CASE DESCRIPTION

A 5-day-old girl, born at term after an uncomplicated pregnancy, was admitted to the hospital after a routine midwife check showed that she had lost 15% of her original birth weight [6.2 lb (2.83 kg)]. She was being fed normal-term formula milk, and an initial assessment revealed only mild dehydration. The working diagnosis was a feeding problem, and her management plan was to be fed 150 mL/kg formula milk per day with regular monitoring of weight. The patient’s serum concentrations of selected analytes were as follows: sodium, 135 mEq/L (135 mmol/L; reference interval, 135–145 mmol/L); potassium, 5.3 mEq/L (5.3 mmol/L; reference interval, 3.5–5.3 mmol/L); and urea, 11.7 mg/dL (4.2 mmol/L; reference interval, 3.5–6.5 mmol/L).

Five days after admission, the patient’s weight was unchanged. Her serum analyte concentrations were now as follows: sodium, 128 mEq/L (128 mmol/L); potassium, 6.7 mEq/L (6.7 mmol/L); urea, 5.8 mg/dL (2.1 mmol/L); creatinine, 0.3 mg/dL (28 μmol/L; reference interval, 60–100 μmol/L); and blood glucose, 77.4 mg/dL (4.3 mmol/L; reference interval, 4–7 mmol/L). These findings prompted more-detailed biochemical and endocrine tests. Her bicarbonate concentration was 30 mEq/L (30 mmol/L; reference interval, 24–32 mmol/L), and her chloride concentration was 94 mEq/L (94 mmol/L; reference interval, 95–105 mmol/L). These results yielded an anion gap of 10.7 mmol/L. The urine sodium concentration was 10 mEq/L (10 mmol/L). Further blood results were available 2 days later: plasma renin, 854 mIU/L (reference interval, 4–190 mIU/L in >7 days to 1 year); serum aldosterone, >5786 ng/L (reference interval, 300–2000 ng/L in neonates). The results of blood gas, serum cortisol, ammonia, lactate, urine culture, and urine steroid profile tests were all normal.

DISCUSSION

WEIGHT LOSS IN A NEONATE

Some weight loss is normal in the first few days of life. A loss of up to 10% can be normal in breast-fed babies, but a weight loss of only 5% is expected in formula-fed babies (1). Babies with excess weight loss in the context of difficulty establishing feeding—especially breast-fed infants—may show evidence of hypernatremic dehydration due to loss of body sodium, but with a greater deficit in body water (2). In this case, the hyponatremia did not correlate with the clinical scenario for a formula-fed baby failing to gain weight, despite the patient following a clear feeding plan.

There are many pathologic causes (3) for faltering growth in an infant, including the following: genetic and chromosomal abnormalities, such as trisomy 21, Turner syndrome, and cystic fibrosis; inborn errors of metabolism; endocrine disorders, such as congenital adrenal hyperplasia (CAH); anatomic abnormalities, such as a large ventricular septal defect or biliary atresia; and psychosocial factors (3), such as emotional deprivation, poverty, neglect, and maternal mental illness.

HYPONATREMIA AND HYPERKALEMIA IN THE NEONATE

This combination in association with excessive weight loss indicates a problem with sodium chloride metabolism. CAH due to salt-wasting 21-hydroxylase deficiency (SW21-OHD) is the most common cause of hyponatremia and hyperkalemia in neonates. SW21-OHD is a genetic disorder that results from a deficiency of the enzyme 21-hydroxylase, which is responsible for converting cortisol into inactive forms. This leads to increased levels of aldosterone, which in turn increases sodium reabsorption and decreases potassium excretion, resulting in hyponatremia and hyperkalemia.

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3 Nonstandard abbreviations: CAH, congenital adrenal hyperplasia; SW21-OHD, salt-wasting 21-hydroxylase deficiency; PHA1, pseudohypoaldosteronism type 1.
sterone crosses the plasma membrane of epithelial cells
and binds to the cytosolic mineralocorticoid receptor.
The receptor–hormone complex activates intracellular
signaling cascades, increasing the luminal epithelial sod-
dium channels in many organs, including kidney, lung,
colon, and sweat and salivary glands. These channels
control sodium absorption at the luminal surfaces of
epithelial cells (5–7). Sodium is then secreted at the
basolateral surface into extracellular space via the
Na\(^+\)-K\(^+\) ATPase pumps. This process is coupled with
potassium secretion at the luminal surface. Therefore,
epithelial sodium channel dysfunction leads to hypo-
natremia and hyperkalemia.

**TYPES OF PHA**
There are 3 types of PHA (Table 1). PHA1 has 2 clinical
subtypes, each with a distinct pattern of inheritance.
Type 2 is characterized by hypertension and hyper-
kalemic metabolic acidosis with low renin and aldoste-
rone values (4, 8); it is therefore excluded in the pres-
tent case. Type 3 is an acquired variety (4), in which
transient aldosterone insensitivity is seen in such con-
ditions as urinary tract infection, obstructive uropathy,
or pyelonephritis. Type 3 PHA resolves with the reso-
lution of the initial clinical condition. In our case, urine
microscopy and renal ultrasound scan results were
normal.

**GENETICS OF PHA1**
The autosomal recessive PHA1 is caused by mutations
within the genetic subunits that code for the epithelial
sodium channel (5–7, 9). It is the most severe
form, because the salt wasting occurs in numerous
mineralocorticoid-sensitive tissues, including the
lungs, kidneys, colon, and sweat and salivary glands.
These patients require lifelong salt-replacement
therapy.

Autosomal dominant PHA1 is the likely expla-
nation for the case described. Salt wasting is re-
stricted to the kidneys, and the mutation lies in the
gene encoding the mineralocorticoid receptor
(9, 10). The mineralocorticoid receptor mutation
leads to a lack of renal sensitivity to aldosterone, and
the prognosis is better than for autosomal recessive
PHA1. Genetic testing is available for PHA, but such
testing is possibly more of academic interest. Genetic
testing was not done in our case in light of a clear
clinical diagnosis and a good response to sodium
chloride supplementation. There was no known
family history of the disease.

**CLINICAL PRESENTATION OF RENAL PHA1**
This disease is a pan-ethnic disorder with equal inci-
dences in males and females, and it usually presents in
the newborn period, often within the first 2 weeks of
life, with excessive weight loss, failure to thrive, feeding
difficulties, vomiting, and dehydration. Laboratory findings include hyponatremia, hyperkalemia, and metabolic acidosis. The glomerular filtration rate is normal, but it is rarely measured in infants. Hypovolemia and hypotension may also occur (4, 7). These presenting symptoms are similar in infants with true hypoaldosteronism and CAH.

MANAGEMENT OF RENAL PHA1
In the acute phase, the neonate may need treatment for hypovolemic shock or correction of hyperkalemia and metabolic acidosis. The glomerular filtration rate is normal, but it is rarely measured in infants. Hypovolemia and hypotension may also occur (4, 7). These presenting symptoms are similar in infants with true hypoaldosteronism and CAH.

Long-term treatment involves judicious fluid management and sodium chloride supplementation. After sodium chloride supplementation is initiated, the potassium concentration will normalize. The adequacy of supplementation can be measured by monitoring the serum potassium concentration (4); however, the plasma renin concentration gives the best estimate of salt replacement and should be measured every 3 to 12 months, depending on age. Total suppression will be seen with excessive sodium chloride replacement, and there may be no other clinical or biochemical indicators.

PROGNOSIS
In autosomal dominant PHA1, the renal tubules mature throughout infancy and urinary sodium wastage gradually decreases, with remission occurring by about 2 years of age because the child will take an adequate amount of salt in the diet by this age. The prognosis is very good (5), with resolution of the electrolyte disturbances. Symptoms may recur at times of sodium chloride restriction and during periods of illness or heat stress.

PATIENT OUTCOME
Regular sodium chloride supplementation (3 mmol/kg per day) was started on day 12, and weight gain was noted from day 21. The patient’s serum sodium and potassium concentrations remain normal. At 10 months of age, she is growing normally, and her weight has increased from the 0.4th centile to the 75th centile.

### Table 1. Types of PHA.

<table>
<thead>
<tr>
<th>PHA type</th>
<th>Genetic or acquired?</th>
<th>Genes involved*</th>
<th>Biochemical abnormalities</th>
<th>Organs involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 PHA (autosomal recessive PHA1 (MTOD))</td>
<td>SCNN1A, SCNN1B, SCNN1G</td>
<td>High serum renin and aldosterone, hyponatremia, hyperkalemia</td>
<td>Lungs, kidneys, colon, sweat and salivary glands</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant (renal PHA)</td>
<td>NR3C2 (MR)</td>
<td>High serum renin and aldosterone, hyponatremia, hyperkalemia</td>
<td>Kidneys</td>
<td></td>
</tr>
<tr>
<td>Type 2 PHA (Gordon syndrome)</td>
<td>WNK1, WNK4</td>
<td>Hyperkalemia, hyperchloremic metabolic acidosis, low aldosterone and renin</td>
<td>Kidneys</td>
<td></td>
</tr>
<tr>
<td>Type 3 PHA (secondary PHA)</td>
<td>No genes known; reverses with treatment of primary pathology</td>
<td>Transient aldosterone insensitivity, hyponatremia, hyperkalemia, metabolic acidosis</td>
<td>Seen with urinary tract infection, obstructive uropathy, pyelonephritis</td>
<td></td>
</tr>
</tbody>
</table>

* SCNN1A, sodium channel, non-voltage-gated 1 alpha subunit; SCNN1B, sodium channel, non-voltage-gated 1, beta subunit; SCNN1G, sodium channel, non-voltage-gated 1, gamma subunit; NR3C2, nuclear receptor subfamily 3, group C, member 2 (also known as MR); WNK1, WNK lysine deficient protein kinase 1; WNK4, WNK lysine deficient protein kinase 4.

** MTOD, multiple target organ defect.

### POINTS TO REMEMBER
- Excessive neonatal weight loss may be associated with hypernatremic dehydration in breast-fed babies.
- Hyponatremia in a neonate with clinically important weight loss warrants further investigation to consider less common endocrine causes, such as PHA or CAH.
- PHA1 may present symptomatically before the development of electrolyte abnormalities.
- PHA1 (autosomal dominant) is managed by sodium supplementation and monitoring of serum sodium and potassium concentrations.
Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References

Commentary

Abby S. Hollander*

The authors describe the interesting case of a 5-day-old girl with poor weight gain, hyperkalemia, and mild to moderate hyponatremia due to resistance to aldosterone—or type 1 pseudohypoaldosteronism (PHA). The diagnosis was confirmed by the demonstration of an extremely increased serum aldosterone concentration at the time of hyponatremia, and the child was successfully treated with sodium chloride supplementation. Adrenal insufficiency is appropriately mentioned in the differential diagnosis. Note that adrenal insufficiency should be empirically treated if it is suspected in a sick neonate.

The diagnosis that is most likely for an infant with hyponatremia, hyperkalemia, and hypovolemia is salt-wasting congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. CAH is an autosomal recessive disorder with an incidence of 1 in 10 000 to 1 in 20 000 births. Females with 21-hydroxylase deficiency typically have clitoromegaly due to excess androgen production, so examination of the genitalia is a crucial part of the evaluation of a baby girl with hyponatremia and hyperkalemia. Newborn screening for 21-hydroxylase deficiency is performed in all US states and at least 12 other countries. This newborn screening has led to earlier diagnosis, thereby reducing the likelihood of a life-threatening adrenal crisis.

The clinical presentations of type 1 PHA and salt-wasting CAH in the neonate can be very similar. As the authors discuss, type 1 PHA can be primary, due to mutations in the gene encoding the mineralocorticoid receptor (autosomal dominant) or in the genes encoding the epithelial sodium channel (autosomal recessive), or it can occur secondary to urologic problems such as obstructive uropathy or pyelonephritis. Careful physical examination for female virilization, evaluation for genitourinary anomalies, and evaluation of results for the appropriate laboratory tests (17-hydroxyprogesterone, cortisol, renin, aldosterone) will lead the clinician to the appropriate diagnosis and treatment for the neonate with hyponatremia and hyperkalemia.

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