Cerebral Edema in a Child after Preemptive Kidney Transplantation

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Abstract

Dialysis disequilibrium syndrome (DDS) is characterized by acute neurological manifestations in patients undergoing first dialysis treatment. The mechanisms for the development of DDS include the reverse urea effect, transient intracranial acidosis, and idiogenic osmoles which can increase intracellular osmolality and promote water movement into the brain. We present a case of a 4-year-old child with chronic kidney disease who underwent a preemptive living unrelated donor kidney transplant. He had a 24 mEq/L drop in his sodium concentration, 92% reduction in blood urea nitrogen (BUN) concentration, and a 67 mOsm/kg drop in serum osmolality within 18 hours after transplant, with concurrent development of symptomatic and radiologic cerebral edema, similar to that described in DDS. Mental status rapidly returned to baseline after administration of 3% hypertonic saline. This case highlights the risk of cerebral edema in patients who have a high pretransplant BUN. It emphasizes the need for close monitoring of vital signs, mental status, and electrolytes in children undergoing renal transplant. Hypertonic solutions can be used to prevent or manage cerebral edema in these patients when serum osmolality decreases rapidly. Pretransplant dialysis is another consideration to proactively reduce serum hyperosmolality.

Keywords

- renal transplant
- fluid management
- hyponatremia
- osmolality
- dialysis disequilibrium syndrome

Introduction

Dialysis disequilibrium syndrome (DDS) was first described in 1962 by Kennedy et al as an acute neurological dysfunction of hemodialysis with variable clinical manifestations.¹ Patients who are just being started on intermittent hemodialysis are at the greatest risk for DDS, particularly if the blood urea nitrogen (BUN) level is markedly elevated.² Pediatric patients with preexisting neurologic conditions are at increased risk of DDS.^{3,4} A few studies have postulated potential mechanisms for the development of DDS, including the reverse urea effect.^{5,6} In normal health, brain and plasma urea levels are similar. The reduction in BUN upon initiation of dialysis lowers plasma osmolality, thereby creating a transient osmotic gradient that promotes water movement into cells. In the brain, this water shift produces cerebral edema and a variable degree of

clinical neurological dysfunction. Urea is generally considered an ineffective osmole because of its ability to permeate cell membranes, but it takes several hours for plasma and cellular equilibration to reach completion. There is insufficient time for urea equilibration when hemodialysis rapidly reduces the BUN. As a result, urea can transiently act as an effective osmole, promoting water movement into the brain.^{7,8} In addition, animal studies have suggested that there may be a decrease in urea transporters and an increase in water channels in uremia, which would increase the reflection coefficient of urea.⁹ It is also hypothesized that paradoxical transient intracranial acidosis with displacement of sodium and potassium by hydrogen ions as well as augmented production of organic acids (idiogenic osmoles) can increase intracellular osmolality and promote water movement into the brain.^{7,8}

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Early symptoms of DDS include nausea, vomiting, headache, disorientation, restlessness, blurred vision, and asterix.³ In general, symptoms are self-limited and usually dissipate within several hours. Some patients, however, may progress to confusion, seizures, coma, and even death.

We present a case of a child who developed mental status changes and radiographic evidence of cerebral edema due to rapid fall in serum sodium, BUN, and osmolality after a renal transplant, similar to that described in DDS.

Case Presentation

A 4-year-old male child with chronic kidney disease stage 5 secondary to congenital ureterovesical junction obstruction and renal dysplasia was admitted to our pediatric intensive care unit (ICU) following a preemptive living unrelated donor kidney transplant. He was not dialysis dependent during the course of his illness. He was normotensive prior to transplant and was not on antihypertensive medications. He had no history of developmental delay or seizure disorder. He underwent a renal transplant from a living unrelated donor who was positive for *Cytomegalovirus* and Epstein-Barr virus antibodies. The human leukocyte antigen (HLA) profile showed a three major and three minor antigen mismatch. Preoperatively, the patient weighed 13.1 kg. The day prior, he was noted to have the following laboratory values: sodium, 134 mEq/L; potassium, 5.1 mEq/L; BUN, 88 mg/dL; creatinine, 4.8 mg/dL; glucose, 161 mg/dL; and hemoglobin, 10.2 g/dL. His calculated serum osmolality was 308 mOsm/kg. Overnight, while not being allowed to take anything by mouth, he was continued on intravenous fluids of 5% dextrose with 0.45% normal saline at 46 mL/hour. Intraoperative, he received 2,900 mL of intravenous fluids (including normal saline and sodium bicarbonate boluses for metabolic acidosis) and 250 mL of packed red blood cells with a hemoglobin nadir of 6.5 g/dL. He was also given methylprednisolone 15 mg/kg and started on antithymocyte globulin 1.5 mg/kg for immunosuppression. During reperfusion of the transplanted kidney, the patient did develop some hypotension and elevated T-waves, but very quickly recovered from these. He made 630 mL of urine in the operating room.

In the ICU, his systolic blood pressures (BP) ranged between 80 and 85 mm Hg and diastolic BP ranged between 42 and 50 mm Hg. Immediate postoperative laboratory tests showed an increased sodium level at 151 mEq/L, attributed to the normal saline and sodium bicarbonate boluses he received during the surgery. He had a postoperative BUN of 56 mg/dL, creatinine of 1.7 mg/dL, glucose of 79 mg/dL, and hemoglobin of 14.9 g/dL. His calculated serum osmolality was 326 mOsm/kg. He was continued on 5% dextrose in water at 17 mL/hour to account for insensible losses and received 1:1 urine replacement with 0.45% normal saline with 22 mEq/L of sodium bicarbonate (total of 99 mEq/L of sodium). He had persistent hypotension (BP 74/37 mm Hg) for which he received three boluses, 150 mL each, of normal saline (each containing 154 mEq/L of sodium), and was started on a dopamine infusion. Two hours later, he was given 1 g/kg of 5% albumin (approximately 130–160 mEq/L of sodium). He received two calcium boluses of 1 g each (2.5 hours apart) for a serum calcium of 6.7 mg/dL and ionized calcium of 1.02 mmol/L. He was started on 300 mg/m²/dose of mycophenolate for immunosuppression.

On the first postoperative night, BP remained in the 115–129/57–77 mm Hg range. Since being in the operating room, he had received 9,738 mL of fluids (3,150 mL given in operating room and 6,588 mL over 13 hours in the ICU after surgery), and total urine output was 5,760 mL (630 mL in the operating room and 5,030 mL over 13 hours, or 28.5 mL/kg/hour, in the ICU), giving him a positive fluid balance of 3,978 mL.

The next morning, his weight was 14.4 kg, BP measured at 122/73 mm Hg, and heart rate was 106/minute. On repeat blood work, his calculated serum osmolality was 267 mOsm/L. Three hours later, he made 895 mL (21 mL/kg/hour) of urine and his fluid balance for the morning was negative 102 mL. BP increased to 151/95 mm Hg and heart rate decreased to 74/minute. Despite stopping the dopamine infusion, BP remained elevated up to 146/103 mm Hg. He was drowsier and had a heart rate of 60 to 70/minute. On repeat laboratory work, the sodium was 127 mEq/L, BUN was 7 mg/dL, glucose level was 104 mg/dL, creatinine was 0.3 mg/dL, and hemoglobin was 12.3 g/dL (► **Table 1**). The serum osmolality at that time was calculated as 262 mOsm/kg. He was given a 10-mg dose of intravenous furosemide. He had a further decrease in

Table 1 Changes in pertinent laboratory tests in our patient

Time (h)	Comments	Sodium (mEq/L)	BUN (mg/dL)	Creatinine (mg/dL)	Osmolality (mOsm/kg)	Hemoglobin (g/dL)
–27	Preoperative	134	88	4.8	308	10.2
0	Allograft anastomosis					
3.5		151	56	1.7	326	14.9
16		130	9	0.2	267	11.2
19		127	7	0.3	262	12.3
22	Neurological changes, hypertension, bradycardia	125	7	0.2	259	13.3
28	Post 3% normal saline	135	8	0.3	278	10.3

Abbreviation: BUN, blood urea nitrogen.

responsiveness, intermittent lip smacking, and an acute decrease in heart rate to the 40s/minute with BP elevated at 146/103 mm Hg. An emergent computed tomography of the head demonstrated diffuse effacement of the cerebral sulci with loss of gray–white matter differentiation, particularly in the middle cranial fossa. The lateral ventricles were slightly prominent with a slit-like third ventricle and nearly effaced fourth ventricle. There was no midline shift or intracranial herniation with medialization of the uncus bilaterally. His electrolytes were rechecked and his sodium had decreased to 125 mEq/L, and had BUN of 7 mg/dL, glucose of 132 mg/dL, and calculated osmolality of 259 mOsm/kg (►Table 1, ►Fig. 1). His urine sodium was high at 130 mEq/L and urine osmolality was 349 mOsm/kg. He was given a bolus of 5 mL/kg of 3% saline, following which BP decreased to 114/81 mm Hg, heart rate increased to 92/minute, and mental status normalized. He was started on a 3% saline infusion at 2.6 mL/hour. His sodium levels gradually improved to 135 mEq/L over 5 hours and his calculated osmolality was 278 mOsm/kg.

Discussion

This case describes a child with no prior history of developmental delay or seizure disorder, who underwent a preemptive living unrelated donor kidney transplant. We believe that the rapid drop in sodium, BUN, and serum osmolality in the patient after transplant led to fluid shifts and development of cerebral edema, similar to that noted in patients reported to have DDS. Mental status rapidly returned to baseline after administration of 3% hypertonic saline. Two years posttransplant, the patient has normal neurological findings and normal development.

There are two case reports of patients having massive polyuria and hyponatremia after renal transplant.^{10,11} The first report described a 11-year-old boy, with underlying neurological damage and minor seizure disorder who developed hyponatremia, seizure, and cerebral edema within 5 hours after a preemptive renal transplant. The second report illustrates the case of a 4-year-old child, depended on peritoneal dialysis, who developed hyponatremia and cerebral edema soon after anastomosis on the allograft while under anesthesia. The outcome in both these patients was death. Our patient was not dependent

on renal replacement therapy prior to renal transplant. As compared with prior reports, he lacked underlying comorbid neurological conditions. He had a favorable outcome with rapid administration of hyperosmolar solution. A recent study showed that after renal transplantation, mild hyponatremia and hence an acute drop in serum osmolality put patients at risk of postoperative neurologic complications.¹²

Pediatric transplant recipients are at increased risk of seizures, the etiology of which appears to be multifactorial.¹³ Patient often have severe hypertension secondary to fluid overload, corticosteroid, calcineurin inhibitor therapy, or from acute allograft rejection. Children with marked polyuria after transplant are at increased risk of biochemical disturbance, including hyponatremia, hypocalcemia, and hypomagnesaemia. Immunosuppression places the child at increased risk of infections, including those of the central nervous system.

Our patient had good graft function and quick drop in his creatinine from 4.8 mg/dL preoperatively to 0.2 to 0.3 mg/dL the next morning. He had a drop in his BUN levels from 88 mg/dL preoperatively to 7 mg/dL, which is a 92% drop in BUN, within 18 hours of renal transplantation (►Fig. 1, ►Table 1). The rapid gain in renal function and hemodilution likely contributed to the rapid fall in the BUN.

The rapid decrease in serum sodium from 151 to 127 mEq/L following surgery likely contributed to the development of cerebral edema, as has been described in other clinical scenarios (►Fig. 1). Several etiologies of hyponatremia are possible in this patient. These include hemodilution from receiving hypotonic fluid and renal sodium wasting. His total sodium intake was ~625 mEq, or 94 mEq/L. He had a positive fluid balance of 3.9 L, slight drop in hemoglobin, and an increase in weight from 13.1 kg (preoperatively) to 14.4 kg (postoperatively). Our patient had an elevated urine sodium level of 130 mEq/L and a relatively high urine osmolality of 349 mOsm/kg in the face of hyponatremia, suggesting renal sodium wasting. Sodium wasting has been known to occur after ischemic injury and tubular dysfunction of the graft.¹⁴ After transient interruption of blood flow to the allograft, the proximal tubular cells exhibit disruption of the cytoskeleton with redistribution of Na^+/K^+ -ATPase from its normal location. The Na^+/K^+ -ATPase pump generates an electrochemical gradient across the cell that is

Fig. 1 Graphical representation of the change in the serum sodium levels, blood urea nitrogen (BUN), and serum osmolality in our patient after renal transplantation.

required for reabsorption of sodium. Redistribution of Na^+/K^+ -ATPase has been proposed as an explanation for the high fraction of filtered sodium noted in patients with postischemic renal injury.

Rapid changes in serum osmolality can be prevented by careful monitoring of patients posttransplant for the risk of developing DDS-like symptoms. Posttransplant intravenous fluid should be optimized for these high risk patients.¹² Since the rate of urine output and clearance cannot be controlled, we recommend using higher tonicity intravenous fluids in patients after a renal transplant, especially if they are not on dialysis. At our institution, for intravenous hydration after transplantation we now use 5% dextrose with 77 mEq/L sodium chloride to replace insensible losses, and 5% dextrose with 77 mEq/L sodium chloride and 22 mEq/L sodium bicarbonate to replace urine output. Furthermore, similar to recommendations to reduce BUN slowly with initiation of hemodialysis to prevent DDS,^{2,4} another consideration is to dialyze patients prior to preemptive transplant if pretransplant BUN levels are greater than 80 mg/dL to ensure a more gradual decrease in serum osmolality after renal transplant.¹²

Patients with mild, nonspecific symptoms of DDS such as nausea, vomiting, restlessness, and headache should be treated symptomatically. Rapid infusion of hypertonic saline helps resolve increased intracranial pressure (ICP). Although intravenous mannitol has been reported to be useful in the treatment and prevention of DDS and increased ICP, it should be avoided posttransplant to prevent exacerbation of the already prominent diuresis.

In summary, rapid changes in electrolytes and BUN levels posttransplant can lead to fluid shift and cerebral edema similar to that seen in DDS. Close monitoring of vital signs and electrolytes of children is required after renal transplant. Direct measurement of osmolality at presentation as well as at multiple points during the clinical course is ideal.

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