Case Report

# Two Qatari siblings with cystic fibrosis and apparent mineralocorticoid excess

**Khalid Zahraldin, Ibrahim Ahmed Janahi, Tawfeg Ben-Omran[1], Reem Alsulaiman[1], Bajes Hamad[2], Abubakr Imam[2]**

*Pulmonary Section, [1]Section of Clinical and Metabolic Genetics, [2]Nephrology Section, Department of Pediatrics, Hamad Medical Corporation, Doha, Qatar*

**Address for correspondence:**
Dr. Ibrahim Ahmed Janahi, Associate Professor of Clinical Pediatrics, Weill-Cornell Medical College-Qatar, Sr. Consultant and Head of Pediatric Pulmonology Section, P.O. Box 3050, Hamad Medical Corporation, Doha, Qatar.
E-mail: ijanahi@hmc.org.qa

Submission: 31-03-2014
Accepted: 25-06-2014

**Abstract:**

Cystic fibrosis (CF) and apparent mineralocorticoid excess (AME) syndrome are both autosomal recessive disorders that result from mutations of specific identified genes for each condition. CF is caused by defects in the Cystic fibrosis trans membrane conductance regulator (*CFTR)* gene which encodes for a protein that functions as a chloride channel and regulates the flow of other ions across the apical surface of epithelial cells. AME is due to the deficiency of 11β-hydroxysteroid dehydrogenase type 2 enzyme (11βHSD2), which is responsible for the peripheral inactivation of cortisol to cortisone. Cortisol excess stimulates the mineralocoritoid receptors (MR) resulting in intense sodium retention, hypokalemia and hypertension. We report on a consanguineous Arab family, in which two sibs inherited both CF and AME. Gene testing for AME revealed previously unreported mutation in the *11βHSD2* gene. This report draws attention to the importance of recognizing the possibility of two recessive disorders in the same child in complex consanguineous families. Moreover, it provides a unique opportunity to highlight the implications of the coexistence of two genetic disorders on patient care and genetic counseling of the family.

**Key words:**

Apparent mineralocorticoid excess, autosomal recessive, Arab, cystic fibrosis, Qatar

**Access this article online**

Quick Response Code:

**Website:** www.thoracicmedicine.org

**DOI:** 10.4103/1817-1737.146892

Consanguinity and endogamy is common in the Middle East region resulting in a higher frequency of autosomal recessive disorders, particularly rare or private syndromes.[1] Apparent mineralocorticoid excess syndrome (AME, OMIM # 218030) is a rare autosomal recessive disorder caused by deficiency of the enzyme type II 11-beta-hydroxysteroid dehydrogenase (11βHSD2; Enzyme Commission number 1.1.1.146) encoded by the 11β-hydroxysteroid dehydrogenase type 2 (*HSD11B2*) gene on chromosome 16q22.1.[2,3] This enzyme is responsible for the peripheral inactivation of cortisol to cortisone, thereby protecting the mineralocorticoid receptor (MR) from inappropriate activation by cortisol.[4] In patients with AME, the cortisol excess stimulates the MR causing intense sodium retention, hypokalemia and hypertension.[5] Cystic fibrosis (CF, OMIM # 219700) on the other hand, is another autosomal recessive disorder caused by mutations in the cystic fibrosis trans membrane conductance regulator (CFTR) gene on chromosome 7q31.2 encodes a protein that functioning as a chloride channel, in addition, controls the regulation of other transport pathways.[6]

To the best of our knowledge, there is no reported relationship or coexistence of these two conditions in the same patient. The purpose of this report is to highlight the importance of considering the possibility of two recessive disorders when dealing with consanguineous population.

## Clinical Reports

This family came to medical attention because of hypertension in the eldest sibling. There were multiple loops of consanguinity [Figure 1]. They have three children in total; one normal and the two affected siblings described below.

### Patient 1

The proband was born at 33-week after an uneventful pregnancy. She had a birth weight of 1430 g (between 3rd-10th % percentiles), length of 41 cm (at 10th % percentile) and head circumference of 23.5 cm (below 3rd % percentile). Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. There were no postnatal complications.

At the age of 16 months, she presented to the Emergency Department with 1-day history of fever and chronic cough (for 3 months duration). Physical examination revealed weight of 6.4 kg and height of 69 cm (both below the 3rd percentile). Blood pressure was high above the 95th percentile (range 110/68-135/85). Otherwise, her systemic examination was unremarkable except for bilateral red and congested tympanic membrane. She was treated for otitis media and admitted to the hospital for further evaluation and management of hypertension. Biochemical analysis showed hypokalemia (serum potassium, 2.7 mmol/L), alkalosis (bicarbonate 27 mmol/L), and normal sodium (145 mmol/L), with normal

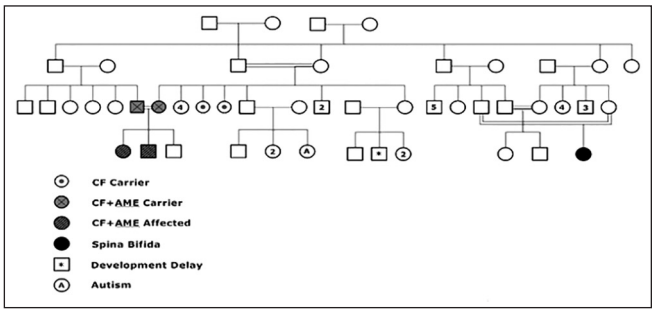


**Figure 1:** Pedigree of the presented family

renal function (serum creatinine 25 μmol/L). Renal Doppler ultrasound revealed bilateral normal sized kidney with increased parenchymal echogencity and resistive indices are at higher level. Because of suspicious of renovascular disease, magnetic resonance angiogram (MRA) of the abdominal aorta and renal arteries were done and reported as normal. Cardiac echocardiography showed hypertrophied left ventricle.

### *Treatment and progress*

The patient's hypertension was managed at pediatrics intensive care with continuous intravenous labetalol drip (0.5 mg/kg/hr) increased up to (2 mg/kg/hr) to control her blood pressure. She has also received intravenous potassium chloride supplement. Despite labetalol therapy, there was persistent elevation of blood pressure, amlodipine 2 mg twice daily (0.3 mg/kg/day) was added and the labetalol was switched to oral at a dose of 9 mg twice daily (2.8 mg/kg/day). She has also received 10 day of amoxicillin /clavulanic acid for otitis media. Because of the history of chronic cough and failure to thrive, sweat chloride test done (63 mmol/L), his genetic study confirmed the diagnosis of cystic fibrosis with two mutant alleles for I1234V known to cause cystic fibrosis in the Qatari population.

### *Clinical follow-up*

The result of renin and aldesterone revealed low levels. The plasma renin activity was 0.33 ng/ml/hour (normal: 0-2 years: 1.7-11.2 ng/mL/hour); serum aldosterone was low at 17 pg/ml (normal: 194.2-2579.8 pg/ml). With these values, low renin hypertension was entertained and the possibility of Liddle syndrome against for apparent mineralocorticoid excess (AME) was considered. Gene testing was done for both conditions and the patient was switched to amiloride (0.7 mg/kg/day).

Two months later, on follow-up, the BP was adequately controlled (below 90$^{th}$ percentile) and the electrolytes were normal (potassium 5 mmol/L, bicarbonate 23 mmol/L) without supplementation. She is currently 3 years and 7 months of age and her weight is 10.7 kg (less than the 3$^{rd}$ percentile), height 92 cm ((less than the 3$^{rd}$ percentile). Her BP is normal on amiloride 2 mg once per day (0.2 mg/kg/day) and with follow-up echocardiogram showing normal heart with no evidence of left ventricle hypertrophy and good biventricular function.

Genetic study has confirmed the diagnoses of apparent mineralocorticoid excess with homozygous variant in exon 2 of the *HSD11B2* gene (c.266G < A p.G89D). This mutation was not reported previously, however, they were detected in homozygous status in both of the affected siblings and as heterozygous status in the parents.

## Patient 2

The younger brother of the proband, was born at 33 week after an uneventful pregnancy. He had a birth weight of 1370 g (between 3$^{rd}$-10th % percentiles), length of 40 cm (between 3$^{rd}$-10$^{th}$% percentile) and head circumference of 28.5 cm (10th % percentile). Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. His neonatal period was complicated by distal ileal obstruction and resection of 12 cm of the small intestine.

Because of consanguinity and positive family history for CF, sweat chloride test was done (78 mmol/L); his genetic study confirmed the diagnosis of cystic fibrosis with two mutant alleles for I1234V. He was followed by the pulmonary and gastroenterology services.

At the age of 5 months, he was admitted to the hospital for acute chest exacerbation with pneumonia. On admission, his weight was 4.4 kg (below 3$^{rd}$ percentile corrected for prematurity), the height was 63 cm (at 50$^{th}$ percentile corrected for prematurity). His vitals showed significantly elevated high blood pressure readings (range 132/85-100/60). The systemic examination was unremarkable except for tachypnea and rhonchi in the chest. He had abdominal scar of the previous bowel resection sugary.

Biochemical analysis showed hypokalemia (serum potassium level was 2.57 mmol/L), alkalosis (bicarbonate level was 34 mmol/L), with normal sodium (144 mmol/L) and normal renal function (serum creatinine level was 15.9 μmol/L). Plasma renin and aldesterone were sent at that time.

Renal Doppler ultrasounds revealed the presence of mild dilation of right renal pelvis, otherwise unremarkable, with normal flow. His cardiac echocardiography showed mild left ventricular hypertrophy.

### *Treatment and Progress*

He was treated with intravenous potassium chloride supplement and later with oral potassium chloride 2 mmol/kg/day. He was started on amlodipine 0.5 mg twice daily (0.1 mg/kg/day) as his blood pressure readings were consistently higher than the 95$^{th}$ percentile for his age, gender and height. His pneumonia was treated with intravenous amoxicillin/clavulanic acid for 10 days. He underwent a flexible bronchoscopy that revealed normal upper and lower anatomy bronchoalveolar lavage send for culture revealed no growth. He was discharged home with follow-up in the clinic.

### *Clinical Follow-up*

Two months later, the patient BP was not adequately controlled with amlodipine and the result of renin and aldosterone were available. The plasma renin activity was 0.1 ng/ml/hour (normal: 2.4; 3-7 ng/ml/h) and serum aldosterone was low 33 pg/ml (normal: 194-2746.3 ng/dL). With these values and the similar presentation of his sibling (case 1), low renin hypertension was entertained and the possibility of Liddle syndrome against for AME was also considered. Gene testing was also done for both condition and the patient switched

to amiloride 0.6 mg/kg/day). Two months later, the BP was adequately controlled (below 90th percentile) and the electrolytes were normal (potassium 4.5 mmol/L bicarbonate 20 mmol/L) without supplementation. He is currently 2 year and 1 month of age and his weight is 9.3 kg below 3rdth percentile, height 87 cm (between5th and 10th percentile). His BP is normal (below 90th percentile) on amiloride 2 mg once per day (0.2 mg/kg/day) and the follow-up echocardiogram showing normal heart without any evidence of left ventricle hypertrophy and good biventricular function.

His genetic study confirmed the diagnosis of cystic fibrosis with two mutant alleles for I1234V, and was also found to have a homozygous variant in exon 2 of the HSD11B2 gene (c.266G < A p.G89D).

## Discussion

The syndrome of AME is a rare cause of hypertension in children. It is due to single gene mutations that are inherited as an autosomal recessive disorder. This monogenic form of hypertension is characterized by low levels of renin and aldosterone, and it is caused by congenital deficiency in the activity of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2).[2,3] Normally, 11βHSD2 enzyme converts cortisol to cortisone, which is a type of steroid that does not bind to the mineralocorticoid receptors (MR). Cortisol, on the other hand, has an affinity to these receptors similar to aldosterone. As a consequence, to the deficiency of 11βHSD2 enzyme, there is a state of excessive plasma cortisol levels that can reach 100-1000 fold higher than plasma aldosterone levels.[7] This excessive cortisol binds the MR and result in significant increase in the mineralocorticoid activity resulting in a physiological state similar to hyperaldosteronism with salt retention, hypertension, hypokalemia and metabolic alkalosis.[7] The end-result of this state is further suppression of renin and aldosterone production and hence the low circulating levels of renin and aldosterone in patients with AME syndrome. The condition was first reported in the 1970, and subsequently several gene mutations have been reported. To date, over 30 different mutations on *HSD11B2* gene have been reported worldwide in many ethnic groups including Caucasians, Africans, Asians, American Indians and Arabs.[4,8,9] However, there has no report of association of this condition with other genetic disease such as cystic fibrosis (CF).

CF is a well-known autosomal recessive disease caused by defects in a protein that functions as a chloride channel and regulates the flow of other ions across the apical surface of epithelial cells.[6] In 1989, the CF locus was localized through linkage analysis to the long arm of human chromosome 7, band q31.[10] Cystic fibrosis trans-membrane conductance regulator (CFTR), functions principally as a cAMP-induced chloride channel and appear capable of regulating other ion channels. The most common mutation, ΔF508, accounting for about 70% of CF chromosomes worldwide and more than 850 mutant alleles have been reported to the CF Genetic Analysis Consortium.[10] CF, similar to AME, can result in hypokalemia, metabolic alkalosis and failure to thrive. However, CF is not associated with hypertension or a state of slat retention and has different clinical presentation.

The typical clinical signs and symptoms of the originally described AME included low birth weight and failure to thrive. Patient with AME are often born with mild to moderate degree of intrauterine growth retardation, as seen in our patients. Although, the reason for this is not known, it seems likely that deficiency of 11βHSD2 enzyme in the placenta permits excessive quantities of maternal glucocorticoids to cross the placenta thus inhibiting fetal growth.[11] In addition to low birth weight and failure to thrive, these children can present with polyuria and polydipsia and nephrocalcinosis.[11-13]

In our patients, both siblings have growth failure and strong family history of CF. The CF was confirmed in the two siblings by sweat chloride test. The two siblings were homozygous for the I1234V mutation of cystic fibrosis gene, which is a known mutation in Qatar. They presented with hypertension, hypokalemia with metabolic alkalosis. The workup for hypertension revealed low renin and aldosterone levels. With such early clinical and biochemical presentation, monogenic hypertension is usually suspected. The gene testing for both siblings excluded Liddle's syndrome and confirmed AME.

There are previous reports of AME in Arab population. Quinkler *et al.*, reported five different mutations for 11βHSD2 enzyme in four families from Oman with sequence analysis revealing new mutations in exon 3 (A221V), exon 5 (V322ins9nt) and exon 1 (R74G and P75Δ1nt).[14] Al-Harbi *et al.*, described a family from Saudi Arabia with three siblings who have mutations in exon 3.[8] In this report, the affected siblings were diagnosed as early as 5 years and presented with failure to thrive, hypertension, hypokalemia and metabolic alkalosis. Unlike our patients, they have hypercalciuria and nephrocalcinosis. Both of our patients were diagnosed in earlier age and were found to have homozygous variant in exon 2 of the *HSD11B2* gene. This mutation was not reported previously.

It has been proposed that oxidation of cortisol or corticosterone by 11βHSD2 to cortisone or 11 dehydrocorticosterone, respectively, represents the physiological mechanism conferring specificity for aldosterone upon the MR. Although cortisol and corticosterone bind the MR well *in vitro*, cortisone and 11-dehydrocorticosterone are poor agonists for this receptor.[7] In AME, the unmetabolized cortisol binds to the MR inducing sodium retention, hypokalemia, hypertension and other clinical features of AME, which already present in both of our patients. The enzymatic activity for 11βHSD2 can be assessed by the urinary excretion ratio of cortisol to cortisone metabolites. In AME, these ratios are usually abnormal, with ratios of 6 to 50, whereas the normal ratio should be between 0.3-1.[15] Unfortunately, neither cortisol nor cortisone urinary metabolites levels could be evaluated in our patients. Therefore, we proceeded directly to the confirmatory test, the genetic testing. We have also ruled out other causes of monogenic forms of hypertension that can also present with similar clinical and biochemical picture, such as Liddle syndrome. Both patients were genetically tested for Liddle and were found to be normal. The activity of 11βHSD2 enzyme can be affected by licorice ingestion; however, there was no history of licorice ingestions in our patients.

The main aim of treating patients with AME is correcting life-threatening hypokalaemia and controlling the blood pressure.

Therapeutically, patients have been treated using a wide range of medications, including potassium supplementations. At the kidney level, it is well known that the distal convoluted tubule and the principal cells of the collecting duct are the main sites for sodium and potassium handling in the distal nephron. Sodium re-absorption in this part of the nephron is regulated by mineralocorticoid hormones. Aldosterone binds to MR and leads to increased activity of amiloride-sensitive epithelial sodium channel (ENaC). Therefore, specific treatment for AME targeted this pathway. Spironolactone, as mineralocoricoid antagonist, has been used and showed variable benefits.[16] This is due to high doses that are required to block the MR from the cortisol activation. Amiloride and triamterene are potassium-sparing diuretics that act by directly by blocking the tubular sodium channels, ENaC. They have shown to be very effective and safe in the treatment of AME.[16] Other therapies such as dexamethasone have had variable success, and works by suppression of cortisol secretion.[16] Our patients' blood pressures and electrolytes were adequately controlled with amiloride.

This report highlights the fact that two recessive disorders could exist in the same child, particularly in the presence of complex consanguinity in the family. This might lead to confusion and difficulty in establishing a diagnosis. Moreover, the presence of two disorders in the same family makes genetic counseling more difficult and challenging task.

In conclusion, we report here a complex consanguineous family of Qatari origin with two children inherited both CF and AME. Both children showed previously unreported mutation for 11βHSD2 gene and were both treated successfully with amiloride. This report draws attention to the importance of recognizing the possibility of two recessive disorders in the same child in complex consanguineous families. Moreover, it provides a unique opportunity to highlight the implications of the coexistence of 2 genetic disorders on patient care and genetic counseling of the family. The clinical impact of this coexistence on each condition remains to be elicited

## Acknowledgment

We are pleased to thank the family for their cooperation.

## References

1. Teebi AS, El-Shanti HI. Consanguinity: Implications for practice, research, and policy. Lancet 2006;367:970-1.
2. White PC, Mune T, Agarwal AK. 11beta-Hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. Endocr Rev 1997;18:135-56.
3. Luft FC. Mendelian forms of human hypertension and mechanisms of disease. Clin Med Res 2003;1:291-300.
4. Morineau G, Sulmont V, Salomon R, Fiquet-Kempf B, Jeunamaitre X, Nicod J, *et al*. Apparent mineralocorticoid excess: Report of six new cases and extensive personal experience. J Am Soc Nephrol 2006;17:3176-84.
5. Albiston AL, Obeyesekere VR, Smith RE, Krozowski ZS. Cloning and tissue distribution of the human 11 beta -hydroxysteroid dehydrogenase type 2 enzyme. Mol Cell Endocrinol 1994;105:R11-7.
6. Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, *et al*. Identification of the cystic fibrosis gene: Chromosome walking and jumping. Science 1989;245:1059-65.
7. Funder J, Myles K. Exclusion of corticosterone from epithelial mineralocorticoid receptors is insufficient for selectivity of aldosterone action: *In vivo* binding studies. Endocrinology 1996;137:5264-8.
8. Al-Harbi T, Al-Shaikh A. Apparent mineralocorticoid excess syndrome: Report of one family with three affected children. J Pediatr Endocrinol Metab 2012;25:1083-8.
9. Wilson RC, Nimkarn S, New MI. Apparent mineralocorticoid excess. Trends Endocrinol Metab 2001;12:104-11.
10. Zielenski J. Genotype and phenotype in cystic fibrosis. Respiration 2000;67:1170-33.
11. Edwards CR Benediktsson R, Lindsay RS, Seckl JR. Dysfunction of the placental glucocorticoid barrier: Link between fetal environmental and hypertension? Lancet 1993;341:355-7.
12. Craigie E, Evans LC, Mullins JJ, Bailey MA. Failure to down regulate the epithelial sodium channel causes salts sensitivity in hsd11b2 heterozygote mice. Hypertension 2012;60:684-90.
13. Knops NB, Monnens LA, Lenders JW, Levtchenko EN. Apparent mineralocorticoid excess: Time of manifestation and complications despite treatment. Pediatrics 2011;127:e1610-4.
14. Quinkler M, Bappal B, Draper N, Atterbury AJ, Lavery GG, Walker EA, *et al*. Molecular basis for the apparent mineralocorticoid excess syndrome in the Oman population. Mol Cell Endocrinol 2004;217:143-9.
15. Paolo F, Zygmunt K. Mineralocorticoid Selectivity: Role of 11 βHSD2 and Other Mechanism. Kidney Int 2000;57:1374-81.
16. Draper N, Stewart PM. 11beta-Hydroxysteroid dehydrogenase and the pre-receptor regulation of corticosteroid hormone action. J Endocrinol 2005;186:251-71.

**How to cite this article:** Zahraldin K, Janahi IA, Ben-Omran T, Alsulaiman R, Hamad B, Imam A. Two Qatari siblings with cystic fibrosis and apparent mineralocorticoid excess. Ann Thorac Med 2015;10:69-72.

**Source of Support:** Nil, **Conflict of Interest:** None declared.