Hypertension With Hypokalemia: A Quiz

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Clinical Presentation

A man in his mid-40s with a history of longstanding, untreated hypertension presented to the emergency department with right-sided neurologic deficits and slurred speech secondary to intracerebral hemorrhage discovered on computed tomography imaging. He was diagnosed with hypertension in his 20s, was not taking any antihypertensive medications, and did not have regular medical care. He did not use drugs, alcohol, or tobacco. Family history was pertinent for his father having hypertension and dying at age 56 years of myocardial infarction, a brother diagnosed with hypertension in his 20s, and his mother diagnosed with hypertension and diabetes. On admission, the patient's blood pressure was 257/159 mm Hg, and he had hypokalemia (potassium level, 3.1 mmol/L), with preserved kidney function (serum creatinine level, 0.83 mg/dL). Bicarbonate level was 27 mmol/L. Coagulation values, lactate, and all other laboratory values were within reference ranges. Ethyl alcohol screening and urine toxicology findings were negative, and troponin test results were unremarkable. Table 1 includes the patient's basic metabolic panel on admission and pertinent laboratory findings during his hospitalization. The patient was admitted to the intensive care unit for a nicardipine drip and initiation of long-acting antihypertensive therapy. His severe hypertension, age, and hypokalemia prompted investigation for a secondary etiology of his hypertension.

Table 1. Patient's Basic Metabolic Panel on Admission and Pertinent Laboratory Values During Hospitalization

	Value	Reference Range
Day 1		
Sodium, mmol/L	136	135-145
Potassium, mmol/L	3.1	3.4-5.0
Chloride, mmol/L	103	99-109
Bicarbonate, mmol/L	27	23-33
Creatinine, mg/dL	0.83	0.5-1.3
Glucose, mg/dL	99	65-99
Urine toxicology	Negative	–
Day 4		
Renin activity, ng/mL/h	2.8	–
Aldosterone, ng/dL	<4	–
Plasma metanephrine, <0.5 nmol/L	0.23	–
Normetanephrine, <0.9 nmol/L	2	–
Day 5		
24-h urine volume, mL	3,150	–
Cortisol, μg/24 h	1,197	–
Cortisone, μg/24 h	473	–
Metanephrine, μg/24 h	237	44-261/<400[a]
Normetanephrine, μg/24 h	1,024	119-451/<900[a]

[a]Reference ranges for normotensive/hypertensive patients.

- **How should the patient's hypertension be managed?**
- **What is the differential diagnosis for the cause of hypertension with hypokalemia and metabolic alkalosis?**
- **What would be the appropriate work-up for this patient?**

Discussion

How should the patient's hypertension be managed?

Hypertension with intracerebral hemorrhage should be managed with intravenous nicardipine (fast-acting, short half-life) to lower systolic blood pressure to 140 mm Hg in the first hour, then to maintain it at 140 mm Hg for 24-48 hours. If systolic blood pressure is >220 mm Hg, as in this patient, there should be a quick lowering to 220 mm Hg, then to 140-160 mm Hg over several hours.[1]

What is the differential diagnosis for the cause of hypertension with hypokalemia and metabolic alkalosis?

Although causes of secondary hypertension include diverse conditions such as chronic kidney disease, glomerulonephritis, pheochromocytoma, thyroid disease, and sleep apnea, the differential diagnosis for secondary hypertension with hypokalemia and metabolic alkalosis includes conditions in which distal tubular sodium exchange for potassium and hydrogen is disturbed. Treatment of hypertension with diuretic agents induces hypokalemia by interfering with this exchange, but, if hypokalemia persists off diuretic treatment, an inappropriate primary increase of aldosterone should be considered. This can be seen in benign adrenal hyperplasia/adenoma or Cushing syndrome. A secondary aldosterone increase may be seen in renal artery stenosis, aortic coarctation, and renin-secreting tumors. Rarely, aldosterone's effect on distal tubular cells can be imitated in the absence of aldosterone by a circulating compound able to bind to its

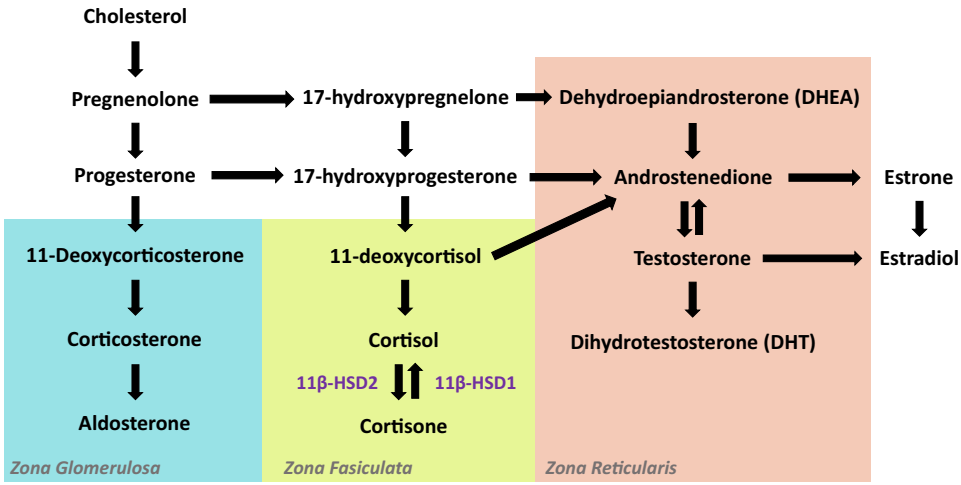

Figure 1. Major steroidogenic pathways in the 3 zones of the human adrenal cortex (based on information in Miller and Auchus[6]). 11β-HSD1, 11-β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11-β-hydroxysteroid dehydrogenase type 2.

receptor or a gain-of-function gene variant that increases distal tubule sodium channel activity. Liddle syndrome is a genetic disorder of increased epithelial sodium channel activity that causes hypertension with low aldosterone and renin levels.

What would be the appropriate work-up for this patient?

Computed tomography imaging ruled out aortic coarctation, renal artery stenosis, and adrenal hyperplasia/adenoma. Plasma renin and aldosterone, measured simultaneously, were within reference ranges, as were plasma free metanephrines. Twenty-four–hour urine studies demonstrated a cortisol level twice that of cortisone. Normally, the conversion of cortisol to cortisone by 11-β-hydroxysteroid dehydrogenase type 2 takes place in the kidney (Fig. 1) and results in a urinary cortisone to cortisol ratio of 2:1.[2]

Careful history was taken to rule out consumption of licorice products, such as in some chewing tobacco, and antifungal drugs. Licorice contains glycyrrhetinic acid, which inhibits the conversion of cortisol to cortisone.[3] Unlike cortisone, cortisol has similar binding affinity to aldosterone for mineralocorticoid receptors. Increased cortisol levels therefore produce some of the same effects as hyperaldosteronism, including increased sodium reabsorption and potassium excretion, resulting in hypertension and hypokalemia characterized as a syndrome of apparent mineralocorticoid excess.[3] The antifungal agents posaconazole and itraconazole also inhibit the conversion of cortisol to cortisone and can cause hypertension with hypokalemia through a similar mechanism.[4] Lacking exposure to 11-β-hydroxysteroid dehydrogenase inhibitors, and considering the family history of early-onset hypertension, a genetic deficiency of 11-β-hydroxysteroid dehydrogenase type 2 was suspected. The syndrome of apparent mineralocorticoid excess is usually autosomal recessive, presenting in childhood with failure to thrive and severe hypertension associated with end organ damage.[5] Presentation of apparent mineralocorticoid excess in adulthood occurs when the enzymatic defects are less pronounced.

Final Diagnosis

11-β-hydroxysteroid dehydrogenase type 2 deficiency.

Article Information

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