Dialysis Disequilibrium Syndrome: A Case Report & Concise Review

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**Research Article**

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**ABSTRACT**

Dialysis Disequilibrium Syndrome (DDS) is characterized by neurological symptoms caused by rapid removal of urea during hemodialysis. It develops primarily from an osmotic gradient that develops between the brain and the plasma as a result of rapid hemodialysis. This results in brain edema that manifests as neurological symptoms such as headache, nausea, vomiting, muscle cramps, tremors, disturbed consciousness and convulsions. In severe cases, patients can die from advanced cerebral edema. Recent advancements in cell biology implicate the role of urea disequilibrium (with a smaller contribution from organic osmolytes) as the pathophysiological mechanism responsible for this syndrome.

**Keywords**: Dialysis Disequilibrium Syndrome, Hemodialysis, urea disequilibrium.

**INTRODUCTION**

Dialysis disequilibrium syndrome is a rare and disappearing entity given the widespread availability of Hemodialysis in most countries currently. A few cases of DDS are reported in patients undergoing their first hemodialysis. Here, we present a case of a patient who stayed off hemodialysis and survived for a long period of time and went into DDS after she finally underwent hemodialysis. This case highlights the need to consider DDS as a potential complication in these specific scenarios and modify therapeutic options conservatively.

**Case Report**

A 69-year old African American female with a past medical history of hypertension, End stage renal disease on Hemodialysis, schizophrenia is sent from nursing home for evaluation of hyperkalemia. Patient did not undergo hemodialysis for past 3 weeks secondary to malfunctioning AV fistula, and fistula repair was not undertaken because patient or patient’s family did not want any further procedures.

On presentation, patient’s potassium was 6.8 with no EKG changes suggestive of hyperkalemia. Patient’s urea was 111 mg/dl and creatinine was 13 mg/dl at presentation. Patient was given potassium binders, insulin and dextrose and plans were made to attain access for Hemodialysis. By the time family’s consent was obtained and access was obtained patient’s creatinine crept up to 18 mg/dl and urea crept up to 229 mg/dl. Patient was at her baseline mental status all this time and hyperkalemia was treated on a daily basis, as needed.

Immediately after hemodialysis, the patient was found to be unresponsive. Patient’s blood pressure, heart rate and saturation were within normal limits but she was not responding to verbal or painful stimuli. Differential diagnoses like CVA, arrhythmia and seizure were entertained. Patient started responding to painful stimuli in few hours and came back to her baseline in next few hours.

CT, MRI and EEG were within normal limits. Blood and urine cultures were negative showing low probability of sepsis. Analysis of patient’s labs post Hemodialysis showed a dramatic drop of BUN from 229 mg/dl to 106 mg/dl, which was attributed to cause a transient cerebral edema that could explain patient’s twitching and unresponsiveness. A diagnosis of Dialysis Disequilibrium Syndrome was entertained based on circumstantial evidence of drastic drop in urea and absence of other incriminating factors.
DISCUSSION

Incidence

Dialysis disequilibrium syndrome has been reported most frequently after rapid haemodialysis and in certain high-risk groups (Arieff, A.I. 1989). This syndrome is often under-reported given the mild nature of DDS-type symptoms. First-time haemodialysis patients are at greatest risk, particularly if the blood urea nitrogen (BUN) levels are markedly elevated (above 175 mg/dL or 60 mmol/L). In addition, patients with a sudden change in their dialysis regime, in particular, cases with increased dialysis flow rates are susceptible. Children and elderly patients may remain at increased risk, in particular those with a sudden change in their haemodialysis regime (Flannery et al, 2008). Patients with pre-existing neurologic disease, such as head injury, stroke or malignant hypertension, are also at greater risk for developing DDS (Peterson et al, 1964).

Pathogenesis

Although DDS has been recognized for more than forty years, the pathogenesis of DDS remains debated and incompletely understood. However, what is established and central to the diagnosis of DDS is a raised intracranial pressure. Three theories are tried to explain the reason for increased intracranial pressure:

1. The reverse urea effect

Haemodialysis rapidly removes small solutes such as urea, particularly in patients who have marked uremia. Urea is generally considered an "ineffective" osmole, because of its ability to permeate cell membranes. However, this ability to cross the cell membrane may take several hours to reach completion. This "lag period" may be particularly relevant in the brain where the blood-brain barrier may contribute to a plasma-brain urea concentration gradient. As a result, urea transiently acts as an effective osmole, promoting water movement into the brain. In addition, the reduction in BUN lowers the plasma osmolality, thereby creating a transient osmotic gradient that promotes water movement into the cells. In the brain, this water shift across the blood-brain-barrier produces cerebral edema and a variable degree of acute neurological dysfunction depending on the severity and speed of BUN reduction (Silver et al, 1996). Absolute increases in brain water content have been demonstrated in a rat model of uremia undergoing rapid haemodialysis that was accounted for by an increase in the ratio of brain to plasma urea (Silver et al, 1992; Silver, S.M. 1995).

2. Intracerebral acidosis

A number of reports suggest that the "reverse urea effect" cannot solely account for the development of cerebral edema in DDS since urea movement out of the brain is sufficiently rapid to prevent a large osmotic gradient developing between the brain and extracellular fluid (Arieff et al, 1973). The rate of removal of urea from brain closely parallels its rate of removal from plasma, but the clearance of urea from the cerebrospinal fluid (CSF) is delayed. Studies in dialysis patients have shown that there is often a substantial rise in the PCO2 of lumbar CSF, with a concomitant fall in its pH during haemodialysis (Arieff et al, 1973). Studies in uremic dogs treated with rapid haemodialysis have shown that, despite a rise in the pH of arterial blood, the pH of the CSF fell. It has been found in animal models that the decrement in the pH of the CSF is associated with a concomitant decline in the pH of the brain, and this finding is probably a factor in the pathogenesis of the DDS (Arieff et al, 1976). This decrease in cerebral intracellular pH, resulting in the displacement of bound sodium and potassium by the excess hydrogen ions can increase intracellular osmolality and promote water movement into the brain. An additional contributing factor to the intracerebral acidosis mechanism is the idiogenicosmole principle proposed by (Arieff et al, 1976). The increased osmolality of the extracellular fluid in uremia may induce an adaptive accumulation of intracellular organic osmolytes to limit cerebral cell dehydration. During haemodialysis, retention of these organic osmolytes contributes to a paradoxical reduction in intracellular pH resulting in increased brain osmolality and cerebral edema (Arieff et al, 1973). These brain organic osmolytes may include glutamine, glutamate, taurine, and myo-inositol. A fall in the pH of CSF may contribute to a depression of the sensorium, and intracellular acidosis of brain cells could result in a rise of brain intracellular osmolality. Such an increase of osmolality could lead to cytotoxic edema. The resulting cerebral edema may be related to a decrease in intracellular pH of the cerebral cortex, probably as a consequence of an increase in intracellular organic acids.
3. Dialysis disequilibrium syndrome-induced interstitial edema

The advent of magnetic resonance imaging (MRI), in particular diffusion-weighted imaging (DWI), has increased physicians' ability to evaluate brain water content. The apparent diffusion coefficient (ADC) measured by DWI, is sensitive in detecting dynamic changes in tissue water. This technique is useful in identifying neurological disorders where there is a derangement in the brain water dynamics e.g. stroke Warach et al, (1995) and has recently been proposed as a useful investigation in patients with suspected DDS Chen et al, (2007). In this study, the authors found that haemodialysis increased the ADC values of brain water, especially in white matter, indicating that interstitial edema rather than cytotoxic edema is more important in the pathogenesis of DDS-related brain edema. Foci of bright areas of white matter were found in all patients on T2-weighted images. The ADC values in white and gray matter in ESRD patients before and after haemodialysis were significantly greater than those of the healthy controls (p<0.005). Regarding the impact of haemodialysis, the ADC of frontal lobe white matter increased significantly after haemodialysis (p=0.036). The authors concluded that because ADC is an indicator of interstitial as opposed to cytotoxic edema, that DDS is a manifestation of an increase in interstitial fluid compartment, especially after first haemodialysis.

Clinical Importance

These symptoms are usually mild, transient and self-limited though, rarely, DDS can be fatal. Symptoms are most often seen in patients with very high plasma urea concentrations, in patients with CKD (versus acute kidney injury), and with aggressive urea removal with the initial hemodialysis treatment Kennedy et al, (1962). It is more common in children, in patients with a history of head injury, subdural hematoma, stroke and malignant hypertension, and in patients with conditions such as hyponatremia that predisposes them to cerebral edema Fine et al, (1970). In rare cases, DDS can be present as either demyelination of the pontine and extrapontine areas or as subcortical white matter lesions in parietal and occipital lobes of brain. The latter lesion is quite similar to the reversible posterior leukoencephalopathy syndrome Agildere et al, (2003).

Dialysis Disequilibrium Syndrome is a clinical diagnosis, occurring in a patient at risk of undergoing hemodialysis. There is no laboratory test or biological marker available to diagnose DDS and it remains largely a diagnosis of exclusion. The clinician needs to consider processes that cause similar manifestations such as uremia, hyponatremia, hypoglycemia, stroke and subdural hematoma. Electroencephalography has been examined as a test to improve the diagnosis of DDS, but is of limited clinical value [Basile et al, (1987) Hampl et al, (1983)]. Although no radiological study is available to make a diagnosis, certain imaging techniques such as diffusion-weighted MRI may be helpful in supporting the diagnosis.

Management

Management of DDS is based primarily on preventative measures to reduce the development of cerebral edema. As (i) these measures have little risk and (ii) there are no guidelines indicating which patients receiving their first dialysis are “not” at risk, interventions to minimize DDS have become common practice for a patient’s initial dialysis. While certain modalities such as peritoneal dialysis and hemofiltration/hemodiafiltration are not associated with DDS, they are not practical or available for all patients initiating dialysis. Interventions that are available during hemodialysis to prevent DDS include: (i) slow, gentle initial hemodialysis, (ii) increasing dialysate sodium levels, and (iii) administration of osmotically active substances.

CONCLUSION

Although severe DDS is less common than initial reports due to improvements in modes of dialysis, milder forms of DDS may go unnoticed by the clinician. It is important to be aware of this diagnosis, particularly in high-risk groups, with the aim of prevention and early detection to limit the potentially more serious consequences of DDS.

REFERENCES


