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BRIEF REPORT

# A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation

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**Abstract** We report the case of a child who died from severe cerebral oedema in the context of hyponatraemia and extreme polyuria immediately after renal transplantation. The patient was treated according to a standard post-transplantation protocol, receiving 0.45% saline solution for urine output replacement. The case highlights the dangers of massive fluid therapy in the context of polyuria and, therefore, the need for intensive monitoring.

**Keywords** Hyponatraemia · Seizure · Cerebral oedema · Kidney transplant · Hypotonic fluid · Polyuria · Salt wasting

## Introduction

We report the case of an 11-year-old boy, who had extreme polyuria shortly after live-related renal transplantation. He developed seizures associated with a serum sodium concentration of 126 mmol/l and his condition rapidly progressed to tonsillar herniation and death. We detail the sequence of events, discuss potential causes of this tragic occurrence and describe how we changed our post-transplantation care protocol to enable earlier detection of such abnormalities.

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## Case report

An 11-year-old boy weighing 30.3 kg was admitted for a pre-emptive live-related transplant. He had suffered meningococcal septicaemia at the age of 34 months, complicated at that time by severe neurological dysfunction, with coma, seizures and peripheral vascular involvement with skin and bone loss. He had been undergoing short-term dialysis for nearly 4 weeks, but his renal function [glomerular filtration rate (GFR) by the chromium-51–ethylene diamine tetra-acetic acid ($Cr^{51}$-EDTA) method was 37 ml/min per 1.73 $m^2$ body surface area at 3 years] had recovered sufficiently to be managed conservatively. He was left with a minor seizure disorder treated with sodium valproate at the time of transplantation. Electroencephalography (EEG) showed discharges over the right temporoparietal area, and a cerebral magnetic resonance imaging (MRI) scan when he was aged 4.5 years showed mild cerebellar atrophy, with normal ventricular size. He attended mainstream school and had learning support.

His renal function deteriorated from the age of 10 years, with his serum creatinine rising from 1.6 mg/dl to 3.8 mg/dl (145–330 μmol/l), so work-up was commenced for renal transplantation. He was polyuric, with a daily urine output of 3–4 l.

He underwent a live-related renal transplantation, with 0,1,1 mismatch, from his mother. He was given 0.25 mg/kg tacrolimus and prednisolone 600 mg/$m^2$ before theatre and had a urethral catheter placed after being anaesthetised. The operation was uneventful; the patient had normal vessel

anatomy. There was good blood flow and immediate urine output. The cold-ischaemia time was 30 min, and anastomosis time was 25 min. Intraoperatively, his systolic blood pressure (SBP) was 100-130 mmHg and central venous pressure (CVP) was 10-15 $cmH_2O$. He was given a total of 2,200 ml of fluid during the procedure [1,000 ml Hartmann's solution (near isotonic sodium lactate) and 1,200 ml 4.5% albumin] and 60 mg furosemide. A dopamine infusion (3 μg/kg per minute) and a patient-controlled morphine infusion were commenced. He received routine immunosuppression with tacrolimus, azathioprine and prednisolone.

Immediately postoperatively, he was warm and well perfused, with a core–toe temperature gap of 2.4°C. He had a normal heart rate (HR; 90-105 beats/min) but was hypertensive (SBP 130-140 mmHg). His CVP was 8-11 $cmH_2O$. He regained consciousness fully and was extubated, with saturations of 98–100% in room air, respiratory rate 25/min. He had mixed metabolic and respiratory acidosis, pH 7.25, with a carbon dioxide partial pressure ($pCO_2$) of 42 mmHg (5.6 kPa) (venous gas). His initial postoperative serum sodium level was 141 mmol/l (see Table 1). A bedside fluid balance sheet was established, which included the volume of urine in the catheter bag (1,180 ml) but not the fluids given in theatre (2,200 ml) or the undocumented losses (urine lost during anastomosis of the ureter to the bladder, and blood losses). These losses were retrospectively estimated by the surgeon to be 300–500 ml.

The patient developed massive polyuria almost immediately after anastomosis, passing urine up to 58 ml/kg per hour. He was treated according to the unit's protocol, with replacement of insensible losses of 400 $ml/m^2$ per day and of the previous hour's urine volume with the same volume of 0.45% saline solution, alternating with 0.45% saline solution/2.5% dextrose. Two hours postoperatively he developed signs of poor peripheral perfusion, with a core–toe temperature gap of 6°C; HR was 90–105 beats/min, and SBP was 130–150 mmHg. It was concluded that he had a fluid deficit, and he was given an extra 1,449 ml 0.9% saline solution over 2 h. At 4 h he had a generalised tonic–clonic seizure, which was terminated immediately following administration of 0.1 mg/kg lorazepam. Blood glucose measured with a stix was 8.6 mmol/l, and central venous gas showed uncompensated metabolic acidosis, with a pH of 7.1. He was hyponatraemic (126 mmol/l), initially thought to be an artefact but confirmed on a repeat sample (121 mmol/l). At 5 h he had a further generalised tonic–clonic seizure, which again responded to lorazepam, but at that time his pupils were fixed and dilated. He was

**Table 1** Results of blood and urine tests and fluid balance

| Parameter | Time after anastomosis | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Preoperative | Postoperative | 1 h | 2 h | 3 h | 4 h Seizure | 5 h Seizure | Normal range | Unit |
| Sodium | 140 | 141 | | | | 126 | 121 | 133–146 | mmol/l |
| Total $CO_2$ | 22 | 18 | | | | 15 | 17 | 20–30 | mmol/l |
| Urea | 97 (34.5) | 76 (27.2) | | | | 38 (13.7) | 33 (11.7) | 7–17 (2.5–6.0) | mg/dl (mmol per litre) |
| Creatinine | 6.0 (528) | 4.3 (379) | | | | 2.0 (178) | 1.6 (143) | 0.4–0.9 (35–80) | mg/dl (μmol/l) |
| Total calcium | 11.3 (2.81) | 9.7 (2.42) | | | | 6.8 (1.7) | 6.5 (1.61) | 8.8–10.7 (2.19–2.66) | mg/dl (mmol/l) |
| Magnesium | 1.9 (0.8) | 2.0 (0.83) | | | | 0.9 (0.36) | 0.7 (0.28) | 1.7–2.3 (0.7–0.95) | mg/dl (mmol/l) |
| Albumin | 42 | 51 | | | | 41 | 37 | 37–56 | g/l |
| Glucose | | 202 (11.2) | | | | 175 (9.7) | | 63–99 (3.5–5.5) | mg/dl (mmol/l) |
| Osmolality | | | | | | | | 270–285 | mosmol/kg |
| Haemoglobin | 11.6 | 9.3 | | | | 8.6 | | 11.5–15.5 | g/dl |
| Urine | | | | | | | | | |
| Sodium | 112 | | | | | | | | mmol/l |
| Osmolality | | | | | | | | | mosmol/kg |
| Fluids | | | | | | | | | |
| In | | 2,200[a] | 1,303 | 1,485 | 2,383 | 2,591 | 1,898 | | ml |
| Out[b] | | 1,240[c] | 1,170 | 1,760 | 1,740 | 1,620 | 1,150 | | ml |
| Cumulative Balance | | +960 | +1,093 | +818 | +1,461 | +2,432 | +3,180 | | ml |

[a] Total amount of fluid given intra-operatively
[b] Except for 200 ml from the wound drain, all output was urine
[c] Immediate postoperative output did not include intra-operative losses, which were not documented (see text)

intubated and ventilated; a computed tomography scan revealed severe cerebral oedema, with uncal and tonsillar herniation; he was diagnosed as being brainstem dead the following morning. Using hypertonic (3%) saline solution, we achieved normonatraemia after 8 h to allow organ donation.

## Discussion

Our case highlights the dangers of massive fluid therapy and biochemical disturbances in the face of extreme polyuria. There are obvious questions regarding the aetiology of the patient's seizures, hyponatraemia and polyuria. Moreover, considering that the patient was treated according to a standard protocol, used for over 15 years in more than 200 paediatric renal transplantations, we describe how the protocol was changed in order to prevent a similar tragedy from occurring.

### What caused the patient's seizures and subsequent tonsillar herniation?

Seizures are a recognised complication after renal transplantation, with a frequency of up to 24%, with potential causes including fluid overload, and corticosteroid and calcineurin-inhibitor therapy [1–3]. Our patient was known to have had seizures previously, indicating that he had a lowered seizure threshold which was reduced further by the hypocalcaemia and hypomagnesaemia after transplantation (Table 1). The first seizure in our patient occurred when the serum sodium level was 126 mmol/l, a level not usually associated with seizure activity. However, hypo-osmolality was likely to have been the key aetiological factor, as the drop in serum sodium level was compounded by the rapid fall in urea after transplantation. His calculated serum osmolality dropped by approximately 80 mosmol/kg between transplantation and first seizure.

### Why was the patient polyuric?

The massive diuresis after anastomosis (58 ml/kg per hour) was extremely unusual. There is one report of an adult with diuresis of 25–50 ml/kg per hour after having received a live-unrelated renal transplant, who was also given fluid replacement with 0.45% saline solution and who developed hyponatraemia [lowest serum sodium (Na) concentration 113 mmol/l] and multiple generalised tonic–clonic seizures [4].

Our patient had 3–4 l/day (4–5 ml/kg per hour) native urine output, and the massive fluid losses after transplantation would have included a proportion from the native kidneys. However, excretion of ~1,800 ml/h requires a GFR of at least 30 ml/min, whilst the estimated GFR in our patient was 6 ml/min, uncorrected for surface area. Therefore, the majority of urine must have derived from the graft. Glucose given in the replacement fluid caused mild hyperglycaemia, with levels of 10–11 mmol/l, leading to osmotic diuresis. However, this leads to free water losses and hypernatraemia and is, thus, probably less relevant here.

### Why did the patient become hyponatraemic?

The patient's venous sodium level had dropped from 141 mmol/l post-operatively to 121 mmol/l 5 h later. Hyponatraemia is due to either a deficiency in salt or an excess of water.

A separate quantitative analysis of water and salt balance, also called tonicity balance, can help identify the pathophysiology of hyponatraemia [5]. From the beginning of surgery till his death, the patient was given 11.8 l and lost 8.6 l (see Table 1), a net positive balance for water of 3.2 l. An expansion of his total body water (estimated at 20 l or 65% of body weight) by this amount is consistent with the observed dilution of his serum sodium from 141 mmol/l to 121 mmol/l ($141 \times 20/23.2 = 121.6$). Based on this first part of the tonicity balance, excess fluid accounted for the hyponatraemia. This fits also with the observed decrease of albumin and haemoglobin in the blood (see Table 1). However, in order to retain the extra 3.2 l as free water, he must have been in equal sodium balance, i.e. the amount of sodium lost in the urine must have been equal to the sodium received. Whilst the urinary sodium was not measured, the amount received can be calculated from the fluids administered, and it totalled 1,140 mmol. An excretion of 1,140 mmol sodium in 8.6 l of urine equates to 133 mmol/l and represents 20% of sodium filtered during that time (assuming a GFR of 100 ml/min), indicating sodium wasting. This compares to reports of fractional sodium excretion ($FE_{Na}$) as high as 46% in deceased-donor renal allografts on the day of transplantation [6].

### Why did the patient have sodium wasting?

Sodium wasting is likely to have been due to hypoxic–ischaemic injury to the graft. The high $FE_{Na}$ reported in deceased-donor allografts was associated with ischaemic changes on biopsy [6]. In another study, hyponatraemia was seen in 88 of 125 adult recipients, also associated with an increased $FE_{Na}$ [7]. The dramatic postoperative decrease of serum calcium and magnesium concentrations (Table 1), which clearly exceeded the 16% dilution explained by the fluid balance, also suggests tubular dysfunction.

Sodium wasting can also be an appropriate physiological response of the kidney to volume overload, but it should not lead to hyponatraemia, as water can be excreted

alongside. However, other factors could have led to water retention, such as stress and morphine, recognised non-osmotic stimuli for antidiuretic hormone [8], or furosemide, which impairs urinary dilution.

How should a polyuric patient be treated?

For a patient with gross polyuria (> 10 ml/kg per hour) we suggest giving a fixed intake of 10 ml/kg per hour, with frequent (two-hourly) clinical and biochemical assessments that include blood pressure, peripheral perfusion, CVP, and serum and urine sodium and osmolality, to guide further replacement. We use 0.45% saline solution, based on our subsequent experience with typical post-transplantation urinary sodium concentrations of approximately 80 mmol/l. Any extra fluid for perceived volume depletion must be given in isotonic form. We use a glucose-containing solution at a steady rate for replacement of insensible losses, but fluids given for urine output replacement and boluses are glucose-free.

## Conclusion

Our patient developed seizures and tonsillar herniation due to hypo-osmolality associated with the administration of large volumes of hypotonic intravenous fluids in the context of extreme polyuria. Other factors, such as his previous brain injury, might have contributed to the fatal outcome. Regardless, the case highlights the importance of close clinical and biochemical monitoring after transplantation, especially in the context of polyuria. Although, in this case, the rapidity of events suggests that these measures might not have prevented death, we hope that lessons from this case will help to modify practice and prevent future tragedies.

## References

1. Awan AQ, Lewis MA, Postlethwaite RJ, Webb NJ (1999) Seizures following renal transplantation in childhood. Pediatr Nephrol 13:275–277
2. McEnery PT, Nathan J, Bates SR, Daniels SR (1989) Convulsions in children undergoing renal transplantation. J Pediatr 115:532–536
3. Qvist E, Pihko H, Fagerudd P, Valanne L, Lamminranta S, Karikoski J, Sainio K, Ronnholm K, Jalanko H, Holmberg C (2002) Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. Pediatr Transplant 6:53–62
4. Montas SM, Moyer A, Al-Holou WN, Pelletier SJ, Punch JD, Sung RS, Englesbe MJ (2006) More is not always better: a case postrenal transplant large volume diuresis, hyponatremia, and postoperative seizure. Transpl Int 19:85–86
5. Carlotti AP, Bohn D, Mallie JP, Halperin ML (2001) Tonicity balance, and not electrolyte-free water calculations, more accurately guides therapy for acute changes in natremia. Intensive Care Med 27:921–924
6. Kwon O, Corrigan G, Myers BD, Sibley R, Scandling JD, Dafoe D, Alfrey E, Nelson WJ (1999) Sodium reabsorption and distribution of $Na^+/K^+$-ATPase during postischemic injury to the renal allograft. Kidney Int 55:963–975
7. Higgins R, Ramaiyan K, Dasgupta T, Kanji H, Fletcher S, Lam F, Kashi H (2004) Hyponatraemia and hyperkalaemia are more frequent in renal transplant recipients treated with tacrolimus than with cyclosporin. Further evidence for differences between cyclosporin and tacrolimus nephrotoxicities. Nephrol Dial Transplant 19:444–450
8. Robertson G (2008) Thirst and vasopressin. In: Alpern R, Hebert S (eds) The kidney. Raven Press, New York, pp 1123–1142