



## EXCEPTIONAL CASE

## Fatal case of hospital-acquired hypernatraemia in a neonate: lessons learned from a tragic error

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### ABSTRACT

A 3-week-old boy with viral gastroenteritis was by error given 200 mL 1 mmol/mL hypertonic saline intravenously instead of isotonic saline. His plasma sodium concentration (PNa) increased from 136 to 206 mmol/L. Extreme brain shrinkage and universal hypoperfusion despite arterial hypertension resulted. Treatment with glucose infusion induced severe hyperglycaemia. Acute haemodialysis decreased the PNa to 160 mmol/L with an episode of hypoperfusion. The infant developed intractable seizures, severe brain injury on magnetic resonance imaging and died. The most important lesson is to avoid recurrence of this tragic error. The case is unique because a known amount of sodium was given intravenously to a well-monitored infant. Therefore the findings give us valuable data on the effect of fluid shifts on the PNa, the circulation and the brain's response to salt intoxication and the role of dialysis in managing it. The acute salt intoxication increased PNa to a level predicted by the Edelman equation with no evidence of osmotic inactivation of sodium. Treatment with glucose in water caused severe hypervolaemia and hyperglycaemia; the resulting increase in urine volume exacerbated hypernatraemia despite the high urine sodium concentration, because electrolyte-free water clearance was positive. When applying dialysis, caution regarding circulatory instability is imperative and a treatment algorithm is proposed.

**Keywords:** brain oedema, brain injury, electrolyte-free water clearance, fluid therapy, hospital-acquired hypernatraemia, hypernatraemia, safety and quality, salt intoxication, sodium

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## CASE PRESENTATION

A 3-week-old boy presented to a large secondary hospital (>900 beds) with fever, diarrhoea and insufficient breast feeding. Later, rotavirus was detected in his stool specimen.

An intravenous bolus of 20 mL/kg (80 mL) of isotonic saline (154 mmol/L) was prescribed. After the bolus, the anterior fontanelle became sunken, the skin mottled and capillary refill time worsened. Laboratory data showed that the plasma sodium (PNa) concentration had increased from 136 to 163 mmol/L and blood glucose from 5.2 to 10.4 mmol/L (Table 1). These findings were interpreted as worsening dehydration and hypovolaemia and another 20 mL/kg bolus of isotonic saline was prescribed. After the second infusion, the neonate became unresponsive, with nystagmus and convulsions. The fontanelle became extremely sunken, like a 'bowl'; blood pooled in the gluteal region, resembling livor mortis; the rest of the body was extremely mottled and capillary refill time increased (4–5 s). Hypertension and large diuresis were observed. Convulsions were treated with intravenous diazepam. Transient bradycardia and hypotension developed and a third bolus of 10 mL/kg was infused (Figure 1). Repeat laboratory data showed plasma sodium of 206 mmol/L and blood glucose of 9.6 mmol/L and it was now discovered that rather than isotonic saline, hypertonic saline had been given in error. The fluid had been drawn from a 100 mL fluid bag containing 1 mmol/mL hypertonic saline, used for adding sodium to hypotonic maintenance fluids. The isotonic and hypertonic fluid bags were similar in shape and labeling and were stored near each other.

To treat hypernatraemia, a total of 50 mL/kg (200 mL) intravenous 10% glucose in water (erroneously thought to be isotonic) was infused, resulting in severe hyperglycaemia with blood glucose >60 mmol/L, and hypertension reoccurred. Echocardiography showed sufficient filling of the ventricles but reduced contractility globally and mitral insufficiency. Fluid therapy was changed to 5% glucose in water. After a total of 50 mL/kg (200 mL) of 1 mmol/L saline (200 mmol of sodium) and 110 mL/kg (440 mL) of 10 and 5% glucose in water (178 mmol of

glucose), hypertension persisted and the skin was still extremely mottled.

Four and a half hours after presentation, the neonate was intubated and transferred to the Pediatric Intensive Care Unit of a tertiary centre and insulin therapy was instituted. Two hours later, laboratory data obtained with the infant on a ventilator (fraction of inspired oxygen 0.25) showed arterial pH 6.89, partial pressure of carbon dioxide 5.9 kPa, partial pressure of oxygen 10.4 kPa, bicarbonate 7.2 mmol/L, lactate 8.8 mmol/L, PNa 180 mmol/L and blood glucose 57 mmol/L. Haemodialysis was initiated and was complicated by an episode of circulatory failure. Amplitude-integrated electroencephalography briefly showed low voltage, but this normalized. Ultrasound showed no evidence of brain haemorrhage or oedema. Following a 1.5-h dialysis, PNa was 160 mmol/L and blood glucose was 14.7 mmol/L. Six hours after dialysis and 16 h after the first hypertonic saline infusion, electrical and clinical seizures (clonic movements of the extremities, blinking and oral automatisms) were observed. The seizures persisted despite treatment with midazolam and thiopental.

Six days after salt intoxication, magnetic resonance imaging of the brain showed subcortical/cortical hyperintensities in large areas of the cerebrum and cerebellum, with involvement of the left thalamus on T<sub>1</sub>-weighted images (Figure 2A). T<sub>2</sub>-weighted and fluid-attenuated inversion recovery sequence changes were most pronounced in the occipital and parietal lobes (Figure 2B). Diffusion-weighted imaging (DWI) revealed restricted diffusion in the same regions in addition to the corpus callosum and in several smaller areas in the brain parenchyma (high DWI, low apparent diffusion coefficient) (Figure 2C and D). There was no mass effect, no sign of brain shrinkage, no dural vein thrombosis and no intraventricular or subdural blood.

Based on the combination of widespread pathology on magnetic resonance imaging and intractable seizures, care was changed to palliative care, and the infant expired a short time later.

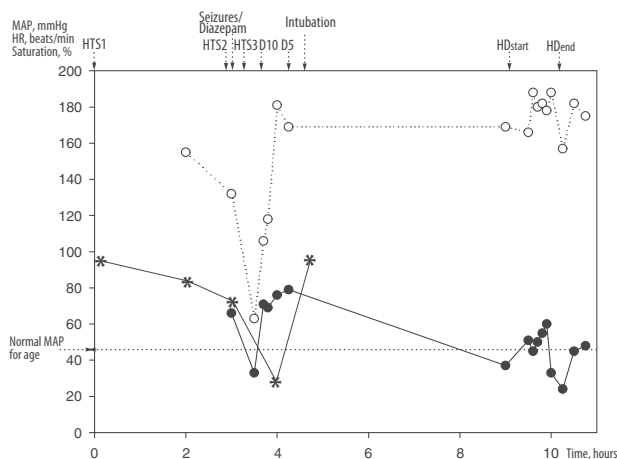
## DISCUSSION

The death of this infant caused by a medical error is unspeakably tragic. The parents encouraged us to report the case, in hopes that others could learn from it. The most important lesson is to avoid recurrence of the error by changing the storage and packaging of intravenous fluids. In addition, there is much to learn about the physiology and treatment of salt poisoning. The case is unique because a known amount of sodium was given intravenously to a well-monitored infant. PNa was known before, during and after the accident. Therefore the findings give us valuable data on the effect of fluid shifts on the PNa, the circulation, the brain's response to salt intoxication and the role of dialysis in managing it.

### Hypernatraemia

The increase in PNa from 136 to 163 to 206 mmol/L was caused by sodium overload. Edelman showed that PNa is a function of exchangeable sodium and potassium (eNa and eK) and total body water (TBW) as depicted by Equation (1) [1]:

$$\uparrow\uparrow\uparrow \text{PNa} = \frac{\uparrow\uparrow\uparrow \text{eNa} + \text{eK}}{\text{TBW}} \quad \text{sodium overload} \quad (1)$$



**FIGURE 1:** Circulation and events. MAP: mean arterial pressure (closed circle), mmHg; HR: heart rate (open circles), beats per minute; capillary blood saturation (asterisks), %; HTS1: first hypertonic saline bolus (80 mL of 1 mmol/L) infusion; HTS2: second hypertonic saline bolus (80 mL of 1 mmol/L) infusion; diazepam 1.6 mg intravenous; HTS3: third hypertonic saline bolus (40 mL of 1 mmol/L) infusion; D10: 10% glucose infusion (200 mL); D5: 5% glucose infusion (240 mL); HD<sub>start</sub>: haemodialysis start; HD<sub>end</sub>: haemodialysis end.

Table 1. Biochemistry

Time (h)	-1	0	3	4	4.5	5	6	7	10.5
Intervention	Before HTS	After 80 mL of HTS	After 200 mL of HTS, seizures, diazepam	D10 infusion	After 200 mL of D10, after intubation	After 240 mL D5, PICU	After insulin	Before HD	After HD, blood infusion
Blood source	Capillary	Capillary	Capillary	Capillary	Capillary	Arterial	Arterial	Arterial	Venous
Hgb, mmol/L	8.8	7.9	5.2	6.6	6.4	7	8.5	7.7	12.3
PNa, mmol/L	136	163	206	206	178	185	186	180	160
SK, mmol/L	6.5	6.4	3.4	3.4	3.2	2.8	4.2	4	5.1
Glucose, mmol/L	5.3	10.5	9.7	25	>60	52	45	57	14.6
pH	7.42	7.37	7.11	6.94	7.15	7.28	6.88	6.89	7.02
pO <sub>2</sub> (kPa)	8.6	6.1	6.2	3.5	65	18.7	10.2	10.4	
pCO <sub>2</sub> (kPa)	5.4	5.3	7.9	9.3	3.4	2.2	6.9	5.9	10.7
HCO <sub>3-</sub> , mmol/L	26	22.5	15.6	10.2	10.5	11.4	8.8	7.2	11.7

Hgb: hemoglobin; SK: plasma potassium concentration; glucose: blood glucose concentration; HTS: hypertonic saline 1 mmol/L; D10: 10% glucose; D5: 5% glucose; PICU: Pediatric Intensive Care Unit.

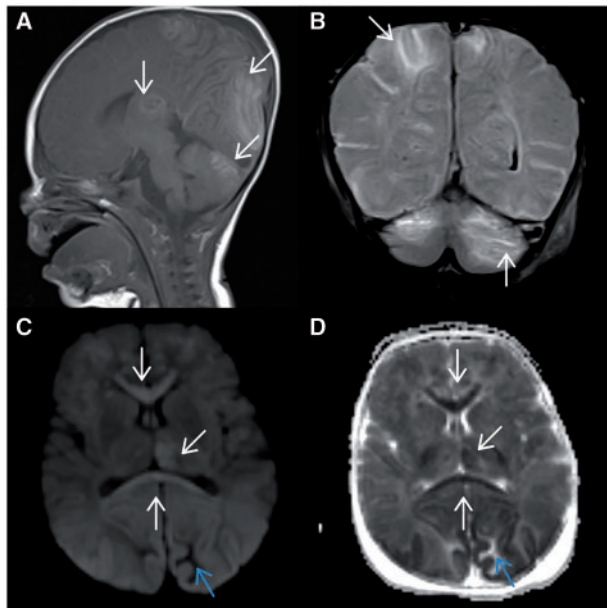


FIGURE 2: Brain magnetic resonance imaging. (A) T<sub>1</sub>-weighted sagittal and (B) coronal fluid-attenuated inversion recovery sequences. Hyperintense areas resembling oedema and blood in cortical and subcortical areas, including the left thalamus (white arrows). (C) Diffusion-weighted imaging and (D) apparent diffusion coefficient images show restricted diffusion in the callosal body and left thalamus (white arrows). Blue arrows show occipital vasogenic oedema.

Changes in PNa (from PNa<sub>1</sub> to PNa<sub>2</sub>) are determined by changes in external cation balances [Δ(Na<sup>+</sup>+K<sup>+</sup>)] and water balances (ΔTBW) according to Equation (2) [2, 3]:

$$PNa_2 = \frac{PNa_1 \times TBW + \Delta(Na^+ + K^+)}{TBW + \Delta TBW} \quad (2)$$

Assuming TBW to be equal to 60% of the 4 kg body weight (2.4 L), the first 80 mL of 1 mmol/mL hypertonic saline would be predicted to increase PNa from 136 to 164 mmol/L (calculation A in Supplementary Appendix). The predicted value is very close to the observed PNa of 163 mmol/L and there is nothing to suggest that any of the infused sodium was sequestered in osmotically inactive stores [4, 5].

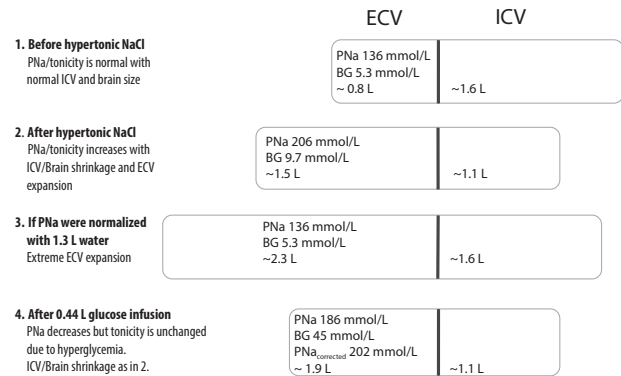


FIGURE 3: Fluid shifts. BG: blood glucose concentration. PNa<sub>corrected</sub> = PNa<sub>measured</sub> + 0.4 × (blood glucose – 5 mmol/L) = 186 mmol/L + 0.4 × (45–5 mmol/L) = 202 mmol/L. See Supplementary Appendix D for flux calculations in 2.

Paediatricians often encounter hypernatraemia due to dehydration:

$$\uparrow\uparrow\uparrow PNa = \frac{eNa + eK}{\downarrow\downarrow\downarrow TBW} \quad \text{dehydration}$$

Thus, in an infant with diarrhoea and mottling, the increase in PNa to 163 mmol/L was interpreted as dehydration and it prompted additional boluses of intravenous fluid, compounding the error. However, an acute increase in PNa of this magnitude could not plausibly be due to dehydration, as it would have required loss of ~0.4 L of water (10% of body weight) in 4 h (calculation B in Supplementary Appendix).

The administration of an additional 120 mL of 1 mmol/mL hypertonic saline would be predicted to increase PNa to 200 mmol/L, very close to the measured value of 206 mmol/L (particularly considering the dilutional effect of the blood glucose of 9.7 mmol/L; see below), offering additional evidence against acute osmotic inactivation of sodium (calculation C in Supplementary Appendix).

### Fluid shifts and hyperglycaemia/tonicity

The sodium load is restricted to the extracellular space, leading to a dramatically increased extracellular tonicity and water flux

from cells, decreasing intracellular volume (ICV) and increasing extracellular volume (ECV) [6]. Clinically, decreased ICV was evidenced by extreme shrinkage of the fontanelle/brain and ECV expansion by a 41% decrease in haemoglobin concentration from 8.8 to 5.2 mmol/L [Figure 3 (2) and calculation D in Supplementary Appendix] [7].

Immediately after the third hypertonic saline bolus, urine sodium concentration (UNa) was 200 mmol/L and urine potassium concentration (UK) was 5 mmol/L. Despite a large urine output (V), excretion of sodium in the urine would not correct hypertonicity because electrolyte-free water clearance (EFWC) was nil [6]:

$$\text{EFWC} = V \times \left(1 - \frac{\text{UNa} + \text{UK}}{\text{PNa}}\right) = V \times \left(1 - \frac{200 + 5}{206}\right) \approx 0$$

In cases of severe salt intoxication, a reduction in PNa with a 5% glucose infusion is advocated [8, 9]. The treatment decreases PNa by increasing the denominator:

$$\uparrow\uparrow\uparrow \text{PNa} = \frac{\uparrow\uparrow\uparrow \text{eNa} + \text{eK}}{\text{TBW}} \Rightarrow \text{PNa} = \frac{\uparrow\uparrow\uparrow \text{eNa} + \text{eK}}{\uparrow\uparrow\uparrow \text{TBW}}$$

Correction of hypertonicity with water would require 1.3 L and ECV would increase from 0.8 to 2.3 L, 2.9 times its normal volume (calculation E in Supplementary Appendix) [Figure 3 (3)].

Expanding ECV with bicarbonate-free fluid causes metabolic acidosis. In this case, after 0.2 L of hypertonic saline and 0.44 L of glucose in water, the resulting increase in ECV from 0.8 to 1.94 L (2.4 times normal size) would reduce the extracellular bicarbonate concentration from 26 to 10.9 mmol/L by dilution alone. The severe metabolic acidosis that occurred (Table 1) resulted from dilution and reduced tissue perfusion (see below).

Intravenous water must be infused with glucose to avoid haemolysis, which will initially exacerbate both ECV expansion and ICV contraction. Hypernatraemia in itself puts the infant at risk of hyperglycaemia—due to reduced glucose utilization and increased glycogenolysis—and hyperglycaemia was already present before the glucose infusions (Table 1) [10]. Even with high doses of insulin, the maximal rate of glucose metabolism is 10 mg/kg/min [11]. Administration of 1.3 L of 5% glucose (50 000 mg glucose/L) to a 4 kg infant over 2 h to normalize PNa would provide glucose at 135 mg/kg/min, by far exceeding the maximal rate of glucose utilization and further exacerbating hyperglycaemia. Hyperglycaemia would partially counteract the effort to correct hypertonicity and would exacerbate ECV expansion. Hyperglycaemia also causes glucosuria, so that some of the administered free water is lost in the urine [6].

In this case, first 0.2 L of electrolyte-free water was given as 10% glucose, providing 111 mmol of glucose. If all of the glucose were unutilized and confined to the ECV (1.5 plus 0.2 L), then the predicted increase in blood glucose would be 69 mmol/L. Indeed, the glucose infusion resulted in severe hyperglycaemia (blood glucose >60 mmol/L). The PNa decreased due to the combined effects of administered water and a glucose-induced shift of water out of cells, but tonicity did not change [Figure 3 (4)] [6, 12].

The first measurable blood glucose was 45 mmol/L when PNa was 186 mmol/L. Correcting measured PNa for hyperglycaemia [Figure 4 (4)] [6, 12]:

$$\text{PNa}_{\text{corrected}} = \text{PNa}_{\text{measured}} + 0.4 \times (\text{blood glucose} - 5 \text{ mmol/L}) \\ = 186 \text{ mmol/L} + 0.4 \times (45 \text{ mmol/L} - 5 \text{ mmol/L}) = 202 \text{ mmol/L}$$

Four hours after the first hypertonic saline infusion and after 10% glucose infusion, urine output was 50 mL/h. Glucosuria would be expected to reduce UNa. Assuming UNa to be 100 mmol/L, urine losses would eliminate only 2.5% of the salt load and 9% of the fluid load per hour and exacerbate hypernatraemia because EFWC would now be positive (UNa+UK>PNa).

Learning points: Treatment of acute salt poisoning with rapid infusions of glucose in water causes severe hypervolaemia and hyperglycaemia; the resulting increase in urine volume will exacerbate hypernatraemia despite high UNa, because EFWC will be positive. Frequent monitoring of PNa, blood glucose, urine volume and composition, with adjustments in the rate of infusion (rather than a fixed calculated input) is essential [13].

## Dialysis

Because intravenous fluids and diuresis could not correct hypernatraemia without hyperglycaemia and fluid overload, dialysis was applied [8, 9]. Haemodialysis was chosen because of our institution's experience with this procedure in neonates and to rapidly improve the severe metabolic disturbance. The strategy was to reduce the PNa to 160 mmol/L (not all the way to normal) to protect both the brain and the circulation.

We need to balance the risk of ongoing brain damage from hypertonicity against the unknown risk of brain swelling from excessively rapid correction of hypernatraemia and hyperglycaemia [14]. In longer-lasting hypernatraemia, the brain accumulates organic osmolytes that persist when the PNa is rapidly reduced, causing cerebral oedema. Accumulation of organic osmolytes requires upregulation of transporters, which requires a few days in experimental animals [14, 15]. Although only 9 h had passed since the first bolus of hypertonic saline, which might have been too soon for organic osmolytes to accumulate, it is not known how rapidly this adaptation occurs after an osmotic insult as extreme as in this case [6, 9, 15].

Despite volume expansion, the neonate's circulation was compromised. Severe peripheral vasoconstriction developed after the second hypertonic saline bolus and it persisted, possibly because of a direct toxic effect of acute hypertonicity on the vasculature. Direct vascular damage and capillary thrombosis have been reported in autopsies of babies dying of salt intoxication [16]. High tonicity directly damages the endothelium [17]. Direct injury to the microvasculature combined with distortion of the circulation due to extreme muscle shrinkage would produce hypoperfusion despite hypertension, as observed in this infant. A catecholamine response to the acute brain injury could produce the same clinical picture. Cardiac function was also compromised, either because of a direct effect of hypertonicity on cardiomyocytes or myocardial stunning from catecholamines [18]. Because of these changes, tissue perfusion was extremely poor, with lactic acidosis, and we wanted to avoid a large change in plasma volume during dialysis.

At the time of dialysis, the neonate had received a total of 0.64 L of fluid intravenously and may have excreted as much as half of this extra volume in the urine. The expanded ECV volume at the time of dialysis was due to the remaining infused fluid and the presence of excess extracellular sodium and glucose. During dialysis, sodium and glucose would be rapidly removed because of concentration gradients between the blood and dialysate and removal of these solutes would be expected to result in a fluid shift from the ECV to the ICV; limiting correction to 160 mmol/L with blood glucose of 10 mmol/L was intended to minimize these fluid shifts [19].



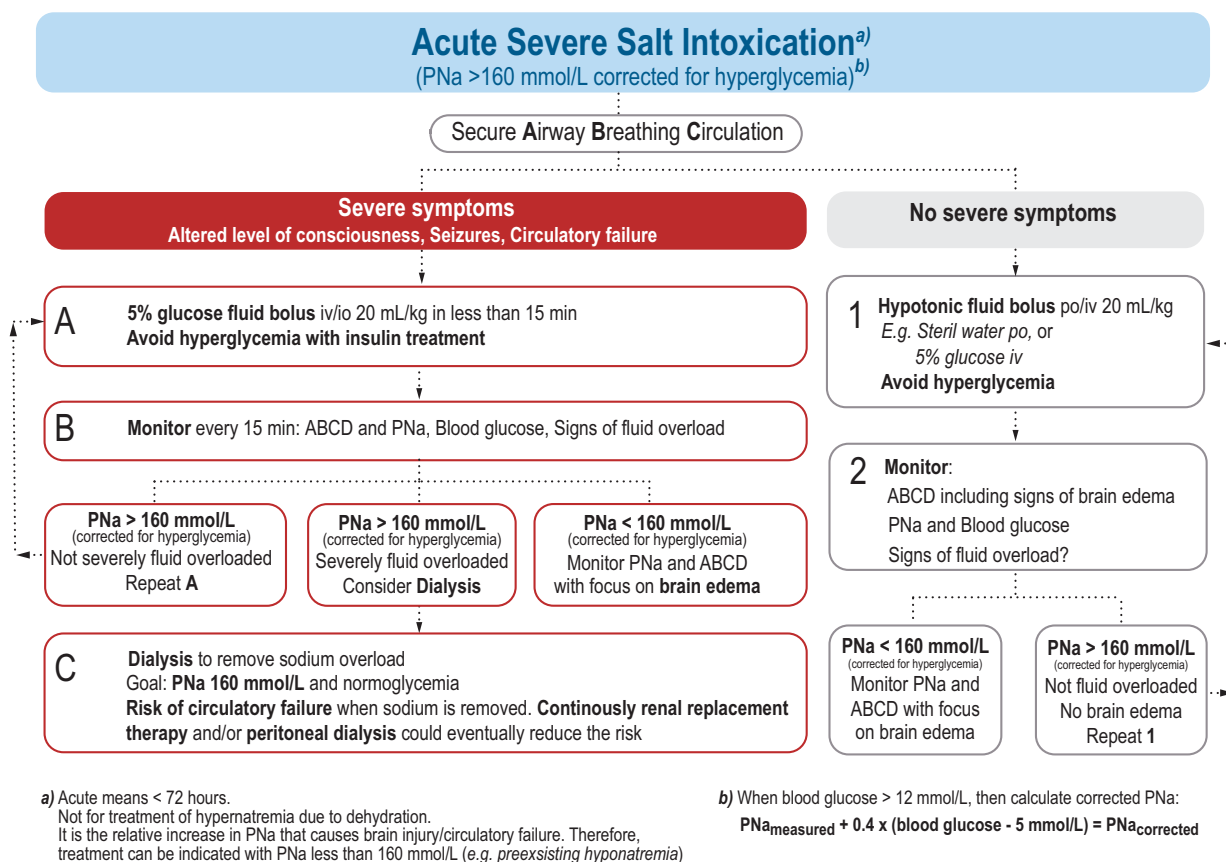


FIGURE 4: Proposed treatment algorithm in acute salt intoxication.

The dialysis system was primed with red blood cells to avoid hypovolaemia. Blood flow was 10–25 mL/min and the dialysate had a sodium concentration of 150 mmol/L, potassium concentration of 4.0 mmol/L, calcium concentration of 1.75 mmol/L and bicarbonate concentration of 38 mmol/L. PNa and blood glucose were measured every 15 min. There was no fluid removal. Despite these precautions, the blood pressure suddenly increased, followed by severe hypoperfusion and hypotension after 90 min of dialysis. The dialysis was stopped and perfusion was stabilized with blood and intravenous epinephrine. After dialysis, PNa was 160 mmol/L and blood glucose was 14.6 mmol/L.

Learning points: When applying dialysis to treat severe salt intoxication, caution regarding circulatory instability—when the excess sodium is removed—is imperative. Using continuous renal replacement therapy or peritoneal dialysis instead of haemodialysis would likely reduce the risk of hypoperfusion caused by sodium removal and fluid shifts and would avoid sudden osmotic stresses on the brain (see below).

### Acute brain response to hypernatraemia

Acute hypernatraemia resulted in an immediate onset of reduced consciousness, nystagmus and convulsions. The symptoms were similar to other cases of severe salt intoxication [14, 20–22]. The acute neurological symptoms could be caused by brain cell shrinkage, anoxic-ischaemic injury due to brain

capillary thrombosis and generalized hypoperfusion [14, 16, 23, 24] or an altered electrochemical environment [6].

Extreme brain shrinkage, with marked depression of the anterior fontanelle, was observed immediately after the hypertonic saline was given. A rapid increase in PNa (and tonicity) reduces cell size in all tissues, including the brain [Figure 3 (2)] [6, 9]. Extreme cell shrinkage distorts the intracellular environment, eventually leading to apoptosis of brain cells [14]. Extreme brain shrinkage could mechanically reduce perfusion and hence cause anoxic-ischaemic brain damage, as seen clinically [16, 23, 24] and experimentally [14]. A direct toxic effect of acute hypernatraemia on brain vessels [17] with capillary thrombosis [16] may also have contributed to anoxic-ischaemic brain injury. The global hypoperfusion in the hours after the accident and the episode of circulatory failure during haemodialysis would aggravate such injury. Severe hyperglycaemia with blood glucose >60 mmol/L could also have worsened the brain injury [25, 26].

Magnetic resonance imaging of the cerebrum (Figure 2A and B) was consistent with laminar cortical necrosis with subcortical oedema and subarachnoid bleeding, findings that have been reported in acute hypernatraemia [23, 27]. Restricted diffusion may be caused by microthrombosis leading to ischaemia but has also been described in osmotic demyelination syndrome in which involvement of the corpus callosum was also seen [14, 16, 24]. The absence of osmotic demyelination is consistent with a magnetic resonance imaging case series in children <3 years of age [28]. In salt-intoxicated adults, osmotic demyelination has

been described more often, probably because the magnetic resonance imaging was performed later (12 days after the accident) or due to a higher myelin content than in this infant [24].

Given time, brain cells gradually adapt to hypernatraemia, restoring their volume by accumulating organic osmolytes. Because these extra solutes are not rapidly shed, rapid correction of the electrolyte disturbance can cause rehydration seizures associated with potentially fatal cerebral oedema. This complication has been reported exclusively in infants with chronic hypernatraemia, and it is associated with a bulging fontanelle, which was not observed in this case. An ultrasound of the brain after haemodialysis did not show any evidence of brain swelling. The neonate did develop seizures, beginning 6 h after dialysis. It is possible that rapid correction of hypernatraemia contributed to the seizures, but rehydration seizures typically occur earlier.

How the route and rate of sodium administration and the age of the patient influence brain injury in severe salt intoxication is not known. It is certain that severe salt intoxication can cause brain damage with a high mortality. Experimentally, fast reduction of PNa substantially reduces mortality [14]. Case reports also describe survival with fast PNa reduction after oral salt intoxication [21, 22]. In experimental models, osmotic demyelination can be aborted by rapidly re-lowering the PNa after rapid correction of chronic hyponatraemia [29]. The mechanism for this phenomenon has not been identified and it is not known if rapid re-lowering of the PNa has a similar protective effect in acute hypernatraemia.

Learning points: Current knowledge of the effects of severe, acute hypernatraemia on the brain is quite limited and deserves further study. Although a rapid, but controlled, decrease in PNa to reduce the toxic effect of hypertonicity on brain cells and the microcirculation appears likely to be beneficial, it is not known whether full normalization of the PNa or limited correction is the best strategy.

## CONCLUSION

Acute salt intoxication increased the PNa to a level predicted by the Edelman equation with no evidence of osmotic inactivation of sodium. The resulting hypertonicity caused extracellular fluid volume expansion and severe shrinkage of the brain. The ideal treatment of the condition is not known and our knowledge of the pathophysiology of the disorder is quite limited. We do not know whether the brain had already been irreversibly damaged before corrective measures were applied. We would still advocate a rapid (hours) decrease in PNa to reduce direct toxicity on vessels and the brain to ~160 mmol/L, compatible with survival without brain damage [14]. The reduction in PNa with hypotonic fluids should be tailored to avoid fluid overload and hyperglycaemia. With extreme sodium overload and/or fluid overload, removing excess sodium with dialysis is advocated. Continuous renal replacement therapy or peritoneal dialysis rather than acute haemodialysis could reduce the risk of exacerbating haemodynamic instability. To avoid secondary brain damage from hypoxaemia, protection of the airway, adequate ventilation and maintenance of adequate circulation are essential. Figure 4 is a proposed treatment algorithm [6, 14, 30, 31].

## PATIENT CONSENT

The parents encouraged us to report the case in hopes that others could learn from it. They have read and approved the

final manuscript including the images. The parents have signed the consent form to publish the case in *Clinical Kidney Journal*.

## SUPPLEMENTARY DATA

Supplementary data are available at [ckj online](#).

## AUTHORS' CONTRIBUTIONS

C.O.S., P.P. and R.S. were responsible for the research idea and study design. P.P. and A.L. were responsible for data acquisition. C.O.S., P.P., C.H., L.S.S., A.V., C.H.H., A.L. and R.S. were responsible for data analysis/interpretation. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

## CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part.

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