Case Report

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Paediatrics Section

Cutaneous and Ocular Findings in Systemic Pseudohypoaldosteronism I: Early Clinical Pointers

NEHA AGARWAL[1], ALPA GUPTA[2], RENU DHASMANA[3], ASHIMA MEHTA[4], NITIKA AGRAWAL[5]

ABSTRACT

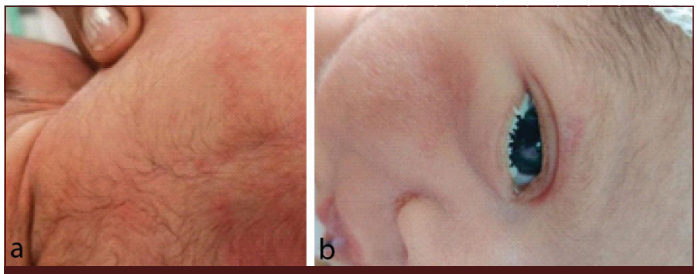
Systemic Pseudohypoaldosteronism type I (PHA I) is an uncommon and an often missed cause of salt wasting crisis in the neonatal period. In addition to dyselectrolytemia, cutaneous findings in the form of miliaria rubra, and ophthalmic findings secondary to abnormal sebum accumulation in the eye may also be present in patients with systemic PHA I. This article is about systemic PHA in a female neonate (birth weight 2.040 Kg, delivered at 34 weeks of gestation), who presented with life-threatening hyperkalemia, along with characteristic cutaneous and ophthalmic manifestations. Normal female genitalia, history of hyperkalemia with similar cutaneous and ophthalmic manifestations leading to death in the previous sibling, provided clue to the diagnosis. All relevant investigations were performed. Blood chemistry in this neonate revealed hyponatremia and hyperkalemia with metabolic acidosis. Plasma renin and serum aldosterone levels were reportedly high. Neonate was followed and electrolytes were monitored twice weekly on outpatient basis. But the life-threatening hyperkalemia led to multiple episodes of vomiting and, refusal to feed for few hours and the baby succumbed to death at age of 2.5 months. Hence, it was concluded that systemic PHA I should be considered in the differential diagnosis of neonates presenting with hyponatremic dehydration, hyperkalemia, and metabolic acidosis. Timely and appropriate electrolyte correction is pivotal for favourable outcome.

Keywords: Hyperkalemia, Neonate, Salt wasting crisis

CASE REPORT

A female neonate (birth weight 2040 g), born to non consanguineous parents, was delivered by Caesarean section at 34 weeks of gestation. The antenatal period was apparently uneventful. Genitalia was normal and no obvious dysmorphism was noted.

She was admitted in the neonatal Intensive Care Unit (ICU) for prematurity and low birth weight. She was asymptomatic at day 1 of life. On day 2 of life, erythematous maculo-papular skin lesions, characteristic of miliaria rubra developed over the back [Table/Fig-1a]. She also developed white thread like discharge from bilateral eyes. Ophthalmologic examination was suggestive of prominent meibomian glands with visible white projections over the superior and inferior lid margins [Table/Fig-1b]. Bilateral eye swab was collected for culture and sensitivity, which was reported to be sterile.



[Table/Fig-1]: a) Miliaria rubra; b) Thready white discharge and prominent meibomian glands.

Further evaluation revealed history of unexplained death in a male sibling, at around 18 days of life (delivered in the same institute). Record analysis of the sibling was suggestive of hyponatremia, hyperkalemia with metabolic acidosis during the course of hospitalisation. A provisional diagnosis of Congenital Adrenal Hyperplasia (CAH) was kept. However, the serum Adrenocorticotropic Hormone (ACTH) and 17-Hydroxyprogesterone (OHP) was reportedly normal. Moreover, there was a similar history of miliaria rubra-like rash and bilateral white thread like discharge from bilateral eyes. In view of these clinical findings and with a positive family history, a possibility of PHA was kept. Blood chemistry revealed eunatremia {Sodium (Na) 136 mEq/L} and hyperkalemia {Potassium (K) 6.97 mEq/L}.

At day 4 of life, baby appeared lethargic and developed refusal to feed. Evaluation for sepsis was negative. Repeat laboratory investigations were suggestive of hyponatremia (Na=129.1 mEq/L) and hyperkalemia (K=7.33 mEq/L) with metabolic acidosis {pH (Concentration of Hydrogen)=7.21, bicarbonate=12.5 mEq/L, Base excess=-10.5}. Subsequent evaluation showed urine sodium of 72 mmol/L, and urine potassium of 9 mmol/l. Plasma renin and serum aldosterone levels were reportedly high [Table/Fig-2]. Further, urine routine microscopy and renal ultrasound was done to rule out other causes of similar electrolyte disturbances, which were normal. A sweat chloride test could not be performed.

Parameters	Observed value	Reference range
ACTH* (pg/mL)	28	<46.00
17-hydroxy progesterone (ng/mL)	1.2	0.14-2.35
Plasma Renin (mcgIU/mL)	267.20	2.8-39.90
Plasma Aldosterone (ng/dL)	1065	2.52-39.2

[Table/Fig-2]: Laboratory parameters.
*ACTH: Adrenocorticotropic hormone

Based on the clinical and laboratory findings, a possibility of systemic PHA I was kept. This was further confirmed on genetic analysis, which showed a known pathogenic homozygous mutation in Sodium Channel Epithelial 1 Subunit Beta (SCNN1B) gene. Meanwhile, electrolyte disturbances were managed with saline boluses, potassium free fluid with additional sodium supplementation and insulin drip with added dextrose.

In view of rapidly rising potassium levels, exchange resin (calcium polystyrene sulphonate) was added at a dose of 7.5 g/kg/day, which was given orally. Serum electrolytes were regularly monitored and dose of exchange resin and sodium supplements were tailored accordingly. Nebulisation with salbutamol and insulin dextrose drip was also used intermittently. By day 20 of life, serum electrolytes reached within the normal reference ranges. At this time, baby was receiving sodium chloride (parenteral and oral)- 40 meq/kg/day, sodium bicarbonate- 3.25 meq/kg/day (oral) and exchange resin (calcium polystyrene sulphonate)- 7.5 g/kg/day.

Subsequently, on day 24 of life, the baby developed respiratory distress in the form of tachypnoea and desaturation on room air. Cardiac examination was apparently normal. Chest auscultation was suggestive of bilateral crepitations and wheezing. Sepsis screen was normal. Nebulisation with distilled water was initiated, in addition to salbutamol and N-acetyl cysteine. Conservative management was continued, gradually oxygen demand and respiratory distress decreased. Baby was successfully discharged on day 45 of life on sodium chloride (oral)- 40 meq/kg/day, sodium bicarbonate- 3.25 meq/kg/day and exchange resin (calcium polystyrene sulphonate)- 7.5 g/kg/day.

Baby was followed and electrolytes were monitored twice weekly on outpatient basis. Dose of sodium supplements and calcium polystyrene sulphonate was adjusted according to the electrolyte levels. Unfortunately, despite good medicine compliance, baby succumbed to death at the age of 2.5 months due to life-threatening hyperkalemia (K-11.52 mEq/L). This was preceded by multiple episodes of vomiting and, refusal to feed for few hours before presentation to the Emergency Department.

DISCUSSION

Salt wasting crisis in paediatric practice is a medical emergency requiring prompt identification of the aetiology and immediate intervention for intact survival. The most common cause of salt wasting during the neonatal period is CAH, characterised by low cortisol and/or aldosterone levels with or without atypical genitalia. Other common aetiologies include renal failure recognised by raised creatinine levels and aldosterone synthase defect which will have low aldosterone levels with normal genitalia. An uncommon and often a missed cause of salt wasting in the neonatal period is PHA, characterised by high aldosterone and high renin levels [1].

The index case presented with lethargy and poor feeding along with cutaneous manifestations of miliaria rubra and presence of dilated meibomian glands with white secretions. Normal female genitalia, history of salt wasting crisis along with similar cutaneous and ophthalmologic manifestations in the previous sibling, provided clue to the diagnosis of systemic PHA I. PHA I is a genetic condition characterised by hyponatremia, hyperkalemia and metabolic acidosis, in the presence of raised aldosterone level [2]. Two forms of disease are known:

(a) Autosomal recessive (systemic PHA I) which is a severe form of the disease and is caused by loss-of-function mutations in genes encoding α (SCNN1A), β (SCNN1B), or γ (SCNN1G) subunits of the amiloride-sensitive epithelial sodium channel [2];

(b) Autosomal dominant (renal PHA I), caused by mutation in NR3C2 (Nuclear Receptor Subfamily 3 Group C Member 2) gene [3]. This form is relatively milder. It is important to differentiate patients with systemic PHA I from those with renal PHA I as these patients present with salt wasting crisis and severely decompensate without treatment [4,5].

Systemic PHA I usually present with characteristic cutaneous and ocular features [6], which was also present in the index case. Defect in sodium channels leads to abnormal sebum accumulation in meibomian glands creating an appearance of white discharge from eyelid [7]. Cause of miliaria rubra like rash in systemic PHA I is hypothesised to be due to damage to eccrine ducts caused by increased concentration of sodium chloride in sweat, because of defective Epithelial Sodium Channel (ENaC). This also explains its exaggeration during a salt losing crisis [6,8]. Other studies have found certain features to be associated with PHA I and defective ENaC expression in other tissues. These include cholelithiasis [9], polyhydramnios [10], and characteristic skin changes [6].

Stabilisation of the initial electrolyte imbalance and giving correction of dehydration is the first step towards management of PHA I. Sodium supplementation to rectify the sodium deficit, is given in the form of sodium bicarbonate, sodium chloride or sodium citrate. Correction of hyperkalemia is achieved through potassium exchange resins and other antihyperkalemic measures including calcium gluconate, sodium bicarbonate, intravenous or nebulised salbutamol, and/or insulin dextrose infusion. Regular monitoring of serum electrolytes and tailoring treatment accordingly is crucial in the management of infants with PHA I. Indomethacin, thiazide diuretics and carbenoxolone therapies are in trial [11]. Gastrostomy can be done for babies with systemic PHA I with poor oral tolerance for large amount of fluid, sodium supplementation and potassium binders [11].

Moreover, patients with systemic PHA I, typically demonstrate recurrent coughing and wheezing without identifiable bacterial airway infection which is postulated to be because of reduced liquid absorption which is sodium dependent, due to inactivation of ENaC the pulmonary epithelium [4]. Al Homyani DK et al., speculates respiratory distress caused due to excessive volume of surface liquid that narrows airway lumens and dilutes surface-active materials that stabilise small airways predisposing the patients to wheezing and airway infections early in life [12]. Amin N et al., described chronic pulmonary syndrome in their study [4]. Similarly, respiratory distress and oxygen dependence was present in the index case without an identifiable cause. Frequent nebulisations with bronchodilators and normal saline was needed to allay tachypnoea and wheezing. Chronic pulmonary syndrome requires symptomatic management. Systemic PHA I carries a very poor prognosis and even with treatment children succumb to death, usually due to hyperkalemia induced arrhythmias. Welzel M et al., studied PHA type 1 in 7 patients. All had salt wasting crisis along recurrent pulmonary infections and two cases died in early infancy due to dyselectrolytemia [13]. Similarly, Manipriya R et al., also reported two cases of systemic type PHA, who were managed with fludrocortisone, sodium supplementation and antihyperkalemic measures. Both of them succumbed to death, out of which one had ventricular arrythmia due to severe hypercalcaemia [9].

CONCLUSION(S)

To conclude, although unusual, systemic PHA I should be considered in the differential diagnosis of neonates presenting with hyponatremic dehydration, hyperkalemia, and metabolic acidosis. This case highlights the importance of dermal and ophthalmic findings in providing clue to the diagnosis of systemic PHA I.

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PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Paediatrics, Himalayan Institute of Medical Sciences, Rishikesh, Uttarakhand, India.
2. Professor and Head, Department of Paediatrics, Himalayan Institute of Medical Sciences, Rishikesh, Uttarakhand, India.
3. Professor and Head, Department of Ophthalmology, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India.
4. Junior Resident, Department of Paediatrics, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India.
5. Associate Professor, Department of Paediatrics, Himalayan Institute of Medical Sciences, Rishikesh, Uttarakhand, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Nitika Agrawal,
Associate Professor, Department of Paediatrics, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Doiwala, Rishikesh, Uttarakhand, India.
E-mail: nitikaagrawal@srhu.edu.in

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