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BRIEF REPORT

Asha Moudgil · Gail Rodich · Stanley C. Jordan
Elaine S. Kamil

Nephrocalcinosis and renal cysts associated with apparent mineralocorticoid excess syndrome

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Abstract Apparent mineralocorticoid excess (AME) syndrome is a rare inherited disorder caused by 11β-hydroxysteroid dehydrogenase (11-HSD 2) isozyme deficiency in the kidney. This enzyme is responsible for oxidizing cortisol to its inactive metabolite cortisone. An elevated tetrahydrocortisol (THF) and allotetrahydrocortisol (aTHF) to tetrahydrocortisone (THE) ratio in the urine is pathognomonic of AME syndrome. Clinical features include hypertension, hypokalemia, alkalosis, reduced plasma renin activity (PRA), low aldosterone levels, and occasionally nephrocalcinosis. Here we describe a 13-year-old boy who presented with severe hypertension, hypokalemia, low PRA and aldosterone levels, and elevated THF plus aTHF/THE ratio in the urine consistent with a diagnosis of AME syndrome. On ultrasound examination, he had severe nephrocalcinosis, and bilateral renal cysts. Renal cysts have not been previously reported in AME syndrome. The development of nephrocalcinosis and renal cysts may be associated with chronic long-standing hypokalemia. An early diagnosis and treatment of AME syndrome could help to prevent these sequelae, and to preserve renal function.

Key words Hypertension · Hypokalemia · Plasma renin activity · Aldosterone

Introduction

Apparent mineralocorticoid excess (AME) syndrome is a rare autosomal recessive disorder that was described nearly 25 years ago in a child with low renin hypertension [1]. Fewer than 50 cases have been subsequently reported [2, 3]. AME syndrome is secondary to 11β-hydroxysteroid dehydrogenase (11-HSD 2) enzyme deficiency, which converts cortisol to cortisone (inactive metabolite) in many organs including the kidney [4]. Excessive cortisol in the kidney binds to the mineralocorticoid receptors, causing features of mineralocorticoid excess with low to undetectable aldosterone levels [4]. These patients excrete excessive amounts of cortisol metabolites [tetrahydrocortisol (THF) and allotetrahydrocortisol (aTHF)], whereas there is reduced excretion of the cortisone metabolite tetrahydrocortisone (THE) in the urine. An elevated THF plus aTHF/THE ratio in the urine is diagnostic of AME syndrome. A number of mutations in the gene encoding this enzyme located on chromosome 16q22 have been identified [2, 3]. The clinical features of AME syndrome include hypertension, hypokalemia, alkalosis, polyuria, polydipsia, and failure to thrive. These children can present at different ages, and some have died in early infancy and childhood. Nephrocalcinosis has been reported in a few patients with AME syndrome [2]. In this report we describe a 13-year-old boy with AME syndrome who had extensive nephrocalcinosis and multiple renal cysts. Renal cysts have not been previously reported in AME syndrome, and may be a result of chronic hypokalemia.

A. Moudgil · G. Rodich · S.C. Jordan · E.S. Kamil
Ahmanson Department of Pediatrics,
Cedars-Sinai Medical Center and UCLA School of Medicine,
Los Angeles, CA, USA

A. Moudgil (✉)
Department of Nephrology, 3.5-300, West Wing,
Children's National Medical Center, 111 Michigan Avenue NW,
Washington, DC 20010, USA
e-mail: amoudgil@cnmc.org
Tel.: +1-202-884-5058, Fax: +1-202-884-3621

Case report

A 13-year-old Caucasian boy presented to the emergency room with a sprained hand and was found to have a blood pressure (BP) of 161/119. His past medical history was significant for occasional headaches, polyuria and polydipsia for a number of years for which no medical attention was sought. The patient was performing poorly in school secondary to behavioral problems. At 7 months of age he was hospitalized with fever, diarrhea, and estimated 7% dehydration. His BP was 94/60 (75th percentile) at admission. No further BP readings were documented. He was born at 41 weeks gestation by emergency cesarean section because of a nuchal cord. His birth weight was 2.9 kg (10th percentile), and length was 49 cm (25th percentile). He was the only child with no

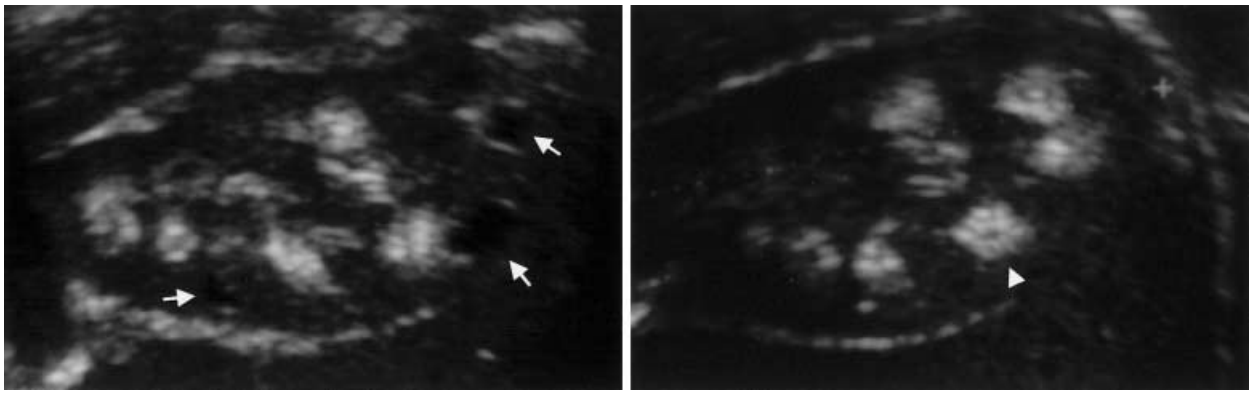

Fig. 1 Renal ultrasound showing hypoechoic areas consistent with cysts *(arrows) in the left panel* and increased echogenicity consistent with nephrocalcinosis *(arrowhead) in the right panel*

family history of hypertension or renal disease. There was no history of consanguinity. On physical examination he was extremely nervous, with rapid eye blinking and pressured speech. He weighed 48.5 kg (50th percentile), and his height was 154 cm (25th percentile). BP was elevated at 160–180/110–120. No BP differences were observed between the upper and lower limbs. The remainder of the physical examination was unremarkable. Laboratory evaluation included: sodium 147 mEq/l, potassium 2.9–3.3 mEq/l, chloride 96 mEq/l, plasma bicarbonate 33–36 mEq/l, blood urea nitrogen 7 mg/dl, creatinine 0.8 mg/dl. Serum calcium, magnesium, phosphorus, alkaline phosphatase, and liver function tests were normal. Routine urinalysis showed specific gravity 1.015, pH 8.0, negative for protein and glucose; no casts and crystals were seen. Thyroid function tests, 24 h urine for vanillylmandelic acid (VMA) and plasma catecholamine levels were normal. An electrocardiogram showed flattened *t*-waves that normalized after correction of serum potassium levels. An echocardiogram showed mild concentric left ventricular hypertrophy. Renal ultrasound showed normal-sized kidneys, bilateral nephrocalcinosis, and three cysts in the left kidney (Fig. 1). Captopril renal scan and magnetic resonance angiography (MRA) failed to show evidence of renal artery stenosis. On magnetic resonance imaging (MRI), two cysts were noted in the upper pole of the left kidney, and one at the upper pole of the right kidney. A single cyst was noted in the spleen.

PRA was low at 0.3 ng/ml/h (normal 4.1–7.7 ng/ml/h), and aldosterone level was less than 2 ng/dl (normal for age 4–31 ng/dl). A 24 h urine calcium excretion was normal at 101 mg. THF plus aTHF/THE ratio measured twice in urine was elevated at 4.9–6.3 (normal 1.0). The patient was subsequently identified to have two mutations, one at exon 4 (A237 V, GCG-GTG), another at exon 5 (328 V, GCG-GTG).

His mother was 56 years old. She had normal BP and urinalysis on multiple occasions. A renal ultrasound was not obtained. She was identified to have a mutation on exon 5 (328 V, GCG-GTG. His father was in good health with normal BP and urinalysis, but did not consent to any further studies including genetic analysis.

The patient was initially treated with potassium supplements and antihypertensive treatment with clonidine, and sustained release nifedipine. After the diagnosis of AME syndrome was confirmed, he was started on amiloride and was taken off potassium supplements. For the last 3 years, his hypertension has been well controlled with oral clonidine (0.05 mg twice a day), sustained release nifedipine (60 mg twice a day), and amiloride 5 mg once a day. His BP ranges between 120 and 125 systolic and between 80 and 85 diastolic. His serum potassium and bicarbonate levels have been normal. Repeat renal ultrasound examinations 10 months, 2 years and 3 years later have remained unchanged with persistent stable nephrocalcinosis and cysts.

Discussion

The patient in this report had typical features of AME syndrome which included hypertension, hypokalemia, alkalosis, low renin and aldosterone levels and elevated THF plus aTHF/THE ratio in the urine [2]. The diagnosis of renovascular hypertension was excluded because of suppressed renin and aldosterone levels, normal captopril renal scan, and MRA. Clinically, patients with AME syndrome are indistinguishable from those with Liddle's syndrome, a rare familial disorder caused by mutations in the β-subunit of the sodium channel in the distal tubule [5]. Patients with Liddle's syndrome present with hypertension, hypokalemia, alkalosis, and undetectable aldosterone levels. However, the urinary steroid profile is normal in these patients [5].

This patient had some unusual clinical features that included bilateral nephrocalcinosis and renal cysts. Nephrocalcinosis has been previously described in a few patients with AME syndrome [2]. The pathogenesis of nephrocalcinosis in this syndrome has not been well investigated. The common causes of nephrocalcinosis such as hypercalcemia, hypercalciuria, and renal tubular acidosis were excluded in this patient [6]. Patients with chronic hypokalemia have been noted to develop interstitial renal scarring secondary to excessive ammoniagenesis [7]. In a large series of patients with chronic hypokalemia due to laxative or diuretic abuse, interstitial fibrosis was noted in the majority [8]. We speculate that nephrocalcinosis as observed in this patient and others may be related to dystrophic calcification in the areas of interstitial fibrosis.

The development of renal cysts in this child may be related to chronic hypokalemia, and has not been previously described in AME syndrome. This child had a negative family history of adult onset polycystic kidney disease (ADPKD). His father and mother (57 and 56 years old respectively) have normal BP and urinalysis, making a diagnosis of incidental ADPKD highly unlikely. A critical factor in cyst formation is the enhanced growth and proliferation of the epithelial cells lining the tubules [9]. Under various experimental conditions, a decrease in the extracellular potassium concentration, and an increase in the intracellular potassium concentration, stimulates protein synthesis and cell division [10]. Renal cysts have been reported in newborn rats in association with severe

hypokalemia [11]. Cyst formation in these animals could be prevented by administration of potassium chloride [11]. In a study by Torres et al., renal cysts were noted in 44% of patients with primary aldosteronism and hypokalemia [12]. The cysts were often multiple and correlated with the presence and severity of hypokalemia [12]. The size and number of cysts decreased markedly after removal of adrenal adenoma, suggesting the role of hypokalemia in renal cystogenesis. The cause of a single splenic cyst in this patient is unclear and has not been described in hypokalemia.

In conclusion, we report a patient with AME syndrome with bilateral nephrocalcinosis and renal cysts possibly related to chronic hypokalemia. An early diagnosis of AME syndrome made by measuring urine steroid metabolites in patients with hypertension and hypokalemia and an early intervention may prevent these structural renal sequelae.

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