Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia

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INTRODUCTION

The serum sodium concentration is the primary determinant of serum tonicity (also known as "effective serum osmolality") (see "Diagnostic evaluation of adults with hyponatremia"). The fall in serum tonicity in patients with hypotonic hyponatremia promotes water movement into the brain and, if the hyponatremia is acute and severe, can lead to cerebral edema and neurologic symptoms. In response to hyponatremia, the brain makes adaptations that lower the cerebral volume toward normal and reduce the likelihood of these complications. The mechanisms responsible for this cerebral adaptation are discussed elsewhere:

- (See 'Brain adaptation to hyponatremia' below.)
- (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Osmolytes and cerebral adaptation to hyponatremia'.)

However, brain adaptations that reduce the risk of cerebral edema make the brain vulnerable to injury if chronic hyponatremia is too rapidly corrected. The neurologic manifestations associated with overly rapid correction have been called the osmotic demyelination syndrome (ODS; formerly called central pontine myelinolysis or CPM). As will be described below, almost all patients who develop ODS present with a serum sodium concentration of 120 mEq/L or less.

Issues related to ODS and the approach to the patient with unintentional overly rapid correction of hyponatremia will be reviewed here. A general overview of the treatment of hyponatremia is presented separately. (See "Overview of the treatment of hyponatremia in adults".)

BRAIN ADAPTATION TO HYPONATREMIA

A decrease in serum tonicity causes water to flow across the blood-brain barrier, increasing brain water content. The decrease in serum tonicity also causes brain cells, primarily astrocytes, to swell. Astrocytes are cells that surround brain capillaries and express water channels on their foot processes; these cells protect neurons from swelling via a cell-to-cell transfer of cellular solutes and water [1,2].

The brain begins to adapt to hypotonicity almost immediately after a fall in serum sodium, and the adaptation is complete within two days. If the brain were unable to adapt, even mild hyponatremia would result in life-threatening cerebral edema. However, within minutes after a fall in serum sodium, increased intracranial pressure forces interstitial sodium and water out of the brain into the cerebrospinal fluid, ameliorating the increased brain volume. In addition, astrocytes begin to lose intracellular solutes, principally potassium and organic solutes (called osmolytes), within hours of a fall in serum sodium and serum tonicity. This process permits these cells to shed excess water and to have the same tonicity as plasma without a large increase in cell water (figure 1). Cerebral adaptation to hyponatremia is discussed in more detail elsewhere. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Osmolytes and cerebral adaptation to hyponatremia'.)

Because the brain is able to adapt to hypotonicity, hyponatremia that develops over more than two to three days is not associated with severe brain swelling; it is therefore much less likely to be complicated by seizures and coma, and is extremely unlikely to produce brain herniation [3]. However, once the brain has adapted to hypotonicity, the rate of correction of the hyponatremia becomes important. Overly rapid correction of severe hyponatremia can lead to the ODS. By contrast, rapid correction is **not** likely to induce ODS in patients with severe hyponatremia that has only been present for several hours, since the cerebral adaptation is at an early stage. Examples include water intoxication in marathon runners, psychotic patients, and users of ecstasy; rapid correction does not usually lead to ODS in these patients.

Demyelination of the central pons (CPM) is one manifestation of ODS. However, brain demyelination that is associated with rapid correction of hyponatremia may be more diffuse, and it does not always involve the pons [3-7].

PATHOGENESIS OF ODS

How the ODS occurs is not completely understood. Chronic hyponatremia is associated with the loss of osmotically active organic osmolytes (such as myoinositol, glutamate, and glutamine) from astrocytes, which provide protection against brain cell swelling. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Osmolytes and cerebral adaptation to hyponatremia'.)

However, organic osmolytes cannot be as quickly replaced when the brain volume begins to shrink in response to correction of the hyponatremia [8-10]. As a result, brain volume can fall from a value that is initially somewhat above normal to one below normal with rapid correction of hyponatremia. Studies in rats have shown that demyelination primarily occurs in areas of the brain that are slowest in reaccumulating osmolytes after rapid correction of hyponatremia [11].

In experimental models, the mechanism by which a rapid fall in brain volume results in demyelination is best explained by direct injury to astrocytes and/or oligodendrocytes (cells of the glial syncytium) that are crucial for normal myelination and remyelination after demyelinative injury and for maintenance of the blood-brain barrier [12-14]. After rapid correction of hyponatremia, the loss of cell water coupled with the movement of potassium and sodium back into these cells lead to an initial increase in cell cation concentration that occurs before the repletion of organic osmolytes [8,9,15]. Within 12 hours, these combined changes cause protein aggregation, DNA fragmentation, and induce markers of programmed cell death. Approximately 24 hours after the osmotic insult, astrocytes and oligodendrocytes begin to die in regions of the brain that are affected by demyelination, and this may be accompanied by release of inflammatory cytokines and activation of microglia [16]. Endothelial damage and breakdown of the blood-brain barrier occur later, after the injury to astrocytes and oligodendrocytes [17].

RISK FACTORS FOR ODS

The ODS primarily occurs with overly rapid correction of severe hyponatremia (serum sodium concentration almost always 120 mEq/L or less) that has been present for more than two to three days, which is the time required for the cerebral adaptation to become maximal [4,5,7,18,19]. However, some patients are particularly susceptible to this complication and can develop ODS with less severe hyponatremia (ie, with initial serum sodium concentrations above 120 mEq/L) and slower rates of correction.

Serum sodium at presentation — The majority of ODS cases occur in patients whose sodium concentrations at presentation are ≤105 mEq/L, and the vast majority of reported cases arise in patients who present with a serum sodium of 120 mEq/L or less [4,5,7,18-21]. In one large study of 83 patients with ODS documented by magnetic resonance imaging (MRI), the mean serum sodium was 104 mEq/L; 75 percent had a serum sodium ≤110 mEq/L, and 26 percent had a serum sodium ≤100 mEq/L [18]. When the initial serum sodium is greater than 120 mEq/L, ODS is rare and typically limited to two clinical scenarios:

- Patients with severe liver disease and moderate hyponatremia, whose sodium levels increase after liver transplantation [22].
- Patients with arginine vasopressin disorders (formerly diabetes insipidus) who have developed a moderate degree of hyponatremia as a complication of desmopressin therapy and then have the desmopressin discontinued. Their sodium level may then increase quite rapidly as a result of a water diuresis.

In one study of patients with serum sodium concentrations that were ≤105 mEq/L, correction by >12 mEq/L in 24 hours or >18 mEq/L in 48 hours was associated with posttherapeutic neurologic complications; over one-half of the chronically hyponatremic patients who were corrected this rapidly developed complications, while all patients who were corrected more slowly had uneventful recoveries [5]. Another study identified only four cases of ODS among 37 patients with a serum sodium that was ≤120 mEq/L who were corrected by >12 mEq/L in 24 hours and no cases of ODS among 218 patients who were more slowly corrected [23]. However, all cases with ODS in this series had an initial serum sodium of ≤105 mEq/L.

The likely reason for these observations is the fact that patients who have more severe hyponatremia at presentation tend to experience a larger increase in the serum sodium concentration during treatment [24]. Cerebral adaptation in patients with very severe hyponatremia (eg, <105 mEq/L) requires greater depletion of brain organic osmolytes, and therefore, these patients are also more likely to develop ODS after rapid correction.

Duration of hyponatremia — Studies in experimental animals showed that brain damage does not occur when hyponatremia of less than one day's duration is rapidly corrected [25,26]. However, if hyponatremia persists for two to three days or more, the same treatment results in usually fatal demyelinating brain lesions [25-35].

Similar findings have been noted in humans. Neurologic deterioration following rapid correction of hyponatremia is unlikely in patients with severe hyponatremia that develops over a few hours, particularly in those whose normal water excretory capacity rapidly and spontaneously returns the serum sodium to normal. Examples include the ingestion of large

amounts of water over several hours by marathon runners, psychotic patients, and users of ecstasy [4,5,19,36]. In these patients, hyponatremia develops rapidly, and the brain does not have time to fully adapt. By contrast, patients who develop hyponatremia more gradually have time for the brain adaptation and may develop the ODS after rates of correction that are well tolerated in patients with self-induced acute water intoxication [3-7,19]. (See 'Brain adaptation to hyponatremia' above.)

Although the duration of hyponatremia is a major determinant of susceptibility to ODS, it is often not known. Thus, clinicians should **assume that the patient has chronic hyponatremia** unless there are available serum sodium measurements that document acute onset or unless the history is notable for acute water intoxication (ie, consumption of a large volume of water over a few hours preceding measurement of the serum sodium). Conversely, an acute onset of severe neurologic symptoms should **not** be interpreted to mean that hyponatremia is acute. While uncommon, a sudden onset of severe symptoms can occur in patients whose hyponatremia developed over several days.

Polydipsia does not always convey resistance to osmotic demyelination, since some polydipsic patients have hyponatremia of sufficient duration to permit cerebral adaptation. As an example, ODS has been reported in malnourished patients with alcohol use disorder who present with polydipsia and chronic hyponatremia [37]. In addition, alcohol use disorder and malnutrition are risk factors for osmotic demyelination. (See "Causes of hypotonic hyponatremia in adults", section on 'Primary polydipsia due to psychosis' and 'Other risk factors' below.)

Overly rapid rate of correction — Studies in experimental animals have shown that osmotic demyelination is caused by correction of hyponatremia and not by hyponatremia itself, and that more rapid rates of correction increase the likelihood and severity of brain lesions [38]. The threshold rate of correction, above which brain lesions may develop, is approximately 15 mEq/L per day in dogs and 16 mEq/L in rats; the incidence of lesions progressively increases with larger magnitudes of daily correction, and the majority of animals will be affected if the correction rate exceeds 25 mEq/L per day [38,39]. The effect of the hourly rate of correction is influenced by the daily rate of correction. Specifically, a more rapid hourly rate of correction is associated with more severe lesions only if the daily rate threshold is exceeded [38,40]. By contrast, if the daily rate of correction remains lower than the threshold for inducing osmotic demyelination, then even extremely rapid hourly rates (as much as 12 mEq/L per hour) can be well tolerated [28].

Observational studies in humans are consistent with experimental studies in animals, showing that more rapid rates of correction of chronic hyponatremia are associated with osmotic demyelination [4,5,14,21,23,37,41-43]. Most of these studies report the total increase in the

serum sodium concentration over a 24- or 48-hour period and not the hourly rate of correction expressed in mEq/L per hour. Thus, our recommendations on the rate of correction of hyponatremia are based upon the daily, rather than the hourly, rate of correction.

It is difficult to define a threshold rate of correction below which ODS will not occur. Some well-documented cases have been reported in which ODS developed after correction by 8 mEq/L per day [44], and a large cohort study has shown that correction by less than 5 mEq/L per day was not associated with neurologic complications [43].

Thus, because there is no proven advantage to correcting severe hyponatremia (serum sodium <120 mEq/L) by more than 4 to 6 mEq/L per day, we and other authors recommend that the rate of correction of hyponatremia should not exceed 6 to 8 mEq/L in any 24-hour period [14,45]. This is not a goal of therapy, but rather a therapeutic limit that should not be exceeded. In the past, it was thought that the serum sodium concentration should be increased to a supposedly "safe" level of 120 to 128 mEq/L. There is no evidence to support this practice, and doing so could result in marked overcorrection of hyponatremia in patients with very low serum sodium concentrations. We recommend a correction goal of 4 to 6 mEq/L per day, no matter how low the initial serum sodium concentration is. (See "Overview of the treatment of hyponatremia in adults".)

Causes of overly rapid correction — Overly rapid correction of hyponatremia is common, particularly in patients with severe hyponatremia (serum sodium <120 mEq/L) [21,46], and can result from two general mechanisms: following therapy that is specifically directed at raising the sodium concentration (such as hypertonic saline or initiation of a vasopressin antagonist) and following cessation of a reversible stimulus to antidiuretic hormone (ADH) release or cessation of exogenous desmopressin therapy. If kidney function is normal, removal of a stimulus to ADH release results in a urine osmolality that is usually below 100 mosmol/kg, leading to rapid excretion of the excess water (called autocorrection).

Autocorrection of the serum sodium can occur in the following settings:

- The administration of saline to patients with true volume depletion. Restoration of euvolemia rapidly suppresses the release of ADH (which has a half-life of only 15 to 20 minutes), thereby allowing excretion of the excess water [21,47,48].
- The administration of glucocorticoids to patients with adrenal insufficiency [49-51]. (See "Hyponatremia and hyperkalemia in adrenal insufficiency", section on 'Treatment'.)
- Discontinuation of drugs that cause the syndrome of inappropriate ADH secretion (SIADH) [24,52,53]. These include a selective serotonin reuptake inhibitor, carbamazepine, or

desmopressin. Desmopressin is used for the treatment of arginine vasopressin deficiency (previously called central diabetes insipidus), nocturnal enuresis in children, nocturia in adults, hemophilia, and von Willebrand disease, and it can lead to hyponatremia in patients who drink large amounts of water [54]. (See "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)", section on 'Drugs'.)

- Discontinuation of thiazide diuretics since they interfere with urinary dilution [55]. (See "Diuretic-induced hyponatremia".)
- Spontaneous resolution of a transient cause for SIADH (eg, surgical stress, nausea, pneumonia).
- Treatment with a vasopressin receptor antagonist. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Vasopressin receptor antagonists'.)

Autocorrection of a reversible impairment in water excretion is an important reason why equations that are used to calculate the serum sodium response to a given fluid regimen frequently fail to predict the actual response. In a study of hyponatremic patients who were treated with hypertonic saline, for example, the actual rate of correction of the serum sodium exceeded the predicted rate in 29 of 39 patients (74 percent) whose pretreatment sodium concentration was less than 120 mEq/L [24]. Ten patients had overly rapid correction; in these patients, the rise in serum sodium was 2.4 times the predicted value and was due to a documented water diuresis (defined as a low urine osmolality) in four.

Another setting in which overly rapid correction can occur is in patients with end-stage kidney disease who are treated with hemodialysis. Although ODS can occur [56,57], it is thought to be a rare event [58]. 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 [30,58]. Urea crosses the blood-brain barrier relatively slowly compared with osmotic water movement and therefore acts as an effective osmole when serum levels are rapidly reduced. Another possible mechanism is that azotemia enhances brain reuptake of organic osmolytes during correction of hyponatremia, minimizing cellular shrinking [31].

Other risk factors — Several other factors appear to increase the susceptibility to osmotic demyelination. When these factors are present, ODS can develop at less severe degrees of hyponatremia and slower rates of correction [4,5,18,25,37,52,59,60]. These include alcohol use disorder, malnutrition, liver disease, hypokalemia, and hypophosphatemia [18,21,61,62]. In a

large study of 83 patients with MRI-documented ODS, for example, 70 percent had an alcohol use disorder and 68 percent had hypokalemia [18]. Females of childbearing age are thought to be more susceptible to fatal cerebral edema associated with acute hyponatremia [63]. However, there is no evidence that sex increases the risk of ODS.

Some authors have emphasized the role of hypoxia in the pathogenesis of brain damage associated with hyponatremia, including the demyelinating brain lesions [64-67]. The genesis of this theory can be traced to a case series that included seven females who exhibited a biphasic neurologic course, typical of osmotic demyelination, following hyponatremic seizures [66]. The author attributed these findings to seizure-induced brain anoxia and a delayed postanoxic encephalopathy, a demyelinating disorder usually associated with carbon monoxide poisoning. However, in addition to an anoxic insult caused by seizures, these patients had also been treated with hypertonic saline and had experienced hyponatremia correction rates exceeding 25 mEq/L in less than 48 hours. It is not clear whether the brain damage sustained in these females was due to hypoxia, which can exacerbate brain swelling in experimental models of hyponatremia and may contribute to a fatal outcome, or whether these females had ODS [64,65,67]. Magnetic resonance imaging (MRI), which was not available at the time, might have detected the characteristic brain lesions of osmotic demyelination [6,25,52].

INCIDENCE OF ODS

The incidence of ODS in patients with chronic, hypotonic hyponatremia depends primarily upon the severity of hyponatremia and the rate of correction. Other factors, such as alcohol use disorder, malnutrition, liver disease, and hypokalemia, further increase the incidence. (See 'Risk factors for ODS' above.)

The incidence is high in patients with severe, chronic hyponatremia who are rapidly corrected. As an example, in one study of 255 patients admitted to two academic teaching hospitals with serum sodium <120 mEq/L, 11 percent of those corrected by >12 mEq/L in 24 hours developed ODS; none of those corrected more slowly developed ODS [23]. In two other studies, approximately 50 percent of patients with serum sodium ≤105 mEq/L who were corrected too quickly developed ODS [4,5].

Based upon an analysis of hospital administrative data, one group has concluded that ODS is rare [68,69]. In one large cohort of patients admitted with serum sodium <130 mEq/L over 10 years, they reported that the incidence of ODS was only 0.05 percent. However, 87 percent of the cohort had an initial serum sodium ≥120 mEq/L, a population known to be at very low risk for ODS. Of those admitted with serum sodium <110 mEq/L, the ODS incidence was 2.6 percent.

Due to multiple limitations of this study, 2.6 percent is likely to be a substantial underestimate of the true incidence of ODS in rapidly corrected patients with this severity of hyponatremia [70]. As an example, ODS was identified using neuroimaging studies (MRI or CT) that were performed during the same hospitalization, or if the patient was readmitted within seven days and had ODS listed as the primary reason for hospitalization. This approach to case finding is likely to miss many patients with ODS because of the following: radiologic images are typically negative at the onset of clinical symptoms and may not be positive until weeks later; not all patients with clinical features of ODS are readmitted within seven days, and those that are admitted may have additional diagnoses listed before ODS; and patients with severe hyperglycemia (up to 450 mg/dL) and those with acute self-induced water intoxication were included in the cohort. Patients with severe hyperglycemia can have hypertonic (not hypotonic) hyponatremia, often have rapid correction of hyponatremia as the hyperglycemia is corrected, and are at low risk for ODS. Similarly, patients with acute self-induced water intoxication often correct rapidly and are unlikely to develop ODS.

CLINICAL MANIFESTATIONS AND DIAGNOSIS OF ODS

Clinical manifestations — The clinical manifestations of ODS are typically **delayed** for two to six days after overly rapid elevation of the serum sodium concentration has occurred (figure 2) [5,7,71-74].

The symptoms include dysarthria, dysphagia, paraparesis or quadriparesis, behavioral disturbances, movement disorders, seizures, lethargy, confusion, disorientation, obtundation, and coma [3,5-7,18,75]. Symptoms in patients with magnetic resonance imaging (MRI)-documented pontine or extrapontine myelinolysis are frequently irreversible. As an example, in one study of 83 patients with ODS, 40 percent died or were functionally impaired at three months; 60 percent were functionally independent although some had persistent mild symptoms [18].

Severely affected patients may become "locked in"; they are awake but are unable to move or verbally communicate. They can usually move their eyes and blink [7]. In patients with pontine involvement, speech abnormalities occur early and persist, and patients often become mute. Corticospinal signs (hyperreflexia and bilateral Babinski signs) and corticobulbar signs (brisk jaw jerk) are common. Swallowing dysfunction may lead to aspiration pneumonia and respiratory failure. Meaningful recovery is possible, even in patients with severe ODS who require ventilator support. (See 'Supportive therapy' below.)

Other common physical findings include increased muscle tone, facial weakness, and snout, grasp, or rooting reflexes [6]. Extrapontine involvement can result in a variety of findings, including psychiatric disturbances, catatonia, postural limb tremor, myoclonic jerks, and a parkinsonian picture with choreoathetosis or dystonia that responds to dopaminergic treatment [59].

Diagnosis — ODS should be suspected in all patients who have risk factors for the disorder and consistent clinical manifestations. ODS is likely to be present if overly rapid correction of hyponatremia has occurred during the previous week. (See 'Clinical manifestations' above and 'Risk factors for ODS' above.)

Patients suspected of having ODS should undergo brain MRI or, if MRI is unavailable, computed tomography (CT) scanning of the brain, although CT scans are less reliable for detecting demyelinating lesions [6,41,76,77]. In one large study of 83 patients with ODS, 51 percent had central pontine demyelination only, 45 percent had both central pontine and extrapontine demyelination, and the remainder had extrapontine demyelination only [18].

However, even MRI may not become positive for as long as four weeks after disease onset [6,41]. In some patients with a clinical course consistent with ODS, neurological findings resolve over a few days or weeks, and no lesions are ever documented by MRI [14]. Thus, an initially negative radiologic study in a patient who develops neurologic symptoms after overly rapid correction of hyponatremia does **not** exclude ODS; if neurological findings persist, a repeat MRI should be obtained after several weeks. Earlier detection may be possible with certain MRI techniques such as diffusion-weighted imaging [77,78].

PREVENTION AND TREATMENT OF ODS

Prevention in patients at risk for ODS — In view of the often severe and permanent adverse consequences of ODS, prevention is essential. Among patients at heightened risk of ODS because of alcohol use disorder, severe malnutrition, or advanced liver disease, and in patients with severe hyponatremia (ie, serum sodium <120 mEq/L) lasting more than two to three days or if the duration is unknown, we recommend that the serum sodium be raised by less than 6 to 8 mEq/L in any 24-hour period to prevent ODS. (See 'Risk factors for ODS' above.)

Although the duration of hyponatremia is a major determinant of susceptibility to ODS, it is often not known. In this setting, it is safest to assume that the patient has chronic hyponatremia unless measurements of the serum sodium document an acute onset or the history suggests acute water intoxication (ie, large volumes of water ingested over a few hours).

Our recommended strategies to correct hyponatremia are presented elsewhere. However, it is often difficult to accurately estimate the effect of a treatment strategy on the serum sodium, and some patients will correct too rapidly due, for example, to the emergence of a water diuresis [24]. Thus, when correcting severe hyponatremia (ie, serum sodium <120 mEq/L) or raising the serum sodium in patients at heightened risk for ODS, careful monitoring of the serum sodium concentration (initially, every two to three hours) is **essential** to avoid overly rapid correction. The urine volume should also be monitored for the emergence of a water diuresis. (See "Overview of the treatment of hyponatremia in adults".)

Some patients, during the course of treatment of hyponatremia, require further therapy to prevent overly rapid correction or to relower the serum sodium if overly rapid correction occurs. Such patients, and the corresponding therapeutic strategies, include [79]:

- **"Proactive (preventive) strategy" in patients who are likely to develop overly rapid correction** – If the cause of impaired water excretion is likely to be reversible (eg, in hypovolemic patients), a water diuresis may develop and cause an abrupt rise in the serum sodium. In these patients, urinary water losses and rapid correction of hyponatremia can be prevented by administering desmopressin at the outset of treatment.

  Repeated use of desmopressin at regular intervals induces a state of iatrogenic syndrome of inappropriate antidiuretic hormone secretion (SIADH); the serum sodium concentration is then increased with the concurrent administration of 3 percent saline [80,81]. (See 'Patients likely to have overly rapid correction (proactive strategy)' below.)

  We use the proactive strategy in patients with reversible causes of hyponatremia whose pretreatment serum sodium concentration is <120 mEq/L or whose risk of ODS is enhanced because of alcohol use disorder, severe malnutrition, or advanced liver disease. We also use the proactive regimen to treat desmopressin-induced hyponatremia in patients with arginine vasopressin disorders, even at serum sodium concentrations >120 mEq/L.

- **"Reactive strategy" in patients with a worrisome trajectory of the serum sodium** – If a water diuresis emerges during therapy, or if the initial trajectory of correction appears likely to exceed maximum recommended goals, urinary free water losses can either be replaced with 5 percent dextrose in water (D5W) or stopped with the administration of desmopressin [82,83]. (See 'Patients with a worrisome serum sodium trajectory (reactive strategy)' below.)

- **"Rescue strategy" in patients who have already exceeded the correction limits** – If the rate of correction has already exceeded recommended limits, further water losses are stopped with the administration of desmopressin, and the serum sodium concentration is relowered [82,83]. (See 'Patients who have exceeded correction limits (rescue strategy)' below.)

The efficacy of desmopressin to inhibit a water diuresis and to relower the serum sodium is presumably reduced in hyponatremic patients who are treated with vasopressin receptor antagonists such as tolvaptan. (See "Overview of the treatment of hyponatremia in adults", section on 'Vasopressin receptor antagonists'.)

Patients likely to have overly rapid correction (proactive strategy) — In patients with reversible causes of hyponatremia who are likely to develop a water diuresis during the course of therapy, or who are at high risk of developing ODS, desmopressin can be given proactively at the beginning of therapy (ie, before any treatment is given to correct the hyponatremia). (See 'Other risk factors' above.)

We usually use 2 mcg of desmopressin, intravenously or subcutaneously, every six to eight hours for a period of 24 to 48 hours, and we simultaneously administer a slow intravenous infusion of hypertonic saline at 15 to 30 mL/hour. The rate of infusion of hypertonic saline is then adjusted to achieve the desired rate of correction [80,81]. Our experience with this strategy is discussed elsewhere. (See "Overview of the treatment of hyponatremia in adults", section on 'Other therapies for chronic hyponatremia'.)

Patients with a worrisome serum sodium trajectory (reactive strategy) — Some patients with an initial serum sodium concentration <120 mEq/L have an initial trajectory of hyponatremia correction that appears likely to exceed the maximum recommended limit of 8 mEq/L in any 24-hour period or 16 mEq/L in any 48-hour period. This often occurs in association with the development of a water diuresis (ie, urine osmolality less than 200 mosmol/kg) when a reversible stimulus to increased antidiuretic hormone (ADH) release has abated [83]. (See 'Overly rapid rate of correction' above.)

In this setting, replacement of urinary water losses with D5W can be attempted, but it is extremely labor intensive and often fails to prevent overly rapid correction [68,83]. Rapid infusions of D5W may also exacerbate hypokalemia and hypophosphatemia, potentially increasing susceptibility to ODS. The best way to prevent overly rapid correction is the administration of desmopressin to concentrate the urine. Two exceptions are patients who cannot be relied upon to curtail water intake and, because they are at low risk of osmotic demyelination, patients with hyperacute hyponatremia developing over a few hours due to a

marked increase in water intake, as can occur in marathon runners, psychotic patients, and users of ecstasy.

The usual desmopressin regimen begins with 2 mcg intravenously or subcutaneously. The maximum desmopressin dose is 4 mcg in patients who do not respond to lower doses. Two potential options for desmopressin administration are as follows (both require fluid restriction and careful monitoring of the urine output and serum sodium):

- One regimen is to give desmopressin every six to eight hours. Since desmopressin produces a concentrated urine, correction of the hyponatremia will slow down or cease. If necessary, a slow infusion of hypertonic saline can then be added (10 to 30 mL per hour) to produce a rise in serum sodium at the desired rate [83,84]. The serum sodium should be measured every four to six hours, and the rate of hypertonic saline infusion should be adjusted if necessary. Desmopressin and, if used, hypertonic saline are continued until the serum sodium reaches 125 to 130 mEq/L. (See "Overview of the treatment of hyponatremia in adults", section on 'Avoid overcorrection'.)

- A second regimen is to give one dose of desmopressin. Subsequent doses may be given after six to eight hours (or more) if the serum sodium is again rising too quickly or if the urine output has dramatically increased. The urine output should be monitored hourly since escape from the antidiuretic effect of desmopressin may be sudden and unpredictable; the serum sodium should be measured every two to three hours.

Several retrospective studies have reported on the reactive or rescue use of desmopressin in a total of 334 patients with serum sodium concentrations that were ≤123 mEq/L [68,79,82,83]. In the first of these studies, administration of desmopressin to 14 patients in whom overcorrection was anticipated uniformly maintained the correction rate below the 24-hour limit in 13 and below the 48-hour limit in all [83]. In the second study, administration of desmopressin reduced the rate of correction from a median of 0.81 mEq/L per hour (before desmopressin) to -0.02 mEq/L per hour (after desmopressin) and decreased urine output from 650 mL per hour to 93.5 mL per hour [82]. The treatment was well tolerated in both series, and no patient developed seizures. There were two deaths, neither of which was related to hyponatremia, and one case of mild ODS in a patient whose serum sodium had already increased by 10 mEq/L before desmopressin was given.

In a larger study, 254 of 1274 patients with severe hyponatremia were treated with desmopressin to slow the rate of correction [68]. A proactive strategy was more successful than a reactive strategy in achieving a safe correction rate of 8 mEq/L or less in any 24-hour period (79 versus 30 percent), but the proactive strategy was used less frequently (11 versus 69

percent). The proactive strategy was applied without the concurrent use of 3 percent saline, which we recommend, and the authors did not specify the frequency of their desmopressin dosing. A rescue strategy was used in 46 patients (18 percent), of whom 38 had their serum sodium concentrations actively relowered by a median of 9 mEq/L without adverse consequences. There were four cases of ODS in this series, two of whom had advanced liver disease. In the two patients without advanced liver disease, one had been corrected by 10 mEq/L in 24 hours and 13 mEq/L in 48 hours using the reactive desmopressin strategy, and one had been corrected by 12 mEq/L in 24 hours in the absence of desmopressin.

Patients who have exceeded correction limits (rescue strategy) — We suggest **relowering** the serum sodium in patients with the following features: chronic hyponatremia (or hyponatremia of unknown duration); a presenting serum sodium concentration of 120 mEq/L or less; and the rate of correction having exceeded the recommended limit (8 mEq/L in any 24-hour period), particularly if the patient has risk factors that make him or her unusually susceptible to ODS (serum sodium of ≤105 mEq/L, alcohol use disorder, liver disease, malnutrition, hypokalemia) [19].

For patients with a lower risk of developing ODS, relowering may be reserved for those whose rate of correction exceeds 10 to 12 mEq/L in 24 hours [19]; however, if the sodium is not relowered, it is essential that correction not be allowed to exceed 16 mEq/L in 48 hours. The regimen for relowering the serum sodium is discussed below. (See 'Regimen to relower the serum sodium' below.)

Animal models provide support for relowering the serum sodium in patients with hyponatremia that has been corrected too rapidly but who do not have signs of ODS. Studies in rats have shown a marked reduction in the incidence and severity of brain lesions and in mortality when overly rapid correction of severe hyponatremia (by 25 mEq/L or more over several hours) is partially reversed within 12 hours [29,34,35]. In one study, for example, rats with a serum sodium less than 115 mEq/L for three days were rapidly corrected by more than 25 mEq/L with a single intraperitoneal infusion of hypertonic saline [29]. The rats treated with therapeutic relowering of the serum sodium survived free of neurologic sequelae. By contrast, all of the control rats died or developed neurologic signs such as hyperirritability and seizures. Significant benefit from relowering the serum sodium has also been described in rats that already had neurologic symptoms of overly rapid correction (ie, established ODS) [35].

Relowering of the serum sodium can reverse the breakdown of the blood-brain barrier that occurs with overly rapid correction and can prevent the infiltration of microglia that is a feature of osmotic demyelination [34]. Relowering after overly rapid correction in rats is much more effective in preventing brain damage than the administration of glucocorticoids [34].

Although human data are limited, relowering the serum sodium concentration with the administration of both desmopressin and D5W may abort osmotic demyelination following overly rapid correction of hyponatremia. The feasibility and apparent safety of relowering the serum sodium using desmopressin and D5W was described in 50 patients reported in three retrospective studies [68,82,83]. The serum sodium was relowered by 2 to 9 mEq/L below the peak level at rates ranging from 0.09 to 1.6 mEq/L per hour. No adverse effects were observed.

Although these observations demonstrate the feasibility of relowering of the serum sodium in patients with marked hyponatremia who have corrected too rapidly, they do not prove better outcomes than watchful waiting. Evidence for improved outcomes after relowering of the serum sodium is provided only by the rat models described above and by case reports of patients with overly rapid correction of severe hyponatremia (less than 110 mEq/L). In these case reports, relowering was performed because of neurologic symptoms compatible with ODS, and such symptoms resolved after relowering of the serum sodium by 12 to 16 mEq/L over 12 to 14 hours with desmopressin and oral or intravenous administration of dilute fluids (figure 2). (See 'Relowering the serum sodium to treat ODS' below.)

Regimen to relower the serum sodium — The relowering regimen consists of both of the following:

- D5W, 6 mL/kg lean body weight, infused over two hours. This quantity of D5W should lower the serum sodium by approximately 2 mEq/L, and the infusion should be repeated until the therapeutic goal, which is discussed below, is achieved.

- Desmopressin, 2 mcg intravenously or subcutaneously every six hours; the dose can be increased to 4 mcg in rare patients who do not respond to lower doses. The desmopressin is continued, even after D5W infusions have ceased, to prevent the serum sodium from rising again due to the excretion of dilute urine.

The serum sodium should be measured after each infusion of D5W to determine the rate of relowering and whether or not the goal serum sodium has been achieved. The goals of therapy are as follows:

- The serum should be lowered at an average rate of approximately 1 mEq/L per hour.

- The goal serum sodium is one that represents a rate of correction of less than 8 mEq/L in any 24-hour period and less than 16 mEq/L in any 48-hour period. Assume, for example, a patient with alcohol use disorder who has an initial serum sodium of 115 mEq/L is corrected to a serum sodium of 127 mEq/L in a period of 16 hours (overly rapid correction). Desmopressin and D5W should be given to lower the sodium to less than 123

mEq/L within the next eight hours, so that the net rate of correction over the 24-hour period is less than 8 mEq/L.

Once the goal serum sodium is achieved, the D5W is stopped, but desmopressin is continued to prevent overly rapid correction.

Rapid infusions of D5W can exacerbate hypokalemia and hypophosphatemia and can precipitate Wernicke encephalopathy in malnourished patients. We monitor for and correct hypokalemia and hypophosphatemia during D5W infusion; in addition, we administer thiamine among patients with suspected malnutrition.

Investigational therapies in experimental models of ODS — Two studies examined the effect of minocycline (a semisynthetic tetracycline) on the prevention of osmotic demyelination in rats that underwent rapid correction of chronic hyponatremia [32,33]. In both studies, minocycline, given concurrently with hypertonic saline and/or within 24 hours of the correction of the hyponatremia, reduced the severity of neurologic symptoms and histologic demyelination.

The rationale for evaluating the efficacy of minocycline was provided by the following observations: minocycline crosses the blood-brain barrier and inhibits microglial activation, thereby reducing microglial production of inflammatory cytokines; and minocycline has neuroprotective effects in experimental models of other demyelinating disorders [85,86]. There are no available data on minocycline use in humans with overly rapid correction of hyponatremia.

Other interventions that have been shown to prevent osmotic demyelination in rats include the administration of dexamethasone or myoinositol at the same time that the serum sodium concentration is rapidly increased [87,88]. Exogenous administration of myoinositol rapidly restores the brain myoinositol content to normal levels; this compound, which is an organic osmolyte, is depleted in chronically hyponatremic animals. There are no data on the use of either glucocorticoids or myoinositol in humans with overly rapid correction of hyponatremia.

Treatment of established ODS — Patients with suspected ODS (ie, onset of symptoms consistent with ODS in a patient with risk factors, such as overly rapid correction of hyponatremia) should have their serum sodium relowered; efforts to relower the sodium should commence without waiting for imaging confirmation of demyelinating lesions (which may take weeks to appear). Relowering of the serum sodium is less likely to be of benefit later in the patient's course.

In addition, patients who have developed ODS as a consequence of hyponatremia correction often require intensive supportive therapy.

Relowering the serum sodium to treat ODS — The optimal approach to the treatment of patients with serum sodium values that have corrected too rapidly and who have developed neurologic manifestations consistent with ODS is unclear. Based upon the ensuing observations of benefit, the absence of other effective therapies, and the poor prognosis associated with ODS, we recommend relowering the serum sodium to a level that is **just below** the maximal 48-hour target value (ie, to a value that is less than 16 mEq/L above the initial serum sodium). The 48-hour goal was chosen because patients with ODS typically present two to six days after overly rapid correction. The efficacy and safety of this approach is unknown.

The regimens used to relower the serum sodium in patients with ODS are the same as those described above to relower the serum sodium in patients who have exceeded correction limits (but who have not yet developed manifestations of ODS). (See 'Patients who have exceeded correction limits (rescue strategy)' above.)

The potential efficacy of relowering the serum sodium after the onset of neurologic symptoms of ODS was demonstrated in a rat model in which severe hyponatremia of three days' duration was rapidly corrected with hypertonic saline by 30 mEq/L at 24 hours [35]. The following findings were noted:

- Among the control rats, only 1 of 13 was still alive at 10 days (mean survival time of 3.3 days).
- The outcomes were much better among rats treated with relowering the serum sodium with distilled water to a total correction of less than 20 mEq/L at 24 hours; seven survived, and the mean survival time was 7.5 days. 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.

Data in humans are limited to case reports that suggest benefit from early relowering of the serum sodium in patients who have developed symptoms of ODS [71-74]. As an example, a 71-year-old female developed symptomatic hyponatremia with a serum sodium of 106 mEq/L in association with thiazide diuretic therapy [72]. The administration of isotonic saline was associated with an elevation in serum sodium of 21 mEq/L in the first 24 hours. After initial neurologic improvement, the patient deteriorated after 72 hours. The administration of hypotonic fluid and desmopressin relowered the serum sodium so that the final elevation was only 9 mEq/L. The patient recovered without neurologic sequelae.

A similar outcome was described in another case report in which the serum sodium was raised by 23 mEq/L in the first 48 hours (figure 2) [73]. Relowering the serum sodium from 132 to 120 mEq/L within the first 12 hours after the onset of neurologic manifestations consistent with ODS was associated with full neurologic recovery over the ensuing 36 hours.

In the few case reports previously described, relowering with desmopressin and D5W was initiated within hours of the onset of neurologic symptoms, and there were substantial reductions in serum sodium (up to 12 mEq/L) within the first 12 hours (figure 2) [72-74]. The optimal target serum sodium and rate of relowering in patients with ODS have not been defined. A reasonable approach is to lower the serum sodium to a value that is less than 16 mEq/L above the lowest level when therapy was initiated. As an example, a patient who presented with a serum sodium of 100 mEq/L and who develops symptoms of ODS with a serum sodium of 130 mEq/L should have their sodium level lowered to approximately 115 mEq/L (ie, an increase just below 16 mEq/L, which is the 48-hour limit). The rate of relowering should be approximately 1 mEq/L per hour, and the patient's neurologic status and serum sodium should be carefully monitored as relowering is performed.

Relowering therapy should be initiated as quickly as possible after the onset of neurologic symptoms that are attributed to ODS. In the rat model described above, initiation of relowering within four hours of symptom onset was associated with better outcomes than initiation within 8 to 10 hours of symptom onset [35]. In the case reports in humans, relowering was initiated within a few hours after the onset of neurologic symptoms (figure 2) [72,73]. There is no evidence of benefit in humans when relowering is begun more than 24 hours after the onset of ODS symptoms, but clinicians may choose a trial of relowering in this setting.

Supportive therapy — Many patients with ODS recover function, at least in part. In some cases, recovery occurs after prolonged periods of severe neurologic impairment. Thus, aggressive supportive therapy should be provided to all patients who were functional prior to the onset of ODS. Since patients with severe ODS frequently develop aspiration pneumonia and respiratory failure, endotracheal intubation and ventilator support are often required. Recovery from seemingly hopeless neurologic deficits can occur, and therefore, supportive therapy should be continued for at least six to eight weeks before concluding that the deficits are irreversible [7,89,90]. As an example, in a study of 36 patients with ODS treated in a critical care unit (32 of whom required mechanical ventilation), 69 percent survived, and 56 percent of the survivors were left with only minimal neurologic sequelae [90]. The initial severity of the illness was not predictive of long-term prognosis.

Immune-modulating therapies — There have been several reports of complete or partial resolution of neurologic deficits in patients with ODS following various combinations of

immunoglobulins, plasmapheresis, and glucocorticoids [91-93]. Immune-modulating therapy is based on the theory that osmotic disruption of the blood-brain barrier allows circulating lymphocytes, cytokines, complement proteins, and vasoactive amines to enter the brain, where they mediate astrocyte and oligodendroglial injury and demyelination. Cytokines secreted from activated microglial cells are also thought to contribute to oligodendrocyte loss.

Although favorable neurologic outcomes suggest a possible benefit from these interventions, they are difficult to interpret since many patients who develop ODS after rapid correction of hyponatremia experience a spontaneous reversal of neurologic impairment. Unlike therapeutic relowering of the serum sodium concentration, immune-modulating therapy has not been studied in experimental models of ODS.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hyponatremia" and "Society guideline links: Fluid and electrolyte disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- Brain adaptations that reduce the cerebral edema associated with hyponatremia make the brain vulnerable to injury if there is overly rapid correction of severe chronic hyponatremia. The neurologic manifestations of this injury have been called the osmotic demyelination syndrome (ODS; formerly called central pontine myelinolysis or CPM). (See 'Introduction' above.)

- The brain begins to adapt to hypotonicity almost immediately after a fall in serum sodium, and the adaptation is complete within two days (figure 1). Because the brain is able to adapt to hypotonicity, hyponatremia that develops over more than two to three days is not associated with severe brain swelling and is therefore much less likely to be complicated by seizures and coma; it is also extremely unlikely to produce brain herniation. However, once the brain has adapted to hypotonicity, the rate of correction of the hyponatremia becomes important. Overly rapid correction of severe hyponatremia can lead to ODS. By contrast, rapid correction is **not** likely to induce ODS in patients with severe hyponatremia that has only been present for several hours, since the cerebral adaptation is at an early stage. (See 'Brain adaptation to hyponatremia' above.)

- Major risk factors for ODS include the following (see 'Risk factors for ODS' above):

- Serum sodium at presentation – The majority of ODS cases occur in patients whose sodium concentrations at presentation are ≤105 mEq/L, and the vast majority of reported cases arise in patients who present with a serum sodium of 120 mEq/L or less. When the initial serum sodium is greater than 120 mEq/L, ODS is rare and typically limited to patients with severe liver disease and patients with arginine vasopressin disorders (formerly diabetes insipidus) who have developed hyponatremia as a complication of desmopressin therapy and then have the desmopressin discontinued. (See 'Serum sodium at presentation' above.)

- Duration of hyponatremia – Neurologic deterioration following rapid correction of hyponatremia is unlikely in patients with severe hyponatremia that develops over a few hours. By contrast, patients who develop hyponatremia more gradually have time for the brain adaptation and may develop the ODS after overly rapid correction. The duration of hyponatremia is often not known. Thus, clinicians should assume that the patient has chronic hyponatremia unless the history suggests acute water intoxication. (See 'Duration of hyponatremia' above.)

- Overly rapid rate of correction – It is difficult to define a threshold rate of correction below which ODS will not occur. Occasional cases have been reported in which ODS has developed after correction by as little as 8 mEq/L per day or 16 mEq/L in 48 hours. We and other authors recommend that the rate of correction of hyponatremia should not exceed 6 to 8 mEq/L in any 24-hour period. This is not a goal of therapy, but rather a therapeutic limit that should not be exceeded. (See 'Overly rapid rate of correction' above.)

- The clinical manifestations of ODS are typically **delayed** for two to six days after overly rapid elevation of the serum sodium concentration has occurred (figure 2). The symptoms, which are often irreversible or only partially reversible, include dysarthria, dysphagia, paraparesis or quadriparesis, behavioral disturbances, movement disorders, seizures, lethargy, confusion, disorientation, obtundation, and coma. Severely affected patients may become "locked in"; they are awake but are unable to move or verbally communicate. Other common findings include increased muscle tone and facial weakness, as well as snout, grasp, or rooting reflexes. (See 'Clinical manifestations' above.)

- ODS should be suspected in all patients who have risk factors for the disorder and consistent clinical manifestations. ODS is likely to be present if overly rapid correction of hyponatremia has occurred during the previous week. Patients suspected of having ODS should undergo brain magnetic resonance imaging (MRI) or, if MRI is unavailable, computed tomography (CT) scanning of the brain. (See 'Diagnosis' above.)

- Among patients at heightened risk of ODS because of alcohol use disorder, severe malnutrition, or advanced liver disease, or in those with severe hyponatremia (ie, serum sodium <120 mEq/L) lasting more than two to three days (or if the duration is unknown), we recommend that the serum sodium be raised by less than 6 to 8 mEq/L in any 24-hour period to prevent ODS (**Grade 1B**). When correcting the serum sodium in patients with hyponatremia, careful monitoring of the serum sodium concentration (initially, every two to three hours) is essential to avoid overly rapid correction in patients at increased risk for ODS. The urine volume should also be monitored for the emergence of a water diuresis. (See 'Prevention in patients at risk for ODS' above.)

- Some patients, during the course of treatment of hyponatremia, require further therapy to prevent overly rapid correction or to relower the serum sodium if overly rapid correction occurs. Such patients, and the corresponding therapeutic strategies, include:

  - "Proactive strategy" in patients who are likely to develop overly rapid correction – If the cause of impaired water excretion is likely to be reversible (eg, in hypovolemic patients), a water diuresis may develop and cause an abrupt rise in the serum sodium. In these patients, urinary water losses and rapid correction of hyponatremia can be prevented by administering desmopressin at the outset of treatment. We use the proactive strategy in patients with reversible causes of hyponatremia whose pretreatment serum sodium concentration is <120 mEq/L or whose risk of ODS is enhanced because of alcohol use disorder, severe malnutrition, or advanced liver disease. We also use the proactive regimen to treat desmopressin-induced hyponatremia in patients with arginine vasopressin disorders, even at serum sodium concentrations >120 mEq/L. (See 'Patients likely to have overly rapid correction (proactive strategy)' above.)

  - "Reactive strategy" in patients with a worrisome trajectory of the serum sodium – If a water diuresis emerges during therapy, or if the initial trajectory of correction appears likely to exceed maximum recommended goals, urinary free water losses can either be replaced with 5 percent dextrose in water (D5W) or stopped with the administration of desmopressin. (See 'Patients with a worrisome serum sodium trajectory (reactive strategy)' above.)

  - "Rescue strategy" in patients who have already exceeded the correction limits – If the rate of correction has already exceeded recommended limits, further water losses are stopped with the administration of desmopressin, and the serum sodium concentration is relowered. (See 'Patients who have exceeded correction limits (rescue strategy)' above.)

- Patients who have developed ODS as a consequence of hyponatremia correction typically require intensive supportive therapy. In addition, such patients should have their serum sodium relowered. (See 'Treatment of established ODS' above.)

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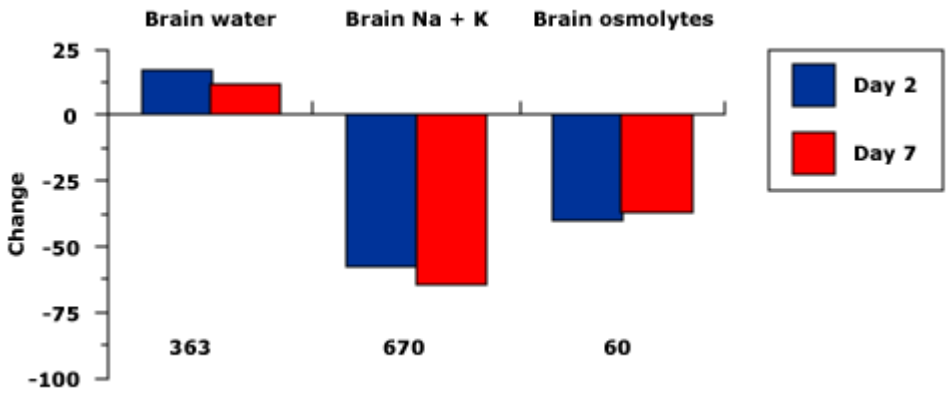
Topic 2317 Version 32.0

GRAPHICS

Cerebral osmotic adaptation to severe hyponatremia

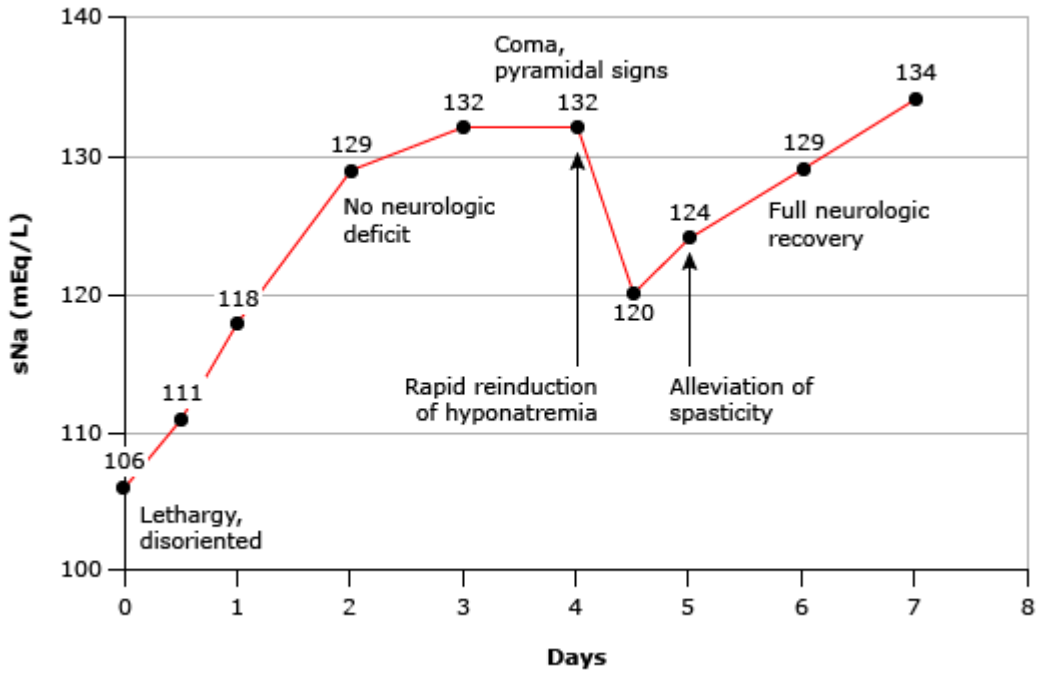


Changes in brain water, sodium-plus-potassium (Na + K) content, and three organic solutes – inositol, glutamine, and taurine – two and seven days after the onset of severe hyponatremia (plasma sodium concentration of less than 110 meq/L). The numbers at the bottom represent the baseline values. The return of brain water toward normal at day 7 is due to loss of sodium, potassium, and the organic solutes (called osmolytes). Although the absolute osmolyte loss is less than that of sodium plus potassium, the fractional loss is much greater – 36 of 60 or 60 percent versus 60 of 670 or less than 10 percent. Preferential osmolyte loss has the added advantage of not interfering with protein function within the cells.

Data from Verbalis, JG, Gullans, SR, Brain Res 1991; 567:274.

Graphic 71152 Version 3.0

Delayed appearance of osmotic demyelination and relowering of the serum sodium



Neurologic symptoms of osmotic demyelination syndrome (ODS) typically occur 2 to 6 days after correction of the hyponatremia. In this patient, severe hyponatremia was corrected too quickly (23 mEq/L in 48 hours), and coma developed 2 days later. The serum sodium was quickly relowered and then slowly corrected. Neurologic symptoms improved, which may have been due to relowering of the serum sodium or may have represented spontaneous resolution.

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sNa: serum sodium.

Graphic 76131 Version 16.0