14 Adrenal Causes of Electrolyte Abnormalities: Hyponatremia/ Hyperkalemia

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Key Points

1. Sodium and potassium homeostasis is tightly controlled by adrenal mineralocorticoid production.
2. Disorders of sexual differentiation are frequently associated with electrolyte disorders.
3. Inborn errors of aldosterone biosynthesis and bioactivity leading to lead hyponatremia and hyperkalemia.

Key Words: Congenital adrenal hyperplasia; Aldosterone deficiency; 17-OHP; aldosterone; plasma renin activity

1. CONGENITAL ADRENAL HYPERPLASIA

An 8-day-old baby boy presents to the emergency department. He is ill appearing, lethargic, and hypotensive. Initial laboratory assessment reveals a serum sodium of 131 mEq/L and potassium of 6.3 mEq/L.

The diseases of the adrenal glands that result in disorders of salt and water metabolism can be classified as diseases of either aldosterone deficiency or aldosterone excess. Further classification of diseases of aldosterone deficiency includes disorders of decreased aldosterone production or decreased activity.

Case Scenario 1: The most common cause of decreased aldosterone production lies within the group of disorders commonly referred to as congenital adrenal hyperplasia (CAH). CAH is a group on inherited disorders of adrenal steroid biosynthesis (Fig. 1). While this group of diseases is commonly thought of only as a disorder of sexual differentiation at birth, the associated disorders in production of aldosterone and its precursors frequently lead to abnormalities in sodium and potassium homeostasis. Eventually, these disorders can lead to issues of severe dehydration, sodium and potassium imbalance, and, ultimately, life-threatening shock (Table 1) *(1)*.

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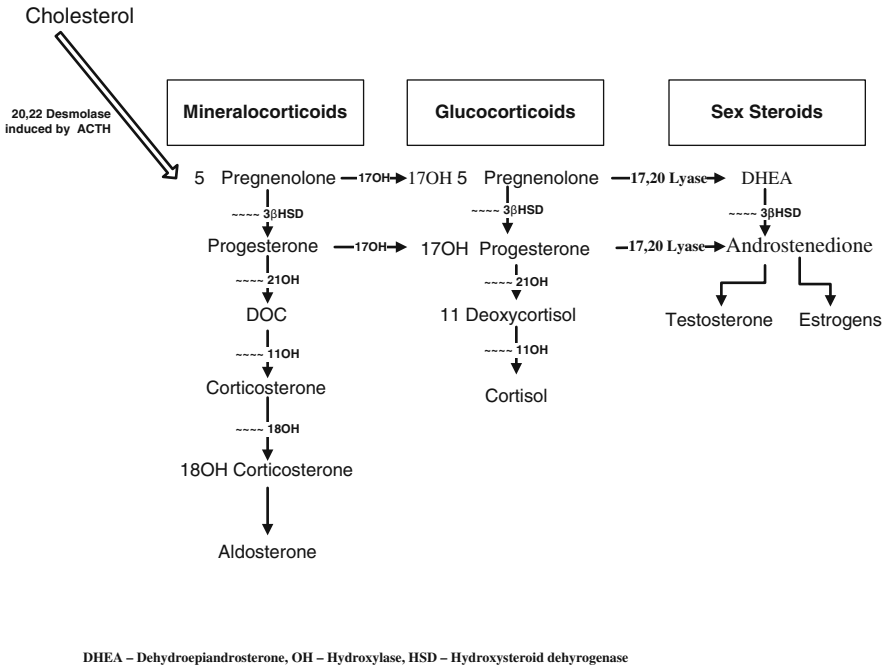

Fig. 1. Pathway of adrenal steroid synthesis.

As noted in earlier chapters, aldosterone is produced by the cells of the zona glomerulosa of the adrenal gland. Its production is regulated by angiotensin II, which in turn is regulated by renin levels. Renin production reflects intravascular volume, as detected by renal perfusion through the juxtaglomerular apparatus. Both potassium and to a lesser degree adrenocorticotropic hormone (ACTH) levels are also important in the regulation of aldosterone levels. Aldosterone in turn acts at the distal tubule, via the mineralocorticoid receptor, resulting in activation of sodium channels and the sodium–potassium pump. This results in resorption of sodium and water and excretion of potassium. This ultimately controls electrolyte and fluid regulation *(2)*.

Table 1
Forms of CAH with Electrolyte Disturbances

Lipoid adrenal hyperplasia (StAR or 20,22 desmolase deficiency)
3β-Hydroxysteroid dehydrogenase deficiency
21-Hydroxylase deficiency
Aldosterone synthetase deficiency

Of the six forms of CAH, 21-hydroylase deficiency is the most common, accounting for 90% of all CAH *(3)*. With an incidence of approximately 1 in 15,000, up to 75% of cases are noted to be "salt wasters." As noted in the adrenal steroidogenic pathway, this disease state is not a primary defect in aldosterone biosynthesis, but rather the inability

to synthesize aldosterone precursors leading to aldosterone deficiency and a consequent inability to resorb sodium and excrete potassium in the tubules. Hence hyponatremic hyperkalemic metabolic acidosis is observed in untreated patients.

The presentation of infants with 21-hydroxylse deficiency may be dependent upon the sex of the newborn. An overvirilized female will frequently be noted to have a disorder of sexual differentiation and generally be observed in the nursery for signs of salt wasting, once the diagnosis of CAH is entertained. However, a newborn male with salt losing 21-hydroxylase deficiency may only have the subtle stigmata of mild hyperpigmentation. Thus, an infant boy may present ill appearing with hyperkalemic, hyponatremic acidosis. This presentation is usually after the first week of life, as the control of fetal electrolytes relies on the placenta and the mother's kidneys. With the institution of newborn screening programs for 21-hydroxylase deficiency throughout the United States, this presentation will hopefully become less common. However, normal newborn screening results do not rule out the possibility of disease.

The other, less common causes of CAH may similarly present with ambiguous genitalia and abnormalities related to salt wasting and hypertension. These include 3β-hydroxysteroid dehydrogenase deficiency as well as StAR (congenital lipoid hyperplasia) deficiency *(4*, *5)*. As noted from Table 1, both of these forms of CAH also lead to decrease production of aldosterone with subsequent salt wasting crisis in the newborn period. Both of these enzyme deficiencies may lead to disorders of sexual differentiation, as males with StAR deficiency and males with 3β-hydroxysteroid dehydrogenase deficiency will be undervirilized while females will be overvirilized.

2. ALDOSTERONE BIOSYNTHETIC DEFICIENCIES

Specific disorders in aldosterone biosynthesis have also been described that are not usually associated with either disorders of sexual differentiation or cortisol production *(2)*. Aldosterone synthetase deficiency, also known as corticosterone methyl oxidase (CMO) I and II, deficiency are among this subgroup. These patients will present with failure to thrive and mild salt-wasting crisis, hyponatremic, hyperkalemic, metabolic acidosis in the first few months of life. The secretory rate of deoxycorticosterone (DOC) is insufficient to meet the mineralocorticoid requirement of a newborn. As they also have normal cortisol production, hypotension and shock are less likely.

3. DEFECTS IN ALDOSTERONE ACTION

With less than 100 cases reported in the literature, a rare resistance to aldosterone has been reported. These patients with pseudohypoaldosteronism type I would present in a fashion similar to those with aldosterone deficiency, but laboratory findings would note elevated aldosterone levels and elevated plasma rennin activity (PRA). As noted in earlier chapters, patients with primary renal disease, including obstructive and infective process, may also present with aldosterone resistant picture, sometimes referred to as type 4 RTA.

4. CONGENITAL SYNDROMES

There are rare syndromes associated with lack of development of the adrenal gland (Table 2). These are not specifically related to enzyme deficiency in the gland, but a lack of development of a normally functioning gland from an anatomic/physiologic perspective. Among these disorders are syndromic disorders, including Smith–Lemli–Opitz and deficiencies of two genes important to adrenal gland development, DAX and SF-1. This specific X-linked adrenal hypoplasia may also be associated with muscular dystrophy and glycerol kinase deficiency.

Table 2
Syndromes Associated with Adrenal Insufficiency

Smith–Lemli–Opitz
X-linked muscular dystrophy/glycerol kinase deficiency/adrenal hypoplasia
Zellweger syndrome
Wolman disease
Adrenal leukodystrophy
Allgrove syndrome

Other congenital syndromes may affect lipid production, and hence an inability to provide the cholesterol precursors necessary for adrenal steroid biosynthesis. These include Zellweger and Wolman syndromes. The adrenal leukodystrophies and the AAA syndrome of achalasia–addisonianism–alacrima often present later in childhood and have variable mineralocorticoid deficiency.

5. ACQUIRED ADRENAL INSUFFICIENCY

Case Scenario 2: A 13-year-old girl with a history of Hashimoto's thyroiditis presents with fatigue and weight loss.

While less common, there are a number of acquired forms of adrenal insufficiency. Included among these are insufficiency secondary to adrenal hemorrhage, either in the newborn period, or secondary to infection, i.e., Waterhouse–Friderichsen syndrome. Viral, fungal, and tuberculin infections leading to adrenal insufficiency have been described, as has infiltrative disorders, including sarcoidosis, amyloidosis, and histiocytosis X *(6)*.

Perhaps more relevant to pediatric practice are those disorders that fall into the autoimmune classification. While frequently isolated, acquired adrenal insufficiency may be associated with other endocrine hypofunction, as well as vitiligo and mucocutaneous candidiasis. Certainly in the setting of other autoimmune disease, as well as a positive family history, an increased index of suspicion will help in making the diagnosis.

It is important to note that those diseases that lead to ACTH deficiency rarely cause disturbances in electrolyte balance, as this system is under the control of the renin–angiotensin–aldosterone system, which is independent of ACTH production.

6. HYPOKALEMIA

While rare, 17α-hydroxylase deficiency presents later in life, usually around the time of puberty, with hypokalemia and hypertension and delayed puberty. Increased substrate, specifically deoxycorticosterone (DOC), which has aldosterone-like effects in the mineralocorticoid pathway, leads to increased production of precursors, hence leading to hypokalemia *(7)*.

7. ACUTE ADRENAL INSUFFICIENCY WITH MINERALOCORTICOID DEFICIENCY

7.1. Evaluation and Treatment

Most commonly acute adrenal insufficiency with electrolyte disturbances presents in the neonatal period.

Referring to the vignette (Case Scenario 1) at the beginning of this chapter, an 8-day-old baby boy presents to the emergency department. He is ill appearing, lethargic, and hypotensive. Initial laboratory assessment reveals a serum sodium of 131 mEq/L and a potassium of 6.3 mEq/L. Serum glucose is 35 mg/dL. Further history reveals persistent vomiting and poor feeding as well as decreased wet diapers. A family history reveals a previous male child died at 3 weeks of age of reported diarrhea, dehydration, and shock. On physical exam, the infant is ill appearing and markedly dehydrated. He is in shock. His weight is 15% below birth weight. He has a generous sized phallus, with hyperpigmented nipples, and scrotum.

The patient's history, physical, and laboratory exam are consistent with the diagnosis of salt losing congenital adrenal hyperplasia (Table 3). The most likely disease in the CAH spectrum is 21-hydroxylase deficiency.

Table 3
Signs of Mineralocorticoid Deficiency

Weakness
Weight loss
Anorexia
Fatigue
Salt craving
Hypotension
Hyperpigmentation
Hyponatremic, hyperkalemic acidosis

As with any patient, the first goal is acute resuscitation. In this case, fluid in the form of normal saline, with or without dextrose, to correct shock is of primary importance. In addition, a stress dose of hydrocortisone should be given, 25 mg/m^2 IV; this may be life saving. During the initial workup, a "red top tube" can be set aside for serum analysis of adrenal steroid precursors, the most important of which is 17-hydroxyprogesterone. Additional laboratory evaluation that may be obtained to help diagnose

mineralocorticoid deficiency include urine electrolytes and a plasma renin activity (obtained in a "purple top" EDTA tube and placed on ice).

Once the patient has been stabilized and is no longer in extremis, the diagnosis is confirmed by elevation of adrenal precursors, either random or after ACTH testing, and DNA analysis, replacement therapy can begin. The goal of therapy in CAH is to decrease adrenal androgen production by replacing cortisol and to insure electrolyte homeostasis by replacing aldosterone. To achieve this goal, hydrocortisone replacement requirements are generally higher than the normal cortisol secretory rate of 7.5–12.5 mg/m^2 divided into every 8-h oral dosing In addition mineralocorticoid replacement is given as 9-alpha-fluorocortisol acetate (fludrocortisone). This dose is titrated to blood pressure, electrolytes and plasma renin activity levels. Infants generally need larger doses than older children. As infants generally receive very little sodium though either breast milk (7.7 mEq/l) or infant formula (18.5 mEq/l), sodium replacement, frequently as 2 g of table salt daily, is needed until enough dietary sodium is ingested daily. The sodium requirement of an infant is 2–3 mEq/kg/day.

CASE SCENARIO 2

A 13-year-old girl with a history of Hashimoto's thyroiditis presents with fatigue and weight loss. History reveals intermittent abdominal pain and occasional vomiting in the afternoon. Upon further questioning there is increased intake of salty foods. Family history is positive for a relative with type 1 diabetes and premature ovarian failure. Upon exam, the girl is cachectic, with a 10-pound weight loss. There is mild hyperpigmentation on the palms, soles, and gums, and no tan lines are noticed. Laboratory evaluation reveals a serum sodium concentration of 131 mEq/L, potassium 5.4 mEq/L. A morning cortisol level is low, 3.2 mcg/dL (3–21), with an inappropriately elevated ACTH of 824 pg/ml (6–48).

This patient appears to have acquired adrenal insufficiency. In the setting of another autoimmune endocrinopathy in the patient, and the family history of a relative with autoimmune endocrinopathy, the history and findings are consistent with polyglandular autoimmune syndrome *(8)*. The autoimmune etiology can be confirmed by measuring anti-21-hydroxylase antibodies. Treatment in this situation is related to long-term replacement of glucocorticoids and mineralocorticoid; as the patient is not in extremis, stress coverage may not be necessary (Table 4). In general, older patients will have their

Table 4
Maintenance and Stress Glucocorticoid and Mineralocorticoid Replacement

Medication	*Maintenance dosage range*	*Stress dosage*
Glucocorticoid replacement (mg/m^2/24 hours)	7.5–12.5 /every 8 hours	25–50
Mineralocorticoid (mg/day)	0.05–1.5	0.05–1.5

Note: no additional mineralocorticoid stress dosage is required, as the increased glucocorticoids will provide enough mineralocorticoid effect.

own "salt seeking" behavior and supplemental sodium is rarely necessary to maintain sodium and potassium in the normal range.

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