Dialysis Disequilibrium Syndrome: Treatment Leading to Fatality

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ABSTRACT

Dialysis disequilibrium syndrome (DDS) is a rare disorder caused by rapid removal of blood urea nitrogen (BUN) during dialysis treatment resulting in adjusted concentrations of the osmotic gradients between fluid compartments inside the human body. The consequential osmotic pressure may cause rapid cerebral edema, leading to headaches, dizziness, seizures, and in severe circumstances, death. If dialysis is stopped immediately when symptoms appear, DDS will often be self – limiting, and will not cause permanent damage. The best prevention of the syndrome is through gentle reduction of the urea concentration by slowly introducing the hemodialysis in brief, frequent intervals. Primary treatment once the condition has been diagnosed is stabilization of intracranial pressure through the administration of mannitol.

ABBREVIATIONS: DDS - dialysis disequilibrium syndrome, BUN - blood urea nitrogen, CSF - cerebrospinal fluid.

INDEX TERMS: Renal Dialysis/mortality, *Pseudomonas aeruginosa*/complications, Azotemia/physiopathology

Clin Lab Sci 2015;28(1):15

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Case Presentation

A 20-year-old Caucasian female, in her normal state of health until a few days prior, presented with a two-day history of nausea, vomiting, headache, and 90-pound unintentional weight loss over the past year. The day before hospital admission, she had visited her dentist for treatment of rapid onset jaw and face pain and was prescribed penicillin for an acute ulcerative gingivitis. Her initial laboratory data revealed serum sodium (Na^+) of 119 mmol/L, serum potassium (K^+) of 7.5 mmol/L, BUN of 234 mmol/L, and creatinine of 21.4 mmol/L (Table 1). In addition, she had an EKG performed that showed abnormalities consistent with hyperkalemia. Urinalysis revealed white blood cells and bacteria, results consistently indicative of urinary tract infections (Table 2). Urine cultures came back positive for Escherichia coli, a common opportunistic pathogen of the urinary tract.

Table 1. Blood/serum laboratory values.

	Day 1: On Admission	Day 2: After Dialysis	Reference Ranges
Blood Urea Nitrogen	234	90	8–20 mmol/L
Serum Creatinine	21.4	4.97	0.6–1.2 mmol/L
Serum Potassium	7.5	4.1	3.5–5.0 mmol/L
Serum Sodium	119	137	135–145 mmol/L
Hemoglobin	6.2	10.1	12–16 g/dL (Female)
Concentration			14 – 18 g/dL (Male)
Hematocrit	30.7	27.2	36–48 % Female
			42 – 54 %Male
Serum Glucose	169	89	70–100 mmol/L

Considering the markedly elevated BUN and creatinine, she was immediately put on hemodialysis for treatment of acute renal failure. During dialysis the patient developed severe respiratory arrest and suffered an acute cerebral hemorrhage. She was subsequently intubated and put on a mechanical respirator. The severity of her neurological compromise led to her removal from respiratory support two days after the onset of symptoms.

Autopsy uncovered diffuse atrophy of both of the patient's kidneys, with histological evidence indicating long-term pyelonephritis and end stage renal disease

with severe glomerulosclerosis. Consequently, she had developed hyperparathyroidism (renal osteodystrophy) secondary to kidney failure. Post mortem blood cultures returned positive for the growth of *Pseudomonas aeruginosa*, a common nosocomial bacterium. An MRI of the brain and lungs demonstrated pulmonary edema and cerebral herniation, two conditions consistent with the effects of dialysis disequilibrium syndrome.

Table 2. Pertinent patient urinalysis results with reference ranges.

	Day 1: On Admission	Reference Ranges
Color	Light yellow	Colorless – light yellow
Clarity	Cloudy	Clear
Leukocyte Esterase	Positive	Negative
pH	5.5	5.0 – 8.0
Protein	100	Negative
Glucose	30	Negative
Ketones	40	Negative
Microscopic Red Blood Cells	72	0 – 2 RBC/hpf
Microscopic White Blood Cells	>182	0 – 5 WBC/hpf
WBC clumps	Moderate	None
Microscopic Bacteria	Many	None

History of the Disorder

First recognized in 1962, dialysis disequilibrium syndrome refers to the subset of symptoms experienced by some patients treated with hemodialysis: the mechanical filtration of blood to restore electrolyte and acid/base balance and to rid the body of nitrogenous waste.[1-4] This treatment is commonly used for patients with acute to chronic renal disease. The most apparent symptoms of DDS are neurological, however, as a syndrome, DDS affects a multitude of the body's chemical components, and can manifest in varying degrees of symptoms, ranging from headache, confusion, and nausea, to blurred vision, and seizures.[2, 4] While the exact rate of incidence for DDS is unknown, it is thought to occur more commonly in patients receiving treatment for the first time, or in patients with extremely elevated urea concentrations.[5,7] A predisposition to DDS development is demonstrated in elderly and pediatric patients, as well as patients with pre-existing seizure-related disorders.[7,8] Although the reason for this is unknown, the predisposition is hypothesized to be a side effect of the higher resulting blood-brain urea gradient after dialysis in these types of patients.[7]

Pathophysiology

The mechanism leading to DDS is still not fully understood by physicians. The current leading theory is known as the "reverse urea effect." This theory dictates that during hemodialysis, rapid depletion of the body's BUN leads abrupt changes in the osmolar gradient between the plasma and blood brain barrier; cerebral edema results from increased pressure on the cerebral cortex related to this new gradient.[4,8,9] Zepeda-Orozco discusses one study performed in 1964, that measured the urea concentrations of cerebrospinal fluid and plasma samples of newly dialyzed patients. After hemodialysis, CSF urea concentrations were higher than the previously elevated BUN concentrations. In this study, the exchange of solutes caused an increased potential for water movement into the neurons in order to equilibrate the new osmotic gradient. This culminated in the altered mental status of the patients.[7] Another alternative theory proposes that elevated extracellular fluid leads to a secondary accumulation of solutes in the neurons, causing water to migrate into the cells.[3] This movement would also result in cerebral swelling and possible hemorrhage. Most often, the signs and symptoms of DDS occur insidiously at the point when the electrolytes regain balance, and severity depends greatly on the urea concentration of each patient prior to dialysis.[7,10] Therefore, the most effective method of prevention is through gradual reduction of BUN concentration using brief periods of dialysis at a reduced rate of flow.[6]

Diagnosis

Sudden onset neurological complications must be evaluated empirically before defining a condition as dialysis disequilibrium syndrome.[11] Other causes of the same subset types of symptoms could include metabolic disorders of glucose and oxygen, hypoglycemia and hypoxemia, or electrolyte imbalances involving Na^+, calcium, magnesium, and phosphorus.[10,11] Therefore, diagnosing DDS relies on eliminating all other possibilities. In the original case, the patient was experiencing neurologic manifestations prior to entering the hospital. These most likely resulted from her decreased serum Na^+ levels. Homeostasis among the cerebral barrier can be maintained if the decrease in Na^+ is gradual, as in many chronic cases of renal failure, but

will become symptomatic when the Na^+ drops below 129 mmol/L.[11] DDS in this case, did not become apparent until her rapid deterioration and sudden onset of severe symptoms only after her sodium levels had normalized and the BUN had decreased by greater than half. In this case, diagnosis of the disorder was not confirmed until after autopsy.

Discussion

Although it was the DDS that ultimately led to the patient's death, many of the laboratory results were indicative of an undiagnosed, underlying condition. An extremely elevated BUN and creatinine, in conjunction with the history of a 90-pound unintentional weight loss over the last year, and severe gingivitis, can suggest a possible undiagnosed diabetic condition, immuno-compromised state, or other disorder that may have contributed to her rapid demise.[12] The patient's glucose levels were only slightly elevated, not indicative of diabetes; however, the unexplained gingivitis and unintentional weight loss, coupled with the lack of previous patient history makes underlying conditions suspect. It is interesting to note how these factors could influence a patient's prognosis when being treated with dialysis.

One theorized correlation for severe adverse reactions, and rapid death following hemodialysis was made following observations of patients hospitalized with acquired sepsis and septic shock. Shiakh et al. suggested that critically ill, septic patients on hemodialysis who develop DDS have a poorer prognosis than other dialysis patients.[3] They presented two patients, both of whom developed DDS after several days of gradual dialysis treatment. Unlike most circumstances of DDS that occur rapidly, both of these patients experienced DDS post – treatment.[3] The authors suggested that severe sepsis may alter the blood brain barrier permeability and contribute to the development of DDS. As a result, these types of patient's are at a greater risk for mortality following dialysis.[3] Correlations can be made between the case described in this report, and the aforementioned study by Shiakh, in regards to the rapid deterioration, and the presence of *P. aeruginosa* in the patient's blood. It is also possible, though uncommon, for patients with pyelonephritis to have the infection spread to the blood stream.[13] It is prudent to note, however, that *P. aeruginosa* is a common cause of nosocomial infections and may have been introduced by the equipment used for dialysis.[14] The positive culture for this organism was dated after the patient's demise, therefore sepsis during her stay at the hospital cannot be confirmed.

DDS, caused by dilutional osmotic shifts, is most often self-limiting with symptoms that dissipate after the patient is removed from dialysis.[5] The disorder is both highly preventable and presently much less common due to increased awareness of the disorder. Despite this, death can still occur, and treating clinicians need to be wary of the risks when working with dialysis patients. By being cognizant of the symptoms, clinicians will be able recognize when the disorder presents itself and implement treatment immediately. When DDS is suspected, removing the dialysis and administering mannitol are currently the most effective treatments .[1,2,]

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