

Severe Hypertension Coexisting with Hypokalaemia in A Young Adult: Case Report and Literature Review

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ABSTRACT

Background: Systemic hypertension, affecting about one billion people worldwide, is the most prevalent modifiable risk factor for cardiovascular diseases and related disability. Secondary hypertension is a common problem among young adults. **Case Summary:** We report a case of a 23-year old man who presented to the emergency room with 8-month history of progressive general body weakness preceded by numbness and paraesthesia initially involving the left then the right lower limbs with family history of hypertension. Blood Pressure was 150/80mmHg. His serum potassium was 1.6mmol/L (Normal range 3.0-5.0) other electrolytes, urea and creatinine were normal. Urinary potassium was 215mmol/24hr (Normal range < 20mmol/24hrs). A diagnosis of severe hypokalaemia in a hypertensive patient with Liddle's syndrome was made. He was commenced on oral Moduretic (contains Amiloride and hydrochlorothiazide because Amiloride or triamterene only formulation is not available) and intravenous potassium replacement. **Conclusion:** Our index case is a 23-year old young man known hypertensive who presented with quadriparesis and spontaneous hypokalaemia with family history of hypertension. The likely cause of his hypertension and hypokalaemia is Liddle's syndrome, however plasma aldosterone concentration, plasma renin activity and genetic studies were not available for us to confirm this diagnosis. Even though this form of hypertension is rare, there is a need for a high index of suspicion for it by the clinicians whenever hypertension is diagnosed in a young individual especially in Maiduguri, Nigeria which have a high prevalence of renal impairment among young individuals' majority of whom have background hypertension.

Keywords: Hypokalaemia, Liddle's syndrome, Quadriparesis, Secondary hypertension, Systemic hypertension

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Introduction

Systemic hypertension, affecting about one billion people worldwide, is the most prevalent modifiable

risk factor for cardiovascular diseases and related disabilities.¹ According to the JNC 8 classification, hypertension is defined as elevated blood pressure measured on at least two separate screenings at rest with appropriate cuff with systolic blood pressure of ≥ 140 mmHg and/or diastolic of ≥ 90 mmHg in patients 18-59 years or systolic blood pressure of ≥ 150 mmHg and/or diastolic of ≥ 90 mmHg in patients 60 years or older without major comorbidities.² Hypertension is traditionally divided into essential or primary hypertension and secondary hypertension. Essential hypertension is the predominant form of hypertension in both children and adults, it is a multifactorial condition, resulting from a complex interaction between lifestyle and genetic factors without a specific aetiology while secondary hypertension is usually due to a specific/definitive identifiable cause which can also be hereditary or non-hereditary. We present a case of a 23-year old male with a severe form of a rare secondary hypertension coexisting with hypokalemia.

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Case Presentation

A 23-year-old man presented to the emergency room with 8-month history of progressive general body weakness preceded by numbness and paraesthesia initially involving the left then the right lower limbs. He had no prior history of fall, trauma to the back, muscle pain or skin lesions. Weakness was not related to ingestion of liquorice, diuretic, heavy carbohydrate meals or strenuous activity. He had no symptoms suggestive of thyrotoxicosis or myaesthesia gravis. He was diagnosed hypertensive about 2 years prior to presentation and had been on Amlodipine and Lisinopril without adequate control despite being regular on them. His mother and three of his siblings were hypertensive. Hypertension was diagnosed between ages of 20 and 22 years in the siblings.

On Physical examination he had no cushingoid facie or renal bruit, had power of 3/5 in both UL and 2/5 in both LL with normal tone and reflexes, other nervous system examinations were intact. Admitting BP was 150/80mmHg. Other systemic examinations were normal.

His serum potassium was 1.6mmol/L (Normal range 3.0-5.0) other electrolytes, urea and creatinine were normal (compensatory mechanism must have played a role for the normal bicarbonate level). Urinary potassium was 215mmol/24hr (Normal range < 20mmol/24hrs) indicating a significant renal loss. Electrocardiogram was normal. Kidneys were normal and equal in size with normal echo-pattern and no adrenal mass on ultrasound scan examination. Facilities for measurement of plasma renin activity, aldosterone or genetic testing were not available in our facility and therefore they were not done.

A diagnosis of severe hypokalaemia in a hypertensive patient secondary to? Liddle's syndrome was made. He was commenced on oral Moduretic (contains Amiloride and hydrochlorothiazide because Amiloride or triamterene only formulation was not available) and intravenous potassium replacement. He started walking with resolution of limb weakness after 6 days on admission, He was later discharged on oral Moduretic and potassium tablet (slow K) on the 8th day while his BP and repeat serum potassium were normalized after 2weeks on his follow up visit.

Discussion

Although the majority of hypertension in the adult population is primary hypertension also known as essential hypertension, in few cases it is reasonable to

evaluate for possible secondary causes of hypertension. Hypertension of new onset in patients younger than 30 years or of sudden onset in those older than age 50 years, hypertension in the absence of obesity, the lack of a strong family history of hypertension, the requirement for three or more medications; one of which is a diuretic with suboptimal control, the acute deterioration of renal function with the initiation of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), paroxysmal symptoms of anxiety, diaphoresis, or palpitations, Cushingoid features, renal dysfunction, and the presence of hypokalaemia and metabolic alkalosis are all findings suggestive of secondary hypertension.³

Hypokalaemia and Hypertension

Potassium is the most abundant intracellular cation in the body with major effect on the resting membrane potential. Excretion of potassium occurs via the kidney (90%) and the remaining 10% through the gastrointestinal tract and skin. Potassium secretion is accomplished via apical potassium channels (ROMK: renal outer medullary K⁺) of the cortical collecting duct via the effect of aldosterone. The secretion of potassium in this nephron segment is indirectly but tightly coupled to sodium reabsorption via the epithelial amiloride-sensitive sodium channel (ENaC).⁴ Therefore increased sodium reabsorption via aldosterone interaction with the mineralocorticoid receptor (e.g. in primary aldosteronism) or increase in the activity of the ROMK (e.g. in Liddle's syndrome) will result into increased potassium secretion causing hypokalaemia while decreased sodium reabsorption (e.g. in aldosterone deficiency) or decreased activity of the ROMK (e.g. in amiloride intake) will decrease potassium secretion and consequently cause hyperkalaemia.

Diuretic use commonly causes hypokalaemia in hypertensive patient by enhancing urinary flow and sodium delivery through the collecting tubule. Potassium secretion is further enhanced in the setting of diuretic-induced intravascular volume depletion and secondary aldosterone stimulation.³ Spontaneous hypokalaemia in a young hypertensive patient, in the absence of diuretic use, deserves further evaluation and hence our index case.

The most common causes of hypertension with hypokalaemia are presented below:



Liddle's Syndrome

A clinical syndrome that mimicked primary aldosteronism was reported by Liddle et al in 1963 as pseudoaldosteronism, subsequently named Liddle's syndrome after Dr. Grant Liddle (1921- 1989), an American endocrinologist at Vanderbilt University in the USA. It is a rare monogenic autosomal dominant disorder characterized by hypertension, hypokalaemic alkalosis, with low plasma renin and aldosterone.⁵ Constitutive activation of the amiloride-sensitive epithelial Na channel (ENaC), result in sodium retention and wasting of urinary potassium and hydrogen ion. The channel is a heteromeric complex constituted of three homologous subunits, α , β , and γ , encoded by the SCNN1A, SCNN1B and SCNN1G genes, respectively. Liddle's syndrome results from germ line mutations in SCNN1A, SCNN1B or SCNN1G genes which prevents the internalization and degradation of the ENaC allowing its accumulation in the distal nephron apical membrane leading to an increase in sodium reabsorption and consequent potassium loss.⁶ The variable expression of the clinical phenotype can make the diagnosis of Liddle's syndrome difficult. It can be distinguished from hypertensive forms of congenital adrenal hyperplasia, primary glucocorticoid resistance, SAME, Cushing syndrome and primary aldosteronism by the presence of normal serum levels of 17α -hydroxyprogesterone, 11β -deoxycortisol, cortisol, PAC, PRA, and normal ratios of urinary THF/THE and failure to respond to dexamethasone suppression of ACTH. Treatment of LS is by K+-sparing diuretics- amiloride and triamterene, which are ENaC blockers. The efficacy of the ENaC blockers is enhanced by dietary low salt intake (2 g NaCl/day). ENaC blockers are effective in normalizing both blood pressure and the typical biochemical alterations.⁶

Our index patient has many clinical features in favour of Liddle's syndrome which included family history of early onset hypertension, hypokalaemia with increased urinary potassium loss associated with severe muscle weakness and response to Amiloride containing diuretics and potassium replacement. However genetic testing and other biochemical tests to confirm this diagnosis and rule out other differential diagnoses were not done because they were not available in our facility.

Primary Aldosteronism

Primary Aldosteronism (PA), also known as Conn's syndrome is the most common form of potentially

reversible mineralocorticoid-induced hypertension characterized by the triad of hypertension, metabolic alkalosis, and hypokalaemia.⁷ The prevalence varies from 0.5% to 10% of hypertensive patients.⁸ The two major subtypes are bilateral adrenal hyperplasia and adrenal adenoma which can be seen on abdominal imaging studies. Our patient had no features of adrenal enlargement.

Conn's syndrome is commonly associated with increased plasma aldosterone and plasma aldosterone: Plasma renin activity (PAC: PRA) has become the most common method of screening for PA. If the morning PAC: PRA is >30 , with PRA expressed as ng/mL per hour, and the PAC is >15 ng/dL, the results are highly suggestive of PA.⁷

Familial forms of PA

1. GRA (FH-1) first reported in 1966 is the most common monogenic autosomal-dominant form of low renin hypertension which is associated with sodium retention and normokalaemia in which aldosterone excess is present under the influence of ACTH rather than angiotensin II as a result of mutation causing aldosterone synthase enzyme being ectopically expressed in the cortisol-producing zone of the adrenal cortex under the regulation of ACTH.⁹ GRA is also a good differential diagnosis in our index patient, however, our patient has severe hypokalaemia and therefore GRA is unlikely.
2. FH-2 is indistinguishable from bilateral adrenal hyperplasia and adrenal adenoma, and the diagnosis can be made only by documenting primary aldosteronism in other family members and excluding GRA with genetic testing.

Syndrome of Apparent Mineralocorticoid Excess (SAME)

SAME is an autosomal-recessive disorder characterized by a defect in the gene that encode for an enzyme - 11β -hydroxysteroid dehydrogenase type 2 (11β -HSD2), which normally inactivates circulating cortisol to the less-active metabolite cortisone. At high concentrations cortisol can cross-react and activate the mineralocorticoid receptor (MR), leading to aldosterone-like effects in the kidney, causing hypertension.¹⁰ Usually patients are children and often present with low birth weight, failure to thrive, short stature, muscle weakness and severe hypertension. A variant of SAME so called type II



SAME has been documented in several patients characterized by a milder phenotype due to some residual functional enzymatic activity with onset in late adolescent or early adulthood and only a mildly deranged urinary THF/THE ratio.¹¹ An acquired form of SAME can be seen with liquorice ingestion which contains glycyrrhizic acid. It has a very low affinity for the MR and competitively inhibits 11 β -HSD2. Symptoms caused by liquorice tends to reverse after discontinuing it.¹²

Cushing's Syndrome

Cushing's syndrome result from excess endogenous glucocorticoid secretion. It presents with hypertension, central obesity, abdominal striae, glucose intolerance, depression, weakness, and characteristic moon facies. It is thought that high levels of endogenously produced cortisol, corticosterone, and deoxycorticosterone stimulate the mineralocorticoid receptor, resulting in hypertension and hypokalemia¹³. ACTH has no direct effect on 11 β -HSD2, but the enzyme is saturated by its substrate and subsequently inactive in ectopic ACTH secretion.

Renovascular Hypertension

Renovascular hypertension, though relatively uncommon in the general hypertensive population, is increased in prevalence in both the younger and older patient of less than 30 and greater than 50 years respectively. The two forms of renovascular hypertension are fibromuscular dysplasia and atherosclerotic which are seen in the young and older patient respectively.¹⁴ Acute renal deteriorations after administration of ACEI or ARB and recurrent episodes of flash pulmonary oedema suggest either bilateral renal vascular disease or disease in a patient with a solitary kidney. The presence of renal bruit on physical examination or a renal sonogram demonstrating marked differences in kidney sizes suggest renal vascular disease.

Conclusion

Any individual presenting with spontaneous hypokalaemia with hypertension requires further evaluation. Our index case is a 23year old young man known hypertensive who presented with quadriparesis and spontaneous hypokalaemia with family history of hypertension. The likely cause of his hypertension and hypokalaemia is Liddle's syndrome, However plasma aldosterone concentration, plasma renin activity and genetic

studies were not available for us to confirm this diagnosis. This highlights the challenges faced by clinicians in developing countries due to lack of adequate diagnostic tools. Our case also tried to highlight the fact that patients with rare syndromes presents to us but we are limited by availability of investigative tools, so that our healthcare administrators and healthcare managers will provide those facilities. Therefore, this form of hypertension though is rare, there is a need for a high index of suspicion for it by the clinicians whenever hypertension is being diagnosed in a young individual especially in Maiduguri, Nigeria which have a high prevalence of renal impairment among young individuals' majority of whom have background hypertension.

Conflict Of Interest: The authors have declared no conflict of interest

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