatremia improves survival in rats with myelinolysis-related neurologic symptoms. J Neuropathol Exp Neurol. 1996; 55: 594-601.

68. Soupart A, Ngassa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. Clin Nephrol. 1999; 51: 383-386.

69. Oya S, Tsutsumi K, Ueki K, Kirino T. Reinduction of hyponatremia to treat central pontine myelinolysis. Neurology 2001; 57: 1931-1932.

70. Changal KH, Raina H, Wani IY. Osmotic Demyelination Syndrome; Treated with Re Lowering of Serum Sodium. Acta Neurol Taiwan. 2014; 23: 138-142.

71. Atchaneeyasakul K, Tipirneni A, Gloria S, Berry AC, Shah K, Yavagal DR. Osmotic demyelination syndrome: plasmapheresis versus intravenous immunoglobulin. Intern Emerg Med. 2016.

72. Bibl D, Lampl C, Gabriel C, Jüngling G, Brock H, Köstler G. Treatment of central pontine myelinolysis with therapeutic plasmapheresis. Lancet. 1999; 353: 1155.

73. Grimaldi D, Cavalleri F, Vallone S, Milanti G, Cortelli P. Plasmapheresis improves the outcome of central pontine myelinolysis. J Neurol. 2005; 252: 734-735.

74. Finsterer J, Engelmayer E, Trnka E, Stiskal M. Immunoglobulins are effective in pontine myelinolysis. Clin Neuropharmacol. 2000; 23: 110-113.

75. Hegazi MO. Treatment of the osmotic demyelination syndrome: the earlier the better? Intern Emerg Med. 2016.

76. Murthy SB, Izadyar S, Dhamne M, Kass JS, Goldsmith CE. Osmotic demyelination syndrome: variable clinical and radiologic response to intravenous immunoglobulin therapy. Neurol Sci. 2013; 34: 581-584.

77. Mastrangelo S, Arlotta A, Cefalo MG, Maurizi P, Cianfoni A, Riccardi R. Central pontine and extrapontine myelinolysis in a pediatric patient following rapid correction of hypernatremia. Neuropediatrics. 2009; 40: 144-147.

78. Chang KY, Lee I-H, Kim GJ, Cho K, Park HS, Kim HW. Plasma exchange successfully treats central pontine myelinolysis after acute hypernatremia from intravenous sodium bicarbonate therapy. BMC Nephrology. 2014; 15: 56.

Cite this article

Hegazi MO, Nawara A (2016) Prevention and Treatment of the Osmotic Demyelination Syndrome: A Review. JSM Brain Sci 1(1): 1004.