Chinese Journal of Evidence-Based Medicine

A case of Pseudohypoaldosteronism Type II

[1] Dr. Vaibhav Patel, [2] Dr. Revathi V, [3] Dr. Jagadeeswari S.

[1]Post Graduate, Sree Balaji Medical College and Hospital

[2]Assistant Professor, Sree Balaji Medical College and Hospital

[3]Professor, Sree Balaji Medical College and Hospital

DOI: https://doie.org/10.0724/Cjebm.2024837639

Abstract:
Gordon syndrome, also known as pseudohypoaldosteronism type II (PHA II), is an uncommon renal tubular disorder characterized by hyperkalemia, acidosis, low plasma renin levels, and hypertension. It is often associated with genetic mutations in WNK1, WNK4, CUL3, and KLHL3 genes. This case report presents a 28-day-old male neonate with symptoms including milky urine, elevated renal parameters, and hyperkalemia. Despite normal sodium levels and mild metabolic acidosis, the patient exhibited elevated serum aldosterone and decreased plasma renin activity. Symptomatic treatment with IV fluids and hyperkalemia correction, followed by Hydrochlorthiazide, led to stabilization and symptom improvement. This case underscores the importance of early diagnosis and intervention in PHA II to prevent long-term renal complications. Understanding the genetic underpinnings of PHA II, especially the roles of WNK and CUL3/KLHL3 mutations, is crucial for managing this rare disorder.

Keywords: Gordon syndrome, pseudohypoaldosteronism type II, hyperkalemia, metabolic acidosis, hypertension, renal tubular disorder, WNK1, WNK4, CUL3, KLHL3.

Introduction:

Gordon syndrome, commonly known as pseudohypoaldosteronism type II (PHA II), is an uncommon renal tubular illness that is inherited autosomally but can be sporadic also.[1] The disease is associated with hyperkalemia, acidosis, low plasma renin level and hypertension. It is frequently linked to high thiazide sensitivity, average glomerular filtration rate (GFR), and salt restriction in the diet.[2] PHA II is caused because of genetic anomalies in the WNK1 and WNK4 types of WNK (WNK; With No K lysine) genes.[3] However, many patients of PHA II showed no signs of a genetic defect in WNKs. PHA II has also recently been linked to genetic abnormalities in Cullin 3 (CUL 3) and Kelch-like 3 (KLHL3).[4] Here we present a case of Pseudohypoaldosteronism type 2 in a neonate.

Vol. 20, No. 1. (2024)
E ISSN: 1672-2531

Case Presentation:
A 28 days old term boy baby born in hospital passed urine and meconium within 24 hrs of life presented with complaints of passing milky urine, minimal in amount. No history of refusal of feeds, abdominal distension, persistent vomiting.

Antenatal history:
Spontaneous conception, booked and immunized. Mother is k/c/o Bronchial Asthma. At 13 weeks of gestation mother was diagnosed with GDM on insulin injection. No h/o fever with rash, lymphadenopathy during pregnancy

Natal History:
Term/ Birth weight: 3.165kg/ Appropriate for gestational age/ Cried immediately after birth/ No h/o NICU admission/ Breastfed within 1hr of birth/ Urine and meconium passed within 24hr of birth/ Double surface phototherapy given i/v/o high bilirubin levels.

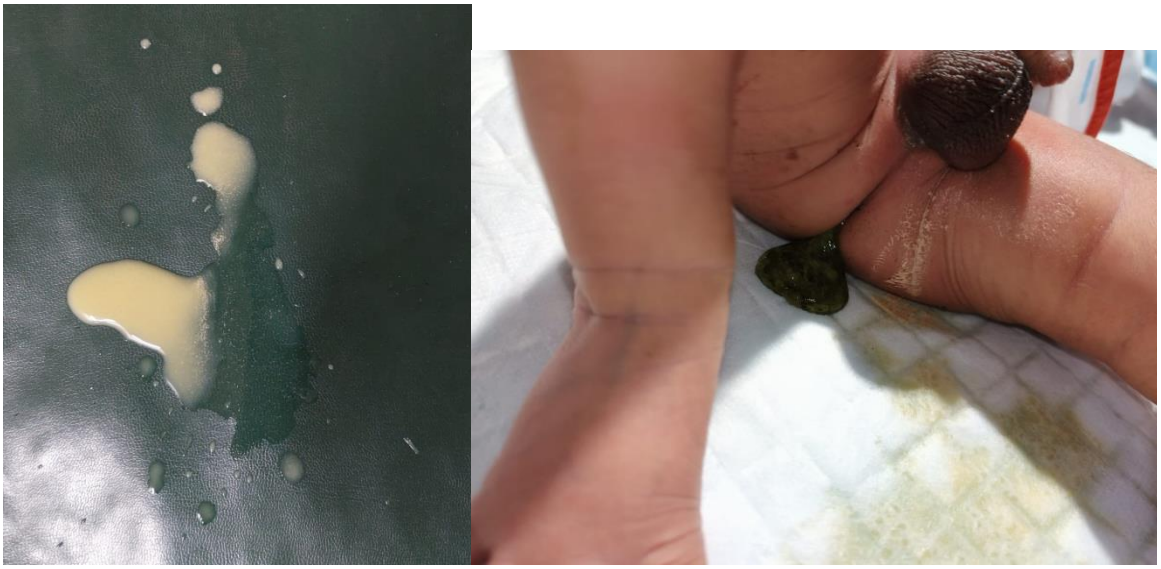
Family History:
Non consanguineous marriage. Mother has a history of 4 previous spontaneous abortions.

General examination was unremarkable. Vitals were stable and blood pressure on day 3 of life was 80/50mmHg. Systemic examination was normal.

Investigations showed elevated renal parameters [Urea-55 mg/dl, Creatinine-1.0]. Echogenic kidney in USG. Normal serum sodium and high serum potassium-5.40 mEq/L. Mild high Chloride-109 mEq/L. Normal anion gap metabolic acidosis [pH-7.33, HCO3-20, pCO2-39] AG-11. Urine calcium creatinine ratio was done which was elevated(1.4) (Ref: < 0.8 for 0-6 months), Serum calcium – 9.9 mg/dl. Urine Na+:40 mEq/L (mildly elevated), Urine K+: 20 mEq/L (normal). Serum Aldosterone- >100 ng/dl (increased), Serum 17 OH Progesterone-20 ng/dl (increased), Plasma renin activity- 1.92 (Ref: 2-25)(Mild decrease).

Treatment:
Symptomatic treatment was given with IV fluids, hyperkalemia was corrected and child was started on Hydrochlorthiazide. Vitals were monitored closely during the hospital stay as child improved symptomatically and hemodynamically, child was discharged. During follow up blood pressure continued to be with in normal range, potassium normalized and no other complaints.
Further genetic evaluation showed WNK1 gene mutation.

Vol. 20, No. 1. (2024)
E ISSN: 1672-2531



Discussion:

Symptoms in PHA II—hypertension, hyperkalemia, and acidosis—are typically brought on by renal insufficiency, a somewhat common reason for increased blood pressure. PHA II is induced by a kinase-dependent mechanism that results from loss-of-function mutations in WNK4 and gain-of-function mutations in WNK1, which eliminates WNK4-mediated tonic inhibition of thiazide-sensitive NCC in the distal convoluted tubule.[3] While some patients develop PHA II due to mutations in WNK1 or WNK4, subsequent research has revealed that KLHL3 and CUL3 are also causal genes for PHA II.[5] The CUL3 protein forms a complex with KLHL3 proteins, which then functions as a ubiquitin ligase. Some studies have recently reported that WNK4 ubiquitination and a decrease in WNK4 protein level are caused by an interaction between KLHL3 and CUL3 and WNK4, whereas a rise in WNK4 protein level is caused by a decrease in the contact between KLHL3 and WNK4.[6][7][8] Because there are so few reports of PHA II in children, the genotype-phenotype association in PHA II is yet unknown.[9][10] Compared to PHA II produced by KLHL3 recessive, KLHL3 dominant, WNK4, and WNK1 mutations, PHA II induced by the CUL3 mutation had an earlier onset and a more severe disease.[4]

Conclusion:

Gordon syndrome or pseudohypoaldosteronism type 2 is a rare disorder of renal tubules that may present with vague symptoms such as milky urine and hypertension along with other typical features such as hyperkalemia, acidosis which may be missed in the initial stages. Timely identification of the disorder using appropriate investigative pannel helps in early intervention and restoration of homeostasis, thus preventing progression of symptoms and safe guarding against long term harmful renal sequelae.

References:

1. Gordon RD, Geddes RA, Pawsey CG, O'Halloran MW: Hypertension and severe hyperkalaemia associated with suppression of renin and aldosterone and completely reversed by dietary sodium restriction. Australas Ann Med 1970, 19(4):287–294.
2. Gordon R.D. Syndrome of hypertension and hyperkalemia with normal glomerular filtration rate. *Hypertension.* 1986;8:93–102.
3. Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Achard JM, et al: Human hypertension caused by mutations in WNK kinases. Science 2001, 293(5532):1107–1112.
4. Boyden LM, Choi M, Choate KA, Nelson-Williams CJ, Farhi A, Toka HR, Tikhonova IR, Bjornson R, Mane SM, Colussi G, et al: Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. Nature 2012, 482(7383):98–102.
5. Louis-Dit-Picard H, Barc J, Trujillano D, Miserey-Lenkei S, Bouatia-Naji N, Pylypenko O, Beaurain G, Bonnefond A, Sand O, Simian C, et al: KLHL3 mutations cause familial hyperkalemic hypertension by impairing ion transport in the distal nephron. Nat Genet 2012, 44(4):456–460. S451-453.
6. Wakabayashi M, Mori T, Isobe K, Sohara E, Susa K, Araki Y, Chiga M, Kikuchi E, Nomura N, Mori Y, et al: Impaired KLHL3-Mediated Ubiquitination of WNK4 Causes Human Hypertension. Cell Rep 2013, 3(3):858–868.
7. Ohta A, Schumacher FR, Mehellou Y, Johnson C, Knebel A, Macartney TJ, Wood NT, Alessi DR, Kurz T: The CUL3-KLHL3 E3 ligase complex mutated in Gordon's hypertension syndrome interacts with and ubiquitylates WNK isoforms: disease-causing mutations in KLHL3 and WNK4 disrupt interaction. Biochem J 2013, 451(1):111–122.
8. Shibata S, Zhang J, Puthumana J, Stone KL, Lifton RP: Kelch-like 3 and Cullin 3 regulate electrolyte homeostasis via ubiquitination and degradation of WNK4. Proc Natl Acad Sci USA 2013, 110(19):7838–7843.
9. Mayan H, Vered I, Mouallem M, Tzadok-Witkon M, Pauzner R, Farfel Z:Pseudohypoaldosteronism type II: marked sensitivity to thiazides, hypercalciuria, normomagnesemia, and low bone mineral density. J Clin Endocrinol Metab 2002, 87(7):3248–3254.
10. Mayan H, Munter G, Shaharabany M, Mouallem M, Pauzner R, Holtzman EJ, Farfel Z: Hypercalciuria in familial hyperkalemia and hypertension accompanies hyperkalemia and precedes hypertension: description of a large family with the Q565E WNK4 mutation. J Clin Endocrinol Metab 2004, 89(8):4025–4030.