Dialysis Disequilibrium Syndrome Revisited

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An aggressive dialysis in a grossly azotemic patient, especially one with severe metabolic acidosis, can lead to dialysis disequilibrium syndrome (DDS). Mild forms present as nausea, vomiting, restlessness, and headache. Severe manifestations include seizures, obtundation, coma, and even death.

This clinical picture is caused by cerebral edema induced by one or more of the following mechanisms:

1. *"Reverse urea effect" – Dialysis removes urea faster from the blood than from the brain; consequently, water enters the brain.*
2. *"Cerebrospinal fluid acidosis" – Correction of systemic acidosis engenders the condition due to a lowering of brain pH.*
3. *"Idiogenic osmoles" – As a response to blood hyperosmolar state, osmoles are produced in the brain. As blood osmolality decreases under relatively quick dialysis, idiogenic osmoles tend to induce brain edema.*

Because the symptoms of DDS can be life-threatening, preventive measures in patients with severe uremia are important. The first strategy relies on raising blood osmolality by introducing solutes (osmoles) into the blood. The second approach, which is the most common, decreases the efficiency of the dialysis treatment by shortening the duration of a dialysis run to 25% – 30% of normal, by lowering dialyzer blood flow or dialysate flow rate, by using a less efficient dialyzer, or by a combination of these maneuvers. Dialysis frequency is increased instead. Anticonvulsant drugs are needed in cases where the preventive measures have not been used or have been unsuccessful.

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Key words

Dialysis disequilibrium, reverse urea effect, brain acidosis, idiogenic osmoles

Introduction

A precipitous fall in blood urea concentration in a grossly azotemic [for example, blood urea level above 60 mmol/L (360 mg/dL)] patient by aggressive dialysis can produce a constellation of neurologic and systemic manifestations collectively known as the dialysis disequilibrium syndrome (DDS). The syndrome can occur during or soon after a dialytic procedure (especially in new dialysis patients), but it can also appear within the 24 hours subsequent to completion of a dialysis session [1,2]. Mild manifestations include anorexia, nausea, vomiting, disorientation, restlessness, muscle cramps, blurred vision, dizziness, asterixis, and headache. Severe manifestations include confusion, seizures, obtundation, coma, and even death [3,4].

The syndrome is particularly common among children and among neurologic patients, such as those suffering from preexisting seizure disorders or brain trauma [5]. The higher incidence in the pediatric population is related in part to the use of dialyzers with a disproportionately high mass transfer area coefficient relative to the child's body size or to the use of a high blood flow rate or a high dialysate flow rate, or both [6]. With regard to neurologic patients, it is possible that insult is being added to injury. Other predisposing factors include older age and severe metabolic acidosis [7]. Finally, it should be noted that DDS is uncommon among peritoneal dialysis patients because of the relatively slower removal of waste products from the body as compared with that in hemodialysis patients [8].

To better understand DDS, a general review of the physiology of the blood–brain barrier is in order.

The blood–brain barrier and reflection coefficients

The blood–brain barrier is a concept that depicts the kinetic aspects of the passage of substances out of the blood into the brain [9]. The general idea of a restriction on the passage of a dissolved substance out of the blood into the brain dates from the studies of Ehrlich [10]. This investigator observed that, whereas many dyes, after intravenous injection, stained nearly every part of the body, the brain was often spared this universal staining.

Urea, by virtue of its physical properties (non polar, non ionized, and water soluble), can traverse most cellular membranes. As a result, at steady state, most body fluids exhibit similar urea concentrations, with the exception of fluids within the ocular and cerebrospinal spaces [11]. In these latter fluids, the steady-state concentration of urea has been found to be lower than that in the blood [12,13]. In the brain, on the other hand, the steady-state level of urea has been demonstrated to be higher than that in the blood [11].

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The permeability kinetics of any solute across the blood–brain barrier, which in turn governs that solute's steady-state concentration, can be studied by measuring the osmotic pressure that the particular solute generates across the blood–brain barrier [14]. The osmotic pressure thus determined can be expressed as a ratio between itself and the ideal osmotic pressure. This ratio is known as the *reflection coefficient.* Reflection coefficient values range from 0 to 1, with a value of 1 signifying complete impermeability. The reflection coefficient of 0.44 – 0.59 for urea (versus, for example, 0.9 for the impermeable mannitol) implies that this waste product has a limited ability to cross the blood–brain barrier. Precisely because of this limited ability, a lag exists not only in the entry of urea from the blood into the brain or into the cerebrospinal fluid (CSF), but also in the reverse process—namely, the exit of urea into the blood from the brain and from the CSF [13, 15,16].

The reverse urea effect

The inherent delay in urea entry into the brain, coupled with the faster movement of water in the opposite direction (the permeability surface area product for water being 0.65 – 1.75 mL/g/min [17] and that for urea being 5×10^{-3} mL/g/min [18]), means that urea can function as a temporary effective osmole [14]. Thus, rapid intravenous infusions of urea have been successfully employed to dehydrate nerve and ocular tissues in patients with cerebral, spinal cord, and intra-ocular lesions [16]. This therapeutic effect can be called the "urea effect".

Conversely, when urea is removed from the blood after equilibration between the blood and the brain has been achieved, the lag in the exit of urea from the brain into the blood can draw water into the brain, thus engendering cerebral edema. This process has been termed the "reverse urea effect" [19]. It is noteworthy that the lag in urea exit from the brain may be magnified in patients with renal failure [20].

Kennedy *et al.* [19] were the first to suggest, in 1962, that DDS is related to the "reverse urea effect". The syndrome was attributed to the delayed exit of urea from the brain in the face of a rapid dialysis-induced decline in blood urea level, thus creating an osmotic gradient that favored the shift of water into the brain from the blood. The researchers based their assertions on the following observation: In patients with dialysis disequilibrium, in common with other azotemic patients, the pre-dialysis levels of urea in the CSF were found to be only slightly lower than those found in the blood. At the end of dialysis, however, the blood urea levels were greatly reduced, while the CSF urea values were only slightly depressed. The group's assertions are in keeping with the lag in urea removal from the CSF and from the brain in the face of an abrupt fall in blood urea concentration [16].

Subsequently, Walters *et al.* [21] were able to show that patients with the highest pre-dialysis blood urea concentration and the greatest absolute reductions in urea had more cerebral edema than those with a lower pre-dialysis urea value and a lesser absolute urea reduction. Moreover, Hu and colleagues [22] found that the delay in urea exit from the brain (due to the low permeability of urea) is aggravated by a great loss (30% reduction in mRNA expression) of urea transporters, agents that normally facilitate urea transport out of brain cells. Lastly, Galons *et al.* [23] discovered that, in uremic rats as compared with controls, hemodialysis could promote a faster movement of water into the brain.

Thus, the combination of a renal failure–related reduction in urea exit from the brain and a dialysis-induced augmentation in water entry into the brain can contribute to the generation of cerebral edema.

Evidence for cerebral edema

With respect to cerebral edema, La Greca *et al.* [24] applied computed tomography to images acquired before and after hemodialysis and found a decrease in parenchymal density, suggesting a relative increase in the hydration of the brain. It has also been shown that, after a conventional hemodialysis treatment, an average increase in cerebral volume of 3% could be detected by magnetic resonance imaging [21].

Additional clinical and experimental data lending support to the presence of cerebral edema have also been forthcoming. For example, an exposed brain flap in a patient was found to swell during the course of a dialysis run [25]. In rapidly dialyzed dogs, brain water content was noted to rise with dialysis [26]. Similarly, Silver *et al.* [13] discovered that rapid dialysis could raise brain water by approximately 6% in nephrectomized rats. Differences in the urea concentration between brain and blood (high brain-to-blood ratio) were incriminated in these changes in brain water content [21].

Elevated intracranial pressure

That cerebral edema is associated with increases in intracranial pressure (ICP) is well described. Thus, measuring ICP can help to detect the presence of cerebral edema. In this respect, a hemodialysis-induced elevation in ICP was observed in a patient harboring an acoustic neurinoma; ICP returned to baseline after completion of the dialysis treatment [27]. In a related study [28], neurosurgical patients suffering from acute renal failure and undergoing hemodialysis treatments were observed by continuous ICP monitoring. An increase in ICP was seen only during dialysis; a similar rise was not noted in the interdialytic interval. Furthermore, by performing studies in uremic dogs and uremic human patients, Sitprija and Holmes [29] were able to conclude that hemodialysis could, respectively, raise the intracranial pressure in dogs and the intra-ocular pressure in humans (changes in intra-ocular pressure are known to correlate with those in ICP).

More recently, in 1990, Davenport *et al.* [30] measured ICP in patients who were suffering from acute oliguric renal failure in association with hepatic encephalopathy, and who were treated with either intermittent or continuous hemofiltration. During the first hour of treatment in patients treated with intermittent hemofiltration, a reduction in plasma osmo-

lality was accompanied by a rise in ICP. Corresponding changes were not seen in patients treated with continuous hemofiltration. The investigators asserted that, in the case of intermittent hemofiltration, a rapid fall in plasma osmolality was responsible for water movement into the brain, producing cerebral edema.

In patients suffering from DDS, serial electroencephalograms have revealed characteristic rhythmic delta-wave abnormalities that are consistent with a rise in ICP [31]. These characteristic waves are believed to be a hallmark of cerebral edema. Avoiding marked falls in plasma osmolality during dialysis can attenuate or abolish these abnormal waves [32].

"Idiogenic osmoles" theory

Idiogenic osmoles are organic osmoles (or osmolytes) produced by the brain to counteract various hyper-osmolal states so that brain shrinkage does not occur [33]. The idiogenic osmoles theory was originally advanced to explain DDS because, in initial studies, the brain urea level was found to be less than that required to produce the degree of cerebral edema seen under experimental conditions [34]. Subsequently, however, Silver *et al*. [14] demonstrated that, if the brains of experimental rats were frozen solid promptly after death, the expected urea gradient between the brain and the blood could be demonstrated. Additionally, no increase in commonly observed idiogenic osmoles has been observed during experimental hemodialysis [34,35]. Because of these findings, the idiogenic osmole theory has lost some of its appeal.

"Cerebrospinal fluid acidosis" theory

It has been suggested that the pH of the CSF falls during hemodialysis [36]. Acidosis of the CSF ordinarily occurs whenever systemic metabolic acidosis is rapidly rectified by alkali therapy [37]. During hemodialysis, existing systemic metabolic acidosis (if any) is promptly corrected, but the corresponding CSF pH level remains low. The low CSF pH may be due to the failure of the higher plasma bicarbonate to enter the CSF (whereas increased plasma CO_2 diffuses rapidly to the CSF, increasing its pCO_2) or to the production of an unidentified organic acid by the brain during dialysis [7]. The CSF and brain acidosis somehow brings about edema of the brain. However, studies lending support to this particular theory are few.

Given the present state of our knowledge, the "reverse urea effect" theory appears the most promising, but neither the idiogenic osmoles theory, nor the CSF acidosis theory can be entirely ruled out.

Management

Prophylactic measures are important in the management of DDS:

1. Solutes (osmoles) are introduced into the blood directly or via the dialysate to raise blood osmolality and to prevent the entry of water into the brain.

   This approach is often employed because the most promising theory regarding the cause of DDS is based on the "reverse urea effect" [19,32]. For example, if a dialysate is enriched with urea in a concentration approximating that in the blood, no appreciable gradient for urea transfer will exist between the brain and the blood. As a consequence, urea will not be lost from the body, the "reverse urea effect" will not take place, and DDS should not materialize [32,38,39].

   A recent testimonial to the success of this approach was demonstrated clinically by Doorenbos *et al.* [40]. Those authors used hemodialysis to treat lactic acidosis and renal failure in a metformin-intoxicated diabetic patient. After 7 hours of dialysis, the blood urea level fell to 10.4 mmol/L (62 mg/dL) from 28.8 mmol/L (172 mg/dL), and the patient promptly developed symptoms of DDS. However, during two subsequent 6-hour dialysis runs, the patient's blood urea concentration was kept constant by enriching the acid concentrate with a 4.4 molar urea solution, in an effort to produce a final dialysate urea concentration approximating that of blood. During the course of the urea-enriched dialysis regimen, the patient was free from manifestations of DDS. The addition of urea to the dialysate enabled the patient to undergo a prolonged dialysis treatment administered to remove metformin from the body and to rectify the lactic acidosis without succumbing to DDS.

   With regard to the concentration of urea in a urea-enriched dialysate, having exactly the same level as that found in the blood is not necessary. One can use a lower dialysate urea value (for example, 10% or so lower), so that, over a series of dialysis treatments, blood urea level can be reduced in a stepwise manner, with less risk of developing DDS.
2. Too-rapid removal of waste products by hemodialysis is prevented.

   To prevent the development of DDS in the event that dialysis is required in a patient with an inordinately elevated blood urea value [for example, 80 mmol/L (480 mg/dL)], an inefficient dialysis treatment can be fashioned by shortening the duration of the dialysis run to 25% or so of normal, by lowering dialyzer blood flow or dialysate flow rates, by using a less efficient dialyzer, or by a combination of those maneuvers. If no untoward effects appear, then, in a stepwise manner, the efficacy of the dialysis treatment can be raised in subsequent dialysis runs until conventional dialysis treatments can be safely offered. By employing less efficient, more frequent dialysis treatments, the biochemical abnormalities associated with uremia are corrected in a more gradual manner, thus reducing the incidence of DDS [41–45].

   It follows, therefore, that daily dialysis treatments or slow continuous therapies such as continuous hemofiltration or hemodiafiltration are ideally suited for the prevention of DDS. These modalities are successful

because they avoid marked reductions in blood waste-product levels, minimize changes in intracranial pressure, and, hence, reduce the risk for the development of cerebral edema [30,46].

In clinical situations in which aggressive dialytic therapy is mandated, exogenously administered solutes such as urea, glycerol, mannitol, or sodium chloride can be used to counteract the urea-lowering effect of the therapy [47–54] (although the use of sodium chloride is controversial [55]). However, in clinical practice nowadays, because most patients are seen relatively early in the course of their disease, when their blood urea levels are not inordinately elevated, the initial management regimen of frequent, ineffective dialysis treatments is often adequate. The introduction of exogenous solutes into the blood to counteract the urea-lowering effect of dialysis is seldom required.

3. Anticonvulsant agents [47] are used.

Anticonvulsant drugs have been used both to prevent and to treat DDS. In general, this therapy may not be the best approach. Because the pathophysiology of DDS is related to the development of brain edema, anticonvulsant therapy only lessens the incidence and duration of seizure disorders; it does not affect the underlying cause. Nevertheless, administration of anticonvulsant agents may be desirable at times, and some agents are more effective than others.

Seizures can be managed by intravenous diazepam therapy with effects commonly lasting between 30 minutes and 1 hour. When compared to barbiturates, diazepam causes less respiratory depression. It cannot be overemphasized that, although diazepam and related drugs are metabolized by the liver, great care should be exercised in their use. Many renal failure patients, especially the elderly, cannot tolerate the dosages ordinarily recommended for patients with normal liver and renal functions.

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