Non-Classical Congenital Adrenal Hyperplasia with Accompanying Congenital Anomalies: Vaginal Atresia, Left Kidney Agenesis, and Urogenital Malformations

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A 16-year-old male-looking patient presented at the emergency room for severe abdominal pain. Physical examination revealed acute abdomen, ambiguous genitalia, empty rectal vault with watery discharge and right lower quadrant palpable mass. Ultrasound showed a uterus and right adnexal mass. General surgery evaluated urethral patency and noted presence of recto-urethral fistula. Surgical exploration, right salpingo-oophorectomy and suprapubic cystostomy were done. Immediate referral to a reproductive endocrinologist was done post-operatively. Retrograde urethrogram and cystogram revealed neurogenic bladder with fistula formation. On follow up, whole abdomen MRI revealed thickened endometrium with fluid levels, tortuous left fallopian tube, multiloculated left adnexal mass and left renal agenesis. Serum levels of 17-hydroxyprogesterone and cortisol were noted to be elevated and karyotyping revealed 46 XX. Patient then underwent psychiatric evaluation and assessment. Patient was readmitted for urology and pediatric surgery diagnostic work up. However, regardless of the findings, patient decided not to undergo further surgeries and opted to be female.

Keywords: Adrenal hyperplasia, vaginal atresia, left kidney agenesis

Introduction

Non Classical Congenital Adrenal Hyperplasia (NCCAH) is one of the three forms of Congenital Adrenal Hyperplasia (CAH) that has a partial deficiency in 21- hydroxylase (21-OHD) functions.

NCCAH presents a wider spectrum of mutations making possible the variation in phenotype and genotype. NCCAH is not life-threatening but can present with serious quality-of-life issues.

The incidence of CAH ranges from 1 in 10,000 to 1 in 20,000 live birth.[1] Among Filipinos, the estimate incidence of CAH is approximately 1 in 7,000.[2,3] NCCAH is more common than the other forms with an incidence of 1: 1000 to 1:2000.[4,5] In the Philippines, no study has been reported regarding the incidence of NCCAH.

The Case

A 16-year-old male-looking patient came in at the emergency room due to severe abdominal pain. Four days prior to admission, he presented with right lower quadrant pain associated with non-billous, non-bloody vomiting and blood-streaked urine. The patient was managed as a case of urinary tract infection. Two days later, there was progression of abdominal pain now associated with fever. Ultrasound revealed a uterus with endometrial contents, fluid in the vaginal canal (Figure 1) and a cystic right adnexal mass (Figure 2). Surgical exploration was advised and the patient was subsequently admitted.

Past medical history of the patient revealed recurrent urinary tract infection which usually presented with abdominal pain and relieved

with a course of unrecalled prescribed antibiotics.

The family history revealed hypertension on both sides of the family. There is gouty arthritis on the paternal side while thyroid disease and bronchial asthma are present on the maternal side. There is no history of cardiac disease, cancer and there are no family members with the same condition as the patient. There is no history of infertility, unexplained neonatal death nor relatives with ambiguous genitalia (Figure 3).

The patient is an elementary undergraduate (grade 6) and was reared as a male because he has a male-looking genitalia. The patient has no known allergies to food and medications neither is he an alcoholic beverage drinker nor a smoker. According to his mother, the patient likes to stay at home and help in household chores. The patient prefers to sit when urinating, wear colorful shirts but plays the male role in school activities. The patient claims to have blood streaks in his urine as well as spotting of blood on his underwear 4 days prior to admission.

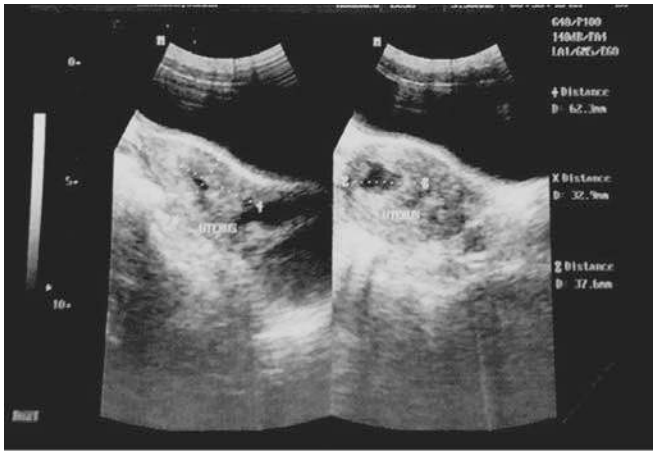

Figure 1. Ultrasound of an anteverted uterus.

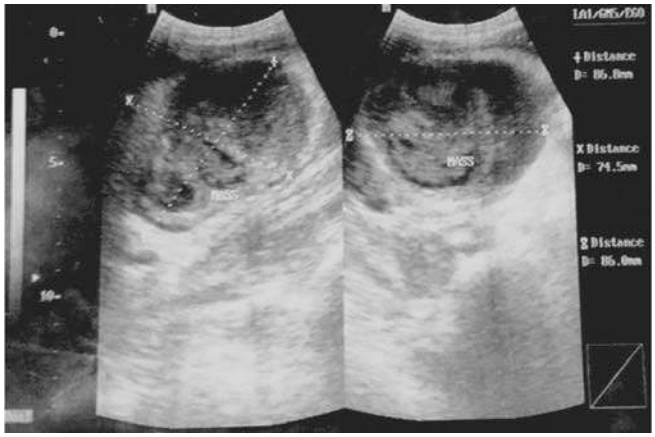

Figure 2. Ultrasound of right adnexal mass.

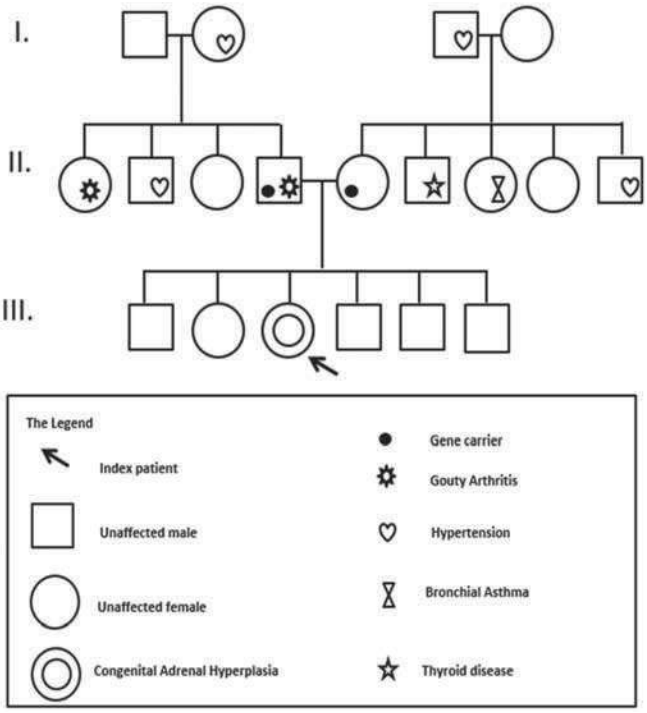

Figure 3. Family genogram.

The patient is the third of six siblings of a non-consanguineous marriage. He was conceived when the mother was 20 years old and the father was 25 years old with no prenatal consultations done during pregnancy. There were no maternal illnesses nor medications taken during the prenatal period. The patient was delivered full term via normal vaginal delivery at home assisted by a traditional birth attendant and no newborn screening was done.

The patient only had BCG at four months old for immunization and no other vaccines were given. At birth, the patient was exclusively breast fed for five months and was able to tolerate complementary feeding at six months. Thereafter, his daily diet is composed of vegetables and fish and occasional poultry, beef and pork. The developmental milestone of the patient was noted

to be at par with a normal child his age. However, the patient entered elementary at a later age due to financial constraints. At the age of six years old, the mother noted pubic hair growth, breast budding and the patient was taller than his playmates. At eight years old, due to his recurrent urinary tract infection and an ambiguous genitalia, an abdominal ultrasound was done which revealed absence of uterus and ovaries. With these findings, the parents were assured that he was a boy and continued to raise him as one.

Facial features include papules and a few on the chest and back (Figure 4) with no exophthalmos. There is a 4cm x 4cm anterior neck mass that moves with deglutition (Figure 5). The armpit has minimal hair growth (Figure 6). There is enlargement of breast and areola but no separation of their contour (Tanner stage 3) (Figure 7) with no masses, no tenderness, nor discharges noted. The abdomen is globular, with direct and rebound tenderness, and abdominal guarding. The genitalia is ambiguous with prominent clitoral hood or fore skin with no vaginal orifice and with a left scrotal sac with no palpable gonads (Figure 8). The pubic hair is coarse and curly but not distributed as widely as in adults (Tanner stage 3) (Figure 9). Rectal examination revealed good sphincter tone, nontender, empty rectal vault with watery discharge and a palpable mass on the right. Bimanual exam revealed tenderness on the right lower quadrant with a palpable mass, slightly movable and measuring 10cm x 12cm.

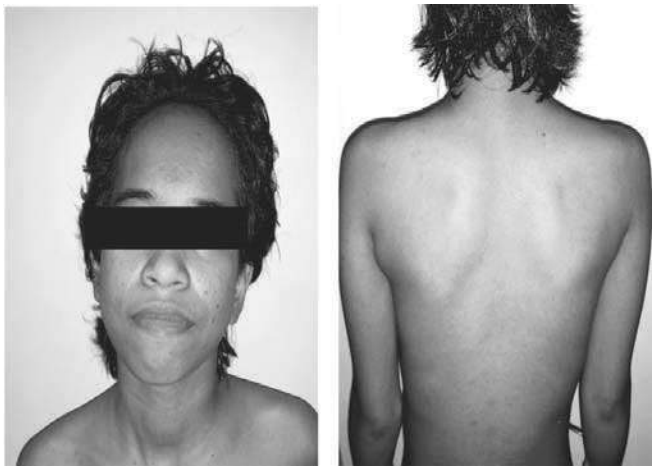

Figure 4. Facial acne (left) and on the back (right).

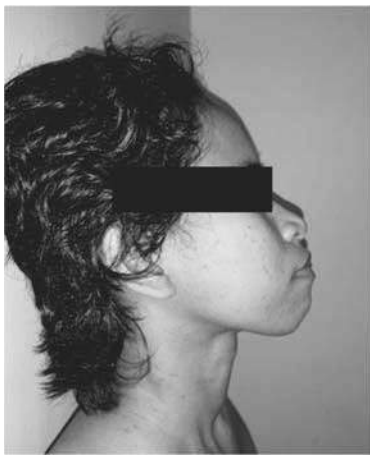

Figure 5. Anterior neck mass

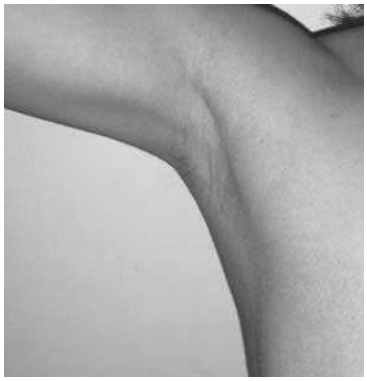

Figure 6. Minimal hair growth in the armpit.

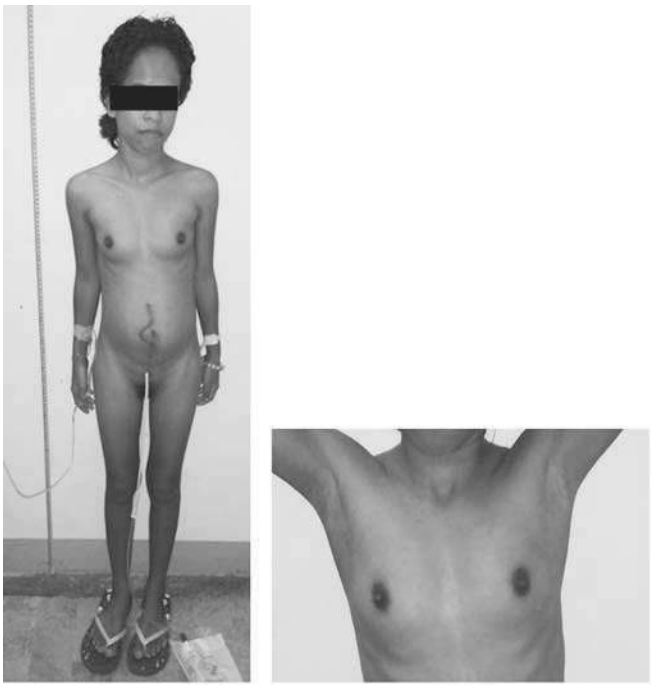

Figure 7. Breast: Tanner stage 3.

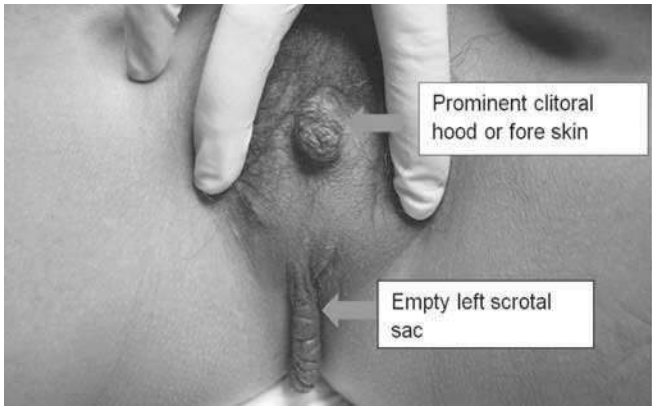

Figure 8. No vaginal orifice and empty left scrotal sac.

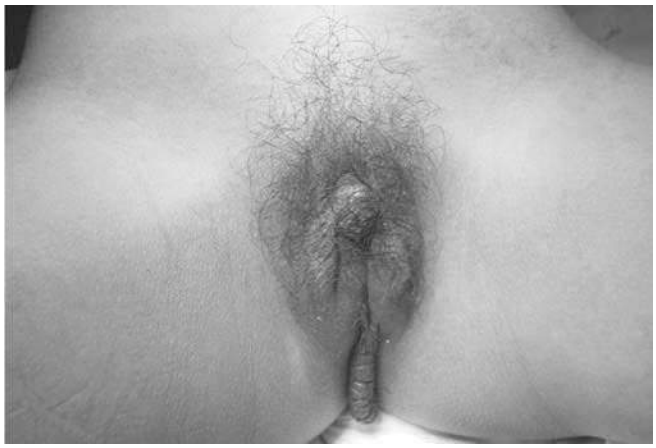

Figure 9. Pubic hair: Tanner stage 4.

The patient was transfused 1 unit of pRBC for correction of anemia prior to operation. Antibiotics were given for urinary tract infection and potassium chloride was also given to correct hypokalemia. When cleared for surgery, the patient underwent exploratory laparotomy under spinal anesthesia. Prior to opening, the general surgeon evaluated the urethra since the patient claims passage of his urine via his anus. Bladder catheterization was done using a French 5 feeding tube through the urethral opening. With further advancement of the tube, its distal end was seen exiting out of the anal canal (Figure 10). Thus, a fistula to the anal opening was noted. The patient was then referred to a Urologist and suprapubic tube cystostomy was done. Thereafter, exploratory laparotomy was done, with the following intraoperative findings: the omentum was matted and adherent to the bowels and pelvic organs. The right ovary was converted into a cystic mass measuring 10cm x 8cm and was adherent to the bowels and the posterior portion of uterus. It has a point of rupture on the anterior aspect measuring 1.5cm revealing foul-smelling whitish fluid. The right fallopian tube was enlarged to approximately 10cm x 5cm, hyperemic with pus draining on its distal end. It was noted to be adherent to the right ovary. The uterus was enlarged to about 12 weeks' size but is grossly normal. The left ovary was not readily visualized as it was covered with bowels and adherent to the pelvic sidewalls (Figure 11). Right salpingooophorectomy was done.

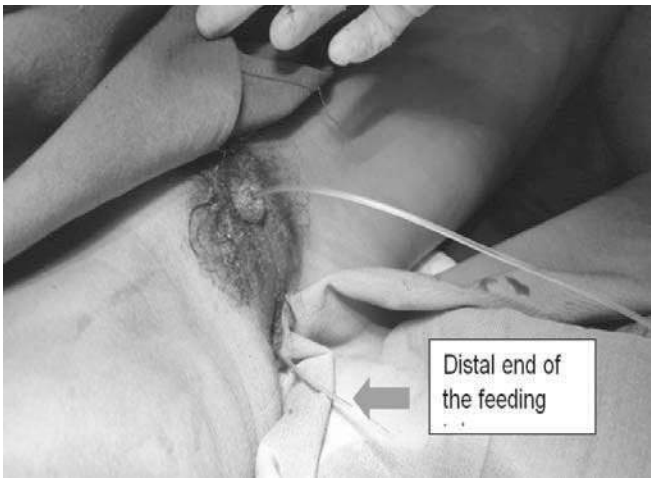

Figure 10. French 5 feeding tube inserted through a urethral opening and exits through the anus.

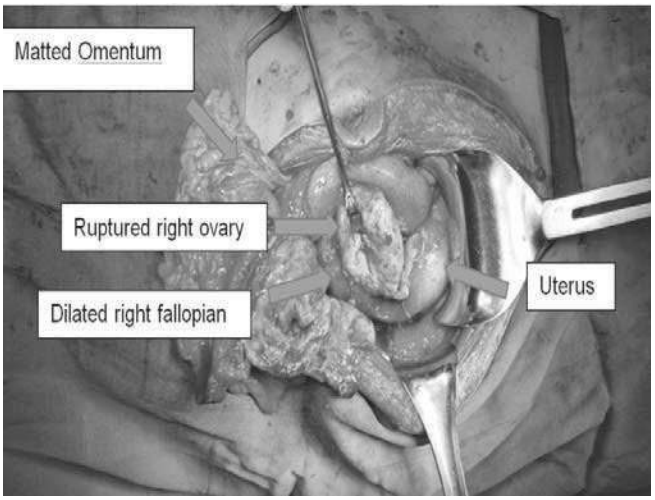

Figure 11. Intraoperative findings.

Chromosomal analysis revealed that patient is genetically female with a karyotype of 46 XX (Figure 12). Hormonal assays were all normal except with increased 17-hydroxyprogesterone and slightly increased cortisol (Table 1)

Patient recovered well and was discharged. Histopathology result of the right adnexal mass revealed a tubo-ovarian abscess with cystic follicle, right.

On follow up, patient had a well-coaptated surgical site, good urine output and with adequate pain control.

The patient also claimed to have a cyclic rectal bleeding which she linked to a probable sign of

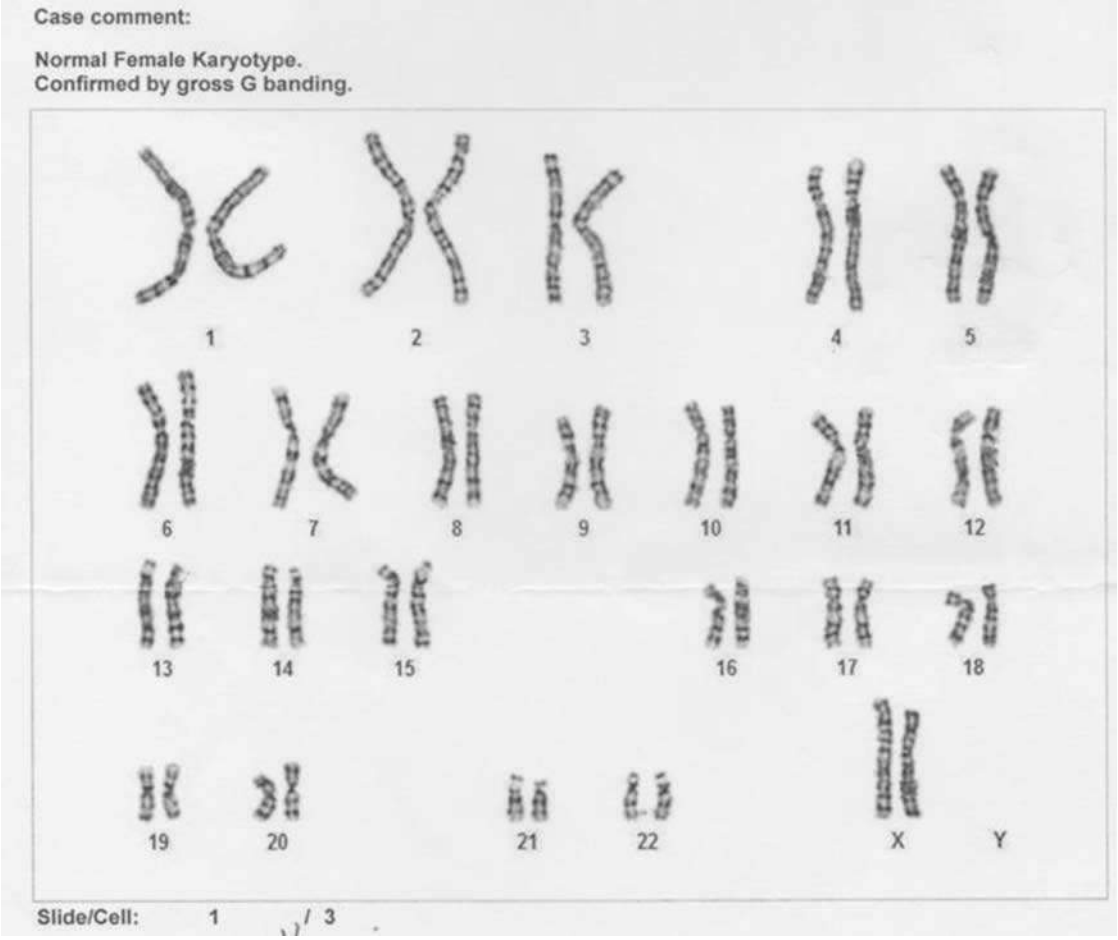

Figure 12. Chromosomal study showing normal female karyotype: 46 XX

Table 1. Hormonal assay.

Parameters	Result	Normal Values
Lutein Hormone	5.20 mIU/ml	1-7.9 mIU/ml
Follicle Stimulating Hormone	4.30 mIU/ml	2.5-13.2 mIU/ml
DHEAS	4.8 umol/L	0.95-11.7 umol/L
Testosterone	6.05 pg/ml	0.05-7.00 pg/ml
17-OHP	92.4 ng/dl	9.9-79.86 mg/dl
Cortisol	634.57 nmol/L	160-620 nmol/L
Aldosterone	125 pg/ml	40-200 pg/ml

menstruation, lasting for 3 days, using up 2 panty liners a day associated with dysmenorrhea.

Patient was referred for psychiatric consult and counseling about her sexual identity. A clinical interview was done revealing no signs of anxiety and depression. The patient accepted her new role in the society as a female

Patient was readmitted for urology and pediatric surgery work up. Following discussion with the multidisciplinary team, patient was offered fistula ligation, temporizing surgery to address present problems and creation of neovagina. The patient with the parents, assisted by a psychiatrist, made an informed decision not to proceed with the proposed surgery given the risks. Proctoscopy was done which revealed 2 openings in the patient's anal area. The upper orifice leads to the bladder and the lower orifice to the rectum. The fistula that connects to the penile structure was not visualized. At this time, they are considering congenital urogenital anomalies.

Stress cystogram revealed neurogenic bladder fistula formation, probably vesico-enteral or uterovesical. (Figures 13 & 14).

MRI of whole abdomen revealed complete absence of the left kidney, low-normal sized right kidney (Figure 15) with a double collecting system (Figure 16) versus crossed ectopy and mild pelvocaliectasia in the upper and lower moiety. Both ureters are dilated and the vaginal vault appears dilated up to the cervix and uterus (Figure 17). There is a thickened endometrium with fluid-fluid levels within (Figure 18). The left fallopian tube is tortuous and dilated (Figure 19). There is a multiloculated and multiseptated structure in the left adnexae probably the left ovary (Figure 20). There is no evident prostate nor testicles.

Diagnosis at this point was non-classical congenital adrenal hyperplasia with accompanying congenital anomalies.

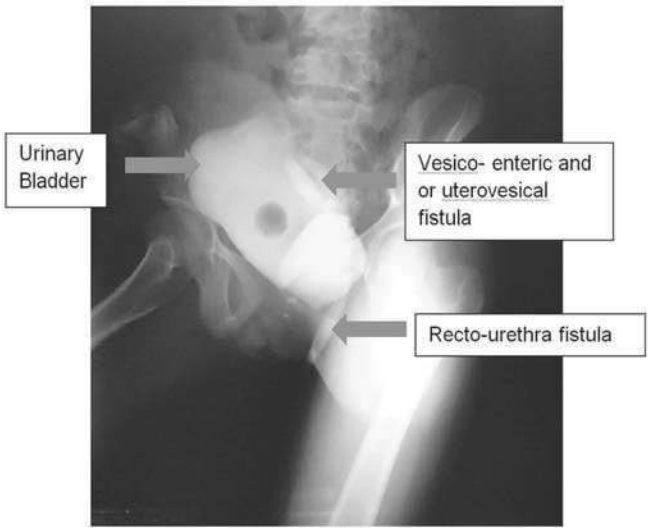

Figure 14. Cystogram: Lateral view.

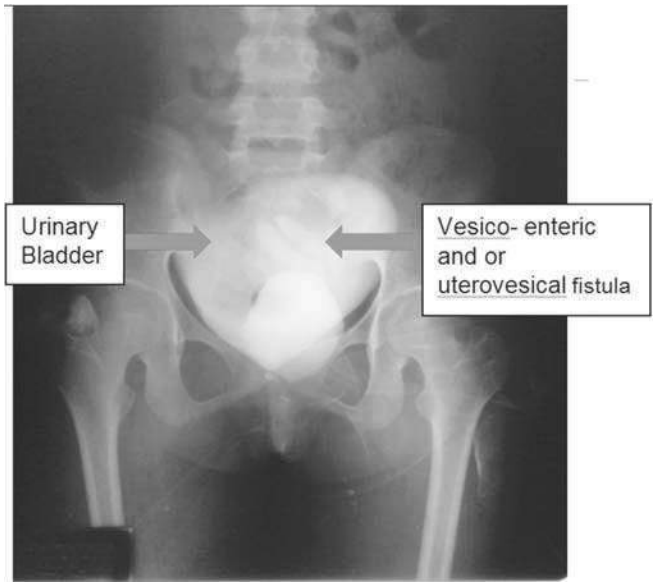

Figure 13. Cystogram: Anterior view

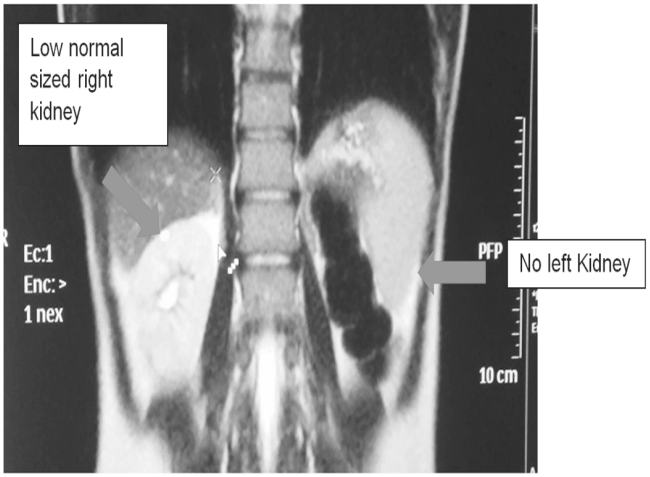

Figure 15. MRI: no normal left kidney, low normal sized right kidney

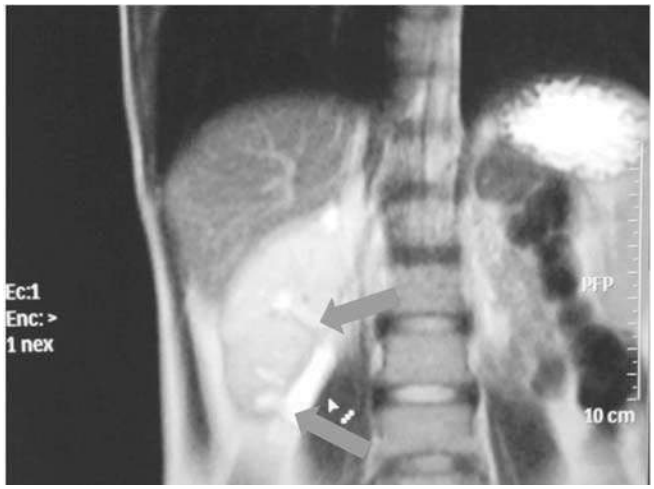

Figure 16. MRI: Double collecting system

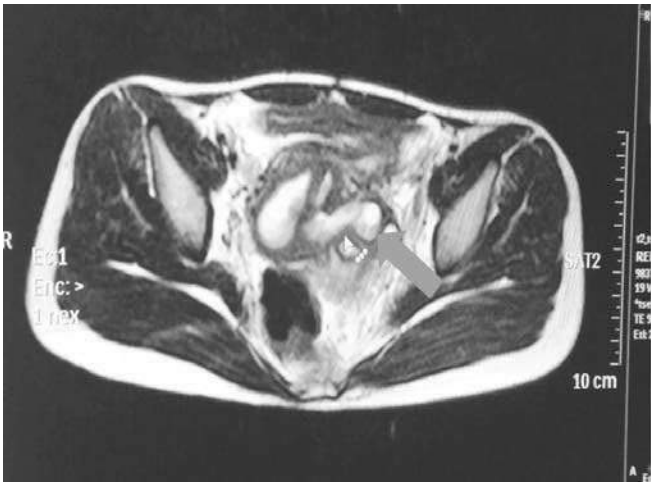

Figure 19. MRI: Tortuous and dilated left fallopian tube (Arrow).

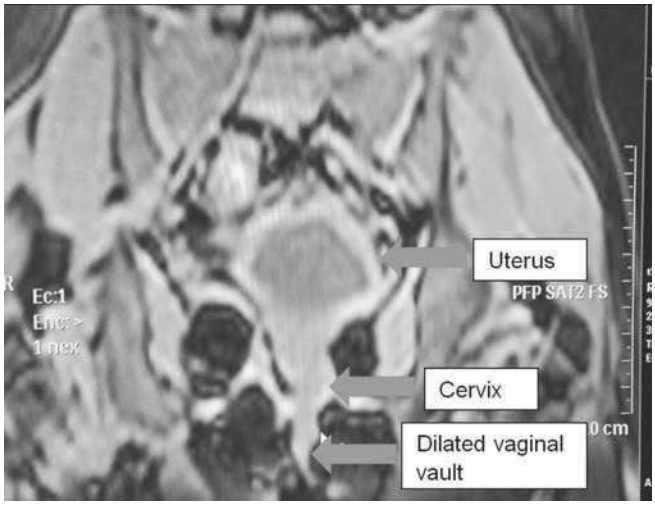

Figure 17. MRI: The vaginal vault appears dilated up to the cervix and uterus.

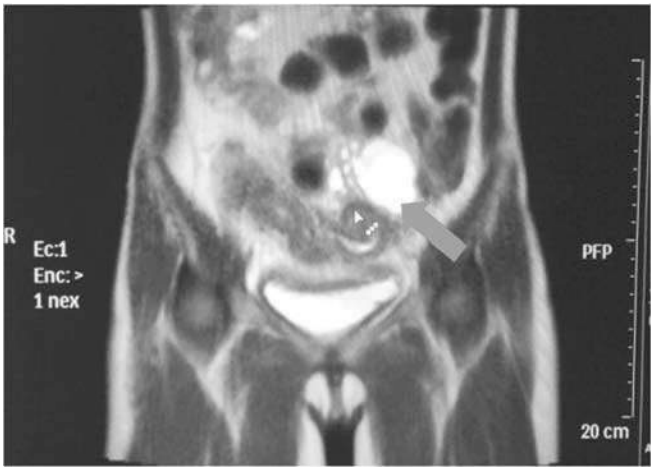

Figure 20. MRI: Multiloculated and multiseptaed structure in the left adnexae probably the left ovary (Arrow).

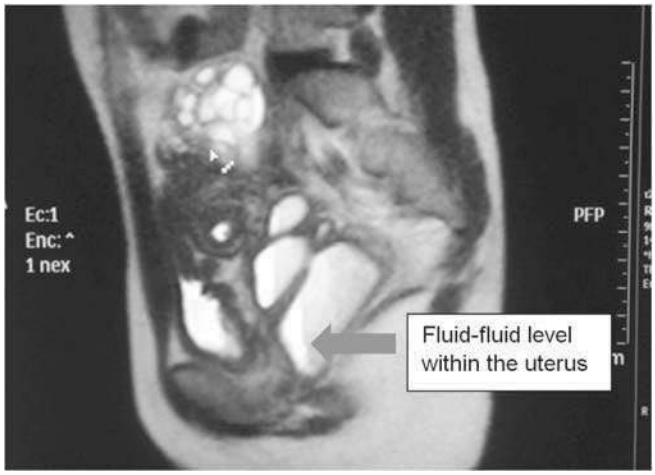

Figure 18. MRI: A thickened endometrium with fluid-fluid levels within.

Discussion

The patient presented with an ambiguous genitalia, precocious puberty, vaginal atresia, unilateral renal agenesis and urogenital malformation. The ultrasound revealed a uterus and bilateral ovaries and no intraabdominal testes. The 17- OHP result is moderately increased. The karyotype revealed a 46 XX making the patient genotypically female.

CAH is considered because it is the most common cause of sexual ambiguity and increased 17-OHP.[5] CAH is a group of autosomal recessive disorders which involves a deficiency in an enzyme in the synthesis of cortisol and aldosterone.[6] CAH

has a variety of genetic mutation that ranges from a point mutation, small deletion or insertion to complete gene deletion that causes abnormalities in steroidogenesis. Absence of enzymes like 17α-hydroxylase leads to increase in androgens resulting to development of sexual ambiguity.[7]

There are three forms of CAH where the clinical presentation depends on the affected enzymes, enzymatic activity, decreased end products and hormonal effects of the increased precursors.[8] First, the classic form which presents with salt wasting, hyponatremia, and hyperkalemia, which leads to acidosis, hypotension, cardiovascular collapse, and even death.[9] Second, the simple virilizing form which has no salt wasting and the 17 Hydroxyprogesterone (17-OHP) level must be greater than or equal to 500 ng/dl.[10] Third, the non-classic form which presents with a wider spectrum of mutations making possible the variation in phenotype and genotype of these subjects.

To confirm the diagnosis of this condition, the measurement of both the plasma 17-OHP and determination of peripheral karyotype is important.[11] Increased level of 17-OHP and DHEAS correlates with CAH (Figure 21).[12] The recent Endocrine Society Guidelines recommend to obtain an early morning serum (7:30am-8:00am) 17-OHP levels.[13] They can be further differentiated into the three forms by measuring the level of cortisol and aldosterone. Decreased cortisol is seen in a salt wasting type of CAH, while normal cortisol is seen in a simple virilising or NCCAH. The simple virilising CAH presents with increased aldosterone while a non-classical type presents with normal aldosterone (Figure 22).[18]

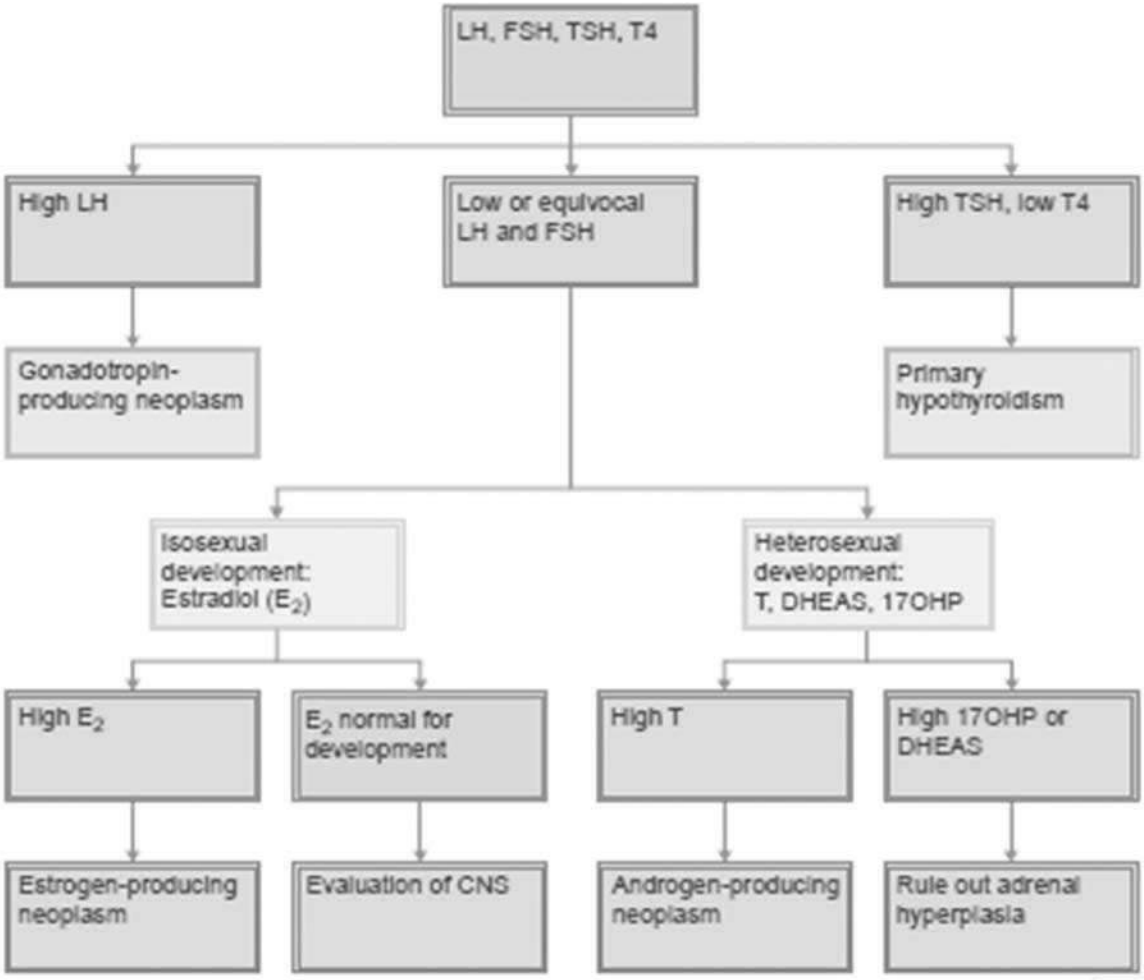

Figure 21. Flow diagram for the evaluation of precocious puberty. From Berek and Novak's Gynecology 14th edition.

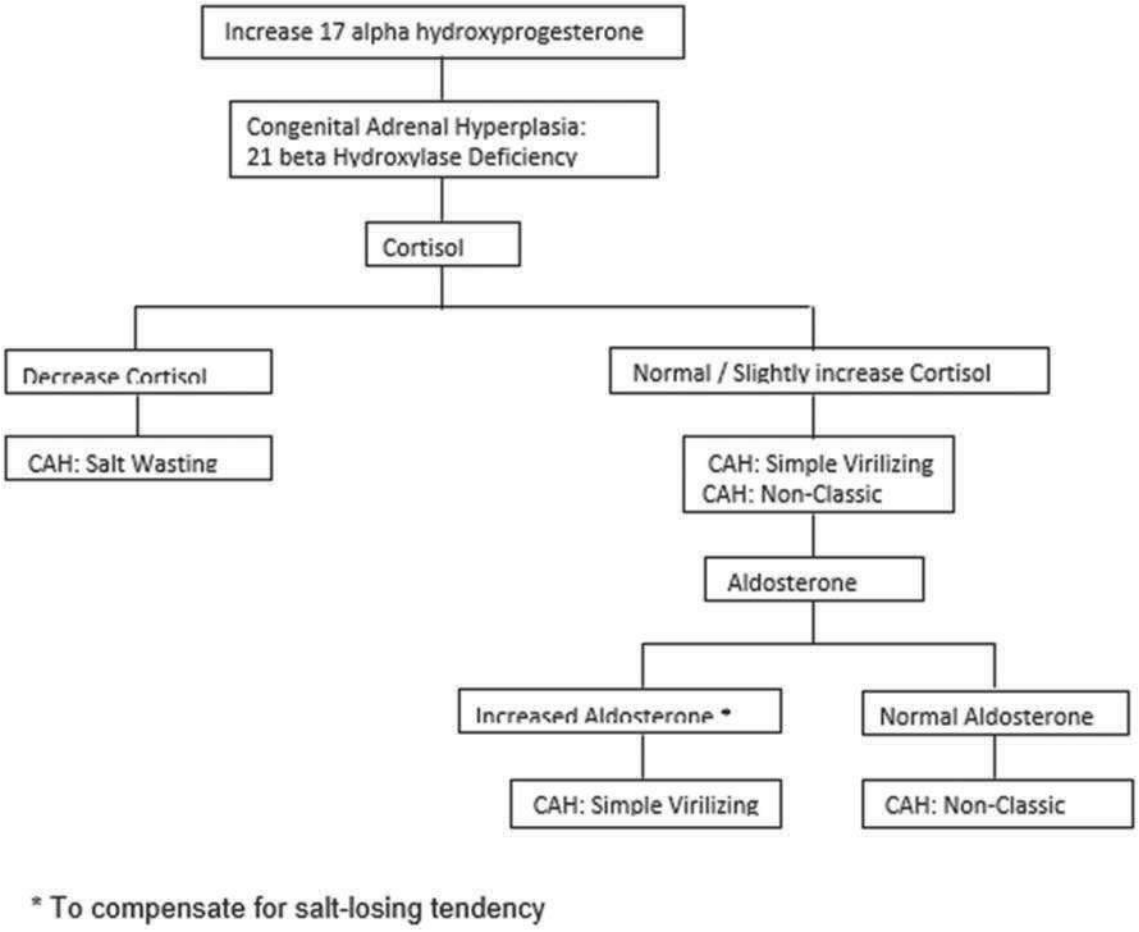

Figure 22. The algorithm to differentiate CAH into its three forms. From Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a guide for patients and their families

NCCAH is not life threatening but can present with serious quality of life issues. Patients with this syndrome may be asymptomatic to mild manifestations which may appear at any time from infancy through adulthood. They can have rapid growth and precocious puberty thus presents with a shorter than expected height due to early closure of epiphyseal plate. Other subjects may have hirsutism, acne, menstrual irregularities and infertility.[9,15]

In this case, the patient has reached the age of 16 years old without having any salt wasting crisis. The breast budding and pubic hair appeared when the patient was six years old, thus presenting with precocious puberty. Patient has short stature due to early closure of the epiphyseal plate. She also has irregular menstrual cycles and acne is present on the face and back of the patient.

Ambiguous genitalia is when one presents with an external genital that do not have the typical appearance of either a male or a female. Ambiguity of the genitalia is not life threatening however it may create social problems for the child and the family. When presented with genital ambiguity, one must first establish the presence of gonads by physical examination and confirmed by intraabdominal ultrasound. In the ultrasound the following are examined: 1) Presence of uterus and streak gonads. 2) Presence of only a uterus. 3) Presence of a uterus and the ovaries.[16] When there is presence of uterus and ovaries, the subject is diagnosed as female pseudohermaphroditism.

The patient's ultrasound result showed an anteverted uterus, normal left ovary and a right adnexal mass hence the patient is a case of female pseudohermaphroditism and karyotyping must be done to determine the genotype (Figure 23).

Androgen receptors have been found in the male external genital structures as well as in the female external genital structures which resemble the distribution in that of the male. This explains why female genitalia can be masculinized if exposed to high androgen levels early in gestation. Virilization may occur from exposure to androgens, either from the mother or through fetal androgens as a result of genetic deficiencies in the steroid biosynthetic pathway as what occurs in congenital adrenal hyperplasia.[12] The patient has a karyotype of 46 XX but presented with ambiguous genitalia and vaginal atresia. During her embryonic period, she must have been exposed to increased levels of androgens thus her genitalia has a male appearance. Vaginal atresia is a congenital defect that results in uterovaginal outflow tract obstruction due to arrest in formation of the sinovaginal bulbs.[12] The patient presented with no vaginal orifice. However, the MRI showed an upper vaginal vault that appears dilated up to the cervix and the uterus (Figure 19). The upper third vagina could be due to arrest in the caudal growth of the vagina.[12]

Patient experienced abdominal pain and intraoperative finding revealed that the right ovary is ruptured with foul smelling fluid. With onset of menstruation, and the absence of a vaginal opening and a small fistula that allows only small amount of blood to egress out of the anus, there is pooling

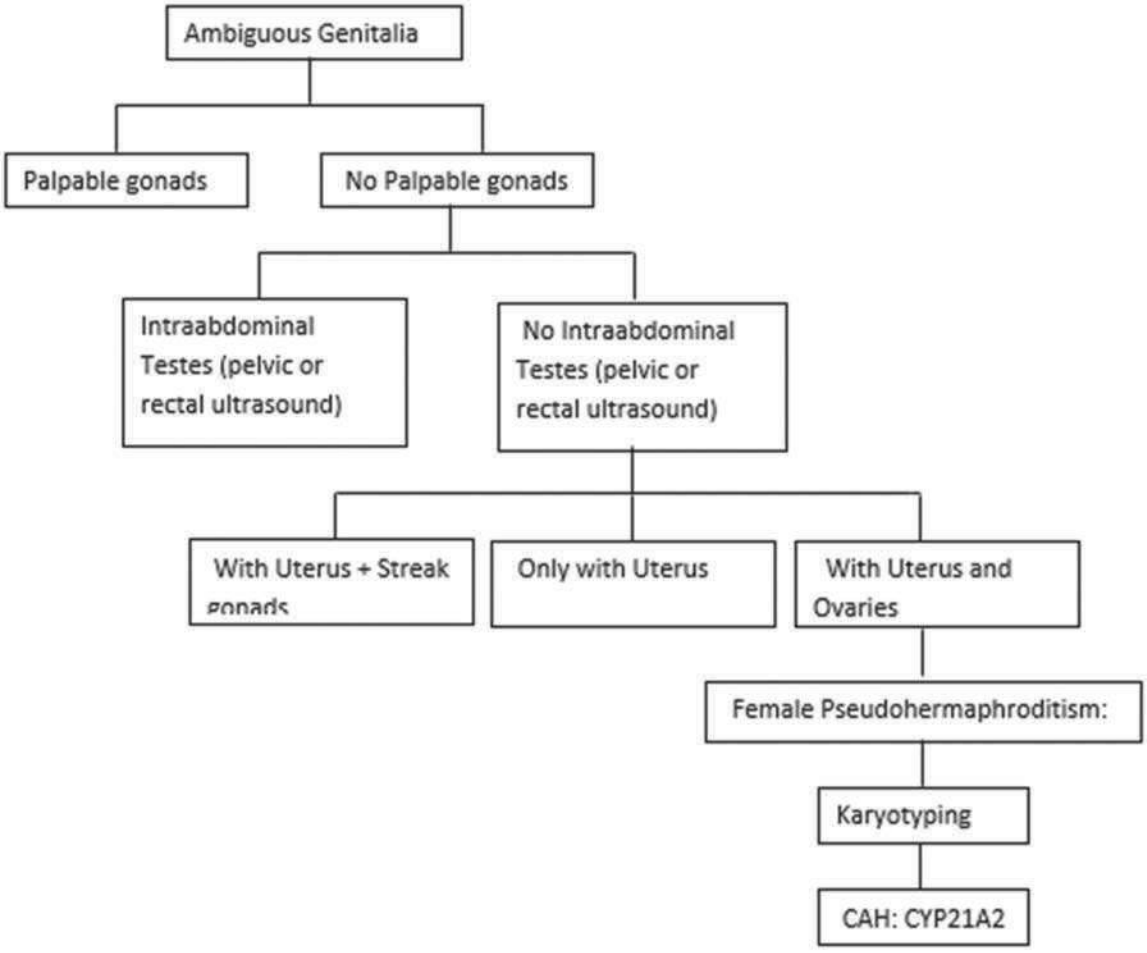

Figure 23. The algorithm of diagnosis with ambiguous genitalia. From From Imaging of Ambiguous Genitalia: Classification and Diagnostic Approach and Berek and Novak's Gynecology 14th edition.

of blood in the uterus. This blood becomes culture media for bacterial growth that may ascend to the fallopian tubes and the ovary causing a tubo-ovarian abscess.

Both the reproductive and urinary systems are derived from the mesoderm, which, beginning at 3rd to 5th gestational weeks, begin to develop into the urogenital tract. This close association of the mesonephric (wolffian) and paramesonephric (müllerian) ducts explains the coexistence of reproductive and urinary tract abnormalities.[17] According to Reichman, renal malformation is most commonly associated with uterine defect such as unicornuate uterus, uterine didelphys, and agenesis syndromes.[18] In the study of Nabhan, et al. the incidence of upper urinary tract anomalies in female with CAH is 5 to 10 fold higher than in the general population (21% vs. 2 to 4% respectively). The reported urinary tract anomalies vary from a hydronephrosis, malrotated kidney, ureteropelvic junction obstruction, vesicoureteric reflux, lower urinary tract obstruction, duplication of collecting system, multicystic dysplastic kidney and only one reported case of agenesis of the right kidney.[19]

To confirm the diagnosis of NCCAH, levels of cortisol and aldosterone were determined. For the patient to be labeled as the simple virilizing type, the 17-OHP must be greater than or equal to 500 ng/dl.[10] However, the patient only has a slightly increased cortisol and a moderately increased 17-OHP at 94.4ng/dl, thus ruling out the classical and simple virilizing CAH forms. The patient's normal aldosterone and moderately increased 17-OHP levels suppors our final diagnosis of a non-classical congenital adrenal hyperplasia (NCCAH) (Figure 24).

Treatment of patients with NCCAH is individualized based on the patient's presenting symptoms. Low dose glucocorticoid treatment is given for individuals with hyperadrogenism. Salt wasting is not one of its features thus mineralocorticoid therapy is not necessary in the treatment of this patient.[4] It is recommended that previously treated patients with NCCAH be given the option of discontinuing therapy if symptoms resolve.[13] Subjects with NCCAH are usually asymptomatic and may not require replacement of hormones however when presented with ambiguous genitalia, this must be addressed early to prevent identity confusion.

Upon follow up checkup, patient claims to have regular cyclic spotting of blood in her underwear and blood streaked urine signifying onset of menstruation, and so the patient does not need any hormonal replacement.

For patient's vaginal atresia, creation of a neovagina was proposed. For her urogenital anomalies, a temporizing surgery was suggested while the team of surgeons plan for her definitive surgery. However, the patient and the parents made an informed decision not to proceed with the surgery given the risks.

On follow-up, the patient appeared more physically feminine for she has grown her hair longer and painted her nails. The patient has accepted her gender as a female and her parents are supportive of her decision. Nevertheless, she firmly chooses not to proceed with any corrective surgeries.Patient was referred for psychiatric consult and counseling about her sexual identity. On clinical interview, she displayed no signs of anxiety and depression. The patient accepted her new role in the society as a female.

It is important to remember that social and psychological factors also play a role in forming gender-related behavior.[12] The endocrine society's clinical guidelines states that the patient must have a complete pyschodiagnostic assessment and have a real life experience fully living the life in the desired gender role before irreversible physical treatment is undertaken.[20] Thus it is important that the assignment of gender is done with active involvement of the patient and the family, careful work up and the patient's voluntary choice.

Conclusion

NCCAH is a common form of congenital adrenal hyperplasia and requires meticulous work up, close follow up and multidisciplinary care with individualized management, involving a team of pediatrician, gynecologist, psychiatrist, urologist and general surgeon. Genetic counselling is encouraged for these patients for they have

increased risk for having offsprings with classic form which carries a poorer prognosis. Patients with this disease may present with ambiguous genitalia and careful work up is done prior to gender assignment because it affects their quality of life. The goal is to correct the visible anatomical anomalies and to create an appearance consistent to the gender the individual has chosen and a function enabling the individual to live a normal life which includes sexual function and if possible, reproduction.[11]

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