CASE REPORT

Ocular and skin manifestations in systemic pseudohypoaldosteronism

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SUMMARY

Pseudohypoaldosteronism type-1 is a rare disorder characterised by end-organ resistance to aldosterone resulting in salt-losing crisis with hyponatraemic dehydration, hyperkalaemia and metabolic acidosis. We report two siblings with pseudohypoaldosteronism type-1 who presented early in neonatal period with hyponatraemia, severe hyperkalaemia and metabolic acidosis. Both babies had miliaria like skin rash which flared up during episodes of hyperkalaemia and hyponatraemia. They had visible dilated meibomian glands from which a white material was protruding. The clinical presentation of pseudohypoaldosteronism type-1 mimics congenital adrenal hyperplasia. As there is often a delay in obtaining hormonal assay results, the eye and skin manifestations may give an important diagnostic clue which in turn will influence management.

BACKGROUND

Pseudohypoaldosteronism type-1 (PHA-1) is a rare syndrome of mineralocorticoid resistance which mainly presents during the neonatal period. There are two primary genetic forms: a renal form of autosomal dominant inheritance due to a mutation of the mineralocorticoid receptor (MR) gene and a severe systemic one of autosomal recessive inheritance due to a mutation of the epithelial sodium channel (ENaC) gene. There is also a secondary form that is usually associated with urinary tract malformation and acute pyelonephritis.¹

CASE PRESENTATION**Case 1**

A male baby was delivered by vacuum-assisted vaginal delivery after full term pregnancy to a 24-year-old primigravida mother. Antenatal period was uneventful. The birth weight was 3880 g, and Apgar score was 8 and 9 at 1 and 5 min, respectively. Parents are second cousins. There was no family history of neonatal deaths, seizures or inborn error of metabolism.

He developed jaundice at 36 h of age which was treated with phototherapy for 3 days. There was no evidence of haemolysis or sepsis. Systemic examination was normal at birth. On day 4, he developed maculopapular erythematous rash over the face and chest, and white projections over the eyelid margins.

On day 6, he became unwell. He was lethargic, had poor suckling, weak neonatal reflexes and delayed capillary refill time. Previously described rash flared up at the same time. He was ventilated for 36 h because of poor respiratory effort. Full septic

screen was performed and antibiotics were given for 5 days till cultures of cerebrospinal fluid, blood and urine were confirmed to be sterile. Blood chemistry revealed hyponatraemia 120 mmol/L (reference 133–146), hyperkalaemia 9.3 mmol/L (reference 3.7–5.9), chloride 86 mmol/L (reference 98–113), blood urea nitrogen 12 mmol/L (reference 1.4–4.3), creatinine 70 μ mol/L (reference 27–88) and calcium 2.3 mmol/L (reference 1.9–2.6). Blood gases analysis showed pH 7.34, partial pressure of carbon dioxide 3.99, partial pressure of oxygen 7.38, bicarbonate (HCO_3^-) 15.7 and base excess -10.1 . Additional evaluation was remarkable for urine sodium 151 mmol/L, urine potassium 17 mmol/L and urine chloride 123 mmol/L. His ECG showed peaked T waves, and broad QRS complexes. Renal ultrasound was normal. Hyperkalaemia was managed with intravenous calcium gluconate, sodium HCO_3^- and glucose-insulin infusion. Considering the possibility of congenital adrenal hyperplasia (CAH), hormonal study was collected. He was treated with intravenous hydrocortisone and oral fludrocortisone. He received normal saline boluses and maintenance fluids. Oral feeding was discontinued.

As the patient's clinical condition and electrolyte values improved, oral feeding was established and gradually increased. Intravenous fluids were decreased accordingly. By day 12, he was on full oral feeds with no intravenous fluids. On day 13, he developed hyponatraemia, hyperkalaemia and metabolic acidosis again with flaring up of the rash. Hyperkalaemia and hyponatraemia were managed as before together with sodium polystyrene sulfonate. Hormonal assays which were sent initially revealed cortisol 1213 nmol/L (reference 64–327), 17-hydroxyprogesterone 3.03 nmol/L (reference 0.45–3), aldosterone 3600 pg/mL (reference 300–1900) and renin 183.2 pg/mL (reference 73 pg/mL). In view of high-serum aldosterone and renin associated with high cortisol, and normal 17-hydroxyprogesterone; diagnosis of PHA-1 was considered. As the baby had no urinary tract infection and no evidence of obstructive uropathy, secondary PHA-1 was excluded. Hydrocortisone was tapered gradually. He was started on high-oral sodium intake (17 mmol/kg/day), sodium polystyrene sulfonate powder (with formula preparation during the first month then orally) and fludrocortisone 0.3 mg/day.

The infant had recurrent electrolyte problems precipitated by respiratory infections and vomiting, requiring repeated hospitalisation. At 1 year of age, he has normal growth parameters (weight: 10.5 kg (>50%), height: 75 cm (50%)) and normal developmental milestones.

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Figure 1 (A) Skin rash on day 2 with normal electrolytes, (B) flaring up of rash on day 3 with hyponatraemia and hyperkalaemia.

Case 2

After 13 months, the same mother gave birth to a 4032 g, full term female baby, with normal Apgar score. She was kept on breast feeding with close observation and regular check-up of serum electrolytes.

She developed similar manifestations like her brother including maculopapular erythematous rash over the face and trunk on day 2 of life (figure 1A) and white projections over the margin of eyelids (figure 2). At the age of 3 days the rash flared up (figure 1B), as she developed hyponatraemia (127 mmol/L), hyperkalaemia (8 mmol/L), metabolic acidosis, elevated urinary sodium (126 mmol/L) and low-urinary potassium (8.5 mmol/L). Renal ultrasound was normal. Hormonal study confirmed the diagnosis of PHA-1.

DISCUSSION

CAH is the commonest cause of severe dehydration, hyponatraemia and hyperkalaemia in neonates. Dehydration and electrolyte abnormalities of CAH respond dramatically to steroid replacement therapy, often making a clinical diagnosis even before

17-hydroxyprogesterone result is available. Poor response to steroids should alert the physician to a possibility of end-organ resistance to aldosterone. In case 1, the pattern of serum electrolytes at presentation raised the possibility of salt-losing forms of CAH which were ultimately excluded by hormonal evaluation. Dehydration and hyponatraemia were corrected by intravenous fluid. Sodium concentration was increased in intravenous fluid to provide sodium intake up to 25 mmol/kg/day. The good response and initial improvement could be explained by the high-intravenous sodium intake with no potassium which the baby received during the initial presentation. The deterioration and second episode of hyponatraemia and hyperkalaemia could be attributed to the decline of sodium and increased potassium intake while shifting the baby from intravenous fluid to oral formula without extra sodium supplementation.

PHA-1 occurs in two forms—renal and systemic. The two forms are genetically different and vary considerably in clinical severity and phenotypic expression. Renal form is autosomal dominantly inherited and is due to mutations in the NR3C2 gene that encodes the MR. This mineralocorticoid unresponsiveness is isolated to the kidney leading commonly to a mild-to-moderate loss of sodium that responds well to sodium supplementation and generally improves spontaneously with age, possibly because of a maturation in the proximal reabsorption of sodium.²

Systemic PHA-1 is inherited as autosomal recessive trait due to mutations of ENaC subunit genes SCNN1A, SCNN1B and SCNN1G. It presents early with severe dehydration, profound electrolyte disturbances. Systemic PHA-1 is characterised by aldosterone resistance and salt wasting in kidneys, colon, saliva and sweat. In general, it carries bad prognosis and patients suffer from recurrent life-threatening episodes of salt loss.³

Miliaria rubra-like cutaneous eruptions present in our patients, which were typically aggravated at the time of salt-losing crisis, are a characteristic feature of systemic PHA-1 and result from the blockage and inflammation of exocrine sweat glands due to high-sweat sodium concentration.⁴

The projections over the eyelids margins in our two patients represented enlarged meibomian glands with rubbery white material extending from it. Our patients demonstrated meibomian glands dysfunction which has been described in few cases of systemic PHA-1.⁵

The presence of elevated aldosterone, raised plasma renin activity, increased urine sodium and decreased urine potassium in the presence of hyponatraemia and hyperkalaemia along with the absence of urinary tract anomalies and infection established the diagnosis of primary PHA-1 in our patients. Although genetic study was declined by parents, early severe presentation associated with ocular and skin manifestations lead to the diagnosis of systemic PHA-1.

Figure 2 Dilated meibomian glands.

CONCLUSION

Biochemical manifestations of CAH and PHA-1 may initially be indistinguishable. There is often a delay in obtaining hormonal assay results. The eye and skin manifestations may give an important diagnostic clue which in turn will influence management and prevent recurrence of severe electrolytes disturbances.

Learning points

- ▶ Biochemical manifestations of congenital adrenal hyperplasia and pseudohypoaldosteronism type-1 may initially be indistinguishable.
- ▶ There is often a delay in obtaining hormonal assay results.
- ▶ The eye and skin manifestations may give an important diagnostic clue which in turn will influence management and prevent recurrence of severe electrolytes disturbances.

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Competing interests None.

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