

Dialysis Disequilibrium Syndrome

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Abstract:

A clinical constellation of neurologic symptoms and signs that can arise during or soon after dialysis, particularly during the initial stages of the procedure, is known as the dialysis disequilibrium syndrome (DDS). This is an exclusion diagnosis that affects people who are hyperosmolar and uremic; quick correction with renal replacement therapy causes cerebral edema and elevated intracranial pressure, which in turn causes clinical neurologic symptoms. Although DDS is most frequently linked to hemodialysis, it can also happen to individuals who need continuous renal replacement therapy (CRRT) due to acute kidney injury. It hasn't been mentioned in relation to peritoneal dialysis as of now. There is a wide range of signs and symptoms, from

headaches and restlessness to coma and death. The specific mechanisms underlying the development of cerebral edema and increased intracranial pressure, which are the principal contributing factors to this illness and the focus of therapy, are still unknown.

Once this illness has manifested, treatment is rarely effective. Therefore, taking action to stop it from developing is essential. This review will look at the pathophysiology of this syndrome and address the things to think about to prevent its development.

Key words: *Dialysis disequilibrium, hemodialysis, cerebral oedema.*

(J Bangladesh Coll Phys Surg 2024; 42: 282-288)

DOI: <https://doi.org/10.3329/jbcps.v42i3.74066>

Introduction:

Dialysis disequilibrium syndrome (DDS) is a neurological condition that can range in severity and is mostly brought on by quick urea elimination during hemodialysis¹. A variety of neurological symptoms linked to cerebral oedema may manifest as DDS. The patients who are just starting HD have the highest chance of getting DDS².

Although it can happen to any patient receiving hemodialysis, it is more likely to happen to those who are receiving it during or right after their first session. The symptoms, which affect the nervous system, are comparable to those of severe hyponatremia or elevated intracranial pressure. These symptoms include coma, headache, restlessness, and mental confusion^{3,4}.

The development of cerebral edema is the primary cause of the DDS symptoms and signs (Table 1)³, which are

related to the dialysis process in terms of time. As cerebral edema deepens and intracranial pressure increases, neurologic symptoms develop one after the other. If left untreated, these symptoms might result in a coma or even death⁵. Chronic dialysis patients frequently experience the earliest symptoms of nausea, headaches, vertigo, agitation, disorientation, confusion, cramping in the muscles, and trembling. Usually, hyper- or hypotension, as well as aggressive or severe ultrafiltration, are the causes of them.

DDS, however, can happen to patients on chronic dialysis and needs to be kept as a differential diagnosis, particularly in cases where the blood urea nitrogen (BUN) is high prior to dialysis and/or there is another cause of hyperosmolality, such as hyperglycemia or hypernatremia⁵. Due to the fact that these symptoms are not exclusive to disequilibrium syndrome, (Table 2)⁶ lists additional diseases that need to be ruled out and taken into consideration.

It is thought that severe DDS with a brain herniation is lethal. There is a case report of a patient who had two low-efficiency dialysis treatments followed by bilateral uncal herniation. And the patient recovered remarkably with vigorous hypertonic saline and mannitol treatment⁷.

The central nervous system (CNS) and urea:

The exchange of solutes and water across the neuronal microenvironment regulates its volume and composition.

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Received: 21 May 2024

Accepted: 8 June 2024

Table-I

<i>Signs and symptoms of dialysis disequilibrium syndrome (DDS)³</i>		
Signs	Nausea	
	Emesis	
	Headache	
	Dizziness	
	Muscle cramps	
	Agitation	
	Disorientation	
	Confusion	
	Tremors	
	Visual disturbances	
	Symptoms	Changes in mental status
		Asterixis
		Seizures
		Coma
Death		

Table-II

<i>Differential diagnosis for signs and symptoms of dialysis disequilibrium⁶</i>
Subdural hematoma
Uremia
Nonketotic hyperosmolar coma
Acute cerebrovascular event
Dialysis dementia
Excessive ultrafiltration and seizure
Hypoglycemia
Malignant hypertension
Hyponatremia

Blood brain barrier (BBB), which is made up of the glial and neuronal plasma membranes as well as those that span the ependyma and pia^{8,9}. The blood-brain and blood-CSF barriers are formed by the brain's microvasculature and the choroid plexus of the lateral and fourth ventricles, respectively. They regulate the chemical makeup of the CSF and the extracellular fluid (ECF) in the brain.

The unfenestrated endothelial cells of the microvasculature, with their intricate tight connections controlling the flow of ions and tiny organic solutes between the blood and the extracellular space, constitute

the actual blood-brain barrier. The microvessels are surrounded by astrocyte foot processes, however they are not sealed, permitting the interstitial fluid to pass through to the basement membrane of the endothelial cell. Comparatively speaking to other circulatory beds, the BBB's endothelial cells exhibit a high solute reflection coefficient, poor ion permeability, and high electrical resistance^{10,11}.

The capacity of a solute to exert an osmotic force is indicated by its reflection coefficient. The van't Hoff equation defines it as the ratio of the actual osmotic pressure to the ideal osmotic pressure. A number of 1 indicates that the osmotic force is at its maximum, while a value of 0 indicates that no osmotic force is being exerted. Urea's reflection coefficient ranges from 0.44 to 0.59, compared to 0.48 for glycerol and 0.90 for mannitol, indicating that it can exert some osmotic pressure across the blood-brain barrier^{12,13}.

Water-soluble and polar chemicals cannot quickly access the brain's interstitial space or the synaptic space when it comes to non-electrolyte compounds because of the tight intercellular connections and unfenestrated endothelial cells. As was previously established, urea enters the brain more slowly than it does other tissues and has a comparatively low permeability in the brain when compared to other organic solutes¹⁴.

Since the paracellular movement of water and solutes is restricted by the tight connections between cells, transcellular transport is necessary and hence controllable. Recent research demonstrates that these cells include particular transporters for water (AQP4 and AQP9) and urea (UT-B1), and that the expression of these transporters is changed in uremia¹⁵. In the brains of rats that had their nephrectomies, it was discovered that the expression of aquaporins increased while the expression of UT-B1 was reduced by half¹⁵. Furthermore, hyperosmolality has the potential to compromise the BBB, which would lessen the control over transport through this area¹⁶.

In healthy rabbits, the BBB's ability to transport urea has been studied^{13,14}. It was shown that although urea can enter the central nervous system, it does so considerably more slowly than it can when it enters muscle tissue. Raffinose was discovered to have a reflection coefficient of 1.0 across the blood-brain barrier (BBB), while urea was found to have a reflection

coefficient of 0.44. These findings suggest that, at the same concentration, raffinose has a greater impact on osmotic water flow than urea¹³.

The predialysis urea concentration in the CSF of the human subjects under study was somewhat lower than the blood concentration¹⁷. This suggests that there existed a small gradient for urea penetration into the CNS between blood and CSF. Following hemodialysis, the CSF's urea concentration exceeded that of the blood, creating an osmotic gradient that allowed water to enter the central nervous system. Rosen et al. observed in their study that patients with higher predialysis blood urea concentrations had a larger discrepancy in the CSF–blood urea concentration¹⁷. Stated differently, patients with higher uremic levels created a greater osmotic gradient that allowed water to enter the central nervous system¹⁷.

Development of brain edema:

Aquaporins (AQPs) have been shown in recent years to control water flow in a variety of tissues. The astrocyte cell membrane is home to AQP4, the aquaporin found in the blood brain barrier¹⁸. The degree of cerebral edema in mice lacking AQP4 is not as high as in wild-type mice¹⁸. As a result, this AQP is essential to the progression of cerebral edema.

Water must travel along an osmotic gradient in order for AQP4 to facilitate the passage of water from the bloodstream into the central nervous system. It was discovered that a guinea pig required an osmotic gradient of 45 mOsm/kg water in order to force appreciable amounts of water into the central nervous system¹⁹. In order to conduct these investigations, the guinea pigs were given an acute water load and vasopressin to prevent water excretion. Understanding the progression of cerebral edema during the dialysis disequilibrium syndrome depends on this osmotic gradient. The main concern has been whether the water transport into the brain can be explained by the gradient created by the differential in urea concentration alone¹².

The “Reverse Urea Effect” and the “Idiogenic Osmoles” theory are the two current theories put forth to explain the osmotic gradient. The theory behind the “Reverse Urea Effect” is that urea diffuses more slowly from the brain to the blood than it does from the blood into the dialysate compartment, which keeps the concentration of urea in the brain elevated. This is basically what the

original researchers discovered when they examined the level of urea in the patients' CSF during hemodialysis and discovered that it was much greater than in the blood.

Similar findings were observed in rats that were rendered uremic by ureteral ligation when precise measurements of blood and brain electrolyte, urea, and water content were done^{20,21}.

Additionally, the investigators' models differed slightly from one another. The animals were examined three days after the ureteral ligation model in dogs, which was employed by Arieff et al.²². Rats were the model employed by Silver et al. and these animals were examined 42 hours following ureteral ligation²². Due to the variation in uremia onset times, it is possible that uremic toxins that would cause the synthesis of “idiogenic osmoles” could develop 48 hours after uremia. Another possibility is that the “idiogenic osmoles” are actually the uremic poisons themselves. There are still unsolved questions in this regard.

Brain radiologic imaging and autopsy data provide evidence of cerebral edema in patients who had developed the dialysis disequilibrium syndrome^{23,24}. After the rats underwent hemodialysis, brain edema was detected by magnetic resonance imaging (MRI) in meticulous investigations of nephrectomized animals²⁵.

More interestingly, the authors determined that the edema was interstitial rather than intracellular based on the findings of their diffusion-weighted MRI investigation²⁵. Chen et al. came to similar conclusions when they studied hemodialysis patients who had diffusion-weighted MRI following their dialysis treatment; they discovered evidence of interstitial edema rather than intracellular edema²⁶.

The impact of cerebral acidosis:

It is unclear how acidosis contributes to the disequilibrium syndrome's development. Research indicates that although the bicarbonate infusion of the dialysate quickly raises blood pH, the brain intracellular pH (pHi) and CSF pH are significantly lower in the quickly dialyzed group²⁷. The fact that the arterial partial pressure of CO₂ did not change indicates that systemic hypoventilation was not the cause of the paradoxical CSF acidosis that resulted from fast hemodialysis.

The CNS's capacity to control the flow of water and solutes across the BBB may be affected by its elevated acidosis. Furthermore, by dislodging cations from their binding sites on intracellular proteins, the ensuing alterations in intracellular organic acids may have an effect on intracellular osmolality²⁷. Thus, the role of changes in CNS acid–base levels is very complex and will need further investigation.

Prevention of dialysis disequilibrium syndrome (DDS):

It is critical to identify individuals who are most at risk for DDS (Table 3) since this gives preventative measures like even more cautious clearance in these populations a chance to be implemented. The old and young, as well as those who have hyperosmolar conditions such as severe uremia, hypernatremia, or hyperglycemia, are among the vulnerable patients. Metabolic acidosis and pre-existing neurologic disorders are additional risk factors³.

Table-III

Risk factors for developing dialysis disequilibrium syndrome (DDS)³

First dialysis treatment
Children
Elderly
High Blood Urea Nitrogen (BUN)
Hypernatremia
Hyperglycemia
Metabolic acidosis
Preexisting neurologic abnormalities
Preexisting cerebral edema
Conditions associated with an increased permeability of the blood brain barrier, eg, meningitis, vasculitis, CNS tumors, hemolytic uremic syndrome or thrombotic thrombocytopenic purpura

Avoiding the development of a substantial osmotic shift is important because the DDS is mostly caused by osmotic fluid shifts into the brain.

Gradient that forms during hemodialysis between the brain and blood should shield against the condition. Three ways can be employed to do this: 1) Decreasing clearance to minimize the drop in plasma osmolality and, consequently, the osmotic gradient after dialysis, 2) Lengthening the duration of clearance; and 3)

Supplementing with an osmotically active substance (e.g., sodium or mannitol) when urea is eliminated by hemodialysis to prevent a substantial shift in plasma osmolality³.

Research conducted on guinea pigs showed that cerebral edema can only occur when there is a 45 mmol/kg shift in plasma osmolality.²⁸ When plasma osmolality is reduced by 48 mmol/kg per day in children with hypernatremia, but not by 24–28.8 mmol/kg per day, cerebral edema develops. In other words, cerebral edema is not caused by a slower correction rate of 0.5–0.6 mmol/L per hour, but rather by a rapid correction of hypernatremia at a rate of 1 mmol/L per hour.^{29,30}

That's why the current guidelines suggest treating chronic hypernatremia at a maximum of 12 mmol/L per day or 0.5 mmol/L per hour. This is the same as lowering plasma osmolality by up to 24 mmol/kg every day.

Consequently, DDS should be avoided by choosing for a longer course of dialysis and limiting clearance so as not to lower plasma osmolality by more than 20–24 mmol/kg weekly. In particular, when dialysis is first started, this can be accomplished by selecting smaller dialyzers and lowering the blood flow rate rate, especially when dialysis is first initiated. Over the course of three to four days, clearance can be progressively raised by 20% each day in order to reach the target urea reduction of roughly 70% during the hemodialysis session.

To treat the volume overload without limiting urea clearance in uremic patients with severe fluid overload, think about using ultrafiltration only and then hemodialysis, or vice versa. Ultrafiltration is a safe alternative because it has been demonstrated that plasma osmolality does not drop during this process.³¹

During the dialysis process, substituting urea with another osmotically active material will reduce the osmotic gradient caused by the quick elimination of urea during hemodialysis and maintain plasma osmolality. The most often used agents are mannitol and sodium; urea and glucose are less frequently employed; glycerol in dialysate has not been examined in humans; and other agents are not as typically used. Hypernatremic dialysate can be used to elevate serum sodium levels during the dialysis process. In a short research, clinical and electroencephalographic (EEG) monitoring was provided to patients receiving extremely efficient hemodialysis, some of whom were receiving it for the first time.

Compared to controls dialyzed against a standard 133 mmol/L sodium dialysate, patients who underwent dialysis maintaining the plasma osmolality using higher dialysate sodium chloride concentrations of 144–154 mmol/L had a significantly lower incidence of EEG changes and none developed symptoms suggestive of DDS³².

The usual 10 mmol/kg fall in plasma osmolality during hemodialysis was found to be reduced by about 50% to 5.2 mmol/kg with the use of high glucose dialysate, to 4.3 mmol/kg with intravenous mannitol, and to 1.7 mmol/kg in patients treated with both in a study evaluating the effects of both on plasma osmolality in chronic dialysis patients. The researchers discovered that these patients' mild DDS symptoms dropped from 67% to 10%, a decrease that was unrelated to the ultrafiltration rate. Intravenous mannitol works better on its own than high glucose dialysate³³.

It may be crucial to address additional factors that may contribute to cerebral edema and hypoxia in addition to hyperosmolality. The negative consequences of fast alkalization may be lessened by using a lower bicarbonate dialysate concentration and treating metabolic acidosis more gradually.

The overall incidence and severity have decreased, partly as a result of early dialysis initiation and prevention measures³⁴. Peritoneal dialysis and continuous kidney replacement therapy (CKRT) may reduce the incidence of DDS, according to some, but not all, studies³⁵.

Treatment of DDS:

The avoidance of DDS is the most important intervention. Table 2 lists the differential diagnosis that includes uremic, toxic, and infectious encephalopathy; electrolyte abnormalities such as hyponatremia, hyper or hypoglycemia; hemorrhagic and ischemic cerebrovascular accidents; subdural hematoma; malignant hypertension; and DDS when neurologic symptoms and signs appear in patients receiving renal replacement therapy, particularly hemodialysis but also CRRT.

DDS is an exclusion diagnosis; there is no diagnostic test for it.

Strong attention should be given to stopping the dialysis treatment if DDS is suspected. Reduce blood

flow rate if symptoms are extremely moderate in order to lower urea clearance.

If symptoms increase or become severe, the patient should be constantly observed and the dialysis session should be stopped right away. It is necessary to evaluate for additional reasons of neurologic decline³.

There are different school of thoughts as well. The first step in treating patients with DDS is to check the delivered dialysis prescription and switch the dialysate sodium bath or activate the dialysis machine's sodium modeling function as soon as possible. It has been suggested by several authors that keeping the patient on dialysis may not be necessary because the clinical improvement following this intervention can happen quickly; typically in less than 30 minutes. For individuals experiencing any level of DDS symptoms, from nausea to unconsciousness, sodium modeling can lessen symptoms. Modeling of sodium is dependent on the patient's predialysis serum sodium level and whether or not the patient is being dialyzed using a machine that can model sodium automatically³⁶.

When it happens, DDS is managed in a supportive manner, just like any other patient who may have cerebral edema, elevated intracranial pressure, or abrupt neurologic decline.

Keep your airway open and be aware of hyperventilation. Furthermore, mannitol or hypertonic saline can be used to raise plasma osmolality in order to decrease the osmotic gradient between the brain and blood in the treatment of cerebral edema.^{37,38} However, DDS has the potential to evolve quickly and be lethal when it is severe and progressed.³⁸

Implementing preventive measures and early identification of DDS risk factors are therefore crucial for patients starting renal replacement treatment for severe AKI and/or advanced CKD.

When sodium modeling is not effective in treating patients who continue to experience severe DDS (such as encephalopathy, coma, or seizures), it makes sense to try hypertonic saline or mannitol, if it is accessible. In order to stop future osmotic shifts and quickly boost the serum osmolality, either 12.5 g of mannitol or 5 mL of 23 percent saline can be used. Since there is currently a dearth of supporting research, this approach is primarily based on anecdotal clinical experience. After

administering hypertonic saline or mannitol, need to stop dialysis and schedule short, daily low-efficiency dialysis sessions, just like when a patient is first started on dialysis. Hemodialysis is usually started with a two-hour session at a blood flow rate of 150–250 mL/min and a dialysate flow rate twice that of the blood flow rate. Dialysis should be started as an inpatient for patients with a very high BUN, such as those with a BUN >100 mg/dL, or neurologic signs including myoclonus, confusion, or somnolence³⁹.

Furthermore, symptomatic management is an option for individuals who still exhibit modest residual symptoms of DDS (e.g., nausea, vomiting, restlessness) even after the prescription has been changed and sodium modeling has been used³⁹.

Conclusion:

Despite being an uncommon and self-limiting condition, DDS should be recognized, especially in high-risk populations. Early identification and prevention of this entity will reduce the likelihood of fatalities and other severe outcomes like comas. Dialysis patients, whether just started or those who miss sessions regularly, should be evaluated for DDS due to its intricate presentation.

Conflict of interest:

We have no conflict of interest to declare

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