Pseudohypoaldosteronism Type 1: Management Issues

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Received: July 19, 2012;
Initial review: September 06, 2012;
Accepted: September 21, 2012.

We report a newborn girl with life-threatening hyperkalemia and salt wasting crisis due to severe autosomal recessive multiple target organ dysfunction pseudohypoaldosteronism type 1 (MTOD PHA1). She was aggressively managed with intravenous fluids, potassium-lowering agents, high-dose sodium chloride supplementation and peritoneal dialysis. Genetic analysis revealed a homozygous mutation of the α- ENaC (epithelial Na^+ channel) gene. She had a stormy clinical course with refractory hyperkalemia and prolonged hospitalization. Eventually, she succumbed to pneumonia and septicemia at 4 months of age. This is probably the first case of PHA1 confirmed by genetic analysis from India.

Key words: *Pseudohypoaldosteronism Type I, Management, Hyperkalemia.*

Aldosterone is central to fluid and sodium-potassium balance in the body through its effects in the distal tubules of the kidney. The hormone acts by binding to the mineralocorticoid receptor (MR) leading to the induction of different signaling pathways and transcriptional cascades modulating the activity of major structural components of ion transport, including the amiloride-sensitive epithelial Na^+ channels (ENaC) [1]. The ENaC is a heterotrimeric protein complex consisting of α, β and γ subunits and is widely distributed in other organs as well including distal colon, salivary and sweat glands [1].

Pseudohypoaldosteronism type 1 (PHA1) is characterized by end-organ resistance to aldosterone resulting in salt-losing crisis with hyponatremic dehydration, hyperkalemia and metabolic acidosis [2]. There are 2 varieties of PHA-1: the autosomal dominant variety and autosomal recessive. The former is characterized by *NR3C2* gene mutations affecting the MR and hence resistance is restricted to the kidney. It has a milder clinical course and generally resolves spontaneously in childhood. The autosomal recessive (AR) variety of PHAI results from homozygous or compound heterozygous mutations in the *SCNN1A, SCNN1B or SCNN1G* genes coding for the subunits of ENaC [3]. This is associated with generalized end-organ resistance or multiple target organ dysfunction (MTOD) involving a more severe clinical phenotype and requires lifelong sodium supplementation [2]. We present a newborn with salt-losing crisis and life-threatening hyperkalemia.

CASE REPORT

A 10-day-old girl was brought to the emergency department with lethargy and refusal to feed for one day. There was no history of fever, diarrhea, seizures or respiratory distress and her urine output was adequate. She was born at term (birth weight 2.9 kg) to a gravida 2 para 1 mother with third degree parental consanguinity. The mother had history of polyhydramnios in the present pregnancy. The 4-year-old elder male sibling was healthy. On examination, the heart rate was 178/minute, respiratory rate 38/minute, the peripheral pulses were low volume with a prolonged capillary refill time (4 seconds). Her weight was 2.5 kg at presentation. There was no evidence of virilization. The rest of the general and physical examination was normal. Investigations revealed hemoglobin 15.7 g/dL, total leucocyte count 12.1 x 10^9/L, platelets 2.56 x 10^9/L, blood glucose 87 mg/dL, serum sodium 124 mEq/L, serum potassium 10.3 mEq/L, blood urea 84 mg/dL (which normalized later suggesting prerenal azotemia) and creatinine 0.5 mg/dL. Arterial blood gas revealed metabolic acidosis (pH 7.15, HCO3 12.7 mmol/L). Blood and urine cultures were sterile and lumbar puncture was normal. Chest *X*-ray and ultrasound abdomen were normal. Shock was managed with oxygen, fluid boluses and vasopressor support. Cardioprotective and potassium lowering measures were immediately started including intravenous calcium gluconate, sodium bicarbonate, glucose-insulin drip, salbutamol nebulisation and potassium-exchange resins (sodium polystyrene sulphonate). She developed ventricular tachycardia and respiratory failure for which

she was intubated and peritoneal dialysis (PD) was started. The urinary electrolytes revealed sodium 97 mEq/L and potassium 18 mEq/L. The trans-tubular potassium gradient (TTKG) at the time of hyperkalemia was 2, indicating mineralocorticoid resistance. Investigations revealed high serum aldosterone 2350 pg/ml (normal 10-150 pg/mL) and direct renin 500 mU/L (normal 2.8-39.9 40 mU/L). Serum 17-alpha-hydroxy progesterone and cortisol levels were normal. An ultrasound (kidneys, pelviceal system and bladder) including Doppler scan of the renal vessels and voiding cystourethrogram were normal. A diagnosis of MTOD PHA1 was considered which was confirmed by genetic analysis which revealed a homozygous nonsense mutation c.1339dup on exon 8 of the *SCNN1A* gene causing a frameshift in the coding sequence, leading to substitution of a tyrosine at position 447 by a leucine, followed by a premature stop codon 12 amino acids downstream (p.Tyr447Leufs*13) resulting in a truncated α–ENaC. The same mutation was found in the heterozygous state in both parents. Serum electrolytes were within normal limits in the parents and sibling.

Her general condition improved and the baby was extubated. Her serum potassium returned to normal and PD was stopped. She was started on high sodium supplementation 30 mEq/kg [sodium chloride salt solution 1 g/kg and sodium bicitrate (Shohl's solution 15mL/kg)] in divided doses and discharged in a stable condition on day 37 of life on the same treatment with potassium binders and mixed feeding (breast milk and formula). She maintained normal serum electrolytes and gained adequate weight in weekly follow up visits over the next one month.

The baby was re-admitted at 2 months of age for pneumonia but no electrolyte imbalance and discharged after 5 days of intravenous antibiotics. Two weeks later, she presented with lethargy, poor feeding and erythematous papular rash all over body (***Fig.* 1**). Investigations showed hyperkalemia (serum potassium 11.4 mEq/L) and hyponatremia (serum sodium 120 mEq/L) despite oral supplements. She was again managed with potassium-lowering agents and cardio-protective measures but hyperkalemia was difficult to control and she required PD. She failed a trial of high dose fluodrocortisone (upto 1mg). High fluid rates (200 mL/kg/day) were required for preventing dehydration. Sodium supplementation up to 40 mEq/L was required to control the hyponatremia initially but later resulted in hypernatremia (serum sodium 150 mEq/L). Though, the hyperkalemia improved initially with PD, serum potassium levels began to rise once it was stopped and PD was repeated on 3 more occasions. The dose of Kayexalate was increased till tolerated (6g/kg divided 4 hourly orally and by rectal enema). Thiazide diuretic (hydrochlorothiazide 2mg/kg) was added and provided transient relief in the hyperkalemia. She developed nosocomial pneumonia during the hospital stay and subsequently required mechanical ventilation. She succumbed to her illness at 4.5 months of age despite aggressive management after more than two months of ICU stay.

DISCUSSION

The presence of hyponatremia and hyperkalemia in the presence of high aldosterone levels pointed to a diagnosis of pseudohypoaldosteronism type 1. Pseudohypoaldostenism in newborns is known to result transiently from urinary tract infection, renal dysplasia or obstructive /reflux nephropathy and should be ruled out as in our case [4]. The severe clinical presentation suggested generalized variety or MTOD PHA1 which was confirmed by genetic analysis of ENCa coding genes.

The erythematous skin rash present in our patient, which was typically aggravated at the time of salt-losing crisis, is a characteristic feature of MTOD PHA1 and results from the blockage and inflammation of exocrine sweat glands due to high sweat sodium concentration [5]. MTOD PHAI is also known to be associated with recurrent pneumonia and can have a clinical presentation similar to cystic fibrosis [6]. The defective transport of sodium in the airway lumens results in accumulation of liquid in the airways predisposing to respiratory disease.

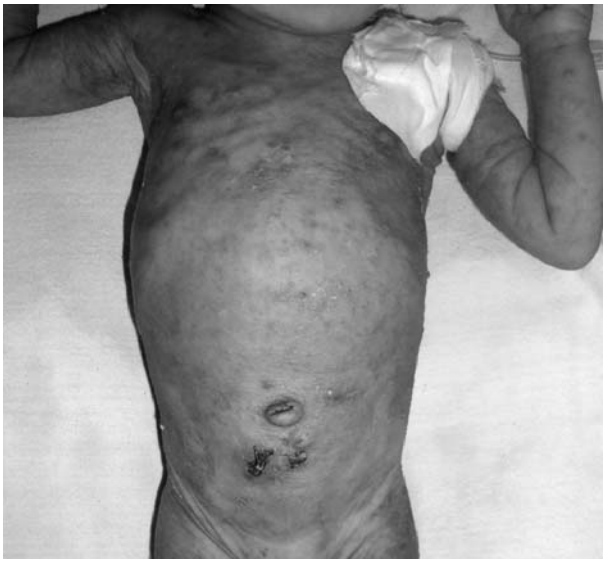

FIG.1 *Erythematous papular rash resembling Miliaria rubra on the abdomen and arms of the baby. The photograph was taken after completion of peritoneal dialysis and sutures can be seen below the umbilicus.*

Long-term survival and catch-up growth are reported in MTOD PHA1 patients treated with NaCl supplementation and potassium-exchange resins [7]. High doses of sodium (around 10 to 40 mmol/kg NaCl/day) enhance Na^+ delivery to the collecting tubules of the kidney and help increase potassium secretion [8]. Patients require low potassium diets (0.5 mmol/kg/day) which can be difficult to achieve with commercial formula milk which contains 15-20 mmol/L of potassium. Breast milk contains approximately 10 mmol/litre of potassium and is ideally suited for feeding. It is difficult to entirely eliminate potassium from the diet as the baby was on mixed feeding (both breast and formula). High doses of potassium binders (upto 8g/kg) may be required but are poorly tolerated orally and may result in rectal bleeding or prolapse when given as enemas [8]. Infants with MTOD PHAI may require gastrostomy due to poor oral tolerance of large quantities of fluid, sodium supplementation and potassium binders [7].

Acute illness can precipitate a salt wasting crisis in patients with MTOD PHA1. Emergency measures including PD are sometimes required to control severe hyperkalemia [8]. It is important to measure serum electrolytes and fluid status closely during the salt-losing crisis. Indomethacin, a potent prostaglandin inhibitor, has been observed to reduce the sodium requirement in patients with MTOD PHA1 though the mechanism of action is not known [9]. It has no affect on the amount of potassium-exchange resins required which has led some authors to use thiazides for the temporary control of hyperkalemia. Though the use of a diuretic in a salt-losing state may appear paradoxical, thiazides are postulated to help in urinary excretion of potassium by increasing the fluid flow to the distal nephron along with creating electronegativity by increasing intraluminal chloride [10]. We tried thiazide diuretics as a last resort to control the dangerous hyperkalemia in our patient and obtained only transient benefit.

In conclusion, MTOD PHA1 can lead to salt-losing crisis and life-threatening hyperkalemia in the neonatal period. Though high-dose sodium supplementation and potassium-binding resins are the standard of treatment, acute illness can precipitate severe fluid loss and dangerous hyperkalemia in these patients which can be particularly difficult to manage.

Contributors: RS, MP and SKK were involved in management of the patient. RS and MP reviewed the literature and drafted the manuscript. SK critically reviewed the manuscript. MCZ provided the molecular genetic testing for the proband. All authors approved the final version of the manuscript.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Furgeson SB, Linas S. Mechanisms of type I and type II pseudohypoaldosteronism. J Am Soc Nephrol. 2010; 21:1842-5.
2. Zennaro MC, Hubert EL, Fernandes-Rosa FL. Aldosterone resistance: structural and functional considerations and new perspectives. Mol Cell Endocrinol. 2012;350:206-15.
3. Riepe FG. Clinical and molecular features of type 1 pseudohypoaldosteronism. Horm Res. 2009;72:1-9.
4. Schweiger B, Moriarty MW, Cadnapaphornchai MA. Severe neonatal hyperkalemia due to pseudohypoaldosteronism type 1. Curr Opin Pediatr. 2009;21: 269-71.
5. Urbatsch A, Paller AS. Pustular miliaria rubra: a specific cutaneous finding of type I pseudohypoaldosteronism. Pediatr Dermatol. 2002;19:317-9.
6. Mora-Lopez F, Bernal-Quiros M, Lechuga-Sancho AM, Lechuga-Campoy JL, Hernandez-Trujillo N, Nieto A. Novel mutation in the epithelial sodium channel causing type I pseudohypoaldosteronism in a patient misdiagnosed with cystic fibrosis. Eur J Pediatr. 2012 Feb 28. [Epub ahead of print]
7. Saxena A, Hanukoglu I, Saxena D, Thompson RJ, Gardiner RM, Hanukoglu A. Novel mutations responsible for autosomal recessive multisystem pseudohypoaldosteronism and sequence variants in epithelial sodium channel alpha-, beta-, and gamma-subunit genes. J Clin Endocrinol Metab. 2002;87:3344-50.
8. Güran T, Deðirmenci S, Bulut ÝK, Say A, Riepe FG, Güran Ö. Critical points in the management of pseudohypoaldosteronism type 1. J Clin Res Pediatr Endocrinol. 2011;3:98-100.
9. Shalev H, Ohali M, Abramson O. Nephrocalcinosis in pseudohypoaldosteronism and the effect of indomethacin therapy.J Pediatr. 1994;125:246-8.
10. Stone RC, Vale P, Rosa FC. Effect of hydrochlorothiazide in pseudohypoaldosteronism with hypercalciuria and severe hyperkalemia. Pediatr Nephrol. 1996;10:501-3.