Pseudohypoaldosteronism Type II: A Young Girl Presented with Hypertension, Hyperkalemia and Metabolic Acidosis

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ABSTRACT

Pseudohypoaldosteronism (PHA) type II is an extremely rare disorder which presents with hypertension, hyperkalemia, and normal anion gap metabolic acidosis. PHA II is also known as familial hyperkalemic hypertension, Gordon syndrome, and chloride shunt syndrome. PHA II is an autosomal dominant disorder and is caused by mutation in WNK1, WNK4, CULLIN3, KLHL3, OSR, SPAK gene. The expression of these proteins is limited to the distal convoluted tube and collecting duct of the kidney. PHA II usually responds to salt restriction and thiazide diuretics. We are reporting here a case of 16-year girl who presented with generalised fatigue and shortness of breath, and blood pressure (BP) of 220/110 mmHg. Laboratory investigation showed hyperkalemia, normal anion gap metabolic acidosis, and hypercalciuria. Workup for secondary causes of hypertension was negative. She responded to thiazide diuretics and her BP is well controlled, and acidosis and hyperkalemia are corrected.

Key Words: *Pseudohypoaldosteronism type II. Gordon syndrome. Hypertension. Hyperkalemia. Hypercalciuria. Metabolic acidosis. Thiazide diuretics.*

INTRODUCTION

Pseudohypoaldosteronism type II (PHA II) is a rare syndrome and is also known as familial hyperkalemic hypertension, Gordon syndrome, and chloride shunt syndrome. It is inherited as an autosomal dominant pattern.[1] It is caused by mutation in WNK1 and WNK 4 genes (with no lysine kinases) on chromosome 12 and 17, respectively. Some researchers have reported the genetic defects in Kelch-like 3 (KLHL3) or Cullin 3 (CUL 3), OSR (oxidative stress-responsive kinase), SPAK (Ste20-related proline alanine-rich kinase) etc. as a cause PHA II.[2] PHA II is manifested by hypertension, hyperkalemia, normal anion gap metabolic acidosis, decreased renal potassium excretion, hypercalciuria, low or low normal plasma renin and variable level of aldosterone, either low or normal. Thiazide diuretics effectively reverse the hypertension and hyperkalemia.[3]

We are reporting a case of PHA II, which responded to thiazide diuretics.

CASE REPORT

A 16-year Kuwaiti girl presented with generalised fatigue and shortness of breath for four hours. She visited a polyclinic and her blood pressure (BP) was 220/110 mmHg. She gave history of seasonal bronchial asthma for which she was taking salbutamol inhaler as per requirement. When she arrived to Emergency Department, her vital signs were: BP of 160/90 mmHg, pulse at 120 beats/minute, and O_2 saturation 96% on room air. Systemic examination, including fundoscopic examination, was unremarkable. She was neither in a state of exacerbation of bronchial asthma nor in hypertensive pulmonary edema.

Investigations showed normal blood counts and renal functions. However, potassium level was 6.1 mmol/L, HCO3 was 18 mmol/L, anion gap was 11.1, and calcium level was 2.3 mmol/L. Arterial blood gases (ABG) analysis showed metabolic acidosis. Coagulation profile urine microscopy and chest X-ray were normal. ECG showed sinus tachycardia with heart rate of 120 beats/minute without left ventricular hypertrophy. 24-hour urinary protein and creatinine clearance was normal and 24-hour urinary catecholamines were normal, whereas 24-hour urinary calcium was high at 8.5 mmol/day (normal 2.5-7.5). TSH, aldosterone (124 pmol/L) and renin (<5.6 ng/L) levels were normal. Echocardiography showed concentric left ventricular hypertrophy with ejection fraction of 65%. Ultrasound of abdomen/pelvis normal, Doppler of renal vessel, MRI of adrenals, MRA of renal arteries and immunological investigations (ANA and ANCA) were all normal.

Initially, she was managed with amlodipine 5 mg OD, and calcium resonium 30 gm TDS with lactulose to treat her hyperkalemia. Later, she was switched to hydrochlorothiazide and amlodipine. Her home BP readings are controlled on thiazide diuretic, and currently she is off the amlodipine. Her electrolytes are shown in Table I.

Her family was screened with serum electrolytes and one of her sisters had high serum potassium levels. She

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Received: September 07, 2016; Accepted: October 29, 2017.

Table I: Comparison of serum electrolytes before and after thiazide therapy.

Electrolytes	Pre-thiazide	Post-thiazide
Potassium	5.7 & 5.8	5.1* & 4.9**
Chloride	116 & 115	117 & 115
Bicarbonate	17	16 & 19

**Done after one week; ** after two weeks of thiazide diuretic.*

need genetic analysis, especially WNK gene, which has not done yet.

DISCUSSION

PHA II is the opposite of Gitelman's syndrome, which presents with low blood pressure, hypokalemia, hypochloremic metabolic alkalosis, and hypocalciuria.[4] Initially, it was considered to be caused by a genetic defect in the NaCl cotransporter (NCC), the target transporter of thiazides. However in 2001, PHA II was reported to be caused by abnormalities in two types of genes known as WNK1 and WNK4 genes.[5] Later, Yang *et al*. confirmed the WNK4 mutation in mice, manifesting hypertension secondary to electrolyte abnormalities, acidosis and increased circulating blood volume.[6] There are reported cases in which PHA II was not linked with genetic mutation in WNKs. Some researchers have reported PHA II is caused by the genetic defects in Kelch-like 3 (KLHL3) or Cullin 3 (CUL 3), OSR (oxidative stress-responsive kinase), SPAK (Ste20-related proline alanine-rich kinase) etc.[2] The expression of these proteins is limited to the distal convoluted tube (DCT) and collecting duct (CD) of the kidney. The WNK1 and WNK4 genes are located on chromosome 12 and 17, respectively.[7] WNK4 gene negatively regulates the thiazide sensitive NCC in the DCT, which leads to volume expansion due to increased sodium and chloride reabsorption; which ultimately results in hyperchloremia and hypertension.[8] Moreover, WNK4 defect also antagonises the aldosterone sensitive renal outer medullary potassium (ROMK) channels of DCT, which leads to decreased potassium secretion through ROMK channels and hence cause hyperkalaemia.[9]

All these findings, i.e. hypertension, hyperkalemia, hyperchloremic metabolic acidosis, hypercalciuria were present in this reported case. Moreover, hypercalciuria typically occurs with WNK 4 gene mutation in subjects of PHA II.[10] In this reported case, hypercalciuria meant that she might have mutation in WNK4 gene. In PHA II, hypercalciuria is caused by increased NCC activity due to defect in WNK genes. Uninhibited NCC activity causes increase sodium reabsorption and decrease calcium reabsorption in PCT which results in hypercalciuria and hypertension. Another mechanism for hypercalciuria is due to down regulation of transient receptor potential V5 channel (TRPV5) activity. It reduces calcium reabsorption in DCT, which may result in urinary calcium loss and osteoporosis.[7]

Thiazide diuretics effectively reverse hypertension and metabolic abnormality in patients of PHA II. Thiazide diuretics are the pharmacological inhibitor of the NCC activity, hence inhibiting the NCC activity normalises hyperkalemia, hyperchloremic metabolic acidosis and hypercalciuria. Moreover, thiazides are six times more sensitive in treating hypertension in patients with PHA II than in individuals with essential hypertension.[7] Hyperkalemia, hypertension, hypercalciuria with hyperchloremic metabolic acidosis in the presence of normal renal function may alert clinician to think of pseudohypoaldosteronism type II. It is associated with mutation of multiple genes, especially WNK genes; and thiazide diuretics effectively reverse the metabolic abnormalities, including hypertension.

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