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Apparent Mineralocorticoid Excess Syndrome: Case Report

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Abstract: Apparent Mineralocorticoid Excess (AME) syndrome is a rare form of high-blood pressure syndrome caused by genetic mutations in the 11b-hydroxysteroid dehydrogenase type 2 (HSD11B2) gene, inherited in an autosomal recessive manner. The condition can be either congenital or acquired. This report presents two cases of AME in children from consanguineous families identified through clinical assessment and whole-exome sequencing (WES). Symptoms included high blood pressure, hypokalemia, and metabolic alkalosis. AME syndrome was confirmed by WES, which revealed a homozygous missense pathogenic mutation c.622C>T p.(Arg208Cys) in exon 3 of the HSD11B2 gene. Treatment with spironolactone, and potassium chloride alone was not effective, so low-dose dexamethasone was added. Post-treatment, both patients showed significant improvement in their blood pressure and electrolyte levels. Diagnosis of AME syndrome can is often challenging because it is an extremely rare autosomal recessive disorder. Only five cases have been reported in Saudi Arabia, and only four case studies discussed treatment plans. This case report provides additional data to support the current literature and treatment protocols.

Keywords: apparent mineralocorticoid excess syndrome (AME), HSD11B2 mutation, hypokalemic alkalosis, whole exome sequencing (WES), spironolactone treatment

Introduction

Apparent Mineralocorticoid Excess Syndrome (AME) is a rare form of high blood pressure that can be caused by genetic mutations in the 11b-hydroxysteroid dehydrogenase type 2 (*HSD11B2*) gene, inherited in an autosomal recessive manner.[1] The clinical symptoms of Apparent Mineralocorticoid Excess (AME) were first documented by Werder et al[1] in a 3-year-old girl. These symptoms included low birth weight, growth delay, polyuria, polydipsia, and hypertension.

Hypertension, plasma volume expansion, hypokalemic alkalosis, and a suppressed renin-angiotensin-aldosterone system are all characteristic features of AME, which is caused by impaired inactivation of cortisol, leading to inappropriate activation of mineralocorticoid receptors. Besides, AME can also be acquired if 11b-HSD2 is inhibited.[2,3] The classification of this condition depends on whether it is congenital or acquired. However, both forms exhibit the same pathophysiological characteristics. Defective 11-HSD2 is responsible for AME, a condition characterized by altered steroid metabolism.[4]

11β-HSD1 and 11β-HSD2 are two enzymes that play a role in tissue- and cell specific cortisol levels.[4] Although both metabolize glucocorticoids, they are quite different, sharing only 18% amino acid sequence identity and oriented toward different cellular compartments.[5] 11β-HSD2 is found in multiple tissues including the brain, placenta, kidney, and colon. It primarily converts the active steroid cortisol into its inactive form cortisone. Mineralocorticoid Receptors (MR) are activated by cortisol and aldosterone. MR exhibit the same affinity for cortisol and aldosterone. However, in living organisms, MR have a much higher preference for aldosterone than for cortisol.[2] The function of 11β-HSD2 in cortisol metabolism is to control the preference of aldosterone for MR. When 11β-HSD2 activity is completely abolished or

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partially lost, cortisol accumulates continuously, leading to excessive stimulation of MR. This results in increased sodium reabsorption, potassium loss, and low-level renin production. Moreover, after the conversion of cortisol fails, there is a noticeable increase in the excretion of the urinary cortisol metabolites tetrahydro cortisol (THF) and allo-THF, accompanied by a decrease in the cortisone metabolite tetra hydrocortisone (THE).[4]

Aldosterone and cortisol have similar affinities for MR but in mineralocorticoid target tissues such as the kidney and colon, 11β-HSD2 inactivates cortisol, which is 500-fold more abundant than aldosterone. This action ensures that aldosterone can regulate electrolyte balance effectively. If 11β-HSD2 is inhibited, cortisol can excessively activate MR, even outside of peak or stress levels. Substances such as licorice and azole antifungals, which inhibit 11β-HSD2, can therefore contribute to this excessive activation.[6]

The feto-placental 11β-HSD2 is commonly referred to as a "glucocorticoid barrier" as it plays a crucial role in strictly controlling the inactivation of maternal cortisol, thus ensuring fetal cortisol homeostasis. Eliminating 11β-HSD2 in the placenta leads to the fetus being overly exposed to maternal glucocorticoids, which in turn causes intrauterine growth restriction. This is associated with alterations in the glucocorticoid receptor phenotype. Moreover, consuming large amounts of licorice and azole antifungals, which are 11β-HSD2 inhibitors, can lead to hypertension caused by MR activation.[4]

Consanguinity is another important factor associated with AME as it is a recessive genetic disorder that indicates close familial relationships. First- cousin marriages are estimated to have a 2–2.5 times higher risk of birth defects in offspring than in the general population, primarily because of autosomal recessive disorders.[7] AME is an extremely rare autosomal recessive disorder that is challenging to diagnose. In Saudi Arabia, only five cases of this syndrome have been reported, with limited information available on the treatment plans. This case study adds to the existing literature and treatment plans by enabling additional research on this disorder.

Case 1

The primary healthcare center referred a 7-year-old girl because of an accidental finding of high blood pressure (154/104) during a routine checkup.

History

The patient was born to consanguineous parents at term with a history of low birth weight. Although the mother could not recall the exact weight at birth, it was documented at another hospital. Throughout pregnancy, no abnormalities were detected, and the child did not require hospitalization. After obtaining a more detailed history from the parents, they mentioned that the child was hyperactive, constantly feeling thirsty, and had a history of bedwetting, frequent urination, and decreased appetite. Additionally, the child had a history of academic struggle.

Clinical Finding

Her blood pressure reading of 154/104 mmHg indicated severe elevation, surpassing the 99th percentile benchmark. The patient's failure to thrive was evident, with a height of 110 cm (below the 3rd percentile on the Centers for Disease Control and Prevention (CDC) growth charts) and a weight of 18 kg (at the 5th percentile on the Centers for Disease Control and Prevention (CDC) growth charts). Examination of other systems revealed no significant abnormalities.

Initial laboratory investigations revealed mild hypokalemia with a serum potassium level of (K 3 mmol/L). Further, metabolic alkalosis was observed at a bicarbonate level of (HCO3 30 mmol/L). Notably, all other serum levels including BUN, chloride, calcium, magnesium, phosphorous, and sodium were within normal range while the creatinine level was at the upper end of the normal range (48 μmol/L), in accordance with the patient's body build. Urine examination results were within the normal range, and the culture test showed no bacterial growth. Renal ultrasonography revealed nephrocalcinosis, but the results of renal micturating cystourethrogram (MCUG), renal Doppler ultrasound, and Dimercapto succinic acid scan (DMSA) were all within normal limits. Echocardiography indicated mild left ventricular hypertrophy, which was potentially attributed to high blood pressure. In addition to the normal thyroid examination results, the lipid profile showed no abnormalities.

Diagnostic Assessment

The parents were informed of the provisional diagnosis, which was based on clinical evaluation. Owing to the unavailability of certain hematological and serological tests at our hospital, we presented two options: either referring the patients to other hospitals for these tests or recommending genetic testing, which is a more accessible alternative in Saudi Arabia. The patients were referred to a genetic clinic for whole exome sequencing, with the consent of their parents.

The likely inherited nature of the condition was explained to the parents, noting that both children appeared to suffer from the diseases. Due to a lack of resources in our hospital (such as tests for urine cortisol level, aldosterone, renin, serum cortisol, and ACTH), we suggested either conducting the tests in other hospitals or sending them to the genetics clinic for whole exome sequencing (WES). Genetic tests are commonly performed in Saudi Arabia due to a high prevalence of genetic diseases. The parents agreed to proceed with genetic tests to identify all possible causes of the pediatric condition.

WES confirmed the diagnosis of AME syndrome, revealing a homozygous missense mutation NM_000196.3: c.622C>T p.(Arg208Cys) in exon 3 of the HSD11B2 gene. Based on these findings, treatment was promptly initiated.

The c.622C>T p.(Arg208Cys) mutation in exon 3 of the HSD11B2 gene is a homozygous missense mutation associated with Apparent Mineralocorticoid Excess (AME) syndrome. This mutation results in a substitution of arginine (Arg) with cysteine (Cys) at position 208 of the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme. The resulting structural alteration impairs enzyme activity, which prevents the proper conversion of active cortisol to its inactive form, cortisone. Consequently, elevated cortisol levels lead to inappropriate activation of mineralocorticoid receptors (MR), resulting in hypertension and electrolyte imbalances. Nunez et al[8] have described how mutations in 11β-HSD2 reduce enzyme activity and contribute to the pathogenesis of AME, offering foundational insight into how variants such as Arg208Cys result in the clinical features of the disease.

Therapeutic Intervention

As part of her initial treatment, she was prescribed potassium chloride supplementation (3 meq/kg/day). Her blood pressure was partially controlled with a maximum dose of losartan (50 mg OD) and amlodipine (10 mg OD). However, during follow-up in the outpatient department (OPD), despite these medications, her systolic and diastolic blood pressures remained high, specifically in the 95th percentile. This led to readmission two months after the last OPD visit. The patient was readmitted with severe symptoms of acute gastroenteritis and dangerously low potassium levels (1.4). Upon admission, the patient exhibited mild dehydration and a blood pressure of 130/87 mmHg.

During this admission, genetic testing results returned positive for Apparent Mineralocorticoid Excess (AME), and she was treated accordingly:

- Symptoms were alleviated by initiating IV fluid with KCL 40 mEq/L and introducing oral KCL along with bolus doses.
- Spironolactone 25 mg PO TID (gradually doses increased till reached to the maximum dose (3.3 mg/kg (75 mg)), in addition to her home medication Amlodipine (10 mg PO OD) and Losartan (50 mg PO OD).
- Initially, the patient responded poorly to treatment during her acute illness, despite receiving the maximum doses of spironolactone, and antihypertensive medications.
- She exhibited high blood pressure, which prompted the initiation of oral dexamethasone at 0.5 mg daily for few days, and the treatment was continued then tapered and discontinued later during her recovery phase as her clinical status improved.

Follow-Up and Outcomes

After treatment, potassium levels showed a steady improvement, increasing from 1.5 to 2.1, then to 2.5, and finally reaching 3.3. Concurrently, the patient's blood pressure normalized, ranging between 108–119 systolic and 65–79 diastolic. At discharge, the patient's blood pressure remained within the normal range (96–100 systolic and 58–72 diastolic), with normal electrolyte levels. The prescribed medication regimens included spironolactone 15 mg orally three times a day, losartan 25 mg orally once a day, and amlodipine 10 mg orally once a day. During subsequent follow-up

visits, the spironolactone dosage was gradually reduced to 12.5 mg three times a day. Regular follow-up evaluations revealed sustained clinical improvement, including weight gain, stable electrolyte profiles, and consistently normal blood pressure.

Case 2

Another patient, aged 3 years, is the younger sibling of the patient in Case-1 above, also exhibited similar symptoms when their family history was examined. These symptoms include hyperactivity, extreme thirst, and a history of low birth weight. Although the exact birth weight was unknown, the patient was born at term without requiring neonatal intensive care. The patient exhibited similar symptoms of his older sister, as indicated by an elevated blood pressure of 138/88. The patient's height was 90 cm (falls on the third percentile, while his weight of 11 KG was below the third percentile). Initial laboratory investigations revealed hypokalemia (K 3 mmol/L) and metabolic alkalosis (HCO3 31 mmol/L). Renal ultrasound and evaluations of parathyroid hormone, thyroid function, and liver function returned normal findings. Based on the confirmed diagnosis of his sibling, the patient was admitted as suspected case of AME. He was initiated on oral potassium supplementation (3 mEq/kg/day), amlodipine 2.5 mg once daily, Spironolactone 10 mg three times daily, and losartan 12.5 mg once daily. Following treatment, there were noticeable improvement, with a blood pressure of 94/54 mmHg and potassium level of 4.7. At discharge, the patient was prescribed oral potassium chloride, spironolactone 12 mg three times daily, losartan 12.5 mg once daily, and amlodipine 5 mg once daily.

AME was later confirmed by genetics tests of the HS11B2 gene, which revealed a homozygous missense mutation− c.622C>T p.(Arg208Cys) in exon 3− consistent with the variant identified in his sister.

In contrast to the first patient, the second patient's blood pressure was more effectively controlled without the need for dexamethasone. This favourable response may be attributable to earlier initiation of spironolactone, male sex, younger age and the absence of aggravating factors such as dehydration or excessive electrolyte loss, despite both siblings harbouring the same pathogenic variant.

Discussion

AME is an uncommon condition, and its prevalence in individuals with hypertension remains unknown. Following the pattern of autosomal recessive inheritance, the primary mutations that cause this condition typically occur in consanguineous or endogamous groups or in families affected by a founder effect.[9] It is difficult to estimate its prevalence, and it likely varies among populations depending on the level of consanguinity. Based on literature, there have been only five documented instances of AME in the Kingdom of Saudi Arabia.[10–12] No sex predominance was observed for this disease. There are two forms of AME, classic and non-classic, which can be distinguished based on the severity of their phenotypic presentation. Researchers have identified a clinical condition called non-classic AME that exhibits a mild range of symptoms. Early onset AME is common in the classic category. Clinical characteristics include severely high blood pressure, an inability to grow and develop properly, and ongoing excessive thirst and urination. Biochemical profiles revealed signs of metabolic alkalosis and extremely low potassium levels. Low plasma renin activity indicates hypertension caused by increased blood volume, which can be treated with a low-sodium diet. Levels of all steroids, including aldosterone, were extremely low.[13]

Individuals who have significant mutations affecting the enzymatic function of 11b-HSD2 often display typical symptoms of AME, such as low birth weight, delayed growth, short stature, early onset of severe hypertension, hypokalemia, reduced testosterone levels, and an elevated ratio of THF + 5α THF/THE in urine. Mutations that result in a partial decrease in the enzymatic activity of 11b-HSD2 can lead to hypertension without low potassium levels.[9] The presence of early onset hypertension with hypokalemia in both reported cases indicate the significance of mutations in this scenario.

In addition to consanguineous recessive cases, compound heterozygous mutations in the HSD11B2 gene can also cause Apparent Mineralocorticoid Excess (AME) syndrome.[14] Such cases are more challenging to detect, thereby complicating diagnosis. For instance, Ding et al[15] reported three pediatric AME cases in China, identifying novel HSD11B2 gene variants thereby expanding the known genetic spectrum of the. Case 1 was found to be homozygous for an HSD11B2 variant, while Case 2 and Case 3 were identified as compound heterozygotes, each carrying two different

HSD11B2 variants inherited from their parents. Compound heterozygotes cases are more challenging to detect during sequencing because compound heterozygosity involves two different mutations, one on each allele, which can complicate diagnosis. Such mutations are often overlooked, especially when detailed sequencing analysis is not performed. It is important to consider both recessive and compound heterozygous mutations in cases where the clinical presentation suggests AME but no clear homozygous mutations are identified. Ding et al,[15] confirmed the compound heterozygotes cases through parental Sanger DNA sequencing and reiterated the importance of early genetic diagnosis.

Biochemical diagnosis of AME involves the analysis of urinary metabolites and determination of the ratio of cortisol to cortisone. However, resource constraints prevented us from conducting biochemical investigations. Clinical evidence indicates that these cases fall under the classic category.[4] Autosomal recessive apparent mineralocorticoid excess was confirmed after the completion of WES. Alzahrani et al[11] observed that spironolactone alone was insufficient to control blood pressure, prompting the addition of dexamethasone.[11] We also followed the same regimen but with a limited dose of dexamethasone for treatment and observed improvements. There are different opinions in the literature on the use of dexamethasone. Some authors recommend this treatment only when mineralocorticoid antagonists fail. We prescribed a low dose of dexamethasone for a short duration, considering its long-term side effects and mode of action of the drug.[16] Albalawi et al[12] not only discussed the rare prevalence of the disease but also delved into treatment options for AME. They highlighted the importance of a low-sodium diet as well as the extended use of spironolactone and amiloride. The major concern in this case report was the diagnosis.[12] Although the two patients/siblings reported had the same HSD11B2 mutation, the younger sibling showed a milder course. This is attributable to earlier diagnosis and treatment, and the absence of aggravating factors.

Conclusions

Genetic forms of AME manifest during childhood and are characterized by high blood pressure, low potassium levels, and decreased renin and aldosterone levels. Spironolactone was administered to inhibit the binding of cortisol and aldosterone to the mineralocorticoid receptor. Potassium supplementation, dexamethasone, and amlodipine are recommended to complement the primary treatment. Dexamethasone suppresse cortisol production by cortisol. Nonetheless, it is not consistently effective in reducing blood pressure and can cause severe side effects with prolonged usage. Timely diagnosis and intervention can prevent or reduce the risk of organ damage and improve long-term outcomes. Further, the differences in clinical outcomes, despite identical genotypes, underscore the impact of treatment timing and the presence or absence of acute illness on disease severity and response.

Declarations

Institutional approval was not required for the publication of this case report. Written informed consent was obtained from the patient's parents, in accordance with the ethical guidelines of the Qassim Region Research Ethics Committee (QREC). No identifiable personal information has been included in this report.

Disclosure

The authors report no conflicts of interest in this work.

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