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Medical therapy refractory salt-sensitive hypertension: Liddle's syndrome

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1. Introduction

Liddle's syndrome, a rare hereditary disease, is characterized frequently by severe early-onset of salt-sensitive hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity and hypo-aldosteronism, caused by disproportionate salt and water reabsorption at the distal nephron [1,2].

It responds to treatment with epithelial Na^+ channel blocker drugs (e.g. Amiloride or Triamterene) and a low sodium diet [3]. As of 2008, there are < 30 pedigrees or isolated cases that have been reported worldwide [4]. We present a case of a 53-year-old male who presented with Liddle's syndrome.

2. Case report

A 53 year-old African male, with known medical history of diet controlled diabetes mellitus and anxiety, presented to Nardone Medical Associates with a diagnosis of hypertension. At the initial visit, his blood pressure was 178/106 mmHg without significant asymmetry or postural variation. His medications included Amlodipine 10 mg only. The initial lab workup, his creatinine level was 1.79 mg/dl, blood urea nitrogen (BUN) 27 mg/dl, serum sodium (Na+) 141 meq/L, serum potassium (K+) 3.5 meq/L, carbon dioxide (CO_2) 28 meq/L, in addition to proteinuria. Electrocardiograph (EKG) showed T wave inversion in the anterolateral leads and left ventricular hypertrophy. However, despite receiving various combinations of beta-blocker, angiotensin-converting enzymes (ACE) inhibitors, thiazide diuretics, and sodium-restricted diet, his blood pressure was not controlled. Follow up visits revealed persistent hypokalemia, which required continuous repletion of potassium.

Additional lab workup showed serum Aldosterone 4.5 ng/dl (upright position), plasma renin activity 3.7 ng/ml/hr (upright position), creatinine 2.0 mg/dl, blood urea nitrogen (BUN) 30 mg/dl, serum sodium (Na+) 142 meq/L, serum potassium (K+) 3.2 meq/L, and carbon dioxide (CO_2) 33 meq/L. Serum protein electrophoresis, complement levels, and P-ANCA and C-ANCA were all within normal levels.

3. Discussion

In a patient with hypertension and hypokalemic alkalosis, primary aldosteronism, Cushing's syndrome, pheochromocytoma, reno-vascular hypertension, essential hypertension with diuretic use, some forms of congenital adrenal hyperplasia, Liddle's syndrome and syndrome of apparent mineralocorticoid excess have to be considered as differential diagnoses [9]. Low serum aldosterone ruled out primary aldosteronism (Conn's syndrome). Pheochromocytoma was excluded on the basis normal serum and urinary metanephrines. The results of serum cortisol, ACTH came back within normal limits, as well. The patient denied any intake of diuretics or licorice. Age of presentation was against the congenital adrenal hyperplasia. Normal USG Doppler results and low-plasma renin activity with low aldosterone ruled out the possibility of reno-vascular hypertension.

With a combined picture of hypertension, hypokalemia with metabolic alkalosis and hyporeninemic hypo-aldosteronism, the possibility of Liddle's syndrome was considered. Response to Amiloride without any recurrence of hypertension and hypokalemia confirmed the diagnosis of Liddle's syndrome.

Liddle's syndrome is a rare autosomal dominant condition

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characterized by a primary increase in sodium reabsorption from the collecting tubule and secretion of potassium in the majority of the cases [9]. Liddle et al. described a familial syndrome of severe hypertension, hypokalemia and metabolic alkalosis mimicking hyperaldosteronism [5]. However, these patients have low renin and aldosterone levels, and there is conservation of sodium and excretion of potassium in the absence of mineralocorticoid excess [9]. Genetic studies have revealed that mutations affecting the cytosolic tail of the β subunit of the epithelial sodium channel (ENaC) could lead to this disorder. These mutations apparently cause constitutive activation of the epithelial sodium channel of the luminal membrane of the collecting tubule and result in excessive absorption of sodium, leading to volume expansion. This in turn causes hypertension, leading to inhibition of renin and aldosterone secretion. Lack of down-regulation of the epithelial sodium channels despite persistent volume expansion is the basis behind the pathogenesis of this syndrome. A similar lack of down-regulation of the activity of the epithelial sodium channels may underlie more common forms of low-renin hypertension [5].

Patients with Liddle's syndrome present with hypertension, often hypokalemia (in most cases) and metabolic alkalosis, similar to that seen in mineralocorticoid excess [5]. Patients mostly present at a young age, although occasionally cases may not be detected until adulthood. However, presentation in the 6th decade of life or later has been reported very rarely [6,7]. Presentation with hypertensive encephalopathy has not been reported in patients with Liddle's syndrome. However, muscle weakness associated with hypokalemia (especially in the lower limbs) has been described, although rarely, in elderly patients with Liddle's syndrome [8]. It is important to screen for this condition in patients with hypertension, hypokalemia and metabolic alkalosis, as the treatment of Liddle's syndrome differs from other forms of essential or secondary hypertension. Potassium-sparing diuretics such as Amiloride and Triamterene, which directly close the sodium channels, are effective in Liddle's syndrome, whereas the mineralocorticoid antagonist spironolactone is ineffective as the increase in sodium channel activity is not mediated by aldosterone in this disorder [3].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jecr.2018.11.001.

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