Secondary Pseudohypoaldosteronism Masquerading Congenital Adrenal Hyperplasia in a Neonate

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INTRODUCTION

Although many diseases can present with hyponatremia, hyperkalemia, and metabolic acidosis in infancy, congenital adrenal hyperplasia (CAH) remains the most common cause. The other less incriminated causes are pseudohypoaldosteronism (PHA), transient mineralocorticoid deficiency of infancy, and cortisol deficiency following adrenal apoplexy.[1] PHA has been classified into 2 types. PHA type 1 can be either primary or secondary. Primary PHA 1 manifests as either an autosomal recessive generalized form (mutation in epithelial sodium channels found in distal nephron, distal colon, salivary glands, and so forth) or an autosomal dominant form (mutation in mineralocorticoid receptor) with only the salt-losing syndrome. PHA type 2 (Gordon syndrome) presents with hyperkalemia and hypertension.[2]

Secondary or transient PHA 1 has been documented in infants with urinary tract (UT) infection, with most cases having concomitant congenital UT malformations.[3,4] The pathogenesis of this condition involves tubular dysfunction stemming from excess intrarenal pressure and intrarenal cytokines.[5] The ensuing interstitial renal damage causes tubular resistance to aldosterone by direct impairment of the cellular responses or indirectly through alteration in renal autacoids, such as prostaglandins. Obstructive uropathy (ureteropelvic junction obstruction, posterior urethral valves) in the absence of any infection also can lead to PHA.[6] All the metabolic abnormalities are readily reversible with medical/surgical therapy if timely intervention is done.

We present here a case report on a female neonate with failure to thrive who presented with vague symptoms and on evaluation was diagnosed with secondary PHA due to pyelonephritis and bilateral grade V vesicoureteral reflux.

CASE PRESENTATION

A 21-day-old preterm female neonate born at 35 weeks to nonconsanguineous parents presented to us with vomiting, lethargy, decreased oral acceptance, and inadequate weight gain since birth. Laboratory investigations showed severe hyponatremia, hyperkalemia, hypochloremia, and non–anion gap metabolic acidosis (Table 1). She was immediately administered 3% NaCl solution, i.v. calcium gluconate, and salbutamol. This was followed by some improvement in her markedly deranged laboratory parameters. Normal 17-hydroxyprogesterone levels, slightly raised serum cortisol, and no evidence of genital ambiguity ruled out the possibility of CAH. Further workup was significant for a raised C-reactive protein (25 mg/l) and total leucocyte count (20,000/mm^3). Urinalysis showed 1+ proteinuria and numerous pus cells. Urine culture was positive for *Klebsiella pneumoniae*. Renal ultrasonography showed bilateral hydroureteronephrosis. The child received i.v. meropenem as per the culture reports for 14 days, and improved. Urinary sodium was 21 mmol/l and urinary potassium was 7.8 mmol/l. She had a non-anionic gap, metabolic acidosis, and her transtubular potassium gradient was <3 (normal 8–9), indicating reduced urinary potassium excretion. Serum renin and aldosterone levels were markedly raised, signifying profound tubular resistance to aldosterone induced by pyelonephritis. Based on the clinical picture, a diagnosis of secondary PHA was made. With the addition of hydrocortisone and fludrocortisone, her electrolytes normalized within 48 hours.

Table 1. Laboratory investigations at presentation

Blood	Laboratory values (normal)
Sodium, mmol/l	103 (135–145)
Potassium, mmol/l	8.2 (3.5–5)
Chloride, mmol/l	66 (102–112)
Bicarbonate, mmol/l	9.4 (20–28)
pH	7.13 (7.35–7.45)
Urea, mg/dl	108 (15–50)
Creatinine, mg/dl	0.8 (0.1–0.4)
Cortisol, μg/dl	48 (3–17)
17-OH progesterone, ng/dl	420 (346–8911)
Renin, ng/ml per h	31 (2.6–9.1)
Aldosterone, pg/ml	2200 (20–1100)

Table 2. Pseudohypoaldosteronism: causes and evaluation

CAUSES

Type 1 (cortical collecting tubule)

Primary

Autosomal recessive: reduced sodium channel activity

Autosomal dominant: mutations in the gene for the mineralocorticoid receptor

Secondary

Uropathies/urinary tract infection: Tubular interstitial disease (lupus, transplant rejection, sickle cell anemia, diabetes mellitus)

Drugs: Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, heparin, ketoconazole, cyclosporin, tacrolimus, trimethoprim, pentamidine, nonsteroidal anti-inflammatory drugs, beta blockers, spironolactone, potassium-sparing diuretics, ketoconazole

Type 2 (familial hyperkalemic hypertension or Gordon syndrome)

EVALUATION

Diagnostic tests

- Hyperchloremic non–anion gap metabolic acidosis in absence of gastrointestinal losses and hyperkalemia
- Negative urinary anion gap
- Investigations for causes as mentioned above
- Rule out congenital adrenal hyperplasia in infants
- Serum cortisol levels; if not done adrenocorticotropic hormone stimulation test to rule out adrenal insufficiency

Clinical examination: blood pressure assessment, genitalia to rule out congenital adrenal hyperplasia

Plasma renin and plasma aldosterone

After discharge, voiding cystourethrogram demonstrated bilateral grade V vesicoureteric reflux, with a normal urinary bladder. Hence, the final diagnosis was established as PHA with bilateral vesicoureteric reflux with chronic kidney disease. Her dimercaptosuccinic acid scan showed bilateral multiple scarred kidneys with impaired function. The child was started on antibiotic prophylaxis, initially cephalexin and later switched to cotrimoxazole. She remained on supportive care for the next 3 years, and ultimately required a preemptive kidney transplant and had an uneventful posttransplant course.

DISCUSSION

UT infections and/or anomalies are frequent among children. Secondary/transient/reversible PHA can occur in patients with immature renal tubular responsiveness to aldosterone during infancy when they have UT anomalies and/or infection; most commonly both. PHA masquerades as CAH, but a comprehensive urologic and endocrinology workup can help in distinguishing the two.[7] Common causes of PHA are summarized in Table 2.

Serum aldosterone, renin levels are markedly raised and serum cortisol, 17-OH pregnenolone levels are normal in PHA, contrary to what is seen in CAH. In addition to 17-OH progesterone, a serum cortisol level also should be done in a hypovolemic, acidotic patient with functioning adrenal glands. If serum cortisol is not measured, an adrenocorticotropic hormone stimulation test can be performed. Failure of rise of cortisol shall suggest adrenal insufficiency. This test is normal in PHA with an appropriate rise of cortisol.[6,7] An attempt should be made to exclude secondary causes, as highlighted in Table 2.

Most cases have nonspecific symptoms (failure to thrive, poor weight gain, and dehydration), making it challenging to diagnose this rare entity. It is imperative to promptly order urinalysis and urine culture and do

renal imaging studies in infants in whom the possibility of CAH has been ruled out.

A case series on 3 male infants with PHA secondary to isolated acute pyelonephritis emphasized that PHA can develop in the absence of vesicoureteral reflux or obstructive uropathy, and ascribed the distal tubular aldosterone resistance to the severe inflammatory milieu stemming from pyelonephritis.[8] Another multicase review on infants with PHA showed that 80% had UT infection with malformation, 12% had only UT anomalies, and the other 8% had isolated UT infection, highlighting the fact that in most cases, pyelonephritis alone cannot cause a clinically relevant sodium loss, unless it occurs on the backdrop of a congenital UT malformation.[9] In addition, literature states that PHA risk diminishes substantially or may disappear after 3 months of age in children with pyelonephritis superimposed on an underlying UT anomaly.[10] Thus, early infancy is itself a risk factor because of inherent immaturity of renal tubules that can be further aggravated by an infection.

The above-discussed patients, as reported in the literature, like our patient, exhibited transient renal tubular resistance to mineralocorticoids. We speculate that severe renal inflammation may cause transient tubular resistance to aldosterone independent of structural anomaly. Also, the fact that addition of fludrocortisone in our patient caused rapid correction of electrolytes implies that high levels of mineralocorticoids may overcome transient tubular resistance.

The overall outlook for patients with secondary PHA is excellent, and mainly hinges on an astute expeditious diagnosis. The treatment focuses on first correcting the fatal dyselectrolemia and then dealing with the underlying infection and/or malformation.

Thus, while treating an infant with a salt-losing syndrome, hyperkalemia, and metabolic acidosis, a vigorous search for a UT infection and/or anomaly ought to be initiated once CAH has been ruled out. If urosepsis and/or UT anomaly is detected, prompt treatment should be instituted, as it guarantees complete resolution.

DISCLOSURE

All the authors declared no competing interests.

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