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Dialysis disequilibrium syndrome: A case report

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Abstract

The dialysis disequilibrium syndrome is a severe, but rare complication that can occur during or after hemodialysis. It primarily arises from an osmotic gradient, between the plasma and the brain, resulting from the rapidity of the dialysis. This gradient leads to the development of cerebral edema and an increase in intracranial pressure, manifesting as various neurological symptoms. Although this syndrome carries risks of morbidity and mortality, it can be prevented by identifying high-risk patients, implementing preventive measures, and ensuring early detection and prompt management of dialysis disequilibrium syndrome. We present a case of dialysis disequilibrium syndrome in a 59-year-old woman, to raise awareness of this uncommon entity. This review focuses on the discussion of clinical features, and prevention of dialysis disequilibrium syndrome, with a particular emphasis on understanding its pathophysiology, as it significantly influences preventive and management approaches.

Keywords

Osmotic gradient, hemodialysis, urea, neurological manifestations

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Introduction

The dialysis disequilibrium syndrome (DDS) presents as a clinical disorder, characterized by acute dysfunction of the central nervous system, occurring in patients with end-stage renal disease undergoing hemodialysis. Dialysis was introduced as a potential therapy for renal failure in humans by Georg Haas in 1924, with the first description of this syndrome occurring in 1962[1,2] in a Lancet publication. It is frequently associated with rapid solute removal by hemodialysis, primarily in patients initiating their dialysis treatment, although it can also occur, less frequently, following maintenance hemodialysis in patients with chronic renal failure.[3,4]

This disorder is explained by the formation of cerebral edema, resulting from the creation of an osmotic gradient between the plasma and the brain.[5,6] Neurological manifestations progress concomitantly with the worsening of cerebral edema, leading to an increase in intracranial pressure, if not rapidly identified and managed, they may progress to coma or, in severe cases, death.[7] The symptoms are typically transient, mild, and time-limited, they are primarily observed in patients with elevated plasma urea concentrations, especially those with chronic kidney disease (as opposed to acute kidney injury), and in patients undergoing initial hemodialysis treatment, with an aggressive approach to urea removal.[2] Severe symptoms like seizures and changes in mental status are the only ones recognized, yet they are high in patients with a history of preexisting neurological disorders.[8]

Herein, we present a case of DDS who was admitted to the medical intensive care unit, due to an altered level of consciousness, following her first hemodialysis session. We also discuss important aspects of presentation, and identifying high-risk individuals is crucial for effective prevention.

Case report

A 59-year-old female patient presented at the emergency with the symptoms of epigastric pain and vomiting, accompanied by a general deterioration of her condition, with a medical history of diabetes type 2, hypertension, inflammatory polyarthritis, and breast cancer. In 2019, she underwent a mastectomy and received radiotherapy and chemotherapy

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Table 1. Laboratory values before and after the initiation of hemodialysis in the intensive care unit.

Parameter	Pre-dialysis value	Post-dialysis value	Reference range
Hemoglobin (g/L)	96	78	137–180
White blood cells /L	11	9	$4.0–11.0 \times 10^9$
Platelets/L	603	486	$150–400 \times 10^9$
Sodium (mmol/L)	138	138	133–145
Potassium(mmol/L)	5.1	3.3	3.5–5.0
Chloride (mmol/L)	95	98	98–111
Bicarbonate (mmol/L)	13	20	21–31
Glucose (g/L)	0.7	0.69	0.8–1.15
Magnesium (mmol/L)	0.88	0.57	0.65–1.15
Osmolality (mosmol/kg)	340	—	280–300
Urea (g/l)	**72.4**	**34.5**	**2.5–9.1**
Creatinine (mg/l)	**1664**	**805**	64–111
Lactate (mmol/L)	0.7	1.3	<2.0

(tamoxifen 20 mg once daily). She also had a hysterectomy in the same year and a cholecystectomy in 2017. Upon arrival at the emergency department, the initial assessment showed a malnourished and afebrile patient. The results of the physical examination revealed signs of tachypnea, tachycardia, use of accessory muscles, and crackles at the base of the left lung. The rest of the examination found diffuse abdominal tenderness, more pronounced at the epigastric level. An abdominal computed tomography scan was performed, revealing stage A pancreatitis. Toxicology and drug screen were negative. In addition, her laboratory tests showed advanced renal insufficiency with a urea level of 4.36 g/l and creatinine level of 188 mg/l. Her serum potassium level was 5.1 mmol/L, and she had an anion gap of 13.

Arterial blood gases showed metabolic acidosis with respiratory compensation. The metabolic acidosis (pH 7.00) continued to be present, but the patient's persistent oliguria raised concerns, even after administering 4 l of crystalloid resuscitation. A right internal jugular catheter was used to initiate emergency hemodialysis, and the treatment was maintained for 2 h. The parameters for hemodialysis included: an FX8 membrane (surface area of 1.4 m^2 and KUf of 50 mL/h/mmHg), potassium at 3 mmol/L, sodium in the dialysate at 136 mmol/L, bicarbonate at 40 mmol/L, calcium at 1.25 mmol/L, and a dialysate flow rate (QD) of 500 mL/min, with a blood flow rate (QB) of 250 to 300 mL/min.

The patient's neurological condition deteriorated post-dialysis, leading to his admission to the medical intensive care unit. The post-dialysis electrolyte panel showed a decrease in urea to 2.08 g/l and creatinine to 91 mg/l (urea reduction ratio was 52.3%). The anion gap was 20, the potassium level was 3.3 mmol/L, and the sodium level was 138 mmol/L (Table 1).

The clinical examination reveals a confused patient with a Glasgow Coma Scale (Table 2) of 10 (OY: 4; RV: 1; RM: 5). The pupils are equal and reactive, the patient is afebrile, and neck stiffness is present. There is no sensory or motor deficit noted. Examination of the cranial nerves raises suspicion of left-sided central facial paralysis with obliteration of the left nasolabial fold. The patient is stable hemodynamically and respiratorily.

Table 2. Glasgow coma scale.[9]

Component tested	Score
Eye response	
Eyes open spontaneously	4
Eye opening to verbal command	3
Eye opening to pain	2
No eye opening	1
Motor response	
Obeys command	6
Localizes pain	5
Withdraws from pain	4
Flexion response to pain	3
Extension response to pain	2
No motor response	1
Verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	

The cerebral CT scan, complemented by cerebral angio-MRI, revealed no abnormalities except for vascular leukoencephalopathy classified as Fazekas 1. An Electroencephalogram was performed, showing slow wave activity suggestive of metabolic encephalopathy with no evidence of epileptic status on the tracing.

DDS was identified as a cause of the altered level of consciousness after excluding other etiologies. The patient's condition demonstrated spontaneous improvement in neurological status, with a Glasgow Coma Scale score of 15 after 7 days of intensive care unit hospitalization. Subsequently, the patient was transferred to the nephrology department and showed good progress.

Discussion

Our understanding of this severe syndrome has improved since the initial description. Studies conducted on both animals and humans demonstrated that DDS is correlated with the development of cerebral edema, leading to an increase in intracranial pressure.[10,11] The crucial question is to clarify whether the gradient resulting from the difference in urea concentration alone can explain the movement of water into the brain. Present hypotheses regarding the osmotic gradient involve the reverse effect of urea, the concept of idiogenic osmoles, and intracerebral acidosis.

It is now well established that specific water channels called aquaporins (AQPs) and urea transporters (UTs) play a

crucial role in facilitating the movement of urea and water across plasma membranes, promoting rapid transmembrane equilibration. Recent data reveal a decline in the expression of the UT-B1 transporter in the brains of uremic rats, suggesting the possibility of a higher reflection coefficient. This could lead to a stronger osmotic force, regardless of the level of urea gradient.[12]

The increased expression of AQP9 and AQP4, combined with the diminished expression of UT-B1 in uremic animals, compared to non-uremic animals, may lead to an elevated urea reflection coefficient. This facilitates increased water movement, with a lower urea gradient. When corrected rapidly through dialysis, or administration of alkaline agents, a paradoxical acidemia of the cerebrospinal fluid (CSF) occurs.[13,14] Due to a rapid increase in bicarbonate and arterial pH, this leads to secondary hypoventilation and an elevation in plasma CO_2. The elevated plasma CO_2 quickly diffuses into the CSF, raising the CSF PCO_2. However, plasma bicarbonate faces difficulty in penetrating the CSF due to slow transport through the blood–brain barrier.[14,15]

As a result, the pH of the CSF decreases. In this case, the patient may have been susceptible to the three mechanisms proposed pathophysiological. The indication for starting renal replacement therapy was to correct refractory metabolic acidosis, in the presence of oliguria. After the initiation of hemodialysis, the patient manifested reversible neurological signs, in line with the post-dialysis cerebral dysequilibrium syndrome. The pre-existing kidney disease, likely underestimated, coupled with an increase in serum osmolality may have induced adaptive modifications in the central nervous system.

Subsequent correction of plasma metabolic acidosis through hemodialysis may have overshadowed a more severe cerebral intracellular acidosis. In addition, hemodialysis effectively cleared approximately 50% of urea, potentially creating a significant plasma-to-brain urea gradient potentially playing a role in the development of DDS. Nevertheless, it is imperative to underscore the unavailability of comprehensive long-term follow-up information for this patient, thus constituting a limitation within our report.

A less effective initial hemodialysis session would lead to a decreased osmolar gradient of urea throughout the central nervous system, consequently reducing the probability of DDS symptoms. These signs are generally mild and time-limited, although rarely, SDD can lead to fatality. They are typically found in patients with elevated plasma urea concentrations, especially those with chronic kidney disease, compared to acute renal failure, and in patients undergoing initial hemodialysis treatment with aggressive urea removal.[2]

The precise incidence remains uncertain, as only severe symptoms such as seizures and alterations in mental state are acknowledged and reported as signs of DDS. However, it is high in patients with pre-existing neurological conditions.[8] Identifying patients with the highest risk of DDS is crucial, providing the opportunity to apply a more careful clearance approach in these populations as a preventative measure. Vulnerable patients include both elderly and young individuals, and those with severe uremic hyperosmolality, hypernatremia, and hyperglycemia. Additional risk factors include pre-existing neurological disorders, undergoing hemodialysis for the first time, and the existence of metabolic acidosis.

-As DDS primarily arises from osmotic fluid shifts in the brain, here are two strategies to prevent the formation of a notable osmotic gradient between the blood and the brain during a hemodialysis session:

(1) Reduce the rate of fluid removal to decrease the reduction in plasma osmolality, consequently reducing the osmotic gradient after dialysis.

-Increase the duration of clearance:

The objective is to achieve a 40% decrease in urea concentration within 2 h of the initial treatment, which is considered a reasonable objective. This would correspond to a urea reduction ratio [(pre-dialysis BUN-post-dialysis BUN)/pre-dialysis BUN] of 0.4. To achieve this goal, the prescription depends on the patient's size, which determines the urea distribution volume. After estimating this volume, blood flow rate and dialysis duration can be established using kinetic modeling of urea.

(2) Introducing another osmotically active agent, such as glucose, sodium, fructose, or mannitol, to the dialysate is another strategy. By incorporating an osmotic agent into the dialysate, it can effectively hinder the movement of urea, thereby preventing a decrease in serum osmolality. None of these agents can be used regularly and repeatedly, due to their tendency to accumulate in the body between dialysis sessions. However, glycerol has a half-life of less than 3.5 h[16] and is not toxic at commonly used doses.[16,17]

Therefore, glycerol could potentially serve as an appropriate agent for preventing dialysis disequilibrium in humans. Therefore, it can be deduced that patients who already have conditions characterized by brain edema will be significantly more vulnerable to the complications associated with DDS. This becomes a significant concern in situations of acute renal failure and concurrent medical or surgical complications, where dialysis is considered essential.

Conclusion

The prevention of DDS has always been the primary therapeutic approach, especially in new patients who have just initiated hemodialysis. In the absence of evidence-based guidelines, the conventional goal is to achieve a gradual

clearance of urea while the exact epidemiology and pathophysiology of DDS remain uncertain.

This syndrome typically presents in patients with end-stage renal failure initiating treatment, critically ill patients may have an elevated susceptibility to developing this syndrome. It is important for emergency physicians, intensivists, and nephrologists to recognize the potential risks associated with DDS.

Author contributions

N.B. Study conception, data collection, data analysis, and manuscript composition; K.Z. Study conception, data collection, and data analysis; L.O. Data collection and critical manuscript review (Assistant Professors); O.S. Data collection and critical manuscript review (Assistant Professors); T.D. Study conceptualization, data collection, data analysis, and critical manuscript review (Associate Professor); A.A.Z. Study conceptualization, oversight, data collection, data analysis, and critical manuscript review (Associate Professor); K.A. Study conceptualization, oversight, data collection, data analysis, and critical manuscript review (Interim Department Head). All authors have endorsed the final manuscript version.

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