

Case Report

A Rare Case of Young Onset Hypertension due to Renal Artery Stenosis Precipitated by Liquorice Ingestion, Which was Cured by Nephrectomy and Auto-Transplantation

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Abstract

Background: Renal artery stenosis accounts for 1-2% of all cases of hypertension, of which <10% is due to Fibromuscular dysplasia. Licorice is the root of *Glycyrrhiza glabra* and is a rare but recognized cause of hypertension.

Case Description: A 26 year old previously healthy female presented with two months of generalized body weakness. She had a high blood pressure of 200/140mmHg. She recalled drinking a herbal drink prior to onset of symptoms, which was found to contain liquorice (*Glycyrrhiza glabra*). Investigations showed persistently low serum K⁺ of 2.9mmol/l, with metabolic alkalosis (pH 7.49). She had a urine protein: creatinine ratio of 965mg/dl, but serum creatinine was 63umol/l. Her serum aldosterone level was 115ng/dl, and plasma renin concentration 1274uIU/ml. Liquorice could not explain hyper-reninemic hyper aldosteronism. Although renal artery doppler showed no stenosis, ultrasound abdomen showed discrepancy of kidney sizes: 10.2cm and 8.4cm. CECT abdomen showed 70% stenosis of the left renal artery. She required intravenous infusion of glyceryl trinitrate to control her blood pressure and was started on four antihypertensives. Hypokalemia correction required oral and intravenous potassium supplements. She underwent laparoscopic left sided nephrectomy and auto-transplantation. Following surgery her antihypertensives were tailed off over 2 months, and she had normal kidney function.

Conclusion: Renal artery stenosis is a rare but recognized cause of hypertension. Not all cases initially have hypertension, but may be precipitated by liquorice ingestion. The two have different mechanisms of causing hypertension and hypokalemia, but they may act synergistically. Kidney auto-transplantation is a successful mode of treatment of renal artery stenosis.

Keywords: Renal Artery Stenosis; Fibromuscular Dysplasia, Liquorice; *Glycyrrhiza*; Apparent Mineralo Corticoid Excess

Abbreviations

RAS: Renal Artery Stenosis; FMD: Fibromuscular Dysplasia; AME: Apparent Mineralo Corticoid Excess; PRA: Percutaneous Renal Angioplasty; RAT: Renal Auto-Transplantation

Introduction

Renal Artery Stenosis (RAS) accounts for 1-2% of all cases of hypertension, and 5.8% of secondary hypertension [1,2]. Atherosclerosis accounts for 90% cases of RAS, and is seen in elderly and those with cardiovascular risk factors. Fibromuscular Dysplasia accounts (FMD) for <10% cases of RAS, and is commoner in young females [3]. Licorice is the root of *Glycyrrhiza glabra*. It has been found to have mineralocorticoid, estrogenic, anti-tumoral, anti-inflammatory, anti-allergenic, and anti-tussive properties, and is being used in herbal medications as a de-stressing agent, for protection against gastric ulcers, and as a sweetener [4]. There are rare reports of chronic occupational inhalation exposure to licorice root

dust causing hypokalemic hypertension. It has an estimated use in the United States of 0.027-3.6mg glycyrrhizin/kg/day. Licorice is a rare but recognized cause of hypertension and hypokalemia, and the Food and Drug Administration (FDA) has issued warnings about its use [5]. Both the above conditions cause hypertension, hypokalemia and metabolic alkalosis via different mechanisms.

Case Presentation

A 26 year old female lawyer presented with a two months history of generalized body weakness. On admission she was found to have a high blood pressure of 200/140mmHg. However her blood pressure during a routine check-up one year ago was 120/80mmHg. She recalled drinking a herbal de-stressing drink on seven occasions over a month period before onset of symptoms. When tracing the ingredients of the drink it was found to contain liquorice (*Glycyrrhiza glabra*). She had a BMI of 18kg/m², with high blood pressure as above and pulse rate was 100. She had no organomegaly and no obvious renal artery bruits. She had no pappilloedema. Investigations showed low serum K⁺



Figure 1: CECT abdomen and CT renal angiogram showed the left kidney being relatively smaller; 8.4cm in diameter, with a short segment (4.0mm) eccentric narrowing causing approximately 70% stenosis 10.4mm from the ostium of the left renal artery, with minimal dilatation of the pre-stenotic segment, and normal flow beyond the stenotic segment.

of 2.9mmol/l, with increased urinary K^+ excretion of 51mmol/L/day. Serum Na^+ was 136mmol/l and serum Ca^{2+} , Mg^{2+} , and Cl^- were normal. She had metabolic alkalosis with a pH of 7.49. She had proteinuria with a urine protein: creatinine ratio of 965mg/g, with low serum albumin of 2.7g/dl. Her serum creatinine was 63umol/l and eGFR >90. Her serum cortisol day curve was: 0800h- 702nmol/l; 1000h- 705nmol/l; 1200h- 584nmol/l; 1400h- 569; 1600h- 423nmol/l. Her Haemoglobin was 14g/dl, white cell count 20×10^3 with neutrophilia, monocytosis, and lymphopenia, and blood picture showed polymorphonuclear leukocytosis. ESR was 10mm and CRP was 6mg/L. 24 hour urinary VMA levels (9.6mg/24 hours) and thyroid function tests were normal. 2D Echocardiogram showed no left ventricular hypertrophy. Ultrasound abdomen showed kidney sizes being 10.2cm and 8.4cm, and no suprarenal masses (Figure 1). Bilateral renal artery doppler showed no evidence of renal artery stenosis. Her serum aldosterone level was 115 ng/dl (2-9 ng/dl), plasma renin concentration 1274 uIU/ml (2.8-39.9 uIU/ml), and aldosterone renin ratio 0.09. The presence of hyper-reninemic hyper aldosteronism with normal renal artery doppler study arose the suspicion of a renin secreting tumor. CECT abdomen and CT renal angiogram showed the left kidney being relatively smaller; 8.4cm in diameter, with a short segment (4.0mm) eccentric narrowing causing approximately 70% stenosis 10.4mm from the ostium of the left renal artery, with minimal dilatation of the pre-stenotic segment, and normal flow beyond the stenotic segment. Tc99m DTPA renal scan showed small sized left kidney with significant renal artery stenosis demonstrating delay in perfusion, moderate to severe functional impairment, and satisfactory sub-renal drainage pattern. She required intravenous infusion of glyceryl trinitrate to control her blood pressure and was later started on losartan 50mg bd, prazosin 7mg tds, nifedipine 20mg bd and methyldopa 500mg bd. Hypokalemia correction required oral and intravenous potassium supplements. A multidisciplinary approach was taken in this patient's management including a general physician, consultant endocrinologist, genitourinary surgeon, general surgeon and Consultant anaesthetist. She then underwent 3D Laparoscopic left sided nephrectomy and auto-transplant. The stenosed segment

of the renal artery was excised, the renal vein was anastomosed to the external iliac vein and the renal artery was anastomosed to the internal iliac artery. The Renal doppler study of the transplanted kidney was normal. Following surgery, her antihypertensives were gradually tailed off over 2 months, maintaining normal blood pressure, and normokalaemia.

Discussion

Decreased renal artery perfusion in RAS leads to increased renin levels, resulting in increased angiotensin conversion and increased aldosterone levels which lead to vasoconstriction, and hypertension [6]. Other mechanisms of hypertension in RAS are exaggerated sympathetic response, endothelial dysfunction, oxidative stress and presence of ischaemic nephropathy [7]. Licorice inhibits 11β hydroxysteroid dehydrogenase type 2, which converts active cortisol to inactive cortisone. This leads to Apparent Mineralocorticoid Excess (AME) resulting in unrestricted sodium and water reabsorption, potassium excretion, and hypertension, thus suppressing the renin-aldosterone axis [8]. This case shows increased aldosterone and renin levels, indicating the effect of renal artery stenosis to be the main culprit to cause hypertension in this case. However, the fact that her blood pressure was normal during a routine check-up one year ago may indicate that the hypertensive effect of her underlying RAS might have been previously masked, but it was precipitated by the ingestion of licorice. Considering her age and gender it is more likely that the cause for her RAS might have been FMD.

Although a renin secreting tumor was suspected as the renin level was very high, the discrepancy of the kidney sizes despite having a normal renal artery Doppler study, RAS was highly suspected and warranted active exclusion. However, a CECT abdomen and CT renal angiogram supported confirmation, of the diagnosis of RAS. A peak systolic velocity of >200cm/sec is the threshold to diagnose reduction in renal artery diameter of 60%, and this has a sensitivity of 85%, and a specificity of 92% [9]. Thus the duplex scan being negative as in this case does not exclude RAS, which is also a learning point from this case.

Though RAS is a rare but recognized cause of hypertension, RAS can be present without renovascular hypertension. Though the stenosed renal artery causes vasoconstriction and increased peripheral resistance, if the non-stenotic kidney is normal the blood pressure can be normalized by salt and water restriction, which does not happen in the case of bilateral RAS. Studies have shown that the renal artery lumen should be obliterated by 75-80% for the development of hypertension [7,10] In this case the stenosis was 70%, which was probably why her blood pressure was previously normal, until the hypertensive episode was precipitated by licorice ingestion. RAS can lead to reduced glomerular filtration resulting in ischaemic nephropathy which progresses to chronic renal failure, which can also lead to secondary hypertension [11]. This patient however had proteinuria indicating early nephropathy, but normal serum creatinine and eGFR indicating preserved renal function. This shows why the blood pressure normalized after revascularization surgery. This would improve her morbidity as the surgery was done prior to development of ischaemic nephropathy and chronic renal failure.

Resistant hypertension as in this case requires further intervention

in addition to medical management. Percutaneous Renal Angioplasty (PRA) is the procedure of choice for ostial or focal, either main or branch RAS due to atherosclerosis or FMD [12]. Barrier et al showed that PRA with or without stenting had initial success rates with improved or cured hypertension in 92% cases, but hypertension recurred later in 42%, likely due to restenosis, and the blood pressure benefit increased to 78% after the second procedure [13]. However some studies have shown disappointing results in revascularization, with no benefit of surgery over percutaneous revascularization [7]. Surgery may be indicated in RAS due to FMD, particularly in recent onset hypertension or with worsening renal function, or for complex lesions such as aneurysms. Surgical revascularization includes aortorenal bypass extra-anatomical bypass procedures, unilateral nephrectomy, extracorporeal microvascular reconstruction and endarterectomy [7]. Renal Auto-Transplantation (RAT) is indicated in young patients with renal artery lesions located in the main artery and intra-hilar segmental arterial branches simultaneously, completely occluded renal artery in functioning kidney, or tight ostial lesions that are not accessed during PRA and stenotic lesions with aneurysms. RAT is more beneficial than PRA as it decreases the number of repeated interventions, and prevents renal function deterioration over long term, and does not require anticoagulation following stenting. Therefore RAT is preferred in younger patients with FMD as in this case [12]. Mhaske et al showed a 87.5% success rate with normalization or improvement of blood pressure following RAT on 2 year follow up [12]. Since this patient had a very short segment stenosis of 4mm it was not suitable for PRA or stenting, and since the stenotic segment was just 10.4mm from the ostium it was too close and not suitable for resection and anastomosis of the stenotic segment. Therefore, nephrectomy and RAT was performed with a good outcome.

Liquorice which is known as “Wel-mee” in the Sinhala language, is used in native ayurveda medicine to treat gastritis, peptic ulcers, and phlegm and as a stress relieving medication, and is used as a sweetener in candy. As explained previously the ingestion of liquorice in this case caused AME leading to precipitation of hypertension. It has been shown that 50g liquorice, which accounts to 100mg glycyrrhizin is required to cause significant hypertension [8]. She consumed a liquorice containing drink on seven occasions for a month, each tea bag containing 100mg glycyrrhizin. Hypertension caused by liquorice alone usually settles soon after cessation of liquorice ingestion, but the fact that the hypertension persisted until revascularization surgery, indicates RAS had a larger impact on her hypertension [8]. The threshold of the dose of liquorice needed to precipitate hypertension in this case was lower than usual, probably because the patient already had an underlying condition which leads to hypertension. There were a few reported cases of liquorice induced hypertension, but this is the first such reported case of hypertension in underlying RAS precipitated by liquorice ingestion [14].

Conclusion

RAS is a rare but recognized cause of hypertension. Not all cases of

RAS have hypertension, but its hypertensive effect may be precipitated by liquorice ingestion and may persist even after withdrawing liquorice. RAS and liquorice ingestion have different mechanisms of causing hypertension but they may act synergistically as in this case. It is important that RAS is diagnosed early and intervention is done to prevent progression of disease, as it is a reversible cause of young onset hypertension. Nephrectomy and auto-transplantation is a successful mode of treatment for RAS with good outcome.

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