CASE REPORT

Reset osmostat: a rare cause of hyponatraemia

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SUMMARY

Neonatal hyponatraemia is common, and related to significant morbidity and mortality. We report a case of a preterm newborn (gestational age of 36 weeks) with hyponatraemia, and with a prenatal diagnosis of cleft lip and palate, with a normal fetal karyotype. On the seventh day of life, a biochemical evaluation for jaundice and mild signs of dehydration showed hyponatraemia of 124 mmol/L. Investigation showed normal adrenal and thyroid functions, plasma hyposmolality (258 mOsm/kg); high urinary sodium (73 mmol/L) and high urinary osmolality (165 mOsm/kg). Despite oral sodium supplementation and fludrocortisone treatment, sodium levels remained between 124 and 130 mmol/L. Cranial ultrasound, brain MRI and renal ultrasound were normal. The diagnosis of hyponatraemia was unpredicted and the investigation was suggestive of reset osmostat, a subtype of the syndrome of inappropriate secretion of antidiuretic hormone, characterised by a subnormal threshold for antidiuretic hormone secretion.

BACKGROUND

Hyponatraemia is defined as blood sodium concentration of less than 135 mmol/L and is associated with significant morbidity and mortality.^{1–4} Hyponatraemia must be distinguished from apparent hyponatraemia (caused by hyperlipidaemia, hyperglycaemia or renal failure) by measurement of plasma osmolality, which is low in true hyponatraemia (<280 mOsm/kg).

Hyponatraemia is caused by one of three mechanisms: an inability to excrete water load, excessive sodium losses or inadequate sodium intake.¹ The main causes of hyponatraemia are related to illnesses that compromise the renal capacity to excrete free water, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), postoperative state, oral water intoxication or diuretics.⁴ In preterm infants, hyponatraemia is usually associated with immaturity of renal salt regulating mechanisms; after 36 weeks of gestational age, the sodium balance is usually positive and sodium regulating mechanisms are mature.⁵

To help determine its cause, hyponatraemia is classified according to the volume status in hypovolaemia, euvolaemia or hypervolaemia. In euvolaemia, plasma renin activity is normal.⁵ The normal response to hyponatraemia is the suppression of ADH secretion, resulting in the excretion of maximally dilute urine. In patients with hyponatraemia and hyposmolality, urine osmolality above 100 mOsm/kg and specific gravity >1003 indicate an inability to normally excrete free water, most commonly because of persistent secretion of ADH. Urinary sodium concentration helps in differentiating between euvolaemic and

hypovolaemic hyponatraemia: a level greater than 40 mmol/L indicates euvolaemia. Causes of hypovolaemic hyponatraemia are gastrointestinal fluid loss, salt-losing nephritis, Addison's disease and salt losing forms of congenital adrenal hyperplasia.⁶ Euvolaemic hyponatraemia is responsible for 60% of all types of chronic hyponatraemia, and SIADH is the most common cause; other causes include hypothyroidism, glucocorticoid deficiency and inappropriate iv therapy.⁶ Causes of hypervolaemic hyponatraemia include heart failure, renal failure and nephrotic syndrome.⁶

There are four subtypes of SIADH, according to ADH secretion. Type A is characterised by high erratic fluctuations in ADH that are not physiologically affected by plasma osmolality. Type B is characterised by a modest and constant leak of ADH. Type C is a rare condition called reset osmostat, which is characterised by a decrease in the plasma osmolality threshold for excretion of ADH, with the plasma sodium concentration adjusted to a lower level, typically between 125 and 135 mmol/L. The diagnosis of this condition is important, as correction of hyponatraemia is unnecessary and ineffective since an increase in plasma sodium and osmolality stimulates the secretion of ADH. Type D is characterised by normal osmoregulation of ADH; these cases seem to be related to mutations in the V2R receptor that lead to constitutive activation of the receptor in the absence of ADH.⁷

In patients with SIADH, the corner stone of diagnosis is hyponatraemia in a state of euvolaemia, in which the rate of sodium excretion is determined by sodium intake.² SIADH is a disorder where the excretion of water is partially limited by an increased secretion of ADH in the absence of an osmotic or hypovolaemic stimulus.^{1 4 7} A child with SIADH is unable to excrete free water, resulting in dilution of serum sodium and hyponatraemia.^{1 7} The degree of water retention leading to hyponatraemia is determined by the amount of liquid ingested and by the severity of the limitation of water excretion.^{7 11}

Hyponatraemia has long-term consequences. Total body sodium is a permissive growth factor and chronic sodium deficiency is associated with poor skeletal and tissue growth, and adverse neurodevelopmental outcome.⁸ Preterm neonates on sodium restricted diets have an increased incidence of hyponatraemia with impaired neonatal growth and worse neurodevelopment at 10–13 years of age. Hyponatraemia has also been found to be a significant risk factor for sensorineural hearing loss, cerebral palsy, intracranial haemorrhage and increased mortality rates in neonates who suffered perinatal birth asphyxia. The degree of hyponatraemia in

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preterm neonates is predictive of both increased salt appetite and dietary sodium intake in adolescence, resulting in hyponatraemic neonates weighing 30% more than their peers.⁹

We report a case of a newborn with persistent asymptomatic hyponatraemia, secondary to a rare subtype of SIADH, reset osmostat.

CASE PRESENTATION

We present a case of a preterm newborn boy of Romani ethnicity (with parental consanguinity), the fifth birth, from a high-risk pregnancy due to maternal diabetes mellitus type 2 on insulin therapy. Prenatal ultrasound showed, at 22 weeks of gestation, a cleft lip and palate, flattening of the mid-face and an abnormal corpus callosum. Karyotype of the amniotic fluid was normal (46, XY). There was no history of drug intake or exposure to known teratogens during pregnancy. Serological maternal investigation was normal.

The baby was born after an induced labour, from vacuum-assisted vaginal delivery, at 36 weeks gestation, due to severe oligohydramnios. Apgar scores were 9 and 10 at 1 and 5 min, respectively. Weight, length and head circumference were adequate for gestational age, 3460 g (P50–75), 50.5 cm (P50–75) and 33.5 cm (P25), respectively. On physical examination the child had a cleft lip and palate with nasal dysplasia. To investigate associated congenital malformations an echocardiogram and cranial ultrasound were performed. Echocardiogram revealed a patent ductus arteriosus and an inter-atrial communication, and cranial ultrasound was normal.

On the fourth day of life, the baby was admitted to the neonatal intensive-care unit (NICU) for intensive phototherapy, because of hyperbilirubinaemia (344.1 $\mu\text{mol/L}$). Owing to his good response to treatment, he was discharged 24 h after to the postnatal ward, alongside his mother. On the seventh day of life, his jaundice worsened again, associated with weight loss of 5% of birth weight, with no other clinical abnormalities such as lethargy, irritability, vomiting or convulsions. On physical examination, he had no signs of dehydration; the abdomen had no organomegaly; his genitalia were normal and had mild axial hypotonia. Analytical investigation revealed serum sodium of 124 mmol/L and the baby was admitted to the NICU for treatment and diagnosis.

INVESTIGATIONS

The subsequent investigation showed: hyponatraemia (131 mmol/L), hyperkalaemia (5.5 mmol/L), low plasma osmolality (258 mOsm/kg), high urine osmolality (165 mOsm/kg), high urinary sodium (73 mmol/L) and a normal renin value (5.9 $\mu\text{UI/mL}$). The diagnostic criteria of reset osmostat include normal renal, adrenal and thyroid function. The remaining studies, which included: glucose, blood urea nitrogen, creatinine, uric acid, capillary blood gas, urinalysis and endocrinological assessment (aldosterone, thyroid-stimulating hormone, FT4, adrenocorticotrophic hormone, 17 OH-progesterone, total testosterone, androstenedione, dehydroepiandrosterone, cortisol, insulin-like growth factor-1 and insulin-like growth factor binding protein-3), were normal.

Brain MRI showed no brain malformations or changes in the morphology of the pituitary gland, the pituitary stalk or hypothalamus. Renal ultrasound was also normal. No fluid or salt overload or water deprivation tests were performed, due to the risks associated with this age group.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of hyponatraemia includes causes of:

- Hypovolaemic hyponatraemia: salt-wasting nephropathy, adrenal insufficiency, proximal renal tubular acidosis, metabolic alkalosis, or pseudohypoaldosteronism.
- Euvolaemic hyponatraemia: SIADH, glucocorticoid deficiency, hypothyroidism, or water intoxication.
- Hypervolaemic hyponatraemia: congestive heart failure, hepatic failure, renal failure, nephrotic syndrome.

TREATMENT

Oral sodium supplementation was started and progressively increased until a maximum dose of 15 mmol/kg/day. Therapy with fludrocortisone (0.05 mg/day) was performed while hypoaldosteronism was not excluded.

OUTCOME AND FOLLOW-UP

Despite oral supplementation with sodium and treatment with fludrocortisone, the serum sodium level remained between 124 and 130 mmol/L, and stayed in this range even after discontinuation of this therapy. During sodium supplementation, urinary sodium excretion ranged between 9 and 182 mmol/L, and urinary osmolality between 135 and 449 mOsm/kg. Diuresis was 3.5 ml/kg/h.

Complementary feeding with a nasogastric tube was initially necessary, with subsequent feeding autonomy and good weight progression. The baby was discharged home from the NICU at 33 days of life, clinically well, with a sodium level of 126 mmol/L. He underwent an uneventful surgical correction of cleft lip and palate at 3 months of age. Evaluation at 16 months of age showed mild psychomotor development delay. Analytical evaluation showed serum sodium level of 130 mmol/L, potassium 4.35 mmol/L, serum osmolality 267 mOsm/kg and urinary sodium 125 mmol/L. Cardiac re-evaluation showed a small patent ductus arteriosus and a therapeutic catheterisation for closure of the intra-atrial communication was performed at the age of 19 months. Ponderal and statural growth with progressive deceleration: weight from P50–75 at birth to <P2 at 19 months and length from P50–75 to P10, respectively. The child was followed in the paediatric clinic in his hometown hospital and in paediatric endocrinology, cardiology and genetic clinics, but failed all his appointments.

DISCUSSION

SIADH is one of the most common causes of hyponatraemia and hypoosmolar hyponatraemia, with high levels of sodium in urine, and is the most common cause of euvolaemic hyponatraemia.^{3–5} SIADH is caused by elevated ADH secretion, which induces water retention and hyponatraemia, since sodium homeostasis is intact. The volume expansion activates secondary natriuretic mechanisms (renin-angiotensin-aldosterone or atrial natriuretic peptide), resulting in loss of sodium and water, and in restoration of euvolaemia.¹⁰ Patients with SIADH are euvolaemic and urinary sodium excretion is equal to dietary sodium intake.^{2–10}

The diagnostic criteria for SIADH have been described by Schwartz and Bartter in 1967 and are: hyponatraemia with plasma hyposmolality; high urinary osmolality relative to plasma osmolality; increased urinary sodium excretion; absence of oedema or volume depletion, and normal renal and adrenal functions.⁶ Our patient meets all the above.

Reset osmostat should be suspected in a patient with SIADH with moderate hyponatraemia (usually between 125 and 135 mmol/L) that remains stable despite variations in water and sodium intake. The diagnostic criteria of reset osmostat are: euvolaemia; normal renal, adrenal and thyroid function; ability

to concentrate urine; ability to excrete fluid overload, and hyponatraemia despite salt overload.^{10 11}

In the case described, endocrinological investigation excluded hypothyroidism and adrenal causes, and renal function was normal, as was urinalysis. The ability to concentrate urine and to excrete fluid overload was not demonstrated because of the associated risks of water deprivation and overload tests in a newborn. The salt overload was not assessed by a salt overload test, however, with an oral sodium intake of 15 mmol/kg/day the child remained hyponatraemic and urinary sodium excretion rose to 182 mmol/L, confirming adequate sodium metabolism.

Reset osmostat diagnosis is important, as patients do not require correction of hyponatraemia, since they are asymptomatic and have stable serum sodium levels.¹⁰ Cases of reset osmostat described in the literature are rare. The majority have associated midline defects, such as cleft lip and palate, agenesis of the corpus callosum and hypothalamic cyst.^{5 11} The cause and long-term outcome of reset osmostat are not known, but the presence of a midline craniofacial defect may be a significant

clue to the diagnosis.⁵ As in the case described, most patients with reset osmostat were asymptomatic. In this newborn, hyponatraemia was identified incidentally in the context of jaundice and weight loss. Natraemia correction is not necessary in these patients.⁵ In this case, growth retardation may be due to chronic hyponatraemia. The psychomotor development is slightly compromised, but there has been progress. Since there are few reported cases, the psychomotor delay, which must be confirmed in the future, may be an aspect to consider in reset osmostat, even in the absence of brain abnormalities.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Reset osmostat, a subtype of syndrome of inappropriate antidiuretic hormone secretion, is a rare cause of hyponatraemia, which is characterised by a decrease of the threshold of plasma osmolality for the excretion of antidiuretic hormone.
- ▶ The diagnosis of reset osmostat must be considered in a child with moderate euvoaemic hyponatraemia, typically between 125 and 135 mmol/L, stable in spite of changes in sodium or water intake, with a normal renal, thyroid and adrenal function.
- ▶ A midline craniofacial defect might be a clue to the diagnosis of reset osmostat.
- ▶ Natraemia correction is not necessary in reset osmostat.

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