Apparent Mineralocorticoid Excess Syndrome: A Case of Resistant Hypertension From Licorice Tea Consumption

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Hypertension is a common medical condition that affects approximately one in three Americans.[1,2] In the United States, a majority of the current cases are classified as essential hypertension related to various behavioral and inheritable risk factors.[2] However, in cases of resistant hypertension, an underlying etiology may be present. Common causes of secondary hypertension include chronic kidney disease, renovascular hypertension (renal artery stenosis), sleep apnea, Cushing syndrome, pheochromocytoma, and primary aldosteronism.[3] Although much more rare, an additional cause of secondary hypertension includes the syndrome of apparent mineralocorticoid excess (AME), which can be the result of a genetic mutation or acquired through the chronic ingestion of glycyrrhizic acid, a component of pure licorice.[4–6]

We present a case of acquired AME secondary to the chronic ingestion of licorice extract tea. While this diagnosis is undoubtedly much less common than most sources of secondary hypertension, it should be considered in the differential diagnosis as it requires simply eliciting a thorough clinical history and may eliminate the need for additional and unnecessary investigations and treatment.

CASE REPORT

Initial Presentation

An otherwise healthy 50-year-old Caucasian woman presented to the outpatient clinic with blood pressure (BP) readings >200/100 mm Hg, headaches, palpitations, and episodic muscular leg pain. She denied any associated chest pain, shortness of breath, orthopnea, or peripheral edema. These pressures were in contrast to her baseline BP of 120/70 mm Hg upon establishing care 3 years earlier. Her medical history was significant for kidney stones and menstrual migraines. She had no family history of hypertension. The patient reported an active lifestyle including running 30 to 45 minutes a day during the previous 2 years and presented with a body mass index of 19.50 kg/m^2. She denied any current use of tobacco, described herself as a social drinker consuming no more than two glasses of wine per week, and denied any recreational drug use.

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Laboratory Workup and Management

The patient was started on lisinopril 10 mg daily and returned 1 week later for follow-up, with a BP of 220/110 mm Hg. At this time amlodipine 10 mg was added for persistent hypertension as well as 60 mEq of potassium chloride for myalgia. Lab reports following this visit were significant for hypernatremia (146 mEq/L; normal 137–144) and hypokalemia (2.9 mEq/L; normal 3.6–5.1) in the setting of low serum aldosterone (<3.0 ng/dL; normal for those ≥15 years 4–31) and low renin (0.2 ng/mL/h; normal 0.2–1.6). Other significant findings from this workup included an elevated intact parathyroid hormone (PTH; 105 pg/mL; normal 15–88 pg/mL), a normal level of ionized calcium (1.25 mmol/L; normal 1.14–1.33), and a normal level of thyroid-stimulating hormone (1.67 mIU/L; normal for those ≥20 years 0.40–4.50). The patient was scheduled for a follow-up appointment 4 days later, at which time her BP continued to be elevated at 174/82 mmHg. The decision was made to increase her dose of lisinopril to 40 mg daily while continuing 10 mg of amlodipine and 60 mEq of potassium chloride. A 24-hour urinalysis was ordered and revealed elevated levels of total free cortisol (170.26 μg/g Cr; normal <24 μg/g Cr). Other significant findings included normal levels of urinary metanephrine (82 μg/d; normal 30–350 μg/d), normetanephrine (211 μg/d; normal 50–650 μg/d), and vanillylmandelic acid (4.7 mg/d; normal 0.0–7.0). Levels of urinary aldosterone were untraceable (normal 1.2–28.1 μg/d).

At this time a more thorough dietary history was obtained and revealed that the patient had been consuming four to five cups of Egyptian Licorice tea on a daily basis. The tea was reviewed and found to contain pure licorice root (*Glycyrrhiza glabra*). The patient was counseled on the effects of pure licorice as it relates to the syndrome of AME and advised to discontinue the use of the tea immediately. She was advised to continue on the 40 mg of lisinopril but to discontinue taking amlodipine secondary to peripheral edema.

One week following this intervention the patient reported feeling well with at-home BP recorded as follows: 111/72 mm Hg, 104/78 mm Hg, and 102/67 mm Hg after 5, 6, and 7 days of discontinuing licorice tea, respectively. Based on these readings her dosage of lisinopril was decreased to 20 mg daily. At 1 month following the discontinuation of licorice tea she presented to the clinic with a BP of 129/85 mm Hg and at-home readings ranging from 100–130/60–80 mm Hg. Repeat lab work at this time revealed normal levels

of sodium (141 mEq/L; normal 137–144), potassium (4.6 mEq/L; normal 3.6–5.1), ionized calcium (1.23 mmol/L; normal 1.14–1.33), and PTH (26 ng/dL; normal 15–88). Repeat 24-hour urinalysis revealed normalized free cortisol levels (16.93 μg/g Cr) (Table). The patient was taken off all hypertensive medications at this time.

PATHOPHYSIOLOGY

The syndrome of AME mimics the findings of primary aldosteronism with resistant hypertension in the setting of hypokalemia, hypernatremia, and low plasma renin.[4,7] The pathophysiological basis of AME is impaired function of the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11-β-HSD2), which converts cortisol (an activator of the renal mineralocorticoid receptors) to cortisone (inactive form).[4,5,7–12] The relative excess of cortisol stimulates the mineralocorticoid receptors in the renal distal tubules and collecting ducts resulting in sodium retention, potassium wasting, and metabolic alkalosis accompanied by low plasma renin and low aldosterone levels.[5,6,9,10,12] The finding of low aldosterone is what distinguishes AME from primary aldosteronism.

There are both genetic and acquired forms of AME. The genetic manifestation is the result of an autosomal recessive mutation in the 11-β-HSD2 gene on chromosome 16 causing a rare but severe form of juvenile hypertension characterized by low birth weight, failure to thrive, hypercalciuria, nephrocalcinosis, and renal failure.[4–6] The acquired form of AME is the result of chronic licorice consumption resulting in the active ingredient glycyrrhizic acid (hydrolyzed to glycyrrhetinic acid in vivo) producing an inhibitory effect on 11-β-HSD2.[4–6]

Liddle syndrome also needs to be considered in cases of suspected secondary hypertension in the setting of hypokalemia, low renin, and low plasma aldosterone.[11,13] As opposed to elevated levels of cortisol causing activation of the mineralocorticoid receptors, Liddle syndome is characterized by an overactivating defect in the epithelial sodium channel resulting in increased sodium absorption and potassium wasting.[11] Differentiation of Liddle syndrome vs AME is most easily accomplished based on urinary cortisol levels (elevated in AME and normal in Liddle syndrome) but can also be distinguished based on the therapeutic response to spironolactone (hypertension is responsive to spironolactone in AME but is not altered in Liddle syndrome).[7]

TABLE. Laboratory Results During Consumption of Licorice Tea Compared With Results After 1 Month of Discontinuation

	Values During Licorice Consumption	Values Following Discontinuation of Licorice
Sodium (137–144 mEq/L)	146	141
Potassium (3.6–5.1 mEq/L)	2.9	4.6
Aldosterone, serum (reference values for patients ≥15 years 4–31 ng/dL)	<3.0	4.2
Renin (adult, normal sodium diet 0.2–1.6 ng/mL/h)	0.2	0.6
Urinalysis		
Urinary cortisol, rate per g of creatinine (for women ≥18 years <24 μg/g creatinine)	170.26	16.93
Metanephrine (24-h, 30–350 μg/d)	82	
Normetanephrine (24-h, 50–650 μg/d)	211	
Vanillylmandelic acid (0.0–7.0 mg/d)	4.7	
Aldosterone, urinary (1.2–28.1 μg/d)	Untraceable	

DISCUSSION

Similar examples of acquired manifestations of AME can be found in the literature dating back to the 1960s and as recent as 2014, with reports including patients consuming pure licorice as a means to quit smoking, chronic use of chewing tobacco containing licorice paste, and chronic consumption of licorice candies containing glycyrrhizic acid.[6,8,14–16] It is important to note that although the chronic ingestion of licorice in the presented case was the result of an extract tea purchased within the United States, ingestion of pure forms of glycyrrhizic acid is rare in our country as artificial licorice flavoring is often used in commercial products.[8] As recent as April 1, 2015, the US Food and Drug Administration has implemented specific limitations for the maximal level of the percentage of glycyrrhizin content in served food.[17]

In addition to resistant hypertension, other reports have implicated isoflavins found within licorice, which have estrogen-like activity, in the modulation of bone metabolism and consequently elevated levels of PTH.[18] A report from Mattarello and colleagues[18] investigated healthy women aged 22 to 26 years who were given commercial preparations of licorice containing glycyrrhizic acid for 2 months. The investigators found that PTH, 25-hydroxyvitamin D, and urinary calcium increased from baseline at the end of this 2-month investigation.[18] The findings of this study may be related to the presented patient's history of elevated PTH and previous kidney stones as discontinuation of licorice ingestion consequently led to the normalization of PTH. However, it is impossible to determine whether elevated PTH levels secondary to licorice were solely responsible for the development of these clinical and laboratory findings.

CONCLUSIONS

The presented case demonstrates a rare but significant cause of secondary hypertension. Identification of the

chronic consumption of licorice tea was essential for the proper diagnosis of secondary hypertension in an otherwise healthy 50-year-old woman and spared the patient from additional and unnecessary medical investigations. Although the diagnosis of acquired AME as the source of resistant hypertension remains a rare diagnosis, it should continue to be considered as its diagnosis simply requires thorough questioning during the clinical interview.

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