

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 -hydroxylase, which converts 11-deoxycorticosterone to deoxycorticosterone, which is then converted to aldosterone;

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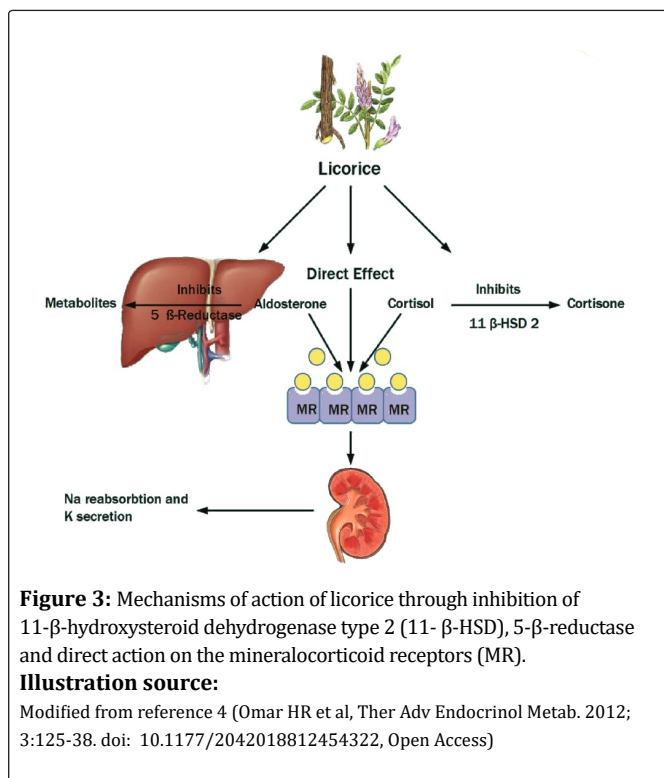
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bone fractures. After the accident he took high doses of Ibuprofen (600 mg 3-4 times daily) for several weeks. His family physician detected high blood pressure (160-170/95-100 mmHg) in several occasions, switched him to Acetaminophen and recommended 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 treated 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 borderline stage 3 renal failure with plasma creatinine 1.35 mg/dL (estimated glomerular filtration rate 58 mL/min/1.73 m², CKD-EPI). At this point he was referred to our Clinic.

The patient was asymptomatic except for muscle weakness, no longer taking any pain medication. He had reduced salt intake and withdrawn smoking. His weight was 77.6 kg, height 176.8 cm, waist circumference 98 cm, body mass index (BMI) 24.8 kg/m², seated office blood pressure 155/88 mmHg, heart rate 72 bpm, without cushingoid features or any other relevant findings in the physical examination. The ECG was normal. The lab tests (with the previous medication) revealed normal plasma glucose, sodium, lipid profile, liver enzymes, cortisol, ACTH, TSH and blood count; but plasma K⁺ was 3.45 mEq/L and plasma creatinine 1.35 mg/dL. In order to study the adrenal axis, we switched the patient to diltiazem 120 mg twice a day for three weeks. The relevant lab results (obtained in the upright position) were: plasma K⁺ 3.6 mEq/L, plasma Cr 1.33 mg/dL, very low plasma 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 licorice 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 64 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 PGE₂ and PGI₂), 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 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 deglycyrrhized liquorice after abstinence 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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