Case Report

CONGENITAL ADRENAL HYPERPLASIA AND OHVIRA SYNDROME: FIRST REPORT OF UNIQUE COMBINATION IN A CHILD

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ABSTRACT

Objective: We present a unique case of congenital adrenal hyperplasia (CAH) combined with a rare Müllerian anomaly characterized by uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis.

Methods: The clinical, laboratory, and imaging findings of the patient are presented with a review of the literature.

Results: An 18-month-old girl diagnosed to have CAH due to 21-hydroxylase deficiency presented for reconstructive surgery of the clitoris and vagina. The patient was known to have right renal agenesis. Preoperative magnetic resonance imaging (MRI) showed unexpected uterus didelphys with obstructed right hemivagina. These findings, together with ipsilateral renal agenesis, constitute the obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome. To our knowledge, this combination of CAH and OHVIRA has not been reported.

Conclusion: In the presence of urinary tract anomalies in patients with CAH, it is important to check for possible associated Müllerian anomalies, which could be accomplished by MRI. This may change the surgical approach and may reduce future morbidities in these patients. **(AACE Clinical Case Rep. 2015;1:e136-e140)**

Abbreviations:
CAH = congenital adrenal hyperplasia; **MRI** = magnetic resonance imaging; **OHVIRA** = obstructed hemivagina and ipsilateral renal anomaly

INTRODUCTION

Congenital adrenal hyperplasia (CAH) describes a group of autosomal recessive disorders characterized by enzyme deficiency in the steroidogenic pathways, most commonly due to 21-hydroxylase deficiency. The resulting excess androgens can cause ambiguous genitalia in newborn girls (1).

Obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome is a rare variant of Müllerian anomalies and is characterized by uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis. Patients with this syndrome are usually diagnosed late in the pubertal period because of nonspecific presentations. They may present with complications such as acute urine retention and endometriosis, which can be severe (2,3).

In this article, we present the case of a young female patient who was diagnosed to have CAH and OHVIRA syndrome concomitantly.

CASE REPORT

An 18-month-old female patient presented to the pediatric surgery clinic for vaginoplasty and clitoroplasty due to ambiguous genitalia and urogenital sinus anomaly. The patient was the child of a 17-year-old primigravida mother who first presented antenatally with ultrasonographic findings of oligohydramnios and a single fetus with ambiguous genitalia, single left kidney, and single umbilical artery. Amniocentesis for karyotyping was performed and revealed a 46,XX karyotype. The patient was born at term by normal vaginal delivery. At birth, the patient had clitoromegaly as well as a single urovaginal opening. Shortly

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after birth, she developed electrolyte imbalance. At 4 days of age, her potassium was 6.7 mEq/L (normal, 3.7 to 5.9 mEq/L) and her sodium was 133 mEq/L (normal, 135 to 145 mEq/L). Her 17-hydroxyprogesterone was elevated, at >60 ng/mL (normally should be <10 ng/mL for age). Dehydroepiandrosterone sulfate was more than 40 μmol/L (normal, 0.4 to 2.61 μmol/L). There was also elevation of adrenocorticotropic hormone to 327 pg/mL (normal, 6.2 to 58.2 pg/mL). Basal cortisol value was 155.6 nmol/L. Subsequently, she was started on hydrocortisone and fludrocortisone, with adequate control.

Genetic testing of the patient showed a homozygous In2cs (intron 2) mutation and 8-bp deletion (exon 3) that, along with laboratory evaluation, confirmed the diagnosis of CAH due to 21-hydroxylase deficiency. Genetic testing of her parents, who were second-degree cousins, showed a compound heterozygous In2cs (intron 2) mutation and 8-bp deletion (exon 3) in both parents. Technetium 99m-dimercaptosuccinic acid scanning was performed and showed an enlarged left kidney with normal uptake, together with the absence of a right kidney. Pelvic ultrasound reported normal uterus and ovaries at that time. The patient is followed in the pediatric endocrine clinic on a regular basis and has remained stable to the time of this report. Her parents were offered genetic counseling regarding future pregnancies.

At the age of 18 months, the patient was referred to the pediatric surgery clinic for reconstructive surgery. Examination under anesthesia with cystovaginoscopy was performed, followed by a urethrogram and vaginogram, which revealed a low confluence of the vagina and the urethra (Fig. 1). Because of the associated right renal agenesis, magnetic resonance imaging (MRI) of the pelvis and abdomen was ordered to exclude other possible anomalies. This demonstrated unexpected uterus didelphys, with widely separated uterine bodies, 2 cervices, as well as double vaginae (Fig. 2). The right hemivagina was short, blind ended, and distended, with high signal intensity on both T1- and T2-weighted images that became brighter on T1-fat suppressed images, consistent with blood. The left hemivagina appeared slightly distended with fluid and tapered distally to open into the urethra just below the symphysis pubis. Both ovaries were identified and appeared normal. Coronal T2-weighted images of the abdomen showed a solitary hypertrophied left kidney (Fig. 3). According to the new findings, vaginal septal resection was planned in addition to vaginoplasty and clitoral recession.

DISCUSSION

CAH represents a group of autosomal recessive disorders of adrenal steroidogenesis. About 95% of cases are caused by adrenal steroid 21-hydroxylase deficiency resulting from mutations in the *CYP21A2* gene. Patients with 21-hydroxylase deficiency are divided into several phenotypes: classical salt wasting (0% enzymatic activity in about 75% of cases), classical simple virilizing (about 1% enzymatic activity), and later-onset nonclassical (20 to 50% enzymatic activity) (4). The enzyme 21-hydroxylase converts 17-hydroxyprogesterone to 11-deoxycortisol and progesterone to deoxycorticosterone, respective precursors for cortisol and aldosterone (1). The excess accumulated precursors shunt into the sex steroid pathway, resulting

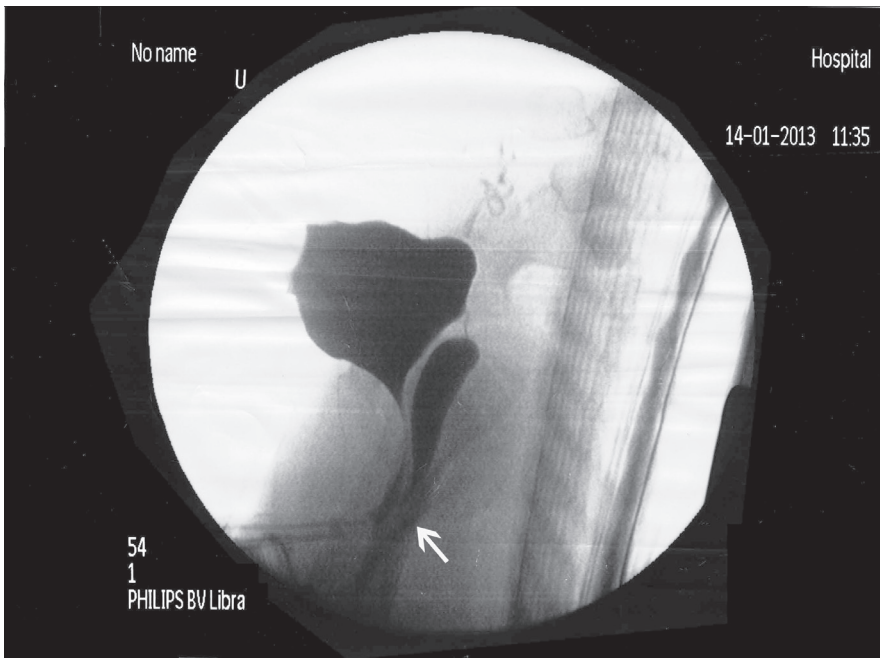

Fig. 1. Cystogram and vaginogram showing the low confluence of the vagina and urethra (arrow), forming a common distal channel.

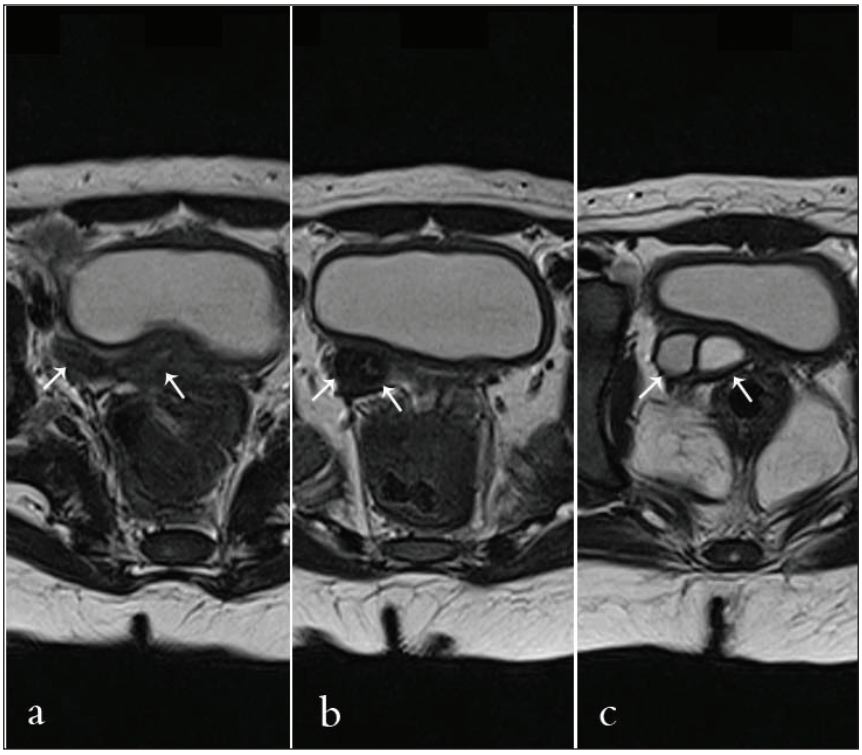

Fig. 2. Consecutive T2-weighted axial images of the pelvis (*A*, *B*, *C*), demonstrating 2 uterine cavities, 2 cervices, and 2 distended vaginae, respectively (arrows).

in increased androgen production. Excess androgens can cause ambiguous genitalia in newborn girls. Concomitant aldosterone deficiency may lead to salt wasting with consequent hypovolemia and shock (5). Reduction of excessive adrenal androgens and replacement of those hormones that are deficient remain the goal of treatment for CAH (6). Regarding feminizing surgery, it is suggested to do complete repair, including vaginoplasty, perineal reconstruction, and clitoroplasty at an early age in patients with low vaginal confluence, although the timing is less certain in patients with higher vaginal confluence. However, there are no data comparing psychosexual health in girls and women who have undergone early and late surgery (1). Few data are currently available to study the association of CAH with upper urinary tract anomalies (7,8). The largest cohort study, by Nabhan et al (7), concluded that the incidence of upper urinary tract anomalies in girls with CAH is 5- to 10-fold higher than in the general population (21% vs. 2 to 4%). The reportewd urinary tract anomalies vary from hydronephrosis, malrotated kidney, ureteropelvic junction obstruction, vesicoureteric reflux, lower urinary tract obstruction, duplication of collecting system, multicystic dysplastic kidney (7,8), and only one reported case of agenesis of the right kidney (7). The exact cause of this phenomenon remains unknown. One hypothesis, however, suggests that it is caused by increased androgen level in utero, based on the observation that implantation of testosterone propionate in the developing female rabbit

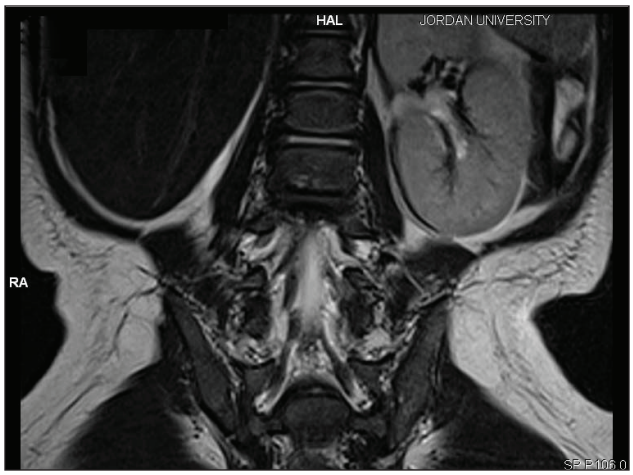

Fig. 3. Coronal T2-weighted image of the abdomen. Note the solitary hypertrophied left kidney.

fetus produces anomalies of the mesonephros (8). Others have proposed that genetic variation in androgen sensitivity and biosynthesis may influence the expression of signs of androgen excess in girls with CAH. This may explain the development of genitourinary abnormalities in some patients and not in others (9).

The syndrome of uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis, OHVIRA (known also as Herlyn-Werner-Wunderlich syndrome) is a rare entity of Müllerian anomalies. It is well-described

in the literature, with many isolated case reports. The incidence of obstructive Müllerian anomalies is unknown; however, it was reported to be between 0.1 and 3.8% (10). Zurawin et al (11) concluded that this condition is underdiagnosed and has no ethnic background predilection but has a right-sided prevalence. The true etiology is unknown. It may be caused by an insult during the first trimester, such as exposure to sex steroids. It may also be caused by polygenic multifactorial inheritance or by an embryologic arrest at 8 week of gestation that simultaneously affect the Müllerian and metanephric ducts (10,11).

Patients with OHVIRA are frequently diagnosed late in the pubertal period due to nonspecific clinical presentation, especially when the patients have regular menstruation from the nonobstructed vagina. They usually present with pelvic pain or vaginal discharge, which are most often treated conservatively before definite diagnosis is made. Some patients present later with more dramatic complications, such as urine retention, endometriosis, pyosalpinx, or adhesions (2,3). Few cases have been reported identifying this anomaly before puberty. These presented with protruded mass through the vaginal introitus (12,13) or with abdominal mass accompanied by pain or urinary retention (13). Timely diagnosis is essential to avoid unnecessary invasive diagnostic tools such as laparoscopy and to preserve normal fertility (2).

Ultrasound and MRI are widely and effectively used in the diagnosis of genitourinary anomalies. Ultrasound is a noninvasive, widely available imaging modality with low cost. MRI is superior to ultrasound in allowing better characterization of anatomic structures (such as the uterine contour and septum characteristics) and their relationship with accuracy in diagnosis, reaching almost 100%. This is important for definite diagnosis and proper surgical planning (14-16). Invariably, surgical intervention is required to excise the septum and relieve the obstruction, with every effort to preserve the obstructed uterus (15). On rare occasions, when complications ensue, this may not be enough, necessitating a hysterectomy (2).

Our patient is a case of CAH combined with OHVIRA syndrome. To our knowledge, there are no previously reported cases of CAH due to 21-hydroxylase enzyme deficiency in association with Müllerian anomalies, based on PubMed and Google searches. Müllerian anomalies were reported in 2 genotypic male patients with CAH due to 17-alpha-hydroxylase enzyme deficiency; both showed persistence of Müllerian duct structures (infantile uterus). Deficiency in 17-alpha-hydroxylase involves both the adrenals and gonads, which leads to lack of sex hormones and subsequently causes infantilism in female patients or pseudohermaphroditism in males (17,18). This type of CAH is different in pathophysiology from CAH due to 21-hydroxylase enzyme deficiency.

CONCLUSION

This association, whether it is a true association or a pure coincidence, highlights the possibility of occurrence of Müllerian anomalies in patients with CAH. These anomalies are usually silent. Early diagnosis may change the surgical approach of a reconstructive procedure and also may prevent future morbidity. The few studies available document the increased incidence of urinary tract anomalies in female patients with CAH compared with the general population. The close association between the genital and urinary systems developmentally warrants the search for Müllerian anomalies in those showing malformation of the urinary tract. MRI is very effective in outlining the genital anatomy noninvasively with a high accuracy rate.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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