Scientific Research Publishing

Open Journal of Nephrology, 2025, 15(2), 167-173
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

# A Rare Encounter: Severe Hypertension and Hypokalemia Due to an Apparent Mineralocorticoid Excess

**Kamel El-Reshaid[1], Emad Abdullah[2]**

[1]Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait
[2]Department of Medicine (Nephrology), Adan hospital, Ahmadi City, Kuwait
Email: kamel@hsc.edu.kw

**How to cite this paper:** El-Reshaid, K. and Abdullah, E. (2025) A Rare Encounter: Severe Hypertension and Hypokalemia Due to an Apparent Mineralocorticoid Excess. *Open Journal of Nephrology*, **15**, 167-173.
https://doi.org/10.4236/ojneph.2025.152016

**Received:** March 10, 2025
**Accepted:** May 10, 2025
**Published:** May 13, 2025



## Abstract

**Background:** Apparent mineralocorticoid excess syndrome (AME) is an extremely rare autosomal-recessive genetic disorder due to deficiency in 11-beta-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2) that converts cortisol to cortisone. The resultant high cortisol level (100-fold higher than aldosterone) avidly binds to and activates the mineralocorticoid receptors leading to hypertension and hypokalemia. **Case:** A 14-year-old girl presented with severe hypertension, unprovoked hypokalemia with high urinary potassium output, and metabolic alkalosis. She did not have a history of parenteral disease, chronic licorice ingestion and lung tumors by FDG-PET scan. Diagnosis was established by; 1) a high 24-hour urinary cortisol to cortisone ratio (>18), 2) low serum levels of renin, aldosterone, 11-beta-HSD and adrenocorticotrophic hormones, and 3) genetic testing showing homozygous pathogenic variants in HSD11B2 gene. **Treatment:** With low-salt diet and daily Amlodipine 5 mg, Amiloride 50 mg and Spironolactone 50 mg, stabilized her disorders up to 6 months of follow-up. **Conclusion:** AME should be considered in children with severe hypertension and unprovoked hypokalemia.

## Keywords

Apparent Mineralocorticoid Excess Syndrome, Hypokalemia, Hypertension, Child, Genetic Testing, 11-Bet-Hydroxysteroid Dehydrogenase Enzyme

## 1. Introduction

Extracellular potassium (K) accounts for only 2% of total body K, and has a major effect on the resting cell membrane excitability especially cardiac muscle that may

culminate in arrhythmogenic death [1]. The kidney excretion is the major route of K excretion and accounts for 90% followed by 10% in gastrointestinal tract. Its narrow and critical range of 3.5 - 5.0 mmol/L, is regulated at apical potassium channels ($Na^+$-$K^+$-$2Cl^-$ cotransporter) in renal cortical collecting ducts via upregulation in $Na^+$-$K^+$-ATPase in apical membrane of the $\alpha$-intercalated cells. Moreover, such upregulation of ATPase increases the activity of another counter transporter, $H^+$-$K^+$-ATPase that leads to $H^+$-loss (alkalosis) in cases of K-depleted states. The excretion of K in this nephron segment is coupled to sodium reabsorption via; 1) the amiloride-sensitive sodium channels and 2) aldosterone action on the mineralocorticoid receptors to increase sodium reabsorption and K secretion [2]. Such pathophysiological basics are essential in diagnosis and management of acquired and congenital renal tubular defects. Moreover, some of those defects result in severe hypertension that is associated with life-threating cardiovascular insults [3]. In this case report, we present our experience in diagnosis and management of a patient with such rare congenital renal tubular disorder that resulted in severe hypertension and hypokalemia.

## 2. The Case

A 14-year-old girl was referred for management of severe hypertension with refractory unprovoked hypokalemia for years. The patient had uncomplicated normal vaginal delivery to first-degree consanguineous healthy parents. She was the 3rd child with no significant disease in the previous or subsequent 2 children. At the age of 5 months; she was noted to have severe hypertension and hypokalemia with high-urinary K-loss. Routine laboratory tests; showed normal kidney function as well as urine routine and microscopy. Moreover, she had negative serological tests for autoimmune diseases viz. serum complements, ANA, ANCA, anti-GBM antibodies, hepatitis B surface antigen and anti-hepatitis C antibody as well as IgA level and protein electrophoresis. Radiological assessment did not show coarctation of aorta and, on ultrasonography both kidneys were normal and without renal artery stenosis as tested with Doppler. Hormonal profile showed normal thyroid stimulating hormone and cortisol. Moreover, without antihypertensive drugs, and at upright position, she had normal levels of direct renin (52 ng/L; Normal: 7 - 57), aldosterone (278 pmol/L; Normal: 271 - 996), and aldosterone/renin ratio (5.3; Normal: 4 - 45). Moreover, she had normal levels of progesterone, pregnenolone, 17-alpha hydroxyprogesterone, 17-alpha-hydroxypregnenolone, and androstenedione. Hence, she was managed as a case of Liddle syndrome. She was treated with Amiloride up to a dose of 20 mg daily and high-dose K-supplementation to keep K level above 3.5 mmol/L. Moreover, and according to her parents, she was not compliant with her medications and medical follow up. At her present assessment, she denied intake of medications and licorice. She was in distress of headache with blood pressure at 170/120 mm Hg. She was afebrile and with body weight at 30 kg. Systemic examination did not show abnor-

mality. Laboratory investigations showed normal peripheral leucocytic, hemoglobin and platelets count. Serum glucose, urea, creatinine, electrolytes and liver functions were normal except for hypokalemia at 2.7 mmol/L and high bicarbonate level at 31 mmol/L. Urine routine and microscopy did not show proteinuria or hematuria. Simultaneous spot urine K was 78 mmol/L. Repeat of radiological assessment confirmed the previous findings except relatively smaller kidneys at 9 cm and with thin and echogenic cortex. Electrocardiogram and echocardiogram showed left ventricular hypertrophy. Repeat hormonal studies and autoimmune work up confirmed the previous findings. Moreover; she had (a) normal FDG-PET scan excluding lung tumors, (b) low serum levels of renin, aldosterone, aldosterone/renin ratio as well as low levels of 11-desoxycortisole at 0.21 ng/ml (Normal: 0.7 - 2.1), (c) high 24-hour urinary cortisol to cortisone ratio (>18), and (d) normal adrenocorticotrophic hormone as tested by plasma copeptin at 7 pmol/L (normal range: 1 - 13.8), and (e) genetic testing showing homozygous pathogenic variants in HSD11B2 gene. 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 – 100 X. Hence, diagnosis of Apparent mineralocorticoid excess was established. She was treated with the same dose of Amiloride and slow K (600 mg) thrice daily with emphasis on low sodium diet. Moreover, to control her severe hypertension she required Amlodipine 10 mg daily with Alpha methyl dopa 250 mg twice daily. Since, she did not have high urinary calcium excretion and/or nephrocalcinosis; thiazides were not added. One week later; serum K increased to 4 mmol/L and urinary K decreased to 23 mmol/L. One month later; her antihypertensives decreased to only Amlodipine 5 mg X1. Her compliance was encouraged by emphasis on; 1) establishment of definite diagnosis, 2) improvement with targeted therapy, and 3) rewarding risk-avoidance of future renal and cardiovascular kidney disease. On such management, she remained stable, clinically and by laboratory testing, up to 6 months of follow up.

## 3. Discussion

Diagnosis of unprovoked hypokalemia (K < 3.5 mmol/L), due to hormonal disorders and/or renal tubular defects, is established only after stabilization of diseases e.g. gastrointestinal losses and control of diabetes mellitus as well as avoidance of drugs viz. laxatives, diuretics, licorice (enzymatic blocker), mineralocorticoids, cortisol and mannitol. Hence; diagnosis requires the following data: 1) history of drug intake (diuretics, mannitol, laxatives and licorice) as well as diarrhea, ureteric diversion and uncontrolled diabetes, 2) blood pressure state, 3) spot or 1-hour urinary K level, 4) arterial blood pH for metabolic acidosis or alkalosis, 5) hormonal testing for plasma renin, aldosterone and renin/aldosterone ratio, cortisol, adrenocortical stimulating hormone or copeptin, 11-beta-hydroxysteroid dehydrogenase, 24-hour urinary cortisol to cortisone ratio, 17-OH-progesterone,

dehydroepiandrosterone, 4-$\delta$-androstenedione, urinary cortisol and urinary androgen catabolites and 6) genetic testing for suspected disorders [4]. Based those data, and using **Table 1**, the etiology of persistent hypokalemia can be established. In our patient; exclusion of certain disorders was done via: 1) high spot urinary K for extrarenal causes viz. poor K-intake, gastrointestinal loss and altered intracellular distribution (periodic paralysis), 2) metabolic alkalosis for renal tubular acidosis and channelopathies viz. Bartter and Gitelman syndromes [4], 3) low renin and aldosterone levels for renovascular disease, malignant hypertension, renin-secreting tumor, adrenal hyperplasia, adenoma and genetic/familial glucocorticoid remediable hyperaldosteronism, 4) normal ACTH and FDG-PET scan for ectopic ACTH tumors [5], 5) low levels of 11-beta-HSD2 and high urinary cortisone/cortisol ratio, as well as genetic testing for Liddle's syndrome which usually shows mutation in one of 3 genes (*SCNN1A*, *SCNN1B*, and *SCNN1G*) [6], 6) normal serum cortisol for glucocorticoid resistance [7], 7) normal levels of androgenic hormones viz. progesterone, pregnenolone, 17-alpha hydroxyprogesterone, 17-alpha-hydroxypregnenolone, and androstenedione for congenital adrenal hyperplasia [8], 8) normal catecholamines for pheochromocytoma [9], and 9) genetic testing for activating mutation in mineralocorticoid receptors [10]. On the other hand, the low level of 11-beta-HSD2 and high urinary cortisone/cortisol ratio established diagnosis of AME and subsequent genetic testing confirmed the diagnosis. AME is an extremely rare genetic disorder with only 101 cases reported worldwide [11]. It is an autosomal-recessive genetic disorder due to an inactivating mutation decreasing production of 11-bet-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2) that converts cortisol to cortisone [12]. The resultant high cortisol level (100-fold higher than aldosterone) avidly binds to and activates the mineralocorticoid receptors leading to hypertension and hypokalemia. Hence, it simulates mineralocorticoid excess with hypertension, hypokalemia, metabolic alkalosis, and low plasma renin activity yet with low/normal plasma aldosterone (pseudohyperaldosterone) [13]. Diagnosis can be established by low-levels 11-beta-HSD2, high 24-hour urinary high free cortisone/cortisol ratio (>5 in children and 18 in adults) and genetic testing [14]. Interestingly, similar disease was not evident in her family members and was confirmed by genetic testing which indicates a new mutation in her. Inadequately treated AME-patients can suffer from severe hypertension in early childhood with target organ damage as seen in our patient with renal impairment and LVH. Moreover, AME can be associated with; 1) low birth weight, failure to thrive, and 2), hypercalciuria and nephrocalcinosis that indicates thiazide therapy [15]. The main line of treatment includes low sodium diet, potassium supplementation and K-sparing diuretics with Amiloride or triamterene are more tolerable than high-dosage of Spironolactone with its side effects. In severe and refractory cases; permeant cure can be achieved with kidney transplantation from a donor with normal 11-beta-HSD2 activity [16].

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 potassium 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 | |
| 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

In contrast to adults, hypertension in children, though uncommon, it is secondary to an identifiable etiology. Renal disease is the most common followed by congenital disorders, hereditary defects and hormonal imbalance. It requires experience in diagnosis and management to avoid long-term and life-threatening complications.

## Authors' Contributions

Prof. Kamel El-Reshaid conceived the study, participated in its design, and drafted the manuscript. Dr. Emad Abdullah 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.

## References

[1] Tse, G., Li, K.H.C., Cheung, C.K.Y., Letsas, K.P., Bhardwaj, A., Sawant, A.C., *et al.* (2021) Arrhythmogenic Mechanisms in Hypokalaemia: Insights from Pre-Clinical Models. *Frontiers in Cardiovascular Medicine*, **8**, Article 620539. https://doi.org/10.3389/fcvm.2021.620539

[2] Palmer, B.F. (2015) Regulation of Potassium Homeostasis. *Clinical Journal of the American Society of Nephrology*, **10**, 1050-1060. https://doi.org/10.2215/cjn.08580813

[3] Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriguez, M., Shah, A.D., Denaxas, S., *et al.* (2014) Blood Pressure and Incidence of Twelve Cardiovascular Diseases: Lifetime Risks, Healthy Life-Years Lost, and Age-Specific Associations in 1.25 Million People. *The Lancet*, **383**, 1899-1911. https://doi.org/10.1016/s0140-6736(14)60685-1

[4] Blanchard, A. (2023) Pathophysiologic Approach in Genetic Hypokalemia: An Update. *Annales d'Endocrinologie*, **84**, 298-307. https://doi.org/10.1016/j.ando.2022.11.005

[5] Walker, B.R., Campbell, J.C., Fraser, R., Stewart, P.M. and Edwards, C.R.W. (1992) Mineralocorticoid Excess and Inhibition of 11 $\beta$-Hydroxysteroid Dehydrogenase in Patients with Ectopic ACTH Syndrome. *Clinical Endocrinology*, **37**, 483-492. https://doi.org/10.1111/j.1365-2265.1992.tb01478.x

[6] Cui, Y., Tong, A., Jiang, J., Wang, F. and Li, C. (2016) Liddle Syndrome: Clinical and Genetic Profiles. *The Journal of Clinical Hypertension*, **19**, 524-529. https://doi.org/10.1111/jch.12949

[7] Chrousos, G. (2011) Q&A: Primary Generalized Glucocorticoid Resistance. *BMC Medicine*, **9**, Article No. 27. https://doi.org/10.1186/1741-7015-9-27

[8] White, P.C., New, M.I. and Dupont, B. (1987) Congenital Adrenal Hyperplasia. *New*

*England Journal of Medicine*, **316**, 1580-1586.
https://doi.org/10.1056/nejm198706183162506

[9] Pacak, K. and Eisenhofer, G. (2007) An Assessment of Biochemical Tests for the Diagnosis of Pheochromocytoma. *Nature Clinical Practice Endocrinology & Metabolism*, **3**, 744-745. https://doi.org/10.1038/ncpendmet0615

[10] Geller, D.S., Farhi, A., Pinkerton, N., Fradley, M., Moritz, M., Spitzer, A., *et al.* (2000) Activating Mineralocorticoid Receptor Mutation in Hypertension Exacerbated by Pregnancy. *Science*, **289**, 119-123. https://doi.org/10.1126/science.289.5476.119

[11] Fan, P., Lu, Y., Yang, K., Zhang, D., Liu, X., Tian, T., *et al.* (2020) Apparent Mineralocorticoid Excess Caused by Novel Compound Heterozygous Mutations in HSD11B2 and Characterized by Early-Onset Hypertension and Hypokalemia. *Endocrine*, **70**, 607-615. https://doi.org/10.1007/s12020-020-02460-9

[12] Speiser, P.W., Riddick, L.M., Martin, K. and New, M.I. (1993) Investigation of the Mechanism of Hypertension in Apparent Mineralocorticoid Excess. *Metabolism*, **42**, 843-845. https://doi.org/10.1016/0026-0495(93)90057-u

[13] Morineau, G., Sulmont, V., Salomon, R., Fiquet-Kempf, B., Jeunemaitre, X., Nicod, J.C.A., *et al.* (2006) Apparent Mineralocorticoid Excess: Report of Six New Cases and Extensive Personal Experience. *Journal of the American Society of Nephrology*, **17**, 3176-3184. https://doi.org/10.1681/asn.2006060570

[14] Palermo, M., Delitala, G., Mantero, F., Stewart, P.M. and Shackleton, C.H.L. (2001) Congenital Deficiency of 11β-Hydroxysteroid Dehydrogenase (Apparent Mineralocorticoid Excess Syndrome): Diagnostic Value of Urinary Free Cortisol and Cortisone. *Journal of Endocrinological Investigation*, **24**, 17-23.
https://doi.org/10.1007/bf03343803

[15] Lu, Y., Zhang, D., Zhang, Q., Zhou, Z., Yang, K., Zhou, X., *et al.* (2022) Apparent Mineralocorticoid Excess: Comprehensive Overview of Molecular Genetics. *Journal of Translational Medicine*, **20**, Article No. 500.
https://doi.org/10.1186/s12967-022-03698-9

[16] Razzaghy-Azar, M., Yau, M., Khattab, A. and New, M.I. (2017) Apparent Mineralocorticoid Excess and the Long-Term Treatment of Genetic Hypertension. *The Journal of Steroid Biochemistry and Molecular Biology*, **165**, 145-150.
https://doi.org/10.1016/j.jsbmb.2016.02.014