Latent Pseudohyperaldosteronism Induced by Salty Liquorice, Unmasked After Sustained High-Dose Ibuprofen Use: Lessons from a Clinical Case

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Abstract
Case Presentation

After treatment with high-dose Ibuprofen during several weeks for a traumatism, a 56-year old male developed resistant hypertension with hypokalemia and mild renal failure, which persisted after Ibuprofen withdrawal. He was referred to our Outpatient Hypertension Clinic for workup. He was diagnosed of acquired pseudohyperaldosteronism, with suppressed renin and aldosterone, and mild metabolic alkalosis. Anamnesis revealed that the patient had been consuming high doses of salmiak (salty liquorice) for many years, maintaining normal blood pressure and renal function. Other causes of pseudohyperaldosteronism were ruled out. One month after salmiak withdrawal, blood pressure, aldosterone, renin activity, potassium, pH and renal function returned to normal without antihypertensive treatment. When the patient resumed consumption of liquorice (but in a non-salty, deglycyrrhizinated variety) blood pressure and laboratory tests remained normal.

Conclusions
This case underscores the relevance of an adequate workup for secondary hypertension in patients who develop resistant hypertension. Diagnosing liquorice-induced pseudohyperaldosteronism is challenging: a high suspicion and a thorough anamnesis are required. Reaching a correct diagnosis is greatly relevant for the patient, because this is a reversible condition, which can usually be corrected simply by withdrawing liquorice, while its complications may be severe, even life-threatening.

The close temporal relationship between Ibuprofen use and development of pseudohyperaldosteronism in a patient who had been consuming high doses of liquorice for years suggests that the renal impairment caused by Ibuprofen unmasked a latent pseudohyperaldosteronism which by itself had caused no previous clinical manifestations. This situation had never (in our knowledge) been reported before.

Keywords
Pseudohyperaldosteronism; Liquorice; Secondary hypertension; NSAID

Introduction
A key effect of the activation of the mineralocorticoid receptor by aldosterone is the stimulation of the epithelial sodium channel (ENaC) in the kidney tubules [1], causing re-absorption of Na⁺ and water, and secretion of K⁺ and H⁺. Pseudohyperaldosteronism is a medical condition that mimics primary aldosteronism, with high blood pressure, low plasma potassium, suppressed renin and metabolic alkalosis. However, in contrast with primary aldosteronism, plasma aldosterone is absent or low [1,2].

The mechanisms and causes of pseudohyperaldosteronism have been reviewed in detail elsewhere [2]. Briefly:
1) Active precursors of aldosterone (primarily 11-deoxycorticosterone) may accumulate in congenital enzymatic deficiencies (primarily 11-β-hydroxilase, which converts 11-deoxycorticosterone to deoxycorticosterone, which is then converted to aldosterone;
also 17-α-hydroxylase). Patients with these deficiencies develop congenital adrenal hyperplasia and hypertension, typically in their childhood. Very rarely, functioning adrenal tumors producing 11-deoxycorticosterone or deoxycorticosterone but little or no aldosterone may develop in adulthood.

2) Very infrequent mutations of the mineralocorticoid receptor which are constitutionally active or over expressed; involved in some cases of preeclampsia.

3) Cushing’s syndrome: Cortisol is able to activate mineralocorticoid receptors, but in aldosterone-sensitive cells the presence of an enzyme, namely 11-β-hydroxysteroid dehydrogenase type II, converts cortisol to cortisone which has very low affinity for the mineralocorticoid receptor. However, in Cushing’s syndrome, the excess of cortisol may overload the enzyme.

4) Apparent mineralocorticoid excess syndrome: Congenital deficiency of the mentioned enzyme 11-β-hydroxysteroid dehydrogenase type II, typically with low birth weight, failure to thrive, severe hypertension since childhood and autosomal recessive heredity.

5) Liddle syndrome: due to mutations that constitutionally activate the epithelial sodium channel (ENaC), mimicking activation of the aldosterone receptor, typically with severe hypertension since childhood and autosomal dominant heredity [2,3].

6) Intake of drugs that directly stimulate the mineralocorticoid receptor (9-α-F-hydrocortisone, fluoroprednisolone), or large doses of glucocorticoids with mineralocorticoid activity (hydrocortisone, etc); rarely, oral contraceptives [1,2].

7) Consumption of excessive amounts of liquorice, or rarely other foodstuffs with similar effect (grapefruit, bitter oranges), or the liquorice derivative drug carbenoxolone [1,2,4].

Liquorice [extracted from the plant Glycyrrhiza glabra, Figure 1] has been appreciated since antiquity for its peculiar sweet flavor, and has been used also as a medicine since the Assyrian and Egyptian civilizations [4]. The plant root contains 2-25% of glycyrrhizic acid (two molecules of glucuronic acid linked to a molecule of 18-β-glycyrrhetic acid [4], Figure 2). Glycyrrhizic acid primarily causes pseudohyperaldosteronism by inhibiting 11-β-hydroxysteroid dehydrogenase type II, thus mimicking the apparent mineralocorticoid excess syndrome [1-4]; it also can directly stimulate the mineralocorticoid receptor and inhibit the liver enzyme 5 β-reductase which degrades aldosterone, enhancing aldosterone action (Figure 3). The sustained intake of > 2 mg/kg/day of 18-β-glycyrrhetic acid is one of the most common causes of pseudohyperaldosteronism [4,5]. Thus, it must be suspected and actively sought given that liquorice is not only consumed as such, but also included in tobacco, liquors, dark beer, candy, ice cream, chewing gum, and baked confectionery [4]. Besides, glycyrrhizic acid has a significant interaction with coumarin anticoagulants, enhancing their degradation. Grapefruit and bitter oranges (also known as Seville oranges and usually consumed as jam) contain naringenin, which also inhibits 11-β-hydroxysteroid dehydrogenase type II [1].

Jerome Conn reported the first known case of pseudohyperaldosteronism in 1968, in a patient consuming large amounts of liquorice [6]. Since then, a few dozen cases have been reported [7,8], often with severe complications: potentially lethal hypokalemia and arrhythmia [9], acute rhabdomyolysis and tetraparesis [10,11], hypertensive encephalopathy [12,13], or life-threatening hypertensive crises with severe retinopathy, kidney and liver damage [14,15]. However, liquorice-induced pseudohyperaldosteronism and hypertension seems to be grossly underdiagnosed [16].

We hereby present a case in which a patient had maintained a large intake of salty liquorice for years without any apparent ill effects; however, he developed resistant hypertension and pseudohyperaldosteronism immediately after the sustained intake of large doses of a non-steroid anti-inflammatory drug (Ibuprofen). We therefore suspect a connection between the NSAID intake and the unmasking of liquorice-induced hypertension, which previously had never (to our knowledge) been reported.

Case Report
A 56 years old Swedish male was referred to our Hypertension Outpatient Clinic for workup of secondary hypertension. He was hypertensive and had died at age 67 due to coronary heart disease. Our patient used to smoke about ten cigarettes daily, but did not have any other previous health issues. He had yearly health checkups and his renal function and blood pressure had always been normal. Seven months before the referral he suffered a skiing accident with multiple contusions and lacerations, but without any...
Bone fractures. After the accident he took high doses of ibuprofen (600 mg 3-4 times daily) for several weeks. His family physician detected high blood pressure (160-170/95-100 mmHg) in several occasions, switched him to Acetaminophen and recommended him to stop smoking and reduce his salt intake. However, his blood pressure remained high. He began treatment with Enalapril 20 mg daily which was withdrawn due to dry cough, and besides, his blood pressure was unchanged. He was switched then to Valsartan 80 mg daily, which was well tolerated, but his blood pressure did not improve. Therefore the patient was switched to a fixed combination of Valsartan + Amlodipine + Hydrochlorothiazide 160/5/12.5 mg once a day, but his systolic blood pressure was still ~150 mmHg; the patient also developed mild hypokalemia (3.32 mEq/L) and alkalosis (venous blood pH 7.56), standard plasma bicarbonate 36 mmol/L). Plasma metanephrine and normetanephrine in the low ranges, aldosterone (1.2 ng/dL), suppressed plasma renin activity (PRA < 0.2 ng/mL/h) aldosterone/PRA ratio not calculable, mild metabolic alkalosis (venous blood pH 7.56, standard plasma bicarbonate 36 mmol/L). Plasma metanephrine and normetanephrine in the low normal range (24 and 14 pg/mL, respectively). A recent abdominal CT scan (after the accident) showed no adrenal or renal anomalies, and a simple chest X-ray was also normal.

With these data and after confirmation of low aldosterone (< 0.9 ng/dL in a separate sample) we concluded that the patient very probably had hypertension secondary to pseudohyperaldosteronism. Liddle syndrome or congenital enzymatic deficiencies were considered very unlikely, due to the age of debut and the apparent lack of family history [3]. An adrenal functioning tumor producing active aldosterone precursors (deoxycorticosterone or 11-deoxycorticosterone) was reasonably ruled out due to the normal CT scan. Clinical and laboratory data were not suggestive of Cushing’s syndrome.

The most likely cause seemed to be a high intake of liquorice. When directly reinterrogated, the patient revealed that he was in the habit of consuming 50-75 g of salmiak (a Nordic specialty based on liquorice with added sea salt and ammonium chloride) daily for many years. We recommended the patient to stop both the salmiak intake and the antihypertensive medication, and check his home blood pressure. One month afterwards, the patient had normal office blood pressure (136/78 mmHg) and mentioned that his home blood pressure was normal one week after stopping the intake of salmiak; new lab tests were also normal or improved (Plasma Cr 1.25 mg/dL, eGFR 46 mL/min/1.73 m², K⁺ 4.8 mEq/L, aldosterone 12.8 ng/dL, PRA 0.9 ng/mL/h, A/PRA ratio 9.7, venous pH 7.42). In a new visit six months afterwards the patient was consuming again daily 25-50 g of liquorice, but in a non-salty, deglycyrrhizinated variety (apparently free of aldosterone-mimetic action); his blood pressure was still normal, with minor changes in his lab tests: Plasma Cr 1.21 mg/dL, eGFR 67 mL/min/1.73 m², K⁺ 4.9 mEq/L, aldosterone 11.6 ng/dL, PRA 1.2 ng/mL/h, A/PRA ratio 9.7, venous pH 7.42).

Discussion

The effects of NSAIDS on blood pressure and renal function have been extensively reviewed elsewhere [17]. Briefly, NSAIDs inhibit the COX-2 cyclooxygenase and the renal synthesis of prostaglandins (primarily PGE, and PGL), decreasing renal blood flow and sodium and water excretion; they may also increase systemic vascular resistance, impair endothelium-dependent vasodilation and enhance the harmful actions of angiotensin II [17,18]. Moreover, the effect of antihypertensive drugs (with the possible exception of calcium-channel blockers) seems to be blunted by the use of NSAIDS [18].

Notwithstanding, in normotensive subjects with preserved renal function NSAIDs seem to elicit small, non-significant increases in their blood pressure; however hypertensive patients suffer significant increases in their mean arterial pressure (in excess of 5 mmHg), according to a large metaanalysis [19]. A recent nationwide longitudinal cohort study involving 32000 Taiwanese subjects showed that hypertensive patients taking NSAIDs have a significantly higher risk (vs. non-NSAID consumers) of developing chronic kidney disease which is time- and dose-dependent [17].

Many people in the world consume large amounts of liquorice and obviously not all of them develop pseudohyperaldosteronism and hypertension [4], although this occurrence is probably much more common than usually thought [16]. It is therefore tempting to consider that a temporary impairment of the renal function (as presumably caused by the consumption of large doses of ibuprofen during several weeks) may have unmasked the effect of liquorice on development of pseudohyperaldosteronism and hypertension in our patient. The effects of NSAIDs and liquorice in the kidney can possibly add up, as both can cause sodium and water retention by different mechanisms. Although we cannot be sure, the close temporal relationship between the NSAID intake and the development of secondary hypertension in a patient who had been consuming a high dose of liquorice for years maintaining normal blood pressure strongly suggests a casual connection and is hypothesis-generating at least. It is remarkable, however, that once pseudohyperaldosteronism and hypertension were established, the removal of ibuprofen did not revert them, but the subsequent abstinence from liquorice brought blood pressure and the renin-aldosterone axis back to normal in a very short time (a month at most, more likely a week according to the patient’s home blood pressure reports).

It is also interesting to remark that the patient was a consumer of salty liquorice (salmiak) which has only rarely been reported in connection with pseudohyperaldosteronism [20]. The extra amount of sodium might conceivably have played a role in the development of Valsartan + Amlodipine + Hydrochlorothiazide 160/5/12.5 mg daily which was withdrawn due to dry cough, and besides, his blood pressure did not improve. Therefore the patient was switched to a fixed combination of Valsartan + Amlodipine + Hydrochlorothiazide 160/5/12.5 mg once a day, but his systolic blood pressure was still ~150 mmHg; the patient also developed mild hypokalemia (3.32 mEq/L) and alkalosis (venous blood pH 7.56), standard plasma bicarbonate 36 mmol/L). Plasma metanephrine and normetanephrine in the low ranges, aldosterone (1.2 ng/dL), suppressed plasma renin activity (PRA < 0.2 ng/mL/h) aldosterone/PRA ratio not calculable, mild metabolic alkalosis (venous blood pH 7.56, standard plasma bicarbonate 36 mmol/L). Plasma metanephrine and normetanephrine in the low normal range (24 and 14 pg/mL, respectively). A recent abdominal CT scan (after the accident) showed no adrenal or renal anomalies, and a simple chest X-ray was also normal.

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of hypertension. However, the main flavoring agent added to liquorice in salmiak is ammonium chloride (7% in average) which has not been linked to hypertension, and the amount of sea salt added seems to be small (less than 1%). We also would like to remark that the use of deglycyrrhizinated liquorice after abstention from salmiak did not bring back any apparent ill effect. Although this could be expected, given that the adverse effects of liquorice are generally attributed to glycyrrhetic acid [1,2,4], the fact had not been reported before (to our knowledge).

Conclusions

• The sudden presentation of resistant hypertension warrants an adequate workup for secondary hypertension; it is not enough to keep adding hypertensive drugs until blood pressure is (hopefully) controlled.
• The occurrence of hypokalemia along with hypertension (even when the patient is taking diuretics) warrants a workup for hyperaldosteronism; and, in case that aldosterone is suppressed, for pseudohyperaldosteronism.
• Most causes of pseudohyperaldosteronism are congenital and typically cause hypertension and hypokalemia since childhood. Acquired pseudohyperaldosteronism in adults is most often caused by Cushing’s syndrome, drugs with mineralocorticoid effect, or foodstuffs (primarily liquorice, also grapefruit and bitter orange).
• Liquorice-induced pseudohyperaldosteronism is a cause of resistant hypertension with very severe, life-threatening complications. It is also easily treatable, simply by avoiding liquorice consumption (plus support measures, if needed).
• However, this condition seems to be overlooked and grossly infradiagnosed. Patients usually consider liquorice to be harmless, or at most are worried about the caloric excess implied by its consumption. Therefore, they are unlikely to report it. A high suspicion and a thorough anamnesis including dietary habits are needed in order to reach a diagnosis.
• The sustained use of a NSAID such as Ibuprofen in high doses might have unmasked a latent liquorice-induced pseudohyperaldosteronism in our patient, due to its renal effects (temporary impairment in renal blood flow and sodium excretion). This is an attractive novel hypothesis, worthy in our opinion of further investigation.

Conflicts of Interest

None

Sources of Funding

None

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