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Severe Hypertension with Hypokalemia and Nephroangiosclerosis Due to Liddle Syndrome's Mutation

—Liddle Syndrome Nephroangiosclerosis

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Abstract

Background: Liddle syndrome (LS) is a rare autosomal-dominant cause of early-life hypertension. It is associated with hypokalemic metabolic alkalosis, hyporeninemia, and suppressed aldosterone secretion. Its morbidity and mortality are associated with hypertension and hypokalemia. **The Case:** An 18-year-old man with severe hypertension, hypokalemia and renal failure for years. He was treated with multiple antihypertensive drugs yet without adequate control. In this patient; LS was confirmed by biochemical and hormonal profiles as well as genetic testing. His close family-members were clinically normal and by genetic testing indicating a new mutation in our patient. He was subjected to kidney biopsy since he had; high serum creatinine at 140 umol/L and bilateral small kidneys at 9 cm, in longitudinal diameter, with thin and echogenic cortex. It showed moderate nephroangiosclerosis. Initially, he was treated with low-salt diet, Amiloride 20 mg daily, slow K and antihypertensives (Amlodipine 10 mg daily and alpha methyl dopa 250 mg twice daily). Subsequently, antihypertensives were reduced to only Amlodipine 5 mg daily. He remained stabilized her disease up to 2 years of follow-up. **Conclusion:** LS should be considered in hypertensive children with hypokalemia since it requires special management to avoid its hypokalemic and cardiovascular complications as well as nephroangiosclerosis.

Keywords

Amiloride, Genetic Testing, Hypertension, Hypokalemia, Liddle Syndrome, Nephroangiosclerosis

1. Introduction

Liddle syndrome (LS) is an autosomal-dominant form of monogenic disorder that typically manifests early in life with hypertension, low potassium (K), metabolic alkalosis, hyporeninemia, and suppressed aldosterone secretion [1]. This condition is primarily caused by gain-of-function mutation in one of 3 genes (*SCNN1A*, *SCNN1B*, and *SCNN1G*) that encode the epithelial sodium channel (ENaC), located on the apical membrane of distal convoluted tubules and collecting ducts of the kidney [2]. The disease is considered rare with less than 80 families reported worldwide [3]. Little is known about the prevalence of LS with many patients being misdiagnosed and die at an early age from complications. In a prospective study of 330 patients with hypertension that lacked secondary causes; 5 patients had hypokalemia and mutations that destroyed the PY motif of ENaC leading to a calculated prevalence at 1.52% [4]. Complications of LS include; 1) hypertensive-induced cerebrovascular, cardiovascular and renal disease as well as 2) those related to hypoK with arrythmias and cardiac arrest [5] [6]. In this case report we describe our diagnostic approach and management of an adult patient with inadequately-treated hypertension and occult renal disease due to LS.

2. The Case

An 18-year-old man was referred for management of persistent headache and progressive renal disease for 1 year. He had uncomplicated normal vaginal delivery to consanguineous parents and was the 2nd child with no significant disease in his parents and their 5 siblings. At his initial examination; he was in distress of headache. His body weight was 60 kg, blood pressure was 180/125 mm Hg and he was afebrile. Systemic examination did not show abnormality. Laboratory investigations showed low hemoglobin at 110 g/L with normal transferrin saturation% and vitamin B12. Peripheral leucocytic and platelets counts were normal. Serum glucose, electrolytes and liver functions were normal except for; 1) high serum urea and creatinine at 8 mmol/L and 140 umol/L, respectively, 2) persistent and unprovoked hypoK at 3.1 mmol/L with high simultaneous spot urine K at 60 mmol/L (and 2.6 mmol/mmol K/creatinine ratio) as well as, 3) high bicarbonate level at 37 mmol/L, 4) normal urine routine and microscopy except for proteinuria that was quantitated at 960 mg/day. His abdominal and pelvic ultrasound did not show abnormality except for bilateral small (9 cm) kidneys with echogenic cortex (**Figure 1**). ECG showed left ventricular hypertrophy. Computerized tomography of abdomen confirmed bilateral smaller than normal kidneys and absence of adrenal lesions. Radiological assessment did not show coarctation of aorta and renal artery stenosis. Serological tests were negative for autoimmune diseases (serum complements, ANA, ANCA, anti-GBM antibodies, hepatitis B surface antigen and anti-hepatitis C antibody as well as IgA level and protein electrophoresis). Hormonal profile showed normal TSH, cortisol, copeptin, catecholamines, progesterone, pregnenolone, 17-alpha hydroxyprogesterone, 17-alpha-hydroxypregnenolone, and androstenedione. He had low levels of direct renin (6 ng/L; Normal: 7 - 57),

and aldosterone (158 pmol/L; Normal: 271 - 996). Moreover, he had normal levels of 11-desoxycortisole and 24-hour urinary cortisol to cortisone ratio. Hence, diagnosis of Liddle syndrome was established. Subsequently; diagnosis was confirmed by genetic testing showing p. Pro617Ser mutation in the SCNN1B gene with a base duplication in the coding region of SCN1B gene that caused a frameshift mutation:c.1789dupC (p.Arg597fs). Genetic testing (Next-generation sequencing) was done on an Ion Torrent S5XL/Prime Machine using ion AmliSeq whole Exorne Sequencing (WES) Kit by Life Technologies to an average coverage depth of 70-100X. Interestingly; genetic testing of his close-family members did not show mutations. Hence; the patient was considered an index case. He was treated with Amiloride 20 mg daily and slow K 600 mg thrice daily to keep K level above 3.5 mmol/L as well as emphasis on low sodium diet. Moreover; to control her severe hypertension he required Amlodipine 10 mg daily with Alpha methyl dopa 250 mg twice daily. After 1 week of therapy; serum K increased to 3.9 mmol/L and urinary K decreased to 19 mmol/L. By 1 month later; his dose of slow K was reduced to once daily and his antihypertensives were decreased to Amlodipine 5 mg X1 only. After his initial clinical stabilization; kidney biopsy was done. It showed a total of 12 glomeruli of whom 7 were globally sclerosed. Viable ones showed 1) wrinkling and thickening of glomerular basement membrane with glomerular collapse, 2) arteriolar medial thickening and subintimal fibrosis as well as 3) tubulointerstitial fibrosis (Figure 2). Immunoperoxidase tests were negative for

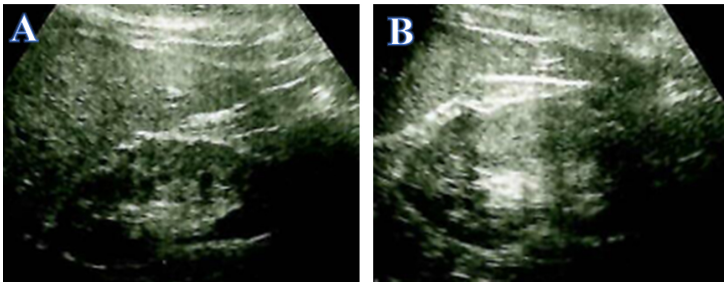

Figure 1. Ultrasound pictures of the right (A) and left (B) patient's 9 cm kidneys with increase cortical echogenicity.

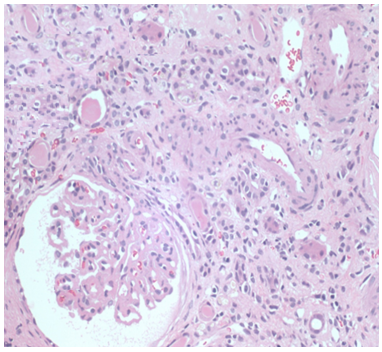

Figure 2. Photomicrograph of a kidney biopsy showing; (a) wrinkling and thickening of glomerular basement membrane with glomerular collapse, (b) arteriolar medial thickening and subintimal fibrosis as well as (c) tubulointerstitial fibrosis.

immune deposits. Such histological picture was consistent with nephroangiosclerosis. In the following 2 years; he was seen every 2 months. He was asymptomatic and with normal blood pressure and fluid status. Laboratory tests showed; serum creatinine was 137 umol/L, serum K at 4.1 mmol/L and proteinuria at 560 mg/day.

3. Discussion

Persistent and unprovoked hypoK indicates a practical pathophysiologic approach as seen in **Table 1**. Concomitant high urinary K (>40 mmol/24 hour or in a spot urine sample that shows K > 20 mmol/L or K/creatinine ratio > 1.5 mmol/mmol K/creatinine ratio) indicates inappropriate kaluresis [7]. It excludes extracellular potassium to the intracellular compartment, related to hypokalemic periodic paralysis, prior diuretics and laxative-use as well as chloride-losing diarrhea. Its association with hypertension excludes Bartter's and Gitelman syndrome. Moreover; low renin and aldosterone levels; excludes renovascular disease and adrenal hyperplasia [8]. In our patient, with low renin and aldosterone hypertension; 1) history excluded prior intake of licorice, Dexamethasone and drugs reducing renin angiotensin aldosterone system viz. Betablockers, Angiotensin converting enzyme inhibitors and Angiotensin receptors antagonists. 2) normal Copeptin excluded ectopic ACTH tumors [9], 3) normal levels of 11-beta-HSD2 and urinary cortisone/cortisol ratio, as well as genetic testing excluded apparent mineralocorticoid excess [10], 4) normal serum cortisol excluded glucocorticoid resistance [11], 5) normal levels of androgenic hormones viz. progesterone, pregnenolone, 17-alpha hydroxyprogesterone, 17-alpha-hydroxypregnenolone, and androstenedione excluded congenital adrenal hyperplasia [12], 6) normal catecholamines levels excluded pheochromocytoma [13], and 7) genetic testing excluded activating mutation in mineralocorticoid receptors [14]. Hence; diagnosis of Liddle syndrome was established that was subsequently confirmed by genetic testing [2]. Interestingly; his parents did not show features of disease and lacked similar mutations on genetic testing. Hence; the patient had new mutation that caused his LS. Historically; the syndrome was first reported by Grant Liddle et al in 1963 [15]. Subsequently, researchers disclosed its genetic mutations in the beta and gamma subunits of the ENaC that amplified their activity independent of aldosterone action [2]. Such pathological derangement results in 3 features; 1) increase in sodium reabsorption leading to chronic volume retention with subsequent hypertensive state and suppression of renin and aldosterone levels and atrophy of juxtaglomerular cells [16], 2) hypoK and metabolic alkalosis due to excessive K-loss in the urine at the expense of sodium reabsorption via increased sodium/K ATPase activity, and 3) improvement with Amiloride and triamterene and lack of response to Spironolactone [17]. Despite its symptomatic and catastrophic complications; patients with LS may asymptomatic and with hypertension and hypoK only in 92.4% and 71.8%, respectively [18]. Genetic testing is essential for disease-confirmation and is also recommended to all first-degree relatives since is; 1) classically autosomal dominant to detect carrier states in first-degree relatives, and 2)

it has variable penetrance with heterogenous phenotypic presentations viz. including age at presentation, degree of HT, presence of hypokalemia and renal/cardiac complications [19]. Our case report confirms; 1) contrary to adults; hypertension in early-life is secondary to specific derangement in renal disease, congenital vascular anomalies and hereditary and/or hormonal defects, 2) practical pathophysiological approach is indicated in diagnosis and management since conventional antihypertensives may be inadequate and drugs such as Spironolactone may not be effective in LS, 3) LS can present as a new mutation, 4) nephroangiosclerosis is a renal complication of LS.

Table 1. Diagnostic algorithm in hypokalemia.

I—Low urinary potassium excretion (<20 mmol/L):	
1) prior diuretic-use	
2) Gastrointestinal loses	
3) Profuse sweating or excessive burn	
4) Translocation (e.g. to muscle in periodic paralysis)	
II—High urinary potasium excretion (>20 mmol/L):	
Normal or low blood pressure	
A—Metabolic alkalosis:	
Low urinary chloride (<20 mmol/L)	High urinary chloride (>20 mmol/L)
1) Vomiting or gastric suction	1) Loop or thiazide Diuretics
2) Congenital chloride-losing diarrhea	2) Bartter's syndrome
3) Villous adenoma	
B—Metabolic acidosis:	
1) Renal tubular acidosis	
2) Diabetic ketoacidosis	
3) Ureteral enterostomy	
C—Variable:	
Diuretic phase of ATN or obstruction	
Hypertension:	
High Renin and aldosterone	High renin & low aldosterone:
1) Renovascular disease	Prior ACEI or ARB
2) Malignant hypertension	
3) Renin-secreting tumor	

Continued

Low renin & high aldosterone	Normal/low renin & aldosterone (R&A)
1) Adrenal hyperplasia, adenoma & tumor	Apparent meniralocorticoid excess (AME)
2) Glucocorticoid remediable hyperaldosteronism (genetic/familial)	Liddle syndrome
	Licorice
	Dexamethasone
	Ectopic ACTH secretion syndrome
	Mineralocorticoid receptor activation mutation
	Glucocorticoid resistance
	Congenital adrenal hyperplasia
	On drugs reducing RAAS

Abbreviations: ATN: acute tubular necrosis; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ACTH: adrenocorticosteroid hormone; RAAS: renin angiotensin aldosterone system.

4. Conclusion

LS should be considered in hypertensive children with hypokalemia since it requires special management to avoid its hypokalemic and cardiovascular complications as well as nephroangiosclerosis.

Author's Contributions

Prof. Kamel El-Reshaid conceived the study, participated in its design, and drafted the manuscript. Dr. Shaikha Al-Bader participated in the study design, follow-up of patients, data collection and tabulation of data.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest

All authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest regarding the publication of this paper.

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