

## CLINICAL VIGNETTE

# Heraclitus Redux: Clinical Consequences of Licorice Ingestion, Once an Ancient Survival Strategy, Now Linked to Overindulgence in Modern Society

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### Introduction

Peripheral edema commonly prompts a patient to seek medical attention. Physicians routinely consider cardiac, renal and hepatic dysfunction as part of the differential diagnosis. Concomitant hypertension is commonly seen in this group of patients. In the case of a patient with edema, hypertension and unexplained hypokalemia, the differential diagnosis should include hyperaldosteronism and pseudohyperaldosteronism. A careful history should also include excess licorice ingestion. Licorice root or black licorice contains glycyrrhizic acid, which inhibits an adrenal enzyme, 11-beta-hydroxysteroid dehydrogenase (11BHS).<sup>1-4</sup> Inhibition of this enzyme leads to activation of the mineralocorticoid receptor by cortisol and results in edema, hypertension, hypokalemia and metabolic alkalosis. Cessation of black licorice ingestion results in complete resolution of symptoms and lab abnormalities. Literature suggests that consumption of relatively small amount of glycyrrhizic acid can cause clinical consequences. This is not a new phenomenon. Even before black licorice was used by confectioners, licorice root was known by survivalists for its ability to lead to water retention and thirst suppression. We describe an interesting case of weight gain, edema, new onset hypertension, hypokalemia and metabolic alkalosis, which resolved after cessation of excessive black licorice candy ingestion.

### Case

A 74-year-old woman presented to her primary physician with a 10 day history of sudden onset bilateral leg swelling. There had been an episode of idiopathic pericarditis 6 years previously, with normal cardiac catheterization. There had been no preceding prolonged travel or immobilization. The patient endorsed lifelong "low blood pressure", however the initial measurement on presentation was 151/74. Edema was noted to be 2+ to the knees bilaterally. Initial laboratory studies, in addition to the those listed in the table below, were notable for normal renal function with a BUN of 9 mg/dl, creatinine 0.48 mg/dl, albumin 3.9 g/dl, normal liver function studies, normal CBC, normal d-dimer, TSH 1.1 mIU/ml, sedimentation rate 21 mm/hr, BNP mildly elevated at 135 pg/ml, and normal urinalysis dipstick negative for protein. The ECG showed low voltage QRS complexes and non-specific T wave abnormalities, all unchanged from 6 years previously. On examination, other than pitting edema to the knees bilaterally, the cardiovascular examination was unremarkable. There was

neither jugular venous distension nor Kussmaul sign. An echocardiogram was normal. After review of the laboratory data showing only unprovoked hypokalemia and metabolic alkalosis, the patient was questioned regarding licorice ingestion. She reported receiving a box of "licorice caramels" from a family member two weeks prior, and had been eating 12 pieces per day since, each the size of a "See's candy". She was advised to discontinue licorice ingestion. No diuretic therapy was prescribed. Two weeks later her edema had resolved and her weight had decreased by 16 pounds. The BNP level decreased from 135 to 15 pg/ml. The potassium level increased and the serum bicarbonate decreased as indicated in the table below. She remained hypertensive with a reading of 148/84. She has remained asymptomatic since and blood pressure readings have only gradually returned to normal.

### Laboratory Results

	During licorice ingestion	4 weeks after cessation
Plasma Renin Activity	0.5ng/mL/hr (0.5-4)	1.3ng/mL/hr (0.5-4)
Aldosterone	<3.0ng/dL (4-31)	9.2ng/dL (4-31)
Potassium	3.0mmol/L (3.6-5.3)	4.6mmol/L (3.6-5.3)
Serum bicarbonate	31mmol/L (20-30)	23mmol/L (20-30)

### Discussion

Cases of pseudohyperaldosteronism typically present with hypertension, hypokalemia, metabolic alkalosis, low renin and low serum aldosterone.<sup>1-4</sup> The underlying pathophysiology is due to the inhibition of the adrenal enzyme 11-beta-hydroxysteroid dehydrogenase (11BHS). 11BHS normally converts cortisol to its inactive form, cortisone. When cortisol is not inactivated it is able to stimulate the mineralocorticoid receptor.<sup>1-4</sup> Because the concentration of cortisol is 100-1000 times higher than that of aldosterone, this leads to increased sodium retention, exaggerated renal potassium loss, low renin, low aldosterone and hypertension.<sup>4</sup>

Differential of pseudohyperaldosteronism typically includes endocrinopathies such as Cushing's syndrome and three monogenic types of mineralocorticoid induced hypertension: Liddle's syndrome, glucocorticoid remediable hypertension, and apparent mineralocorticoid excess which is an autosomal recessive disorder with mutations in 11B-HSD2 gene.<sup>3-4</sup> In this case, cessation of licorice ingestion led to resolution of her presenting symptoms. Furthermore, the plasma renin and aldosterone were no longer suppressed following cessation of licorice candy, therefore, these differential diagnoses were not entertained. Monogenic forms would be unlikely to present in the 7<sup>th</sup> decade.

The world health organization suggests that consumption of glycyrrhizic acid should be less than 100mg/day and the Dutch Nutrition Information Bureau has advised limiting intake to less than 200mg/day. As an example, consuming one 50 gram black licorice candy containing 0.2% glycyrrhizic acid can be enough then to cause significant side effects.<sup>2-4</sup> Our patient was ingesting approximately four times the recommended limit by consuming twelve, 21 gram, licorice caramels containing 0.35% glycyrrhizic acid. Each piece, therefore, contained 74mg of glycyrrhizic acid per piece, totaling approximately 888mg glycyrrhizic acid daily. Red licorice does not contain this compound, therefore the adverse effects are limited to black licorice and licorice root containing products.<sup>4</sup>

According to the ancient Greek historian Diogenes Laertius, Heraclitus, a pre-Socratic philosopher living in the 5<sup>th</sup> century BCE, became disgusted by humans and decided to withdraw to the desert, where he survived by eating only herbs and roots. During this time he became affected by hydrops (a diffuse state of edema) and died at the age of 60. In that period, licorice root was abundant in the Mediterranean area, and was popular for desert survival due to its ability to reduce hunger and thirst. The suppression of thirst is related to the mineralocorticoid-like effect of glycyrrhizic acid. The hydrops of Heraclitus could be interpreted as a consequence of the exaggerated intake of licorice roots, leading to severe sodium and water retention, hypertension and congestive heart failure, leading to his death.<sup>5</sup> Excess glycyrrhizic acid ingestion is an ancient problem that still presents in clinical practice and may only be recognized after a careful history.

## REFERENCES

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