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PSEUDOHYPOALDOSTERONISM TYPE II: THE RELEVANCE OF A CHALLENGING DIAGNOSIS

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ABSTRACT

Pseudohypoaldosteronism type II (PHA II) is a rare genetic syndrome caused by mutations in the *WNK1*, *WNK4*, *KLHL3* and *CUL3* genes, leading to hypertension, hyperkalaemia, and hyperchloremic metabolic acidosis. Each mutation confers a different phenotype, with a large spectrum of clinical presentations, which can delay the diagnosis. We report a case of a 31-year-old female with hypertension. She had uncharacteristic facies, average height and no family history of hypertension or hyperkalaemia. Laboratory data showed hyperkalaemia, hyperchloremic metabolic acidosis, hypercalciuria and suppressed renin. Genetic testing revealed a c.478G>T, p.(Asp160Tyr) variant in the *KLHL3* gene, in apparent homozygosity. Based on clinical history, laboratory findings, and genetic testing, a diagnosis of PHA II was made. This is a representative case of a mild PHA II phenotype, with a non-previously reported *KLHL3* mutation, highlighting the importance of a high level of suspicion for PHA II.

KEYWORDS

Pseudohypoaldosteronism type II, Gordon syndrome, hyperkalaemia, low renin hypertension, *KLHL3* gene

LEARNING POINTS

- We report a case of a young woman with PHA II caused by a novel variant in *KLHL3*, that highlights the importance of a high level of clinical suspicion for PHA II diagnosis in patients with milder phenotypes and without family history.
- PHA II should be considered in all patients with low-renin hypertension, hyperkalaemia, hyperchloremic metabolic acidosis and hypercalciuria, regardless of age, clinical features, or family history.
- Early diagnosis is extremely important because PHA II can be effectively treated with low dose thiazides, avoiding end organ damage onset.

INTRODUCTION

Pseudohypoaldosteronism type II (PHA II), also known as Gordon syndrome, is a rare genetic syndrome characterized by hypertension, hyperkalaemia, and hyperchloremic metabolic acidosis[1]. PHA II is caused by mutations in the *WNK1*, *WNK4*, *KLHL3* and *CUL3* genes[2]. These mutations affect thiazide sensitive NaCl cotransporter (NCC), in the distal convoluted tubule (DTC), increasing

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sodium reabsorption and leading to volume expansion and hypertension. Sodium reabsorption decreases the lumen negative potential that is required for potassium excretion by renal outer medullary potassium (ROMK) channel, decreasing potassium excretion and causing hyperkalaemia. In response to hyperkalaemia and volume expansion, renin activity is decreased, with variable aldosterone levels. Calcium reabsorption in DCT is decreased leading to hypercalciuria[3]. The term "pseudohypoaldosteronism" was originally used to describe cases of persistent hyperkalaemia with elevated serum aldosterone and volume depletion — a condition now referred to as PHA type I. In contrast, PHA II is not a true form of PHA, as it presents with hyperkalaemia and hypertension rather than volume depletion[4].

Mutations in *WNK1*, *WNK4* and *CUL3* genes are dominant, while mutations in *KLHL3* can be either dominant or recessive. Mutations may be inherited or sporadic[5]. Each mutation confers a different phenotype, with a large spectrum of clinical presentations. *CUL3* mutations are associated with a more severe phenotype, leading to clinical manifestations at younger ages, more severe hyperkalaemia and metabolic acidosis, short stature, myalgias, periodic paralysis and dental abnormalities. Dominant *KLHL3* mutations are associated with late onset hypertension and mild hyperkalaemia, which can hinder the diagnosis. *WNK1* and *WNK4* mutations are also associated with milder phenotypes[6].

We introduce a case of a young woman with a mild PHA II phenotype caused by a previously unreported *KLHL3* mutation.

CASE DESCRIPTION

A 31-year-old female was referred to our hospital for evaluation of hypertension that was diagnosed when she was in her mid 20s. She was otherwise healthy. There was no history of myalgias, periodic paralysis, weakness or paraesthesia. She took methyldopa 250 mg (since she was breastfeeding at the time) with poor blood pressure control. Family history was negative for hypertension, hyperkalaemia, renal disease and premature cardiovascular disease. Her parents were non-consanguineous. Physical examination findings included uncharacteristic facies and an average height.

To evaluate secondary causes of hypertension methyldopa was changed to doxazosin. Arterial blood gas analysis revealed a compensated metabolic acidosis (pH 7.362, partial pressure of carbon dioxide 34.8 mmHg, bicarbonate 19.3 mmHg). Laboratory results showed hyperkalaemia (6.2 mmol/l, reference range 3.5–5 mmol/l), hyperchloremia (115 mmol/l, reference range 95–108 mmol/l) and normal serum sodium, calcium and magnesium. The serum creatinine level was 0.8 mg/dl (reference range 0.5-0.9 mg/dl) and estimated glomerular filtration rate was 101 ml/min/1.73m^2. Thyroid function tests and parathyroid hormone were normal (thyroid stimulating hormone 2.36 mU/l, reference range 0.27-4.2 mU/l; parathyroid hormone 43.7 pg/ml, reference range 15-65 pg/ml), as well as cortisol levels (10.3 ug/dl, reference range 6.24-18 ug/dl). Plasma renin activity was depressed (1 pg/ml, reference range 2.4-21.9 pg/ml) with a high aldosterone concentration (17.78 ng/dl, reference range 1-16 ng/dl), leading to an aldosterone-to-renin ratio of 17.8 (reference range <5.4). A saline infusion test was performed, excluding primary aldosteronism (plasma aldosterone decrease: 9.86 to 3.33 ng/dl). Urinary metanephrines were normal. Spot urinary calcium was high (29.6 mg/dl, reference range 6.6-21.3 mg/dl), leading to a high urinary calcium-to-creatinine ratio (0.177, reference range <0.14). Twenty-four-hour urine cortisol, sodium and potassium were normal. There was no albuminuria or proteinuria. Renal ultrasound showed kidneys with maintained topography and dimensions, with regular contours. Doppler showed normal vascularization of renal arteries, without stenosis. Twenty-four-hour ambulatory blood pressure monitoring showed moderate systolic-diastolic hypertension and a dipper pattern.

The presence of hyperkalaemia, hyperchloremia and high urinary calcium with metabolic acidosis led to the hypothesis of PHA II. A genetic test was ordered, revealing a c.478G>T, p.(Asp160Tyr) variant in the *KLHL3* gene, in apparent homozygosity. This variant was not reported in disease or population databases but was localized in the functional domain where other disease-associated variants are described. Based on clinical history, laboratory changes, and genetic testing, a diagnosis of PHA II was made.

Initiation of therapy with indapamide 1.5 mg led to symptomatic hypotension and was discontinued and replaced by nifedipine 30 mg, with good current blood pressure control and no symptoms. The patient was referred to genetic counselling.

DISCUSSION

PHA II is a rare genetic disease but its prevalence in general population remains unknown. Patients with family history and more severe phenotypes can be easily diagnosed but patients with milder forms may go unnoticed. Hypertension, hyperkalaemia, hyperchloremic metabolic acidosis, suppressed renin, and hypercalciuria should lead us to consider PHA II[7].

Hyperkalaemia distinguishes PHA II from other forms of monogenic hypertension that normally occur with hypo or normokalaemia, such as Liddle syndrome, congenital adrenal hyperplasia, aldosterone-producing adrenal adenomas, and syndrome of apparent mineralocorticoid excess[8]. In PHA II hyperkalaemia and volume expansion decrease renin activity, with variable aldosterone levels; low renin hypertension also occurs in primary aldosteronism, a more common condition than PHA II, and may lead to misdiagnosis. However, in contrast to PHA II, primary aldosteronism results in hypokalaemia and a positive saline infusion test[9]. Chronic kidney disease is often associated with hypertension, hyperkalaemia and metabolic acidosis but with concurrent changes in serum renal function markers and renal imaging[5]. The presence of hyperkalaemia

and metabolic acidosis in the absence of kidney disease, in combination with a suppressed renin, should be a red flag for PHA II[10].

When PHA II is suspected, and after more common causes of secondary hypertension have been excluded, a single-gene testing or a multigene panel that includes *CUL3*, *KLHL3*, *WNK1*, and *WNK4* should be considered[4]. Accurate diagnosis of PHA II is essential, as the condition responds remarkably well to low-dose thiazide therapy. Thiazides not only provide effective blood pressure control but also correct the associated electrolyte and acid–base disturbances, since they act as NCC antagonists and directly counteract the underlying pathophysiologic mechanism of PHA II[7,10]. This explains the marked thiazide sensitivity observed in our patient, a characteristic feature that further supports the diagnosis. The patient was initially treated with indapamide 1.5 mg, a thiazide-like diuretic selected for its favourable metabolic profile and lower risk of hyponatremia. Chlorthalidone is also a thiazide-like diuretic with minimal metabolic effects; however, its higher potency makes it less suitable for patients with marked sensitivity to thiazide therapy. Hydrochlorothiazide has been associated with less favourable metabolic effects and could also result in hypotension. Angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists should be used with caution as they may worsen hyperkalaemia[6]. Therefore, indapamide was switched to nifedipine, a calcium-channel blocker.

After switch to nifedipine 30 mg, blood pressure remained well controlled and potassium levels remained within normal range under potassium-lowering dietary measures. As calcium channel blockers do not target NCC, they are not expected to normalize potassium or calcium excretion, and salt and potassium dietary restriction remains an important adjunctive measure.

As previously discussed, PHA II is not a true form of pseudohypoaldosteronism[4], as it presents with hyperkalaemia, sodium retention, volume expansion and hypertension rather than volume depletion. Therefore, exogenous mineralocorticoids have no therapeutic role in this condition, as they would further enhance sodium reabsorption and exacerbate hypertension without correcting hyperkalemia[3].

We present a case of a patient with typical PHA II features, who received a final diagnosis of PHA-II after 6 years. The delayed diagnosis could have led to poor blood pressure control and potential end organ damage. The rarity of this syndrome and the mild phenotype of our patient justify this hiatus, reenforcing the need for a high level of suspicion. The absence of a family history makes diagnosis more difficult, but mutations can be sporadic or inherited in an autosomal recessive manner and therefore the absence of a family history does not exclude a diagnosis of PHA II[5].

Genetic testing revealed a c.478G>T, p.(Asp160Tyr) variant in the *KLHL3* gene in apparent homozygosity, consistent with the mild phenotype that our patient presented. This variant has not previously been reported in disease or population databases but was localized in the functional domain where other disease-associated variants are described, suggesting pathogenicity. Therefore, to our knowledge, our patient is the first to present this specific mutation associated with PHA II.

Genetic counselling is important to detect family members who were previously undiagnosed, or in the autosomal recessive cases, identify the carriers of a *KLHL3* pathogenic variant, who are typically asymptomatic and do not show traits or symptoms of PHA II[4]. Since our patient had a *KLHL3* variant, her parents could be the carriers.

This case illustrates a mild phenotype of PHA II, in which a high index of suspicion was required to reach the diagnosis. Identifying the disorder is essential, as thiazide diuretics provide an effective and specific therapeutic option.

REFERENCES

1. Riepe FG. Pseudohypoaldosteronism. *Endocr Dev* 2013;**24**:86-95. doi: 10.1159/000342508
2. Mabillard H, Sayer JA. The molecular genetics of Gordon syndrome. *Genes (Basel)* 2019;**10**:986. doi: 10.3390/genes10120986
3. O'Shaughnessy KM. Gordon syndrome: a continuing story. *Pediatr Nephrol* 2015;**30**:1903-1908. doi: 10.1007/s00467-014-2956-7
4. Ellison DH. Pseudohypoaldosteronism type II. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023 [updated 2017 Feb 16; cited 2025 Sep 26]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6575/ PMID: 22073419.
5. Etges A, Hellmig N, Walenda G, Haddad BG, Machtens JP, Morosan T, et al. A novel homozygous KLHL3 mutation as a cause of autosomal recessive pseudohypoaldosteronism type II diagnosed late in life. *Nephron* 2022;**146**:418-428. doi: 10.1159/000521626
6. Park JS, Park E, Hyun HS, Ahn YH, Kang HG, Ha IS, et al. Three cases of Gordon syndrome with dominant KLHL3 mutations. *J Pediatr Endocrinol Metab* 2017;**30**:361-364. doi: 10.1515/jpem-2016-0309
7. Zhang R, Zhang S, Luo Y, Li M, Wen X, Cai X, et al. A case report of pseudohypoaldosteronism type II with a homozygous KLHL3 variant accompanied by hyperthyroidism. *BMC Endocr Disord* 2021;**21**:103. doi: 10.1186/s12902-021-00767-w
8. Toka HR, Dhir R, Toka O, Hariri A, Schieffer B, Williams GH, et al. The molecular basis of blood pressure variation. *Pediatr Nephrol* 2013;**28**:387-399. doi: 10.1007/s00467-012-2206-9
9. Athimulam S, Lazik N, Bancos I. Low-renin hypertension. *Endocrinol Metab Clin North Am* 2019;**48**:701-715. doi: 10.1016/j.ecl.2019.08.003
10. Glover M, Zuber AM, O'Shaughnessy KM. Hypertension, dietary salt intake, and the role of the thiazide-sensitive sodium chloride transporter NCCT. *Cardiovasc Ther* 2011;**29**:68-76. doi: 10.1111/j.1755-5922.2010.00180.x