Review Article

Central Pontine Myelinosis and Osmotic Demyelination Syndrome

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Summary

Background: Osmotic demyelination syndrome (ODS), which embraces central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM), is often underdiagnosed in clinical practice, but can be fatal. In this article, we review the etiology, pathophysiology, clinical features, diagnosis, treatment, and prognosis of ODS.

Methods: Pertinent publications from the years 1959 to 2018 were retrieved by a selective search in PubMed.

Results: The most common cause of ODS is hyponatremia; particular groups of patients, e.g., liver transplant recipients, are also at risk of developing ODS. The pathophysiology of ODS consists of cerebral apoptosis and loss of myelin due to osmotic stress. Accordingly, brain areas that are rich in oligodendrocytes and myelin tend to be the most frequently affected. Patients with ODS often have a biphasic course, the first phase reflecting the underlying predisposing illness and the second phase reflecting ODS itself, with pontine dysfunction, impaired vigilance, and movement disorders, among other neurological abnormalities. The diagnostic modality of choice is magnetic resonance imaging (MRI) of the brain, which can also be used to detect oligosymptomatic ODS. The current mainstay of management is prevention; treatment strategies for manifest ODS are still experimental. The prognosis has improved as a result of MRI-based diagnosis, but ODS can still be fatal (33% to 55% of patients either die or remain permanently dependent on nursing care).

Conclusion: ODS is a secondary neurological illness resulting from a foregoing primary disease. Though rare overall, it occurs with greater frequency in certain groups of patients. Clinicians of all specialties should therefore be familiar with the risk constellations, clinical presentation, and prevention of ODS. The treatment of ODS is still experimental at present, as no evidence-based treatment is yet available.

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Osmotic demyelination syndrome (ODS) was first described in 1959 by Adams and Victor, who reported “pontine myelinolysis” in alcoholic patients (1). On pathophysiological considerations, and as an increasing number of manifestation sites in addition to the pons were detected, central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) were combined into “osmotic demyelination syndrome”. Exact epidemiological data are still lacking, as there is not always a clear distinction between ODS and a prior or underlying disease. Furthermore, ODS is not always detected radiologically. As a result, the introduction of magnetic resonance imaging (MRI) led to increasing incidences of ODS, with the demonstration of oligosymptomatic as well as asymptomatic manifestations. Overall, ODS accounts for 0.4% to 0.56% of all neurological admissions to tertiary referral hospitals and 0.06% of all medical hospital admissions (2–4). MRI-based studies describe

incidence of 0.3% to 1.1%. In contrast, at-risk groups show incidence of 9.5%, with rates of 9.8% to 29% after liver transplantation (5). A 2015 clinical study found a 2.5% incidence of ODS among patients in intensive care units (6).

ODS usually manifests itself between the ages of 30 and 50 years; 51.8% to 77.0% of patients are men, and 23% to 48.2% have had a liver transplant (6, 7). Early studies found that the syndrome was localized mostly at the pontine in 67% of the cases, was strictly extrapontine for 6%, and had a mixed location in 27%. More recent, MRI-based studies have resulted in a shift to EPM (with CPM in 40% to 56% of cases, pure EPM in 13% to 35%, and mixed in 23% to 31%). This manifests as myelinolysis in the basal ganglia (especially in the striatum; 34%), cerebellar white matter (33% to 55%), thalamus, or hippocampus (6–8).

FIGURE 1

Pathophysiology of hyponatremia:

- Initial situation
- Changes in acute hyponatremia. Depending on the osmotically activated sodium gradient, the volume of brain cells initially increases, leading to cerebral edema and subsequent hospitalization.
- Compensation mechanisms in prolonged hyponatremia: to regulate cell volume, so-called osmolytes—osmotically active, inorganic ions (approximately 30% potassium and 20% chloride) and organic substances (with myo-inositol as the most important representative)—are released from cells. Inorganic osmolytes are transported via volume-sensitive potassium and chloride channels (00) while organic compounds diffuse along the concentration gradients via so-called leakage pathways (17). The cell volume then normalizes, and the osmotically activated gradient between intra- and extracellular space equalizes.
- Conditions in chronic hyponatremia
- Processes of correction for chronic hyponatremia. Cells are in a relatively hypertonic milieu and are exposed to osmotic stress, as on the one hand intracellular osmolytes are not replicated quickly enough, and on the other hand the reuptake of organic osmolytes via the bidirectional leakage pathways is much slower than their loss (18). Cells contract as a result of osmotic stress, and apoptosis is triggered.

Etiology

Etiologically, there are a large number of underlying causes and relevant comorbidities. Common to all is the development of ODS as a result of a severe prior disease or its treatment. While most of the early publications (up to the mid-1980s) described chronic alcohol use and alcohol withdrawal as the decisive comorbidities (>40%), more recent work as well as some of the older work describes foregoing hyponatremia as the most common cause, occurring in 30% to 78% of cases (7–10). Severe hyponatremia (serum sodium levels <120 mmol/L) is often present, in around 47% of cases; however, the majority of cases have additional concomitant cofactors, each of which alone can trigger ODS (8). In summary, almost any electrolyte imbalance can be the cause. Severe hypokalemia is especially important as a sole determining factor as well as a cofactor, particularly for patients in intensive care units (6, 11).

Another common etiological factor is liver transplantation (LTx), for which the most relevant cofactor is hyponatremia (67%, but severe in only 3.7%).

Further risk factors for LTx (12) are described in the *eSupplement*.

Pathophysiology

Histopathological basis

In pathological sections as well as in imaging, ODS occurs in typical locations. These have a characteristic histological structure (*eSupplement*) and are characterized by symmetrical expression. Histopathologically, there is noninflammatory demyelination with concurrent preservation of neurons and associated axons. In addition, there is a loss of oligodendrocytes, mainly due to apoptosis, and a significant infiltration of myelin-degrading macrophages (13, 14).

Pathophysiology in hyponatremia and correction of hyponatremia

The most common cause of ODS is hyponatremia. However, despite the osmotic stress not every patient who has hyponatremia develops ODS. Simply expressed, the only patients at risk for ODS are those who have experienced chronic hyponatremia (e.g., duration

TABLE

Common clinical symptoms by site of manifestation and syndrome classification (4, 20, 24)

CPM	EPM	
Pontine symptoms	Movement disorders	Neurobehavioral and general symptoms
Vigilance disorders, coma	Akinetic-rigid symptoms	Encephalopathy
Locked-in syndrome	Tremor	Epileptic seizures
Paresis	Dystonia	Mutism
Dysarthria	Chorea, choreoathetosis	Catatonia
Dysphagia	Myoclonus, opsoclonus	Apathy, lethargy
Pupillary and ocular motility disorders	Gait disorders	Depression
Loss of reflexes	Ataxia	Frontal lobe disinhibition, emotional instability, dementia, primitive reflexes

CPM, Central pontine myelinolysis; EPM, extrapontine myelinolysis

>48 h, or progression at a rate <0.5 mmol/h [15]) and correction of hyponatremia. The background for this is the sequential changes during the regulation of cell volume: a decisive role for transition from acute to chronic hyponatremia is played by the removal of inorganic and organic osmolytes from cells, with subsequent normalization of cell volume. The same process occurs during correction of extracellular sodium without rapid regeneration of osmolytes, leading to a decrease in the cell volume along the osmotic gradient, with consecutive cell death (16, 17) (*Figure 1, eSupplement*).

Clinical

Clinical course

ODS is highly variable in its clinical manifestation. In contrast, its time course is characteristic and central to diagnosis. The triggering factor precedes demyelination and its symptoms by 1 to 14 days. A symptom-free or stable clinical interval is then followed by ODS-induced secondary deterioration (8, 15). The symptoms usually correlate with the site of manifestation, differentiated into pontine and extrapontine. The most common clinical manifestations (CPM and EPM) are encephalopathies, characterized by vigilance disorders, qualitative impairment of consciousness, delirium, and disorders of drive, memory, and concentration, among others. The course can also be oligosymptomatic or asymptomatic (18).

Central pontine myelinolysis

If the pons and the corticospinal and bulbar tracts are affected in CPM, patients present with frequent encephalopathies and signs of damage to the brainstem. With corticobulbar pathway involvement, patients are affected by dysarthria and dysphagia (3.2% to 11.5% of ODS cases) (8). If the corticospinal tracts are affected, initially flaccid and later spastic tetrapareses of varying severity appear (in 9.8% to 28.8% of cases) (8). If tegmental lesions are present, ocular and pupillary motility

may also be affected (about 8% of all ODS) (8). In severe cases, the symptoms may even lead to locked-in syndrome (15). Severe disorders of consciousness occur in 6.1% to 14% of cases (8).

Extrapontine myelinolysis and movement disorders

Improvements in MRI have revealed numerous extrapontine sites of demyelination syndromes. As a result of demyelination of the basal ganglia, a wide range of characteristic extrapyramidal motor symptoms have been found, including dystonia, myoclonus, rigor, akinesia, and tremor (5, 18). The course of movement disorders in EPM is often biphasic. Early onset of extrapyramidal symptoms is followed by a second peak that often involves choreoathetoses or dystonia (4, 19). Little is known about the rates of occurrence of the individual symptoms. In a small case series of patients with EPM, 60% had extrapyramidal motor symptoms (4). Much less frequently described (8–14% of cases) are ataxias, generally as part of a cerebellar syndrome with lesions of the cerebellar peduncles (8, 20).

Neurobehavioral disorders

Recent case series and case reports have described the occurrence of cognitive deficits associated with ODS. Lesions can be found in the area of the cortex (cortical laminar necrosis) or at the transition between gray and white matter (21). Cognitive symptoms include frontal dysfunctions (e.g., problem-solving, planning what to do, drive, impulse control, and emotional control), concentration disorders, and psychiatric disorders (such as depressive or manic syndromes, emotional lability, catatonia, and mutism). A further group of patients (12–24%) presents with epileptic seizures that persist longer than potential epileptic seizures in the acute phase of hyponatremia (8, 22).

In summary, the presumptive diagnosis of ODS is usually based first on the clinical picture and course. The following factors suggest the presence of ODS: biphasic clinical course, initial electrolyte imbalance

or other risk factors, and the appearance of pontine or extrapyramidal symptoms after 1 to 14 days.

Factors that do not support a suspected diagnosis of ODS are symptom onset during the phase of electrolyte imbalance, cortical symptoms, and lateralizing symptoms (*Table*).

Diagnosis

A suspected diagnosis of ODS or, more specifically, CPM should be based on the presence of risk factors and a compatible clinical course. Suspicion is confirmed by MRI demonstration of demyelination sites, typically localized in pons, cerebellum, lateral geniculate body, thalamus, and external and extreme capsules. Damage to the brainstem can be detected by electrophysiological diagnostics as supportive evidence. No correlation can be made between diagnostic findings and clinical outcome, due to insufficient research data (22, 23).

Laboratory diagnostics: triggering factors

The principal predisposing factors are electrolyte disturbances (especially rapid correction of a chronic hyponatremia), chronic alcohol abuse, and malnutrition, as well as previous LTx. Therefore, a suspected diagnosis of ODS should be supplemented or completed by the appropriate laboratory diagnostics and medical history. The laboratory parameters to be examined are serum sodium, serum potassium, and liver values, as well as parameters for evaluation of the nutritional status (e.g., vitamin B12, methylmalonic acid, folic acid, and phosphate in serum). If possible, the previous course should be evaluated, especially with regard to serum electrolyte values.

Imaging

As a rule, MRI is more sensitive than computed tomography for detecting the typical demyelination lesions as a morphological correlate of ODS (3, 24). MRI is also successful in providing evidence for milder courses of disease. This has significantly improved assessment of the prognosis of ODS, as diagnosis is no longer restricted to autopsy-verified ODS after a fatal outcome.

MRI: course and sequences

Demyelination sites show hyperintensity in T2-weighted and T2 fluid-attenuated inversion recovery (FLAIR) sequences, and hypointensity in T1-weighted sequences (3, 25). The sensitivity of diffusion-weighted imaging (DWI) is unclear. On the one hand, early DWI changes without T2 or T2 FLAIR demarcation have been described (26). On the other hand, some studies have shown that DWI lesions as well as T1, T2, or T2-FLAIR lesions were detectable (24, 27). Accordingly, DWI, T2, and T2 FLAIR sequences should be considered equivalent for purposes of detection (27, 28).

Likewise, no clear recommendations can be made with regard to the optimal timing of MRI imaging.

BOX

Calculation of adequate sodium correction with specified limits

1. Prepare a 3% sodium chloride solution containing 514 mmol/L sodium chloride by mixing 100 mL of a 10% sodium chloride solution with 318 mL of a 0.9% sodium chloride solution
2. Calculate the sodium deficit to reach a serum sodium level of 120 mmol/L: $0.5 \times \text{body weight [kg]} \times 120 \text{ serum sodium [mmol/L]}$
3. Infusion amount [mL]: $\text{sodium deficit} / 514 \times 1000$
4. Infusion rate [mL/h]: maximum increase rate of serum sodium is 12 mmol/L/d, so divide infusion rate by 24
5. Outcome-relevant limit specification: sodium correction with $<0.5 \text{ mmol/L/h}$ corresponding to $<12 \text{ mmol/L/d}$

Positive MRI findings can sometimes be present as early as the first day after onset of symptoms (27, 28). However, cases have also been reported where the MRI findings were initially inconspicuous and first pointed to the diagnosis at a follow-up examination (24, 27).

In general, in the case of an early (<7 days) inconspicuous MRI examination, follow-up imaging should be carried out 1 to 2 weeks later (3). MRI alone is insufficient for assessment of the prognosis, as neither initial lesion size nor changes in size during the course correlate reliably with clinical outcome (23, 24).

Cranial computed tomography

Cranial computed tomography (CCT) can also be used to confirm clinical ODS, but has significantly lower sensitivity than MRI (initial detection rate: 25% to 28.5%) (3, 28). The rate of positive CCT findings increases over the course of development, although the detection rate does not match that of MRI (28). In contrast, however, CCT imaging is faster than MRI and is ubiquitously available. This makes it especially useful for swift exclusion of differential diagnoses. If the CCT findings are inconspicuous, however, ODS cannot be ruled out at either an early or a late stage.

Nuclear medicine

Nuclear medicine methods contribute more to the pathophysiological understanding than to confirmation of the diagnosis. For instance, based on metabolic analysis by means of ^{18}F -FDG-PET scanning, an early focal hypermetabolism was described that showed partial reversal towards hypometabolism over the course of disease (29). To evaluate the nigrostriatal dopaminergic system in EPM, $^{99\text{m}}\text{Tc}$ -TRODAT-1 and ^{123}I -IBZM

FIGURE 2

Preventive measures to avoid osmotic demyelination syndrome

SPECT can be used. With this method, bilateral reduced uptake of metabolites in the striatum, corresponding to ODS lesions, has been observed (30).

Electrophysiology

Although electrophysiological diagnostics may allow ODS to be detected, especially in the case of a pontine or other brainstem lesion, they do not provide consistent, specific findings. Indeed, not even a correlation with the current clinical symptoms or the outcome has been consistently described.

Therapy

General

The small low amount of evidence on treatment of overt ODS is based purely on case reports and small case series. A preventive approach in hypo- and hypernatremia of varying severity is better documented. Important issues for prevention are diagnostic determination of the cause of electrolyte derangement (and, where appropriate, treatment of the causative underlying disease) as well as the acuity of derangement and the associated symptoms.

Prevention

The severity of the initial electrolyte imbalance and the rapidity of its correction appear to play a critical role. In severe hyponatremia (<20 mmol/L), ODS incidence is significantly reduced by very slow correction of sodium, limited to <0.5 mmol/L per hour and <12 mmol/L per day (31). For hyponatremia (>120 mmol/L), the rate of sodium correction does not seem to be quite as decisive (15). In the case of severe

hyponatremia with relevant neurological symptoms, infusion of a hypertonic solution of 3% sodium chloride should be considered (32). In contrast, if neurological symptoms are not present, increasing the serum sodium with respect to the cause of hyponatremia is of primary importance. For raising the serum sodium levels, the infusion rate and amount can be calculated according to the limits given in the Box.

The goal of every treatment for hyponatremia is initially to achieve euvolemia and then to attain balanced osmolality. If hypokalemia is also present, it must be treated first (33). It is important to closely monitor the levels of sodium and potassium as well as osmolality in serum and urine. If there is significant derangement, monitoring should be done every hour. In addition, fluid intake should be limited and reliably balanced.

Depending on the cause of the hyponatremia, another potential approach is the use of vasopressin antagonists to enhance elimination of water without concomitant loss of electrolytes. The selective V2 receptor antagonist tolvaptan has been approved for this indication (34). Due to the associated risks and a lack of outcome data (35), however, the use of this antagonist is reserved for severe refractory cases after careful consideration. The risks include danger of overcorrection, onset of hyperkalemia, and dangers associated with an initially critical, highly frequent monitoring of electrolyte and volume status (Figure 2).

Clinical manifestation

It should first be noted that in a significant proportion of cases, good spontaneous remission occurs (3). The

described treatment options all have a low level of evidence and can only be characterized as experimental. Animal studies have shown that overly rapid sodium correction has a myelinotoxic-inflammatory component. Based on animal experiments, case reports and small case series have tested early treatment with dexamethasone (36), plasmapheresis, and/or immunoglobulins (37, 38), among others, with unanimous reports of rapid positive outcomes. However, whether this was a consequence of the respective therapeutic measure or merely the spontaneous course (independent of treatment) remains an open question.

Minocycline is another interesting substance with anti-inflammatory and anti-apoptotic effects for which data exist for other demyelinating diseases, such as multiple sclerosis. Among other effects, it inhibits the activation of microglial cells. In animal models, minocycline has been shown to have a protective effect against the development of ODS after rapid sodium correction for chronic hyponatremia (39). Furthermore, in experimental studies and case reports, reinduction of hyponatremia after initial excessively rapid correction for sodium showed higher rates of prolonged survival (40).

Prognosis

While studies up to the mid-1980s reported mortality of 90% to 100%, more recent work describes a much better prognosis, with a good outcome in about 33% to 50% of cases. About 24% to 39% of patients reach *restitutio ad integrum*; another 16% to 34% are self-sufficient in all activities of daily life (5, 23, 24). In contrast, approximately 33% to 55% of patients will require some care, be fully dependent on care, or die. Predictors of a poor outcome are severe hyponatremia of <114 mmol/L, hyponatremia with concomitant hypokalemia, and a notable reduction in vigilance. LTx patients who have clinically noticeable symptoms have the worst outcome: ODS is a relevant outcome factor, with mortality of 63% (LTx with ODS) versus 13% (LTx without ODS) and a morbidity/mortality rate of >77% (8, 12).

The currently more favorable prognosis is due to several factors, including earlier detection of ODS by MRI, the considerable progress achieved by modern intensive care medicine (such as more precise fluid and electrolyte management, among other things), and a more detailed pathophysiological understanding. Patients benefit from improved care programs and early rehabilitative measures in intensive care. A large proportion of patients improve early in the disease course. As significant improvements have also been reported in the long term, after up to 4 years, the prognosis of ODS remains open for a long time (5).

The change in the prognosis of ODS over the years has also been significantly affected by the greater use of MRI-based diagnostics in oligosymptomatic/asymptomatic patients. Furthermore, recent work in the MRI era has revealed a significantly higher proportion of patients with predominant EPM and

Key Messages

- In general, ODS is rare. However, in high-risk patients (e.g., liver transplant recipients), incidence of up to 29% has been described.
- Etiologically, hyponatremia is usually the underlying cause, but other imbalances in osmolytes can also cause ODS (such as hypernatremia, hypokalemia, hypophosphatemia, etc.). These imbalances are often accompanied by further etiologically relevant comorbidities.
- ODS is characterized by a biphasic course of disease, with a variable clinical course that depends on the site of manifestation. MRI is considered the diagnostic gold standard; in the case of suspicion but initially inconspicuous MRI findings, follow-up MRI should be performed after 1 to 2 weeks.
- The prognosis is usually good. The primary aim is to treat the triggering underlying reason for the osmolyte imbalance. Especially in severe hyponatremia, careful correction of sodium levels (< 12 mmol/L/24 h) is important to prevent ODS.
- No evidence-based treatment for overt ODS is currently available. In severe cases immunotherapy can be used, and vaptans should be considered. Overly rapid initial sodium correction can lead to reinduction of hyponatremia. In the future, treatment with minocycline may be possible.

extrapyramidal motor symptoms. In contrast to the severe motor deficits of CPM, these are amenable to symptomatic dopaminergic treatment, which yields good response rates (15).

Outlook

Despite the continuing significant proportion of patients with a poor outcome, overall the prognosis of ODS has improved due to various factors. A significant amount of improvement can also be expected in the long term.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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► Supplementary material

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Supplementary material to:

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eSUPPLEMENT

Etiology

Many causes and relevant comorbidities of ODS have been described in the literature. In the early publications (up to the mid-1980s), chronic alcohol consumption/alcohol withdrawal was described as the predominant comorbidity, present in over 40% of cases (7); according to more recent work, however, this no longer applies. Common to all publications is that the development of ODS is considered to be a consequence of a distinct, severe underlying disease or its treatment.

The most common cause of ODS, in 30% to 78% of cases, is prior hyponatremia (8, 9). Severe hyponatremia (serum sodium levels <120 mmol/L) is disproportionately prevalent (47%) (6).

Is ODS therefore solely a consequence of hyponatremia or its treatment? Looking at the vast majority of recent publications, especially those published after 2000, hyponatremia is the leading pathology; in most cases, however, concomitant cofactors are found, all of which are associated with ODS in normonatremic patients; thus, a monocausal correlation with hyponatremia does not appear to be assured (6). In addition to hyponatremia, other electrolyte imbalances can be the cause of ODS. General electrolyte dysequilibria and osmotic imbalances have been described, especially hypernatremia, hypophosphatemia, and hypokalemia. Severe hypokalaemia is both a significant cofactor and a sole cause of ODS (10), especially in intensive care patients (up to 41% of cases) (5). Patients with renal failure and/or hemodialysis are also at high risk due to significant electrolyte and osmolality fluctuations, accounting for 9% of cases described (6).

The third most common etiological factor is liver transplantation. Here too, hyponatremia is a relevant cofactor, found in 67% of cases. Severe hyponatremia, however, accounts only for 3.7% of cases. For liver transplantation, the following factors are associated with ODS: marked hyponatremia and sodium correction >12 mmol/L/d, transfusion of blood products, and bleeding complications. If two or more risk factors are present, the likelihood of ODS is significantly increased (11).

Diabetes mellitus with hyperglycemia may also be associated with ODS: diabetic ketoacidosis or hyperosmolar hyperglycemia can lead to marked changes in osmolality with increased vulnerability to ODS, either with or without concomitant hyponatremia (6).

Pathophysiology

Histopathological basis

Based on pathological sections as well as its presentation on imaging, ODS is characterized by typical localization and symmetrical expression. Histopathologically, CPM shows a symmetric, noninflammatory loss of myelination with simultaneous preservation of neurons and their associated axons in the central pons (12). In addition to loss of myelin, the examined

lesions are conspicuous for having a strong reduction in oligodendrocyte levels and significant infiltration by myelin-degrading macrophages (13).

But why does ODS have a high affinity especially for the pontine structures? The explanation may be found in the characteristic morphology of the region, with strong interweaving of descending and crossing fibers, together with the proximity of intimately connected gray and white matter with a high concentration of oligodendrocytes. This pattern is also the common feature of all other affected regions (cerebellum [with 33% of EPM], lateral geniculate body, external and extreme capsules, thalamus, basal ganglia, hippocampus, transition from cortical gray matter to white matter) (14). Histopathologically, therefore, oligodendrocyte-rich and myelin-rich regions seem to be particularly vulnerable to the development of ODS.

The loss of oligodendrocytes is mainly due to apoptosis. Overall, oligodendrocytes have a high level of vulnerability to a large number of influencing factors, and in particular physical ones (for instance, changes in the cell volume) that trigger apoptosis. In ODS, osmotic stress is usually the factor that triggers programmed cell death (15). Among other things, a part seems to be played by a potassium channel relevant for apoptosis, which, however, also has a crucial role in the regulation and homeostasis of oligodendrocytes (16).

Pathophysiology of hyponatremia and its correction

Etiologically, a large proportion of patients affected with ODS present hyponatremia. However, not every patient with hyponatremia develops ODS, despite having hyponatremia-related osmotic stress. Thus, one can simplistically state that, as a rule, a risk of ODS occurs only in patients with chronic hyponatremia who have it corrected.

At the point of regeneration of intracellular organic osmolytes, the frequent comorbidities of patients with ODS (malnutrition, chronic alcohol abuse, liver cirrhosis, status post liver transplantation, etc.) may manifest together with a reduced or wholly absent ability to replicate intracellular organic osmolytes. This also offers a possible explanation for the previously described cases of occurrence of ODS despite extremely slow correction of hyponatremia (17, 18).