American Journal of Medical Case Reports, 2018, Vol. 6, No. 4, 68-71
Available online at http://pubs.sciepub.com/ajmcr/6/4/4

DOI:10.12691/ajmcr-6-4-4

Dialysis Disequilibrium Syndrome

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Abstract Dialysis disequilibrium syndrome (DDS) is a rare complication of dialysis leading to neurological symptoms which can vary in severity from a simple headache to coma and death. The debate continues on the specific causes of DDS and centers around two main theories; the reverse urea effect and cerebral acidosis. It can be a challenge to predict in which patients DDS will occur, and an even more difficult syndrome to treat while the best known treatment is prevention. A case where DDS led to irreversible brain damage despite preventative measures in place will be discussed along with a discussion of current literature surrounding dialysis disequilibrium syndrome (DDS) and its treatment.

Keywords: *dialysis, disequilibrium syndrome, cerebral edema, osmolality*

Cite This Article: Christina George D.O, Sreelatha Penumalee M.D, and David Minter D.O, "Dialysis Disequilibrium Syndrome." *American Journal of Medical Case Reports*, vol. 6, no. 4 (2018): 68-71. doi: 10.12691/ajmcr-6-4-4.

1. Introduction

Dialysis disequilibrium syndrome is a complication of dialysis that can vary in presentation and can often go unnoticed. Symptoms vary from mild: nausea, vomiting, headache to severe: coma, cerebral edema and death. This syndrome goes often under-reported due to mild symptoms that can present, however increased awareness of this syndrome can help prevent the more serious side effects from occurring. On a literature review there has never been a reported etiology of DDS. This syndrome is thought to be related to electrolyte and protein imbalance leading to cerebral edema increased intra-cranial pressure and the subsequent neurological symptoms. The exact mechanism leading up to cerebral edema continues to be unknown however there are several proposed mechanisms including the reverse urea effect and cerebral acidosis. The most plausible mechanism continues to be the reverse urea effect. We will report a severe case of DDS, review the current literature, mechanisms and treatments to increase the awareness and encourage reporting of DDS no matter how mild the symptoms.

2. Case Discussion

A 39 year old Caucasian male with a chief complaint of anxiety and tachypnea presented to the emergency department via EMS. History of present illness is limited due to severe conversational dyspnea however critical information was able to be obtained. Patient was only able to nod yes or no and was unable to give verbal responses. Patient had a cough for seven days which has progressively gotten worse. The cough was productive with yellow sputum; he had associated fevers and chills, exertion makes the cough and shortness of breath worse, and he denied any prior treatment. All other review of systems were negative.

Past medical history includes stage IV chronic kidney disease, with a previous GFR noted to be 16 in 2013. Patient had a history of acute renal failure from NSAID use and previous dialysis treatments. Patient was not currently following a nephrologist or receiving dialysis. Past surgical history includes short term dialysis catheter, patient was unable to tell us his current medications, denies medication allergies, alcohol use, tobacco use, or illicit drug use.

Physical exam demonstrates a patient in moderate distress with tachypnea. Initial vital signs HR: 120, RR: 30, blood pressure: 96/50, temperature 97.4. Patient appears anxious and pale. He has dry mucous membranes, rhonchi on the left side of his chest, tachycardia with no murmurs, soft abdomen and no lower extremity edema.

Initial laboratory values are included in Table 1. Pertinent labs include ABG: pH 7.05 pCO2: 9.1, HCO3 <5, lactate of 2.85 BUN 211 and Cr 17.6. A chest x-ray demonstrated a left lower lobe infiltrate.

It was deemed the patient was in severe metabolic acidosis secondary to sepsis, lactic acidosis and acute renal failure. Patient was admitted to the step-down unit and a trialysis catheter was placed by general surgery for emergency dialysis. The patient was given two amps of bicarb secondary to worsening tachypnea before being transported directly to dialysis. The patient also received a one liter bolus of normal saline while in the emergency department. Most notable from the dialysis session is the flow rate was at 250, which is significantly slower than standard dialysis, and the time of dialysis was only two and a half hours. The hospital course continue as follows; post dialysis patient had a witnessed PEA arrest with

ROSC; total down time was approximately 10 minutes without evidence of hypoxia. Patient was transferred to the ICU and repeat labs were obtained. Repeat BUN: 108, Cr: 8.8. Patient was stabilized and monitored overnight. On morning neurological exam: patient had fixed and dilated pupils, no gag reflex and was on full ventilator support. A STAT head CT was ordered, which showed severe cerebral edema. There was no previous head CT to compare, however patient had normal mentation prior to intubation. A discussion occurred on whether to start mannitol vs. hypertonic saline to attempt cerebral edema reversal, however due to poor prognosis the family decided to withdraw care. Patient was terminally extubated and passed away; cause of death; herniation secondary to severe cerebral edema. The patients post dialysis lab values are provided in Table 1 and the head CT is provided in Figure 1.

Table 1. Laboratory values pre-dialysis taken in the emergency department and post-dialysis taken in the intensive care unit following PEA arrest

Lab	Pre-dialysis	Post-dialysis	Reference Range
WBC	34.17	29.05	4.8-10.80
RBC	2.89	2.35	4.7-6.10
HGB	7.7	6.4	14-18
HCT	23.3	18.5	42-52
MCV	80.6	78.7	80-94
PLT	496	376	150-450
PT	12.2	13.6	10.2-12.5
INR	1.08	1.2	0.9-1.10
aPTT	32	44	24-31
Na	123	136	136-145
K	5.7	2.8	3.5-5.1
Cl	86	91	98-107
Glucose	114	92	65-139
BUN	211	102	7-18
Creatinine	17.6	8.8	0.8-1.3
Ca	8.6	6.7	8.5-10.1
pH	7.05	7.33	7.35-7.45
pCO2	9.1	20.7	35-45
pO2	148	344	70-200
HCO3	2.5	10.6	22-26
Anion Gap	-	29	5-15
UDS	negative		

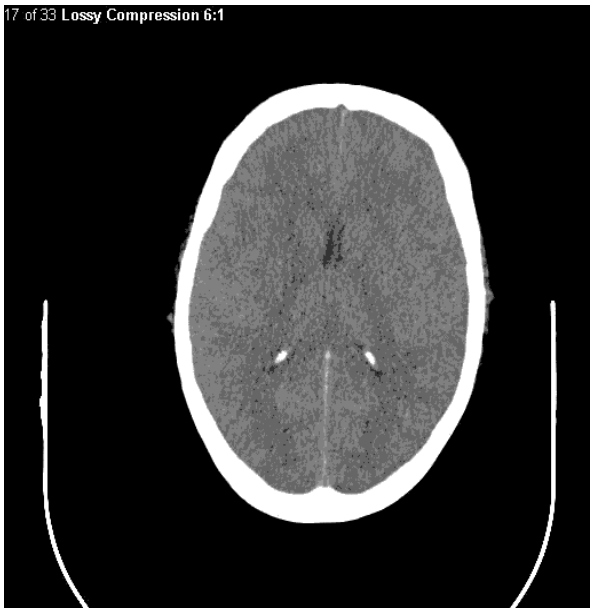

Figure 1. (B) The CT scan of patient on hospital day 2, post-dialysis.

3. Discussion

Our patient was very sick however we believe his death was related to dialysis disequilibrium syndrome secondary to the large shift in BUN compared to pre and post dialysis. The mechanisms of how DDS develops and possible treatments are discussed below.

There are currently two main theories surrounding the development of DDS. The first is the reverse osmotic effect [16,17] and the second involves cerebral acidosis [3,4]. There is no clear cut pathogenesis of the disease process; however the reverse osmotic effect is the more accepted theory. In patients with acute renal failure, urea continues to build up in the plasma and CSF. Depending on the length of time a person is in renal failure, urea is transported across the blood brain barrier via up-regulation of urea transporters (UF-B1). Urea has a reflection coefficient of 0.44-0.59, giving it limited ability to diffuse across the BBB without transporters and requires UF-B1 for transport in both directions. Once on the CSF side, urea can act as an osmotic element if there becomes a discrepancy between CSF and plasma solute concentrations. The body will always move toward homeostasis and maintain equal levels of urea in the plasma and CSF. When urea is removed from plasma, the plasma concentration drops quickly; and the body attempts to maintain a balance between plasma urea concentration and CSF concentration. Urea UF-B1 channels are down regulated during severe acidosis and uremia preventing the movement of urea out of the brain [8]; the mechanism behind this is unknown. AQP4 channels are readily inserted into the membrane and are up-regulated [12]; water moves down its concentration gradient and diffuses into the CSF to dilute the urea solute. This movement of water into the brain leads to edema and swelling [13]. The CSF and brain cells can only compensate enough water until their own intracellular mechanisms are compromised and cell death occurs. A proposed diagram of the reverse urea effect is shown in Figure 2. The pathogenetic importance of urea in dialysis disequilibrium syndrome has been demonstrated by experiments in uremic rats [7,17,18]. Some studies have suggested that the reverse osmotic shift cannot account for the development of cerebral edema in DDS, since the urea movement out of brain is sufficiently rapid to prevent a large osmotic gradient between the brain and extracellular fluid [4]

The second proposed mechanism involves the severe metabolic acidosis during renal failure. Hydrogen ions continue to build up in the blood stream and are not excreted properly by the kidneys secondary to failure [3]. Hydrogen ions have a positive charge and can displace other positively charged ions as the body tries to compensate for the acidosis. Bound sodium and potassium ions are displaced by positively charged hydrogen ions increasing intracellular osmolality and leading to an osmotic gradient [1]. Again water moves down its concentration gradient into the cell to dilute the increase in intracellular osmolality leading to cell swelling and possible cell burst. There also appears to be an upregulation of intracellular organic acid production to help displace the excess hydrogen ions further increasing intracellular osmolality.

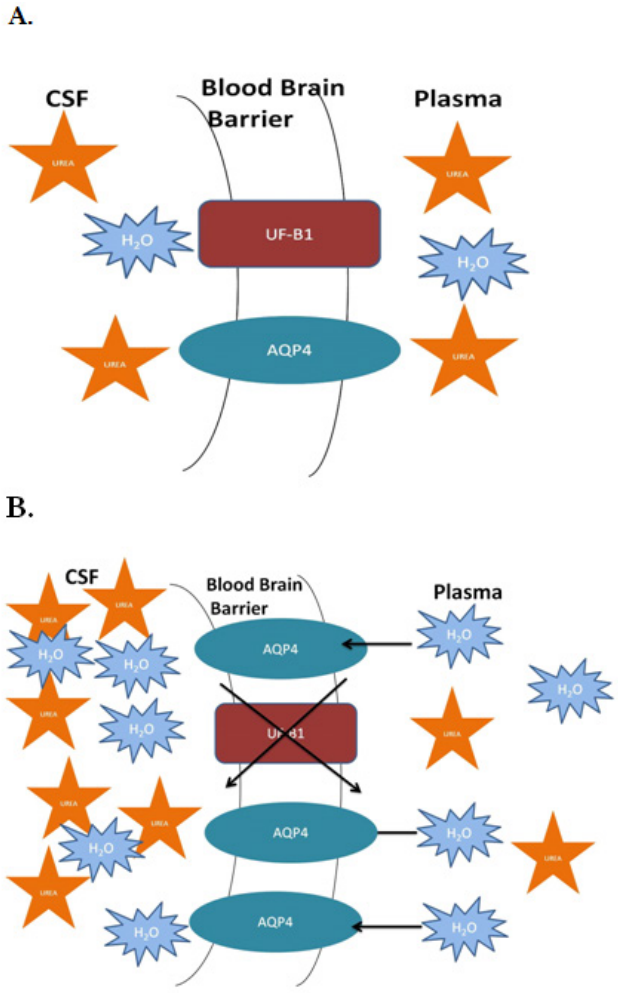

Figure 2. (A) Normal physiologic state, urea and water are equal in concentration and UF-B1 channel is functioning. (B) The reverse urea effect: increased BUN in the CSF, down-regulation of UF-B1 channel blocking BUN inside the CSF. Increased AQP4 channels inserted into the BBB allowing the movement of water across the BBB.

A third mechanism, that is poorly understood and mainly hypothesized, involves an 'unknown' organic molecule that changes the osmolality of the CSF compared to the osmolality of the plasma. Researchers have not been able to prove that this molecule exists however it does remain a reasonable mechanism [16].

None of the above methods have been proven and continue to be debated however DDS may be a combination of all three mechanisms. None seem more plausible than the others. We believe in our patient, secondary to the large shift in BUN, that the reverse urea effect predominates, but with the severe acidosis, CSF acidosis may have played a part. Knowing how DDS works has not help with any treatments of this syndrome and prevention remains the mainstay.

Any dialysis patient is at risk of developing DDS. There are a few situations that increase this risk. Any sort of stress on the body, traumatic or infectious, can decrease the permeability of the blood brain barrier, allowing for easier transport of water and solute across, worsening potential edema. This syndrome is particularly common in pediatric patients and patients with pre-existing neurological conditions [5]. The risk in pediatric patients is secondary to high mass transfer area coefficient or more simply because children are smaller. Severe metabolic acidosis also seems to increase the risk; the mechanism behind this is unknown. Additional risk factors include: first dialysis treatment, marked elevated BUN pre-dialysis, chronic kidney disease and older age.

Treatments are often limited and prevention appears to be the best management. Prophylactic measures regarding the dialysis regime include: increased dialysate osmolality, shorter dialysis sessions, lower dialyzer blood flow rates, less efficient more frequent dialysis sessions [2]. Exogenous solutes such as glycerol, mannitol, and hypertonic saline have been proposed to counter-act the urea lowering effect, and anticonvulsant therapy such as diazepam [15]. Taking these measures into account is not always possible in patients with severe acute renal failure when dialysis is emergent. It is recommended to perform hemofiltration rather than dialysis which uses convective removal of solute rather than diffusive removal of solutes; decreasing the difference of osmolality between fluid compartments in the body [10]. The recommended goal is to decrease the BUN level by 40% to decrease the likelihood of DDS. This decrease in BUN is not only related to amount, but to time as well. The faster the solutes are removed the increased opportunity for fluid shifts within the body compartments.

Our patient had some preventative precautions put in place for the initial dialysis session including a slower blood rate and a shorter dialysis session. Despite these precautions our patient still developed severe cerebral edema secondary to large shift in plasma and CSF osmolality.

Post dialysis treatment is very limited. The only medications shown to have any benefit are mannitol and hypertonic saline to reduce intracerebral pressures; however these have very limited use and the outcomes are variable. It is unknown whether these agents would have provided any benefit in our case.

The exact mechanism continues to be debated. Due to the variability of symptoms, DDS can often go unrecognized and under-reported. It is important to be aware of the risk of DDS so preventative measures can be put in place where appropriate. Continued reporting will overall increase recognition and may provide opportunities for further research to improve outcomes of severe manifestations of DDS.

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