Successful Management of Systemic Pseudohypoaldosteronism Type 1 in an Infant

Pseudohypoaldosteronism (PHA) type 1 is characterized by end organ resistance to the action of mineralocorticoids and manifests as neonatal salt wasting [1]. The autosomal dominant and less severe form, also known as renal PHA type 1 (PHA 1a) is caused by mutation in mineralocorticoid receptor (MR) in the kidney, with isolated renal salt wasting. Mutations in any of the three subunits (alpha, beta or gamma) of the epithelial sodium channel (ENaC) results in the autosomal recessive systemic PHA type 1 (PHA 1b). This form is characterized by sodium wasting in the kidneys, lungs, colon, sweat and saliva. In contrast to the renal form, patients have recurrent respiratory infections and a more severe disease that requires lifelong therapy [2,3]. PHA type 2 (Gordon syndrome) is a rare renal tubular defect that results from mutation in WNK1 or 4, and is characterized by hypertension and hyperkalemic metabolic acidosis in the presence of low renin and aldosterone levels. Herein, we report a neonate with systemic PHA type 1 who was managed successfully despite a tumultuous course.

An 18-day-old baby boy was under treatment for poor weight gain, electrolyte imbalance, metabolic acidosis and sepsis. The baby was born as late preterm through non-consanguineous marriage with a birth weight of 2.5 kg and an uneventful perinatal period. He was symptomatic since day 8 of life in the form of lethargy and poor feeding. There was no history of fever, cough, respiratory distress, vomiting, loose stools, skin lesions, seizures or decreased urine output. He was managed with intravenous fluids and antibiotics, and potassium lowering measures (calcium gluconate, potassium binding resin and insulin infusion). The baby was resuscitated after an episode of cardiac arrest on day 10 of life due to severe hyperkalemia (11.6 mEq/L). Peritoneal dialysis was initiated and continued for 7 days in view of persistent hyperkalemia. He was started on hydrocortisone and fludrocortisone for suspected classical congenital adrenal hyperplasia (CAH). He was then referred to us for further management.

At presentation, he was sick looking, lethargic and had dehydration and acidotic breathing. His weight was 2.3 kg, length 52 cm and head circumference 34 cm. Genitalia was normal male phenotype and there was no hyperpigmentation. The differential diagnosis considered were late-onset neonatal sepsis, CAH with adrenal crisis, aldosterone synthase deficiency, congenital adrenal hypoplasia, and PHA. Laboratory evaluation showed metabolic acidosis, sodium 114 mEq/L, potassium 6.5 mEq/L and normal renal function tests. Blood glucose was normal and sepsis screen was negative. Ultrasonography showed normal renal and adrenal size. Hormonal profile revealed normal cortisol of 12 mg/dL, adrenocorticotrophic hormone (ACTH) level 15 pg/mL, 17-hydroxyprogesterone level 17.27 ng/mL, DHEAS (dehydroepiandrosterone sulphate) 8.28 ng/mL, and elevated aldosterone levels >100 ng/mL and elevated PRA (plasma renin activity) >500 ng/mL/h (normal range 2-35 ng/mL/h). Sweat chloride was elevated (148 mEq/L). Cultures of blood and urine were sterile. CAH was ruled out and a provisional diagnosis of systemic PHA type 1b was considered. He required normal saline boluses, 3% hypertonic saline, oxygen support, intravenous fluids (dextrose-normal saline at 1.5 times maintenance) and intravenous antibiotics. Hyperkalemia was treated with sodium bicar-bonate, insulin-dextrose drip and per rectal potassium-exchange resin (calcium polystyrene sulfo-nate). Hydro-cortisone and fludrocortisone were tapered and dis-continued. He was discharged after 2 weeks of hospital stay on sodium supplementation at a dose of 7.5 mEq/kg/day (in the form of sodium bicarbonate suspension and 3% saline administered orally), and potassium binders (4 g/kg/day).

He was re-admitted at 7 months of age with pneumonia, acute gastroenteritis and salt losing crisis. He was managed with intravenous antibiotics and supportive therapy. At discharge, sodium supplementation was increased to 10 mEq/kg/day and potassium binders to 6 g/kg/day. He subsequently had four hospitalizations with respiratory tract infections and mild metabolic decompensation in the first two years of life, requiring high doses of sodium (20-25 mEq/kg/day) and oral potassium binders (up to 2.2 g/kg/day). Clinical exome sequencing revealed two novel heterozygous variants in SCNN1A gene on chromosome 12. A heterozygous single base-pair duplication in exon 7 [c.1516dup (p.Tyr506LeufsTer13)] and heterozygous single base-pair deletion in exon 3 [c.1041del. (pCys348AlafsTer42)] were identified. Both variants were novel and as they resulted in frameshift and premature truncation of protein (alpha subunit of ENaC), they were classified as pathogenic for PHA type 1b.

At present, the child is aged 5 years and has been asymptomatic for past two years. His electrolytes have remained normal on sodium supplementation at 15-20 mEq/kg/day (table salt and oral sodium bicarbonate suspension) and potassium binder (calcium polystyrene sulphonate) 1g/kg/day. His blood pressure was normal (50th-90th centile). His anthropometry and developmental milestones are age-appropriate. Biochemical profile at last follow up was normal (sodium 136 mEq/L, potassium 4.5 mEq/L).

This presentation of systemic PHA type I can be mistaken for salt-wasting CAH. Elevated aldosterone levels and PRA with normal 17 OHP can help to establish the diagnosis of PHA. Transtubular potassium gradient (TTKG) is also useful in assessment of mineralo-corticoid bioactivity in patients with hyperkalemia [2]. Cystic fibrosis (CF) is another close mimicker, as affected children may have recurrent wheezing and chest infections with poor growth in presence of a positive sweat test [3]. Secondary PHA can occur in the setting of urinary tract infections, renal dysplasia and reflux nephropathy, mandating urine culture and renal ultrasound as a part of work-up [3,4].

The management of systemic PHA remains symptomatic. Acute management includes intravenous fluids, sodium supplementation (using hypertonic saline and/or sodium bicarbonate) and potassium lowering measures. Long-term therapy comprises of oral administration of sodium up to 10-40 mmol/kg/day (hypertonic saline, table salt, oral sodium bicarbonate), along with kayexalate and low potassium diet [5]. Low potassium diets (0.5 mmol/kg/day) can be difficult to achieve with commercial formulas which contain 15-20 mmol/L of potassium. Breast milk has low potassium content (10 mmol/L) and is ideal for feeding. High doses of potassium binders (up to 8 g/kg) are often required but are poorly tolerated orally and may result in rectal bleeding or prolapse when given as enemas [5]. Children who do not tolerate these therapies may require gastrostomy tube placement. Fludrocortisone does not have a role in management because of target organ resistance to aldosterone action. Indomethacin, a potent inhibitor of prostaglandin synthesis, has been used to reduce urine output and thereby urinary sodium losses [3]. However, its exact mechanism of action is not clear and it seems to have limited role in management of hyperkalemia [5]. Synthetic peptides, like Solnatide and its congener, AP318 are novel agents, which have been shown to directly activate the mutant ENaC and hold promise for systemic PHA [6].

There is limited data on long-term follow up in patients with systemic PHA. Most patients continue to require lifelong high dose salt supplementation [7]. The clinical course among patients is variable and associated with the type of genetic mutation [8]. Patients with compound heterozygous mutations in genes encoding ENaC had less severe disease, while those with homozygous mutations suffered frequent metabolic decompensations [4,7]. The favorable disease course in the index case could be attributed to the presence of compound heterozygous mutation; however, a longer duration of follow up would be required.

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