Pseudohypoaldosteronism Type 1: A Rare Cause of Severe Dyselectrolytemia and Cardiovascular Collapse in Neonates

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ABSTRACT
Severe hyperkalemia is a medical emergency and occurs due to a variety of underlying illnesses. We present a 7 day old neonate who presented with life threatening hyperkalemia due to pseudohypoaldosteronism type 1 (PHA1). The clinical picture resembled congenital adrenal hyperplasia (CAH). Very aggressive management including peritoneal dialysis was required to control hyperkalemia. It is important to differentiate PHA1 from CAH since the former does not respond to corticosteroid therapy and may require peritoneal dialysis for control of hyperkalemia. A discussion on the types, clinical course, and management of pseudohypoaldosteronism type 1 is presented.

Key words:
Cardiovascular collapse, hyperkalemia, neonate, pseudohypoaldosteronism

INTRODUCTION
Pseudohypoaldosteronism type 1 (PHA) is a rare inherited disorder, resulting from end organ resistance to the action of aldosterone. Children presented with failure to thrive, dehydration, and electrolyte disturbances are often misdiagnosed to have congenital adrenal hyperplasia (CAH). Our case presented dramatically with circulatory collapse and very high potassium level. However, prompt diagnosis and aggressive treatment ensured that the baby survived.

CASE REPORT
A 7 day old male child was brought to emergency department with poor feeding for 72 h and progressive lethargy for 24 h. He was the second child of non-consanguineous parents and had a birth weight of 2.7 kg. There was no family history of sudden infant deaths or children on hormone replacement. At admission, he was pale and lethargic with poor capillary refill suggestive of shock. His weight was 2.1 Kg (weight loss of 22%). There was mild icterus. The heart rate was 160/min; respiratory rate was 60/min; and mean arterial pressure was 56 mm Hg. He was resuscitated with fluid boluses and phototherapy had begun. Meanwhile, wide QRS tachycardia was noticeable in the ECG tracings. Complete blood count, sepsis work up, blood culture, serum electrolytes, and serum bilirubin were sent. The serum level of potassium was reported to be very high (8.96 mEq/L). There was hyponatremia, acidosis, and hyperbilirubinemia. The test results are summarized in Table 1.

Baby was immediately started on measures to reduce serum potassium like intravenous calcium, sodium bicarbonate, and insulin dextrose infusion. While arrangements were being made for dialysis, he developed ventricular arrhythmia and had cardiac arrest. He was revived with cardiopulmonary resuscitation and emergency peritoneal dialysis was instituted, after which the potassium level began to decline.

| Investigation            | Result (normal range) | After peritoneal dialysis |
|--------------------------|-----------------------|--------------------------|
| Serum sodium             | 122 mEq/L (135-145)   | 134 mEq/L (135-145)      |
| Serum chloride           | 97 mEq/L (96-106)     | 94 mEq/L (96-106)        |
| Serum potassium          | 8.96 mEq/L (3.5-4.5)  | 6.84 mEq/L (3.5-4.5)     |
| Serum bicarbonate        | 13 mEq/L (20-25)      | 26 mEq/L (20-25)         |
| Serum bilirubin          | 19 mg/dL (<12 mg/dL)  | 20.6 mg/dL (<12 mg/dL)   |
| Blood sugar              | 68 mg/dL              | 76 mg/dL                 |
| Blood urea               | 82 mg/dL (14-40)      | 53 mg/dL (14-40)         |
| Serum creatinine         | 0.71 mg/dL (0.3-1.0)  | 0.9 mg/dL (0.3-1.0)      |
| Urine sodium             | 140 mEq/L (20-40)     |                          |
| Urine potassium          | 5.42 mEq/L (<20)      |                          |

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We thought of adrenal insufficiency in view of hyperkalemia, hyponatremia and acidosis. Appropriate hormonal studies were sent, and the results of which are presented in Table 2. The level of 17-OHP was normal, whereas serum aldosterone and plasma renin activity were raised, thereby excluding CAH. He had high urine spot sodium and low spot abdomen excluding obstructive renal tract anomaly.

As the clinical course and investigations were suggestive of PHA type 1, hydrocortisone was stopped. Initially, the baby required parenteral rehydration, but subsequently oral rehydration with common salt (30 mEq/kg/day) added to breast milk was sufficient. Potassium level was kept under check with the use of potassium binding resin (kayexalate) in a dosage of about 2 to 3 g/kg/day, (dosage adjusted according to potassium level). Baby was discharged after his blood sodium and potassium levels were stable for 96 h without intravenous fluids, and there was consistent weight gain.

During the initial follow period, baby developed recurrent skin infections with staphylococcus aureus which were treated with oral antibiotics. Baby had mildly elevated calcium: creatinine ratio (0.8), hence hydrochlorothiazide was added in the hope that it will protect against nephrocalcinosis as well as reduce the requirement of kayexalate. During the next 5 months, his requirement of salt supplementation decreased considerably. At 6 months of age, he was on 2 gram/day of common salt (6 mEq/kg/day), apart from the sodium present in kayexalate (10 mEq/kg/day). He weighs 5.8 kg and the development mile stones were appropriate for this age. He required one more hospital admission at 3 months of age for dehydration accompanying a respiratory illness during which he needed intravenous rehydration.

**DISCUSSION**

Hyperkalemia is a well recognized cause of “near miss” sudden infant death syndrome.[1] It can also cause fatal cardiac arrhythmia.[1] Early recognition and aggressive treatment are life saving. A combination of hyperkalemia and hyponatremia with metabolic acidosis is very much suggestive of adrenal insufficiency and treatment with hydrocortisone gives excellent response. However, when the response to corticosteroids is poor, or if the clinical picture is atypical, peripheral resistance to aldosterone should always be considered.[3,4]

PHA is a condition in which there is an apparent unresponsiveness of the renal tubules to the action of aldosterone. Type 1 PHA occurs in two forms – renal and generalized.[5] The two forms are genetically different and vary considerably in clinical severity and phenotypic expression. Renal form (ad-PHA1) is autosomal dominantly inherited and is due to heterozygous mutation of mineralocorticoid receptor gene NR3C2 located at 4q31.1. Clinical spectrum may vary from asymptomatic patients diagnosable only by elevated aldosterone levels to patients with salt losing nephropathy. It usually presents with failure to thrive, vomiting, and dehydration in early infancy. Hyperkalemia is usually mild and sodium supplementation alone may suffice to counter it. This form tends to improve with age and carries good prognosis. Although it is comparatively milder, Geller et al. have suggested that ad-PHA1 could be potentially lethal in neonates.[6] Multiple type 1 PHA (ar-PHA1) is inherited as autosomal recessive trait due to mutations of epithelial sodium channel (ENaC) subunit genes SCN1A located in 12p13.31, SCN1B, and SCN1G, both situated in the locus 16p12.2.[5] It presents early with severe dehydration, profound electrolyte disturbances, and even cardiovascular collapse as in our case. Here, aldosterone resistance is not restricted to kidneys, and there can be chronic recurrent pulmonary infections and wheezing episodes, sodium loss through sweat and salivary glands, thus creating confusion with cystic fibrosis. In addition, milia rubra like skin rash, recurrent skin infections have been described. Our case had recurrent skin infection. In general, it carries bad prognosis and patients suffer from recurrent life threatening episodes of salt loss. Interestingly, a novel missense (Gly 327 Cys) in the alpha ENaC gene had been described that had only mild salt loss after infancy.[3] A transient form of PHA can sometimes occurs secondary to UTI or obstruction in urinary tract and is categorized as PHA type 3.[1,5,6]

The presence of elevated aldosterone raised plasma renin activity along with the increased urine sodium and decreased urine potassium in the presence of hyponatremia and hyperkalemia established the diagnosis of PHA type 1 in our case. Considering the presentation, severity of hyperkalemia, need for continued potassium binding resin, and skin infection, we assume that our case could be multiple type 1 PHA (ar-PHA1). Genetic analysis was not feasible in our set up.

Treatment of PHA type 1 comprises adequate rehydration, replacement of salt loss, and correction of hyperkalemia and acidosis in the acute phase. After initial stabilization,
Salt supplementation and potassium exchange resins are the mainstay of treatment. Sodium polystyrene sulfonate is the preferred potassium binding resin as it corrects sodium loss to some extent, thereby bringing down the daily salt requirement.\textsuperscript{[10]} Renal form (ad-PHA1) may need treatment until 18 to 24 months of age after which it generally improves. Multiple type 1 PHA (ar-PHA1) poses a therapeutic challenge. Treatment need to be continued lifelong. Apart from this, drugs such as indomethacin and thiazide diuretics are tried with the variable success rate.

PHA1 should be kept in mind as a rare cause of electrolyte emergency in neonates.

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