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CASE REPORT

Difficulties in diagnosing the cause of hyponatraemia in an extremely premature boy

Aleksandra Bryłka[1], Omar Bjanid[1], Wojciech Korlacki[2], Maria Nowak[3], Marta Nowak[3], Marcela Sobecka[3], Majka Jaszczura[4], Piotr Adamczyk[5], Maria Szczepańska[5]

[1]Department of Paediatric Nephrology, Teaching Hospital No. 1, Medical University of Silesia, Zabrze, Poland
[2]Department of Paediatric Malformations Surgery and Traumatology, Teaching Hospital No. 1, Medical University of Silesia, Zabrze, Poland
[3]Students' Scientific Circle at the Department and Clinic of Paediatrics, Teaching Hospital No. 1, Medical University of Silesia, Zabrze, Poland
[4]Department of Paediatrics, Teaching Hospital No. 1, Medical University of Silesia, Zabrze, Poland
[5]Chair and Department of Paediatrics, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Zabrze, Poland

ABSTRACT

We present the history of a nine-month-old male infant born prematurely with extremely low birth weight, who was admitted to the paediatric nephrology department with dehydration, acute kidney injury, hyponatraemia, hyperkalaemia, and metabolic acidosis. While the crucial first step in the diagnosis of hyponatraemia includes the assessment of the patient's fluid status, we focus in the discussion on the causes, diagnosis, and treatment of hypovolemic hyponatraemia. With the notable exception of congenital adrenal hyperplasia (CAH) and other primary adrenal diseases, in which there is a deficiency in aldosterone synthesis, many other salt-losing disorders share the common feature of inducing secondary hyperaldosteronism. In the presented case hyponatraemia was caused by NEC-related ileostomy with, typically, hyperkalaemia despite secondary hyperaldosteronism. The clinical picture can be very similar to pseudohypoaldosteronism type 1 (PH 1), with the renal handling of sodium being the key differentiating feature.

KEY WORDS:

prematurity, hyponatraemia, ileostomy, pseudohypoaldosteronism type 1.

INTRODUCTION

Hyponatraemia and dehydration are potentially serious threats to the health and life of young children. In infants, especially those born prematurely, the regulatory mechanisms of homeostasis are not fully developed yet, and therefore water and electrolyte imbalances can occur faster and have a more severe course than in older children. Clinical symptoms of hyponatraemia are non-specific, and their severity depends on the onset dynamic of the disturbance. Chronic hyponatraemia may be less expressed or even asymptomatic. The spectrum of possible symptoms of hyponatraemia consist of nausea, vomiting, headaches (in older children), and alteration of consciousness. When the disorders exacerbate, cerebral oedema and hypoxia occur and manifest through emesis, convulsions, bradycardia, and, in extreme cases, respiratory distress and coma [1].

Dehydration in children, which often occurs together with disturbances in sodium balance, is characterised by dryness of the mucosa, sunken eyes, reduced skin turgor

ADDRESS FOR CORRESPONDENCE:
Aleksandra Bryłka, Department of Paediatric Nephrology, Teaching Hospital No. 1, Medical University of Silesia, Zabrze, 13-15 3 Maja St., 41-800 Zabrze, Poland, e-mail: brylkaalex@gmail.com

and body weight, tachycardia, and sunken fontanelle in infants [2]. In the case of hypovolemic hyponatraemia the management is focused on rehydration, correction of the sodium deficiency, and, if possible, treatment of the underlying disease. While dehydration in children is most frequently caused by acute gastrointestinal infections, numerous other less common endocrine, renal, or gastrointestinal conditions can cause sodium loss and hypovolaemia, and are discussed in the differential diagnosis of the presented case.

CASE REPORT

A nine-month-old male infant was admitted to the Department of Paediatric Nephrology in Zabrze due to electrolyte disturbances. The boy was born prematurely in the 25th week of pregnancy from a preterm spontaneous vaginal delivery, with extremely low birth weight (760 g). He received 5/6/6/6 points in the Apgar scale. The pregnancy was complicated with maternal urinary tract infection and marginal placenta praevia. Spotting and vaginal bleeding occurred from the 12th week of gestation, and progesterone and lutein were administered to maintain the pregnancy. Two days before delivery a fever occurred in the mother caused by urinary tract infection. The delivery was complicated with perinatal hypoxia and intracranial 4th grade haemorrhage. The newborn required mechanical ventilation due to respiratory distress. Screening tests for metabolic diseases and, notably, cystic fibrosis were negative.

In the second month of life, the boy was operated due to gastrointestinal tract obstruction, caused by a persistent meconium plug located in the distal ileum, which was evacuated. In the third month of life another episode of obstruction occurred accompanied by necrotising enterocolitis (NEC) and perforation. Faecal peritonitis was observed intraoperatively, with a necrotic and perforated ileal segment located 10 cm before the ileocaecal valve.

TABLE 1. Results of selected parameters performed on admission to the nephrology department for children

Laboratory parameter	Result	Reference range
eGFR	58 ml/min	40–90 ml/min/1.73 m^2
In blood		
HCO_3	24.2 mmol/l	21–27 mmol/l
Urea	18.6 mmol/l	1.43–6.78 mmol/l
Creatinine	35 µmol/l	15–37 µmol/l
Aldosterone	795 pg/ml	17.6–232 pg/ml
Plasma renin activity	65 ng/ml/h	2.4–35 ng/ml/h
24-hour urine collection		
Albumin	19.21 mg/24 h	0–30 mg/24 h
THAldo	127.2 µg/24 h	6–34 µg/24 h

Fifteen centimetres of the necrotic small intestine was resected and a double-barrelled ileostomy performed. The patient's condition after surgery was severe, and he again required mechanical ventilation for one week. During the postoperative period in the paediatric ICU periodical convulsions and myoclonus were observed.

Additional disorders related in part to prematurity were also diagnosed: respiratory distress syndrome (RDS), chronic lung disease (CLD), persistent pulmonary hypertension of the newborn (PPHN), emphysema, and oesophagitis, which led to the perforation of the oesophagus in the fourth week of life and the formation of oesophagopleural fistula with mediastinal inflammation. The last complication was treated conservatively. The child was also diagnosed with transient liver failure, cholestasis, systemic inflammatory response syndrome (SIRS), anaemia, thrombocytopaenia, retinopathy of prematurity, dilatation of the inguinal canal, and bilateral hydrocele.

After stabilisation and discharge from the hospital, the infant was subsequently hospitalised five times due to dehydration and electrolyte disturbances, mainly hyponatraemia. The lowest recorded sodium concentration value was 117.9 mmol/l.

During hospitalisation in the nephrology department (at the age of nine months) the physical examination revealed features of dehydration of more than 10% of body weight. Laboratory tests showed hyponatraemia (124 mmol/l), hyperkalaemia (6.15 mmol/l), compensated metabolic acidosis, and eGFR of 58 ml/min/1.73 m^2. The inflammatory markers were negative and the urinalysis was normal. The fractional excretion of sodium (FeNa) was 0.02% and consistently low, which allowed kidney sodium loss to be ruled out. Serum aldosterone level and plasma renin activity were elevated (795 pg/ml and 65 ng/ml/h, respectively). ACTH and cortisol secretion were in the normal range (respective morning values of 63 pg/ml and 10 µg/dl, and night values of 14 pg/ml and 2.8 µg/dl). An increased excretion of tetrahydro-aldosterone was found in a 24-hour urine collection (THAldo – study was performed in the Children's Memorial Health Institute, Department of Biochemistry, Radioimmunology, and Experimental Medicine) (Table 1). A sweat chloride test was also carried out, and was normal. No abnormalities were found at abdominal ultrasound, with notably a normal kidney and urinary tract appearance.

On the basis of those findings, kidney tubular disorders and endocrine causes of hyponatraemia were excluded, and a diagnosis of high drainage ileostomy related dehydration, salt loss, and secondary hyperaldosteronism was established.

After clinical stabilisation the child was discharged for further ambulatory follow-up with the prescription of oral sodium chloride and sodium bicarbonate supplementation. The follow-up electrolyte values and gas acid-base balance results were satisfactory with periodical dose adjustments.

At the age of 17 months an attempt to restore the continuity of the gastrointestinal tract was made. Due to the significant ileal lumen disproportion, anastomosis was performed side to side. In the postoperative period symptoms of intestinal obstruction were observed and required reoperation with a further resection of 15 cm of the small intestine along with the previous anastomosis and cecum with the ileocecal valve. A double layer end-to-end ileocolic anastomosis was performed and proved to be efficient. After this second operation no further complications were observed, with effective restoration of the natural route of defecation. The boy's subsequent follow-up is unknown because he did not attend control visits.

The graphs show changes in body weight (Fig. 1) and changes in the serum concentration of sodium and potassium (Fig. 2) within the available period of observation lasting for eight months.

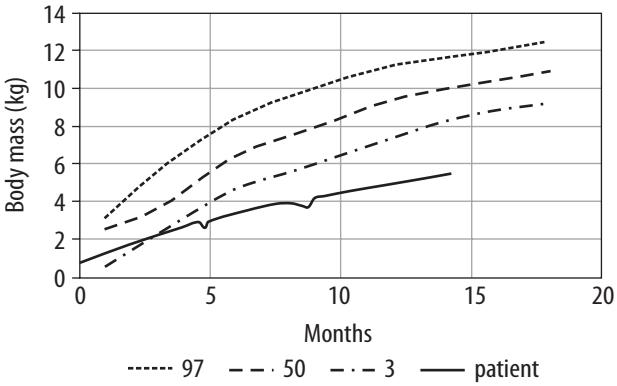


FIGURE 1. The weight gain shown in centile chart during 8 months of follow-up

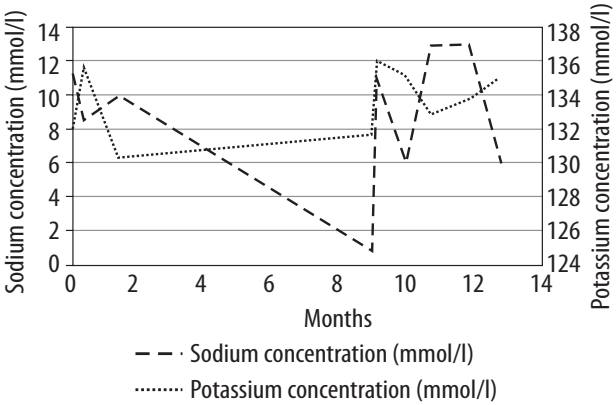


FIGURE 2. Sodium and potassium concentrations during 8-month observation

DISCUSSION

Mild transient hyponatraemia is observed quite frequently in infants and does not constitute a threat to their health [3]. In the case of relapsing or chronic hyponatraemia, especially when the sodium concentration values are less than 130 mmol/l, a thorough workup and comprehensive differential diagnosis is warranted. The kidneys play a central role in the sodium homeostasis, notably by excreting 95% of the dietary sodium load. Thus recurrent water-electrolyte disturbances suggest a possible primary or secondary impairment of renal function [4]. By comparison, the digestive tract and the skin excrete, respectively, 4.5% and 0.5% of the sodium load. An excessive loss of sodium by any of the three above-mentioned systems can lead to volume depletion, which in turn can stimulate the non-osmotic release of antidiuretic hormone (ADH) and water conservation, and enhance the hyponatraemia in consequence. Renal salt and water depletion can occur in tubular disorders, or may be caused by osmotic diuresis or diuretics. With regard to the gastrointestinal (GI) tract, hypovolaemic hyponatraemia can occur in result of diarrhoea, vomiting, intestinal obstruction, and fistulas.

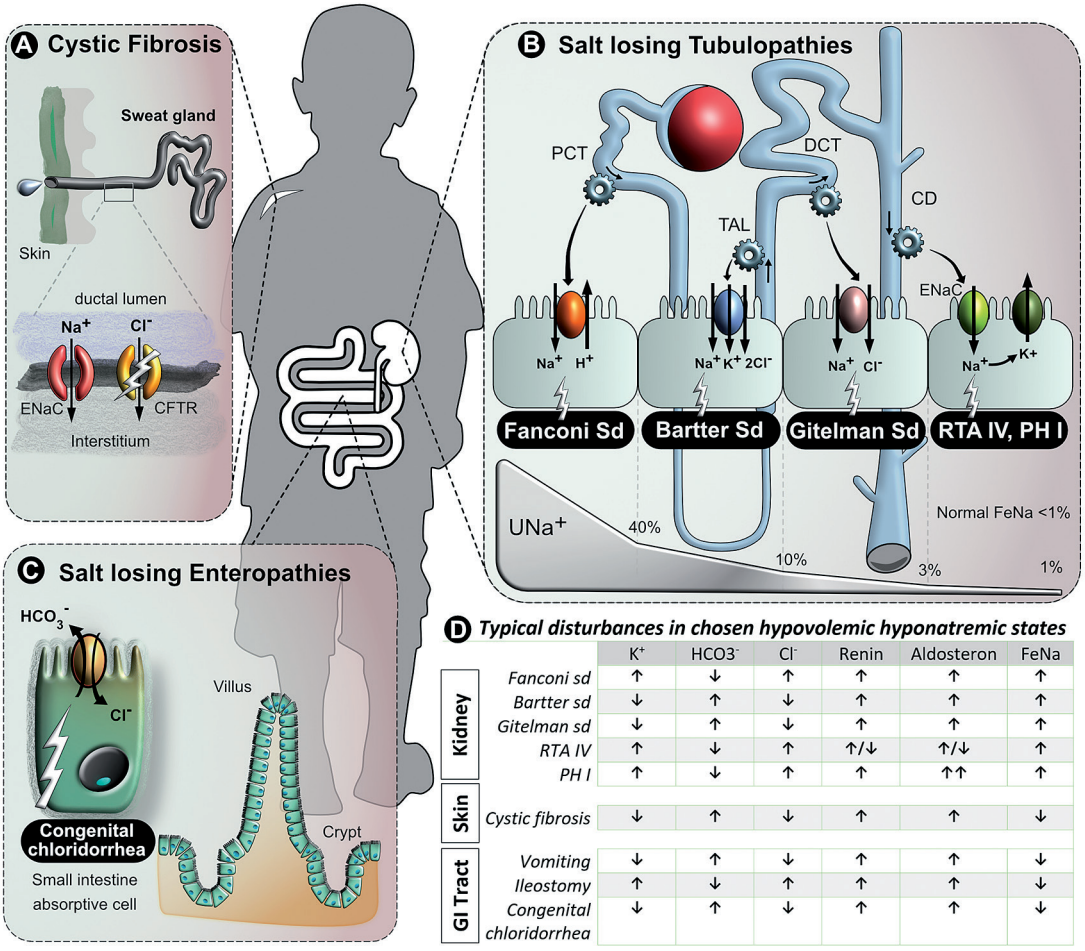
Although hypovolaemic hyponatraemia is the most common dysnatraemia in paediatric patients, sodium concentration disturbances are by no means obligatory associated with hypovolaemia. They merely reflect a disproportion between water and sodium in the extracellular fluid compartment, and can occur with only subtle or no alteration of volaemia, or in oedematous, overtly hypervolaemic states, like cardiac or liver failure and nephrotic syndrome [1]. Common causes of normovolaemic hyponatraemia are inadequate secretion of antidiuretic hormone, hypothyroidism, and adrenocortical insufficiency.

Premature infants are particularly prone to developing hyponatraemia, due to several factors like reduced sodium reabsorption in the proximal and distal renal tubule, limited salt supply, e.g. during breastfeeding, and immaturity of other water-electrolyte homeostasis mechanisms [3]. Acute GI complications such as NEC constitute an additional challenge to homeostasis in that population. A temporary ileostomy is a recognised treatment modality in newborns with acute abdomen, most often NEC [5]. The length of the small intestine in full-term newborns is estimated at about 2.5–3 m, in premature children it can be even half of that length. The minimal small intestine length after resection necessary for feeding autonomy, and thus a major determinant of parenteral feeding dependency and survival prognosis, is estimated at 15 cm if the ileocaecal valve is preserved, and 40 cm otherwise [5]. In infants with ileostomy fed enterally, high output stoma (secretion of more than 50 ml/kg/day) is often observed, and can lead to a shift in the proportion of sodium excreted by the digestive tract and the kidneys [6]. Due to the immaturity of the kidneys that hampers their capacity to compensate the increased extrarenal salt waste, even a small increase in enteral input can stimulate secretion and lead to high watery stoma output with dehydration and electrolyte depletion [7]. Another complication in ileostomy-related sodium depletion is the observed poor weight gain despite adequate caloric intake [8]. The mechanism of the sodium depletion impact on weight is still unclear; however, some studies have suggested ineffec-

tive glucose absorption due to impaired sodium-glucose co-transportation through SGLT-1 as a possible cause [8]. According to performed studies ostomy closure and restoration of continuity of the intestinal tract resolved the chronic diarrhoea and reduced susceptibility to electrolyte imbalance [9].

When the mechanism of water and salt depletion is different from primary mineralocorticoid deficiency, compensatory hyperaldosteronism is expected. Not surprisingly, in patients with ileostomy elevated aldosterone and 18-OH-corticosterone are reported, as was also the case in the presented patient [10]. What can be surprising, on the other hand, is the frequently observed hyperkalaemia despite secondary hyperaldosteronism in those patients. At least three factors contribute to this status. First, the nature of dyselectrolitaemia in GI tract disorders is determined by the composition of the wasted fluid. Ileostomy drainage contains relatively small amounts of potassium (5 mmol/l) and high sodium (40–90 mmol/l), compared to other GI fluids (for example: in normal stool the sodium concentration is 20-30 mmol/l and potassium concentration is 55–75 mmol/l, whereas in inflammatory diarrhoea expected concentrations for sodium and potassium are 50–100 mmol/l and 15–20 mmol/l, respectively) [11]. Second, metabolic acidosis is often observed (despite hyperaldosteronism) and it is caused by the loss of high amounts of bicarbonate in the ileostomy fluid. Acidosis promotes potassium shift from the intracellular to the extracellular compartment and this transmineralisation leads to hyperkaliaemia. And finally, the third factor is the impaired renal excretion of potassium in the distal tubule, caused by volume depletion in conjunction with the flow dependency of the sodium epithelial channel (ENaC). Despite its up-regulation by aldosterone, the ENaC activity is limited by the diminished urine flow in the distal tubule, and cannot build up a sufficient electro-negative gradient in the tubule lumen, necessary to excrete K+ and H+ effectively [12].

The differential diagnosis of chronic hyponatraemia in infants must include salt wasting syndromes related to congenital or acquired insufficient synthesis or function of aldosterone. Congenital defects of adrenal biosynthesis are the most common causes, including congenital adrenal hyperplasia (CAH), which is in 90% of cases due to 21-hydroxylase deficiency [13] and in 75% is manifested as the classic type with salt loss. Laboratory findings in



ENaC – epithelial sodium channel, CFTR – cystic fibrosis transmembrane conductance regulator, PCT – proximal convoluted tubule, TAL – thick ascending loop, DCT – distal convoluted tubule, CD – collecting duct, RTA IV – renal tubular acidosis type IV (hyperkalaemic), PH I – pseudohypoaldosteronism type I, Una – urine sodium, FeNa – fractional excretion of sodium

FIGURE 3. The differential diagnosis of salt-loss disorders

CAH include significant deficiency of cortisol and aldosterone and elevated levels of androgens [1, 14].

In the discussed case the levels of cortisol and ACTH were in the normal range at presentation, which made a diagnosis of CAH highly improbable. Adrenal disorders were definitively ruled out in the ulteriorly obtained urinary steroid profile results. The patient had also high aldosterone, high plasma renin activity, and elevated level of tetrahydroaldosterone (TH-aldo) in urine, which raised the suspicion of pseudohypoaldosteronism type 1 (PH1) [15]. In this disorder renal salt wasting, dehydration, hyperkalaemia, and metabolic acidosis are present, as well as failure to thrive [16, 17]. The milder, autosomal dominant (adPH1), renal type of the disease is caused by an inactivating mutation of the mineralocorticoid receptor (MR), whereas the more severe, autosomal recessive (arPH1), generalised form of PH1 is caused by a loss of function mutation of the effector, the epithelial sodium channel (ENaC). The clinical course of arPH1 is worse, and spontaneous improvement does not occur [18]. This type is associated with the risk of death immediately after birth. A number of other non-genetic, mainly urologic causes of injury to the distal tubule, such as urinary tract anomalies, urinary tract infections [19], amyloidosis, and tubulo-interstitial injury after kidney transplantation, can cause a state of – usually transient – renal insensitivity to aldosterone [18].

Despite the presence of symptoms suggestive of arPH1, this diagnosis was excluded in our patient, because of the consistently low concentrations of sodium in the urine, with a fractional excretion of sodium (FENa) of persistently less than 1%, which ruled out a renal cause of the salt loss. In cystic fibrosis (CF) salt depletion can occur via the skin, but manifests usually as a Bartter-like syndrome, with alkalosis and hypokalaemia. We did, however, actively exclude CF in genetic and chloride sweat tests because, among other symptoms, the recurrent episodes of GI tract obstruction and meconium plug were observed. After ruling out renal and skin salt waste, the cause of hyponatraemia was established as high output NEC-related ileostomy with, typically, hyperkalaemia despite secondary hyperaldosteronism.

Salt wasting disorders that can cause hypovolemic hyponatraemia are summarised in Figure 3.

DISCLOSURE

The authors declare no conflict of interest.

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