CASE REPORT

Two Cases of Ambigious Genitalia

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ABSTRACT

The term "Ambiguous genitalia" applies to confusing appearance of the external genitalia. Sex assignment becomes essential for the parent's peace of mind, and in turn depends on anatomy and functional endocrinology rather than karyotype.[1] Two cases with all different genetic sex, gonadal sex and phenotypic sex are described.
First case is that of congenital adrenal hyperplasia (CAH) in a month old baby whose genotype was female with laboratory investigations exposing her diagnosis. She is doing well with oral hydrocortisone and fludrocortisone. Second case is that of probable 5-alpha reductase deficiency who would probably need future surgery.

Key words: Ambiguous genitalia, congenital adrenal hyperplasia (CAH), 5-alpha reductase deficiency, intersex.

INTRODUCTION

Intersex conditions vary in frequency. CAH is the most common cause of ambiguous genitalia in the newborn. Mixed gonadal dysgenesis (MGD) is the second most common cause of intersex conditions. Clinicians should suspect the possibility of an intersex condition if hypospadias and cryptorchidism occur in the same patient as 50% turn out to be intersex conditions.[2]

Disorder of Sex Development (DSD) is the new terminology replacing intersex with their main advocate being the intersex society of North America in order to avoid conflating anatomy with identity.[3] This has been accepted in a consensus meeting on management of intersex disorder.[4,5,8,10]

Genital ambiguity includes an infant with:[1]

1. A phallus but bilaterally unpalpable testes.
2. Unilateral cryptorchidism and hypospadias
3. Penoscrotal or perineoscrotal hypospadias even if the testes are descended.

Male phallus needs to be 2.5cm in length and clitoris <1cm with no posterior fusion in order to be labeled normal.[1]

Early intervention has been criticized by experts citing individual's experiences of interventions and the lack of follow-up studies shows clear benefits.[6-15]

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Modern treatment of infants with ambiguous genitalia involves a multidisciplinary approach. This gender-assignment team usually involves neonatologists, geneticists, endocrinologists, surgeons, counselors, and ethicists. The goal is to provide appropriate medical support and counseling regarding care and therapy. The topic of early gender reassignment is currently under debate.[2]

CASE NO. 1

Sabeen a 30-days-old baby was referred from a private hospital with complaints of undetermined sex. Mother was a booked case with regular antenatal visits. She had routine ultrasound (obstetrical) examinations, she was prescribed oral iron and folic acid supplements during pregnancy. Beside, she also received regular antiepileptics (Phenobarbitone and Epival) for epilepsy treatment. Delivery was uneventful as was the post natal period. She is the 4th product out of a consanguineous marriage. On examination the child was active, alert with stable vitals (H/R: 120 beats/min, R/R: 40breaths/min, Afebrile, BP: 55/35mmHg) and anthropometrically WNL(Ht: 54 cm, Wt: 2.5 kg, FOC: 35 cm). Examination of genitalia revealed phallus size: 1.3 cm, labioscrotal folds fused, gonads not palpable, single opening at the base of phallus. Systemic examination was unremarkable.

Working diagnosis was that of a virilized female. Investigations revealed 46xx karyotype, Ultrasound pelvis revealed uterus present measuring 3.2 x 1 x 1.8 cm, right ovary measuring 1 x 0.75 cm, left ovary 1 x 0.8 cm ie normal uterus & ovaries. Serum electrolytes were Na^+ 139meq/l, K^+ 5meq/l., 17-OH Progesterone: 33.7 ng/ml(n= 0.20- 3.30), Serum Renin: 34.59 ng/ml/hr(n= 0.15 – 2.33)

Diagnosis of CAH was made and immediately hydrocortisone and fludrocortisone was started. Her labs improved with the treatment. A good follow up plan was communicated at discharge.

CASE No. 2

3-years-old Humaira weighing 13kg came with fever for 15 days. Ambiguous genitalia noticed by mother at age of 2 months. On examination she was vitally stable with good anthropometric measurement. Local examination revealed bilateral partially fused labial swellings, stretched phallus size 1.5cm, single ventral urethral opening, gonads are bilaterally palpable in labial swellings either is around 1.5 cm, no rugae pigmentation at labia, no vaginal opening with anus normal.

Investigations showed uterus, ovaries and vagina were not visualized, hypoechoic areas in lower part of both inguinal regions likely testicular tissue, maximum diameter was 1.5 cm on either side on ultrasound pelvis. MCUG showed well developed elongated male type urethra and no Mullerian remnants. Karyotype was 46xy, Base line testosterone was < 20 ng /dl (male 0-4yr 10 -160 and female <12yr upto 20 normally). After HCG stimulation S. testosterone 44.9ng/dl. Final diagnosis was made of an Undervirilized Male with 5-alpha reductase deficiency or Partial Androgen Insensitivity Syndrome

Management plan advised multidisciplinary consultation with endocrinologist, pediatric surgeon & urologist with a view to reconstructing the child for male sex.

DISCUSSION

At around eight weeks of gestation, under the influence of gene located on Y chromosome (SRYgene) the gonads of an XY embryo differentiates into functional testes, secreting testosterone. Ovarian differentiation , for XX embryo, does not occur until approximately week 12th of gestation. In normal female differentiation, the Mullerian duct system develops into uterus, fallopian tubes and inner third of the vagina. In males the Mullerian duct inhibiting hormone (MIH) causes this duct system to regress. Next, androgen causes the development of the Wolffian duct system, which develops into the vas difference, seminal vesicles, and ejaculatory ducts.[16]

Causes of ambiguous genitalia are virilization of female infant and undervirilization of male infant.

Causes of undervirilization of male infant are, defect in testicular differentiation, testicular hormone and androgen action.

Defects in testicular differentiation include, Deny –Drash syndrome, WAGR syndrome, Camtomelic syndrome, XY pure gonadal dysgenesis and XY gonadal agenesis.

Defects in testicular hormone includes, Leydig cell Aplasia, Congenital adrenal hyperplasia.

Defects in androgen action may either be, 5 alpha reductase deficiency or Androgen insensitivity syndrome.

Congenital Adrenal Hyperplasia is a rare autosomal recessive disorder. Cortisol deficiency increases ACTH causing adrenal hyperplasia and overproduction of intermediate metabolites. Depending upon the enzyme deficient, there may be clinical and laboratory findings of mineralocorticoid deficiency or excess, incomplete virilization, or premature puberty in affected males and virilization in affected females.

More than 98% CAH causes are due to 21 OHlase deficiency. Classic type occurs in 1 in 15000- 20000 births. 75% of infants have salt losing form. 25% have simple virilizing form. Non- classic has prevalence of 1/1000 in general population (more common in Jews) shows mild elevation of androgens & signs of androgen excess postnatally. Decreased production of cortisol leads to loss of feedback on pituitary causing increased ACTH leading to stimulation of adrenal hyperplasia giving increased production of steroids above blockage including androgens.

Excessive androgen production leads to virilizing symptoms in females. Progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, old hyponatremia, hyperkalemia. Prenatal androgen excess causes affected females to have masculinized external genitalia, enlargement of clitoris, labial fusion, and common vaginal & urethral opening (urogenital sinus). Severity of virilization is greatest in females with salt losing form of 21 OHlase deficiency. Internal genital organs are normal.

Prenatal exposure of brain to high levels of androgens may lead to sexually dimorphic behavior in affected females. Males appear normal at birth. Diagnosis can not be made until signs and symptoms of adrenal insufficiency develop. Postnatal androgen excess causes rapid somatic growth, accelerated skeletal maturation. Affected patients are tall in childhood, but premature closure of epiphysis causes growth to stop early, adult stature is stunted. Muscular development is excessive. Pubic & axillary hair may appear. Acne & deep voice may develop. Patients with non classic type have normal genitalia at birth, but may present with precocious puberty.

Investigations for CAH include Karyotyping, U/S pelvis, Serum electrolytes, 17 OH Progesterone, Renin, Aldosterone, ACTH.

Prenatal diagnosis in parents already having affected child can have CVS late in 1st trimester for analysis of DNA; during 2nd trimester by amniocentesis. The goal is to facilitate appropriate prenatal treatment of affected females by Dexamethasone 20ug/kg daily (2-3 divided doses) which suppresses secretion of steroids by fetal adrenals.

Treatment of case is hormone replacement by Oral Hydrocortisone 10-20 mg/m^2/24hrs in 3 divided doses; double or triple doses indicated during periods of stress such as infection or surgery. Monitoring growth along percentile lines, higher height percentile indicates under treatment, loss of height percentile means over treatment. Excessive weight gain suggest over treatment, periodic pubertal development monitoring, serial x-rays of hand & wrist for bone age. Fludrocortisone : 0.1-0.3mg (2 divided

doses) with sodium supplements. In older children 0.05-0.1 mg daily is adequate. Monitoring serum electrolytes frequently especially in early infancy, and plasma renin level. Surgical management of ambiguous genitalia is done usually at 4 -12 months of age.

Case 1 was that of typical CAH 21OHlase deficiency type with virilized female proven by karyotyping, imaging and biochemistry. She was advised lifelong salt supplements along with oral hydrocortisone and fludrocortisones and a life long monitoring plan.

5 alpha reductase deficiency as an autosomal recessive disorder. In neonate phenotypic findings are limited to genitalia. External genitalia exhibit labial appearance to labioscrotal folds with mild rogation or pigmentation, phallus size fall between 1 to 2 cm, urethra may open from tip of phallus to perineum, uterus fallopian tubes and vagina are absent.

In Androgen Insensitivity Syndrome (AIS) the features of partial insensitivity vary from infertility to hypospadiasis, hypogonadism unilateral or bilateral cryptorchidism. In complete AIS, internal genitalia are of male type external are female type, frequently bilateral inguinal hernia are present, testis may be any where along their pathway. Risk of gonadoblastoma is about 20%.

Workup shows XY karyotype, low LH and low Testosterone / Dihydrotestosterone (DHT) in hypothalamopituitary defect, normal to high LH with normal testosterone but low DHT in 5 alpha reductase deficiency and in androgen insensitivity high LH low T / DHT is found. In healthy pre pubertal children baseline T/DHT ratio is 1:2 after HCG stimulation it become 8:1 to 14:1. Imaging studies include ultrasonography, genitogram / vaginogram, also gonadal biopsy is sometimes indicated.

Gender assignment should be deferred until the initial diagnostic evaluation has been completed and the condition clarified. Treatment includes hormone replacement therapy, psychosocial support and reconstructive surgery.

The 2nd case was that of 5-alpha reductase deficiency supported by karyotyping, imaging and relatively normal testosterone levels. DHT levels are not done here so final diagnosis cannot be confirmed nor can partial androgen insensivity be ruled out. Only time can tell the ultimate fate of such cases as hormonal potentials become evident during puberty time.

In short management of ambiguous genitalia needs timely and multidisciplinary approach and a life long followup plan.

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