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Resistant Hypertension in Two Siblings: A Rare Case of Apparent Mineralocorticoid Excess Syndrome

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Abstract: ***Introduction**: Apparent mineralocorticoid excess (AME) is a rare syndrome with an autosomal recessive inheritance characterized by monogenic hypertension, nephrocalcinosis, low birth weight, failure to thrive, and short stature. AME is caused by mutations in the HSD11B2 gene, an enzyme responsible for the conversion of cortisol to cortisone. Based on 100 AME cases reported to date, 20 different mutations in the HSD11β2 gene have been identified. This case study aims to describe the clinical, genetic, and therapeutic aspects of two pediatric siblings diagnosed with AME syndrome. **Discussion**: This study adds to the limited clinical literature on pediatric AME and underscores the value of genetic testing in early diagnosis and treatment planning. AME is characterized by low birth weight, failure to thrive, and renal involvement, including renal failure and early childhood hypertension with severe target organ damage. Long-standing hypokalemia can lead to nephrocalcinosis along with renal cysts, which can be prevented with early diagnosis and management. A limited-salt diet is recommended as a treatment for patients. In addition, mineralocorticoid receptor antagonists, along with potassium-sparing diuretics, are strongly recommended. Glucocorticoids can suppress endogenous adrenocorticotropic hormones. **Conclusion**: We here report cases of AME in two siblings who presented with hypertension. This case report emphasizes the clinical relevance of early genetic screening in pediatric hypertension cases with family history. The confirmation of AME through whole exome sequencing in both siblings guided tailored treatment approaches, leading to improved patient outcomes. Continued follow-up is essential to mitigate long-term risks.*

Keywords: Apparent mineralocorticoid excess syndrome, resistant hypertension, nephrocalcinosis

1. Introduction

Apparent mineralocorticoid excess (AME) is a rare syndrome with an autosomal recessive inheritance characterized by monogenic hypertension, nephrocalcinosis, low birth weight, failure to thrive, and short stature (1, 2). AME is caused by mutations in the *HSD11B2* gene, which encodes 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (2), an enzyme responsible for the conversion of cortisol to cortisone. In individuals with 11β-HSD2 deficiency, cortisol accumulates inside the renal distal tubular cells, activating the mineralocorticoid receptor, causing sodium reabsorption and excretion of potassium and hydrogen, and resulting in the typical clinical features of hypertension (HTN) and hypokalemic metabolic alkalosis (3, 4). Based on 100 AME cases reported to date, 20 different mutations in the *HSD11β2* gene have been identified (1). This case study aims to describe the clinical, genetic, and therapeutic aspects of two pediatric siblings diagnosed with AME syndrome.

Case 1

The patient was a 6-year and 7-month-old boy with a known history of right crossed ectopia umbilical hernia. He was first seen in the pediatric intensive care unit (PICU) at the age of 2 years and 3 months when he was admitted for gastroenteritis with severe dehydration and sepsis. During his stay in the PICU, he had high blood pressure (Figure 1) and pre-renal acute kidney injury (AKI) with hypernatremia, normal anion gap hyperchloremic metabolic acidosis, and high urea (

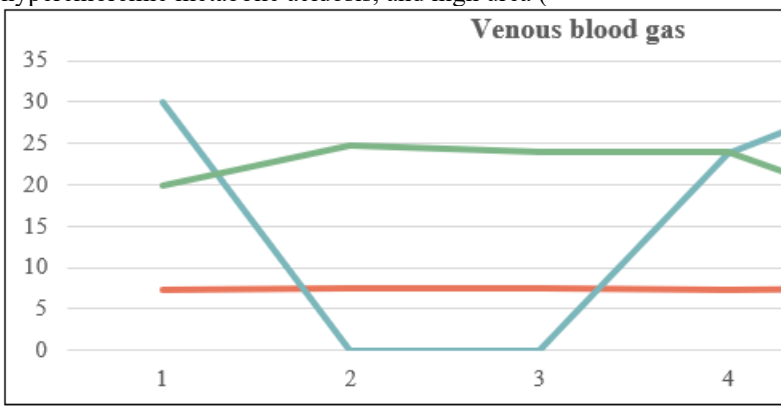


Figure 2), along with failure to thrive.

He was started on labetalol IV (0.3 mg/kg/h), gradually increasing it to 2 mg/kg/h, and hydralazine IV 0.1 mg /kg PRN Q6 h. The cardiology team was consulted. Following an ECHO that showed left ventricular hypertrophy, amlodipine was administered. Doppler renal ultrasound (US) showed no evidence of renal artery stenosis, while the abdominal US showed a right ectopic kidney with grade one nephropathy (

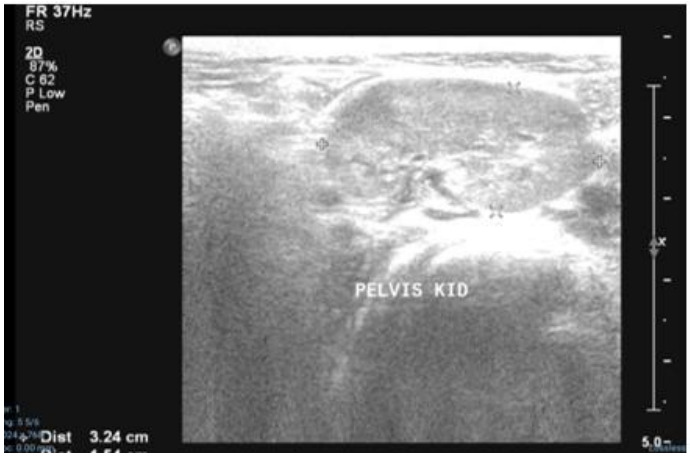


Figure).

Nephrology was consulted to rule out renovascular HTN. CT angiography ruled out renal artery stenosis but indicated right crossed ectopia and a bizarre arterial supply to the ectopic kidney originating from the aorta and right common iliac artery. The renal artery originating from the aorta was slightly kinked near its origin and stretched along its course anterior to the capsule of the ectopic kidney. However, there was no CT angiographic evidence of focal or segmental stenosis or aneurysmal dilatation. The nephrology team recommended starting the patient on captopril 0.3 mg/kg/dose TID, gradually increasing it to 2.5 mg TID. The patient was discharged to go home after his renal and aldosterone levels returned to normal.

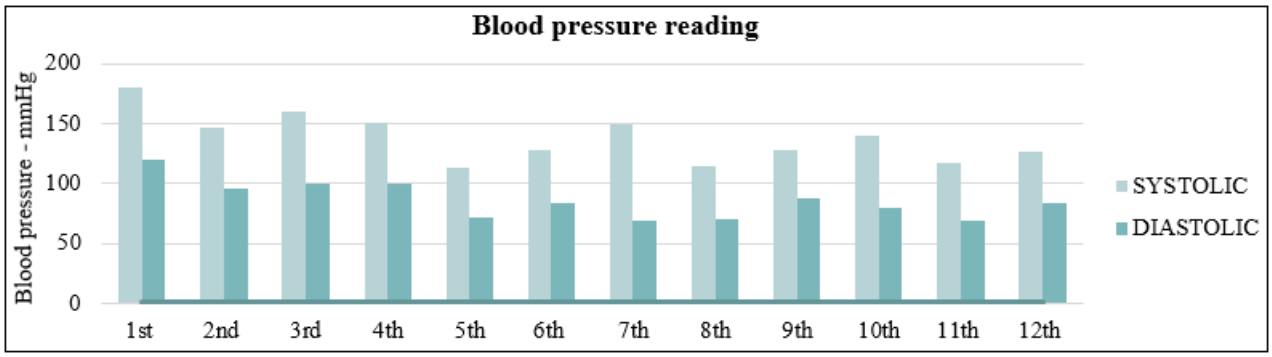


Figure 1: Blood pressure reading in the first inpatient course

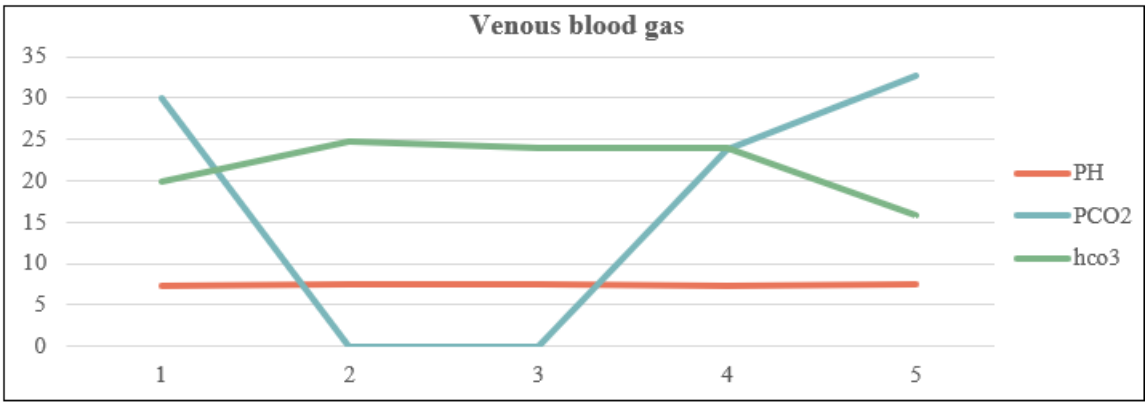


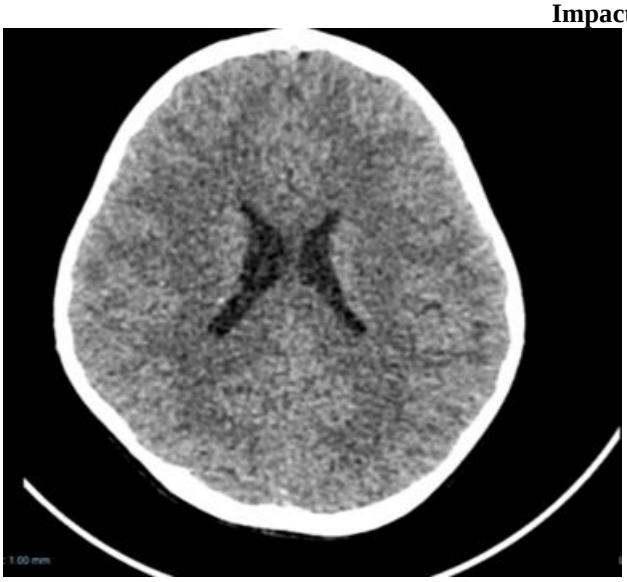
Figure 2: Blood gas reading in the first inpatient course

Subsequently, he was followed up regularly in the nephrology clinic. His blood pressure was still high on his first follow-up visit (Figure 4). A DMSA scan showed a small triangular scar.

After ruling out renovascular HTN, renin-induced HTN, and vasculitis, Liddle Syndrome was considered the cause of monogenic HTN. We added spironolactone 9 mg PO once daily to his medications. However, after a few visits to the clinic, the patient still had low potassium levels and was started on KCL solution, which was discontinued after the potassium levels normalized. He was referred to a higher center for genetic testing to rule out Liddle syndrome. A gene study of whole exome sequencing (WES) for his sister, who had the same complaints and history, revealed a likely pathogenic homozygous variant in the HSD11 B2 gene, confirming autosomal recessive AME disorder. His medication was adjusted since the blood pressure continued to be high. The patient was lost to follow-up almost 10 months later.

The patient was readmitted to the PICU for a second time when he was 6 years and 7 months old for emergency hypertension. The brain CT scan was normal (

Figure 6:).



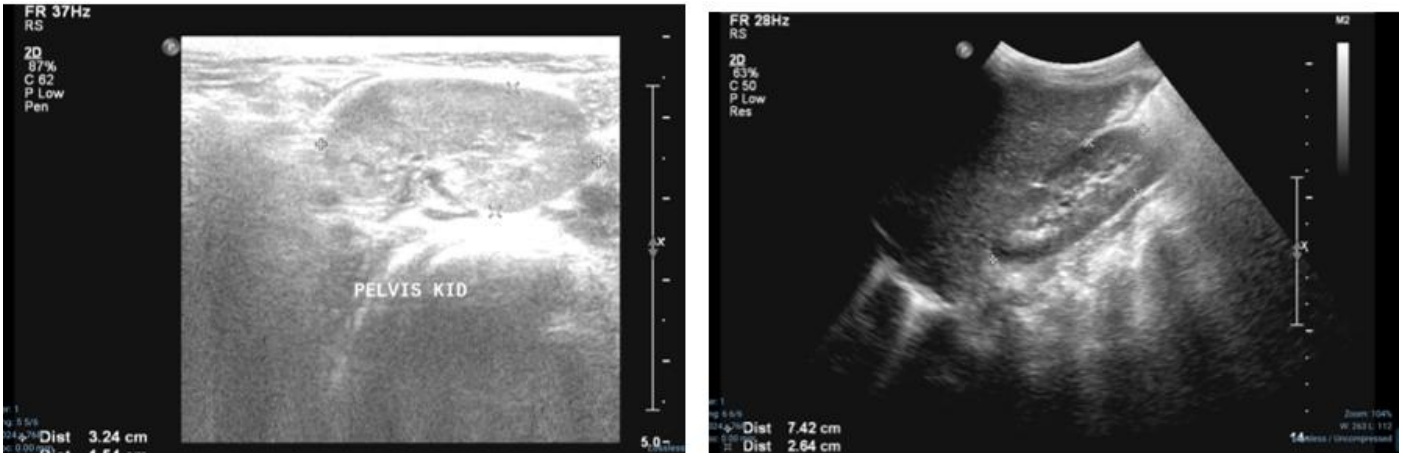


Figure 3: Doppler renal US shows right ectopic kidney with grade one nephropathy.

The endocrine team was involved, and hydrocortisone was initiated. After stabilization of the patient and a few days of admission, he was discharged on the regular medication captopril (1 mg/kg/dose), spironolactone (2 mg/kg/day), propranolol (1.6 mg/kg/day), and hydrocortisone (BID).

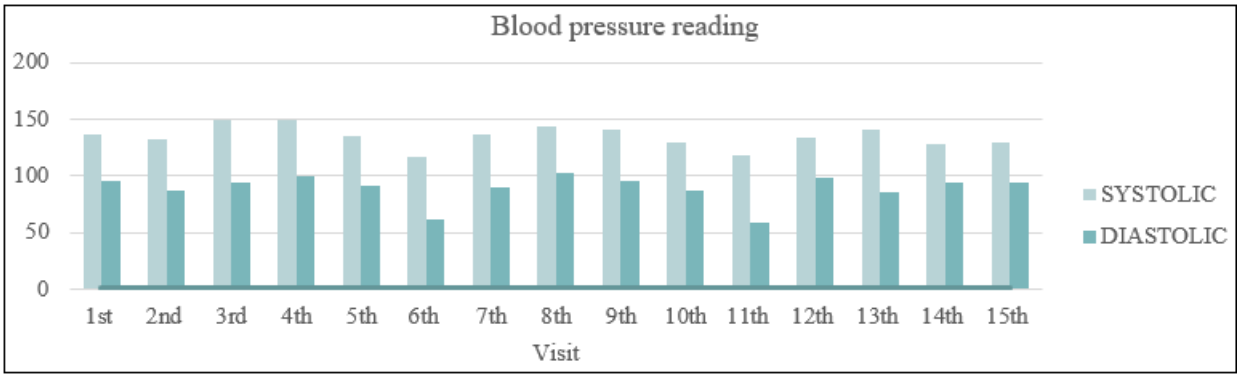


Figure 4: Blood pressure reading during the clinic visit

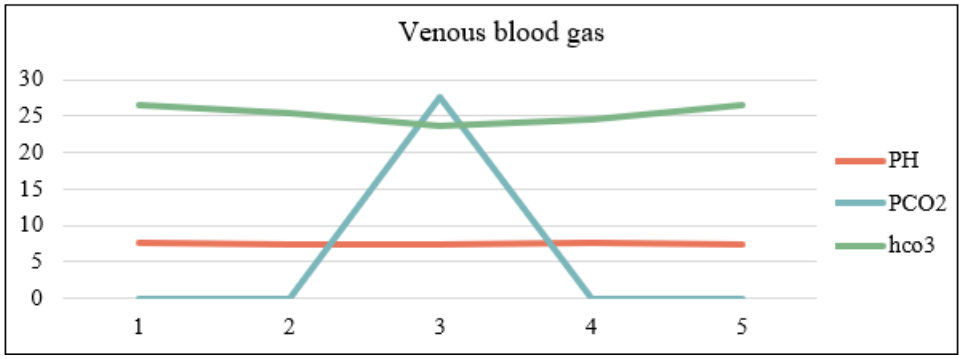


Figure 5: Blood gas during the clinic visit

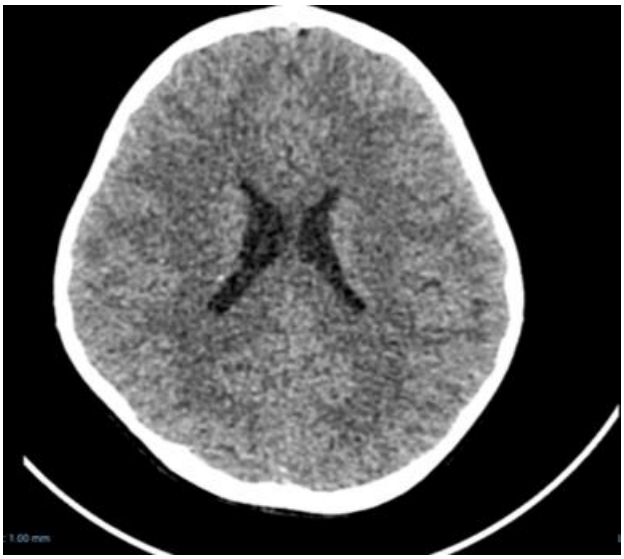


Figure 6: CT brain scan is unremarkable

Case 2

The patient was a 2-year-old girl with a family history of ectopic kidney and hypertension. She was the sibling of the patient described in Case 1. She was seen for the first time in the general clinic because she failed to thrive. During her second visit to the general clinic as a follow-up, high blood pressure of 138 /90, 140 /95, and 141 /95 were recorded, all of which exceeded the 95th percentile +12 mmHg.

She presented at the nephrology clinic for the first time with an accidental diagnosis of nephrocalcinosis. Her blood pressure readings were 102/74 and 134/91 mmHg. A renal ultrasound revealed bilateral nephrocalcinosis (

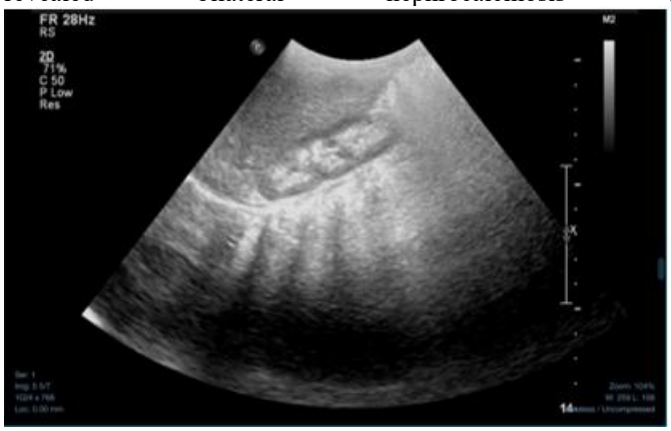


Figure), and she had a normal hormonal profile. She was initially started on hydrochlorothiazide 0.5 mg /kg/day. Following an ECHO during a cardiology consultation, which showed mild hypertrophy, she was started on amlodipine and captopril (6.25 mg) PO. The patient had regular follow-ups with the nephrology clinic, during which she remained asymptomatic with high blood pressure. Gene study WES identified a pathogenic homozygous variant of *HSD11B2* in this patient, confirming AME diagnosis. After an endocrine consultation, she was started on hydrocortisone. Subsequently, her home blood pressure readings were in the normal range, and she remained asymptomatic.

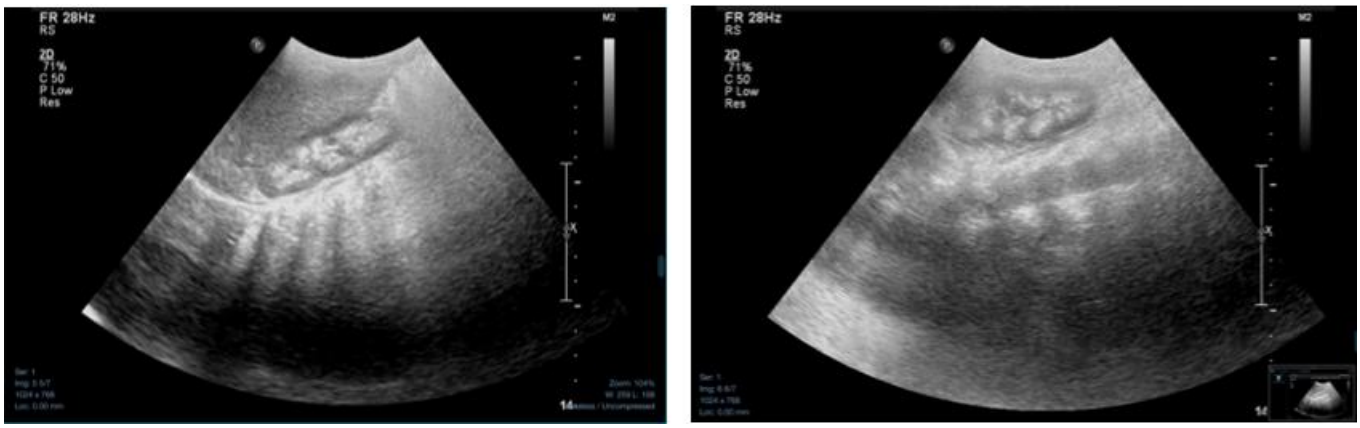


Figure 7: Renal ultrasound shows bilateral nephrocalcinosis

2. Discussion

This study adds to the limited clinical literature on pediatric AME and underscores the value of genetic testing in early diagnosis and treatment planning. AME is characterized by low birth weight, failure to thrive, and renal involvement, including renal failure and early childhood hypertension with severe target organ damage (1). Due to unknown reasons, patients with AME can present early in life with mild to moderate intrauterine growth retardation. The most likely cause for this is mutations in the *HSD11B2* gene, resulting in a deficiency of the 11β-HSD2 enzyme, allowing excessive maternal glucocorticoids to cross the placenta and inhibiting fetal growth. The low birth weight is one of the risk factors for developing hypertension later in the adult life (5).

Depending on the mutations in the *HSD11B2* gene, some patients exhibit fewer symptoms of AME (6). The 11β-HSD2 enzyme has two isoforms. The first is the liver (L) or typeIisoform, which is not found in patients with AME, while the second isoform, found in the mineralocorticoid tissue, has a high affinity for steroids and corresponds to the *HSD11K* or *HSB11B2* gene located on 16q22 chromosome (7). Gene study WES identified a pathogenic homozygous variant of *HSD11B2* in the second patient, confirming AME diagnosis.

Long-standing hypokalemia can lead to nephrocalcinosis along with renal cysts, which can be prevented with early diagnosis and management (8). A limited-salt diet is recommended as a treatment for patients. In addition, mineralocorticoid receptor antagonists (spironolactone or eplerenone), along with potassium-sparing diuretics, are strongly recommended (2). Glucocorticoids can suppress endogenous adrenocorticotropic hormones (2).

We used spironolactone and hydrocortisone to maintain normal blood pressure in the first patient, while hydrochlorothiazide and hydrocortisone were used for the second patient.

A 2017 study describes the long-term outcomes of AME, which include persistent nephrocalcinosis (89%), cardiovascular mortality (19%), and kidney failure (15%) (9). Stroke is a major cause of death in patients with AME (10).

3. Conclusion

We here report cases of AME in two siblings who presented with hypertension. This case report emphasizes the clinical relevance of early genetic screening in pediatric hypertension cases with family history. The confirmation of AME through whole exome sequencing in both siblings guided tailored treatment approaches, leading to improved patient outcomes. While the first patient was treated with spironolactone, a mineralocorticoid receptor antagonist, and hydrocortisone, the second patient received hydrochlorothiazide and hydrocortisone. Continued follow-up is essential to mitigate long-term risks such as nephrocalcinosis, cardiovascular complications, and renal failure.

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