

Pseudohypoaldosteronism Type 1—An Exercise in Clinical Deduction and Critical Management

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- ▶ pseudohypoaldosteronism type 1
- ▶ hyperkalemia
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- ▶ autosomal recessive

Pseudohypoaldosteronism type 1 (PHA1) is a life-threatening disorder for two reasons, first because it causes severe hyperkalemia and second because the rarity of the disorder means that diagnosis is often delayed due to the lack of clinician familiarity with this condition. In this case report, we have described how even to an unsuspecting mind and eye, a systematic approach can lead to reversal of the severe hyperkalemia and arrive at the diagnosis of PHA1 as a cause of hyperkalemia. Long-term management can be successful only with dedicated care, and the prognosis is unfortunately worsened by the lack of availability of sodium-K resin in many countries, including India.

Introduction

Pseudohypoaldosteronism type 1 (PHA1) is a rare condition; due to its rarity, a majority of reports have been in the form of case reports or case series. What makes this entity worth reporting yet again is the lesson it gives on a systematic approach to diagnosis and management of life-threatening hyperkalemia. Long-term management of PHA1 is also tricky, and the experiences of other authors have been found to be highly variable.¹ We would like to present our experience of managing a newborn with PHA1 and her clinical course.

Case

A 1-month-old phenotypically female infant presented with:

1. *Failure to thrive*: weight on admission 2.5 kg (birth weight of 3.1 kg).
2. *Severe jaundice*: serum bilirubin done a few hours prior to admission found a total bilirubin of 19.2 mg/dL, indirect bilirubin of 18.4 mg/dL, and direct bilirubin of 0.8 mg/dL.
3. *Lethargy*: infant was conscious but dull and not feeding well.

The infant was born to consanguineous parents (third cousins). There was a family history of two infants who presented similarly, and who suffered sudden deaths in the neonatal period while undergoing phototherapy for jaundice.

Upon hospitalization, blood was drawn for repeat bilirubin, complete blood count, thyroid function tests, reticulocyte count, glucose-6-phosphate dehydrogenase assay, electrolytes, creatinine, and phototherapy was started. The infant was euglycemic.

Very soon the alert resident noted a wide QRS tachycardia on the monitor. The infant had a palpable pulse but had poor perfusion. The infant was immediately given calcium gluconate 10% intravenously at a dose of 0.5 mL/kg slowly over 5 minutes. The tachycardia reverted and laboratory reports showed that sodium was 115 mEq/L and potassium was 12 mEq/L. Serum creatinine was 0.6 mg/dL (95th percentile value at 1 month of age is 0.57 mg/dL), mildly elevated for her age, but insufficiently high to explain the severe hyperkalemia. A repeat examination of the infant's external genitalia again revealed a normal phenotypic female with no clitoromegaly, effectively ruling out the more common types of congenital adrenal hyperplasia (CAH). The differential diagnosis was now narrowed down to non-CAH-related adrenal insufficiency and one rare type of CAH, congenital lipoid adrenal hyperplasia.

After immediately starting intravenous sodium bicarbonate and glucose insulin drip for treatment of severe hyperkalemia, a sample was drawn for serum cortisol and intravenous hydrocortisone bolus and infusion was started. Arterial blood gas revealed severe metabolic acidosis, which was treated by titrating the sodium bicarbonate infusion. Over the next

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few hours, serum potassium declined insufficiently, from 12 to 10 mEq/L; therefore, peritoneal dialysis was performed for hyperkalemia.

The serum cortisol level subsequently returned at 39.4 µg/dL (normal range: 2.8–23 µg/dL), effectively ruling out adrenal insufficiency. The hydrocortisone infusion was stopped, and an early morning blood sample was sent for plasma aldosterone and plasma renin activity levels.

While an intravenous glucose and insulin infusion help decrease the fraction of potassium in the extracellular space, it does not decrease the total potassium content of the body. For this, all potassium intakes should be stopped and potassium-binding resins have to be used. Of the two resins available, the sodium polystyrene resin is preferable, as it helps in correcting the concomitant hyponatremia seen in many of these patients, while the calcium polystyrene resin (K bind) has the disadvantage of causing hypercalcemia. We were forced to use the calcium polystyrene resin as the sodium polystyrene resin was unavailable.

For long-term management of hyponatremia, the infant was started on oral 3% saline (22 mEq/d) and this with the oral sodium bicarbonate tablets helped maintain sodium in the normal range. For control of serum potassium, the infant was started on K bind (calcium polystyrene resin enema) 24 g/d in four to five divided doses with alternate day monitoring of serum potassium. Despite the fact that there is resistance to action of aldosterone at the receptor level, high dose of oral fludrocortisone has been recommended,² and therefore, it was started in this infant at a dose of 1 mg/d.

Diagnosis

In the absence of hyperkalemia due to increased intake or transcellular shift of potassium which occurs in conditions easily picked up by history alone, disorders of the renin-angiotensin-aldosterone axis constitute an important group where hyponatremia is associated with hyperkalemia and simple clinical deduction helped us rule out most of the causes.

- CAH with concomitant mineralocorticoid deficiency is seen in 21 hydroxylase deficiency, 3 β hydroxysteroid dehydrogenase deficiency, and congenital lipoid hyperplasia. The first two also cause virilization in female neonates. The other conditions causing CAH, 11 hydroxylase deficiency and 17 hydroxylase deficiency, have mineralocorticoid excess and hence lead to hypokalemia rather than hyperkalemia, along with glucocorticoid deficiency.
- Congenital adrenal hypoplasia can be diagnosed by a low serum cortisol.
- Congenital defects in aldosterone synthesis will present biochemically with hyponatremia and hyperkalemia but will have very low aldosterone level and elevations in plasma renin activity.

However, laboratory evaluation revealed markedly elevated aldosterone and renin values: plasma renin activity of >37.0 ng/mL/h (reference range: 1–4 ng/mL/h) and serum aldosterone of 769 ng/dL (reference range: 7–99 ng/dL),

ruling out all of the above possibilities. This leaves us with a very rare condition:

- Disorders of aldosterone resistance or PHA helped us come to the final diagnosis of PHA1.

Genetic studies are planned for confirmation of PHA subtype, subject to availability of financial resources.

Discussion

This case report provides some important learning points in the diagnosis and management of a complex and often life-threatening neonatal condition.

- Hyperkalemia management: When confronted with a life-threatening emergency in the form of a cardiac arrhythmia, IV calcium boluses can be lifesaving, as happened in our case.
- Clinically, salt-wasting variants of CAH can be indistinguishable from PHA. Although the former is far more common, the latter should be suspected in a female neonate with normal genitalia in the setting of severe salt wasting and failure to respond to initial hydrocortisone therapy.

PHA1 has two subtypes. Autosomal dominant-type PHA1 (renal PHA1) occurs due to loss of function mutations in the mineralocorticoid receptor gene *NR3C2* (nuclear receptor subfamily 3 group C member 2), and hence is restricted to renal salt wasting and is reported to improve with age,³ autosomal recessive type (systemic PHA1) occurs due to a loss of function mutation in the epithelial sodium channel. This channel, which is regulated by aldosterone, comprised an α subunit, β subunit, and γ subunit, respectively, encoded by the genes *SCNN1A*, *SCNN1B*, and *SCNN1G*. Autosomal recessive PHA1 occurs due to mutations in *SCNN1G*. As this channel is expressed in multiple organs (including the distal nephron), manifestations are due to involvement of several target organs, including the colon, salivary glands, and sweat glands in addition to the kidney. Skin changes and increased respiratory infections have been reported, and the disease tends to persist into adult life.⁴ In view of the poor genotype-phenotype correlation reported in PHA1,⁵ it is difficult to prognosticate from the clinical course alone. Our case had a stormy neonatal course with a definite history or mortality in two siblings, and with clinically asymptomatic parents with distant consanguinity, suggesting an autosomal recessive inheritance. However, this infant did not manifest any skin lesions as reported in the literature^{1,6} and has not yet developed any respiratory infections at the time of submission. The infant was breastfed and weight gain has improved at 3.5 months of age, the infant's weight is now 4 kg, still well below the 5th weight percentile on the WHO curve but improved considerably from the time of presentation.

Conclusion

PHA1 is unique not just because of its rarity but also because it demands a high degree of clinical acumen in diagnosis as

well as management. From management for acute life-threatening arrhythmia to drug manipulations for long-term control of electrolytes, this case is a lesson in clinical deduction and algorithmic management of hyperkalemia.

Authors' Contributions

M.G. and R.K. were responsible for case management and writing the article, Y.B. helped in reviewing the literature and discussion, and P.P. and A.J. helped in critical revision. All authors contributed toward final approval of article and take responsibility for accuracy and integrity of the work.

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Conflict of Interest

None.

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