



Ambiguous genitalia: A spectrum from iatrogenic to genetic disorder, report of two cases

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Introduction

Intersex conditions are among the most fascinating conditions encountered by the clinician. The ability to diagnose infants born with intersex has advanced rapidly in recent years. In most cases today, clinicians can promptly make an accurate diagnosis and counsel parents on therapeutic options. However, the paradigm of early gender assignment has been challenged by the results of research in clinical and basic sciences, which show that development of gender identity probably begins *in-utero*. While the techniques of surgical genital reconstruction have improved remarkably, the understanding of the psychological and social implications of gender assignment remains poor. Here, we report two cases of ambiguous genitalia, at one end due to iatrogenic cause and at the other end due to genetic defect. This report considers the current status of the evidence relevant to treating children with intersex conditions, with particular emphasis on psychological and methodological issues.

Case 1

A 13-year old girl was admitted on 13th June, 2002 with complaints of short stature, hirsutism and clitoromegaly. Taking her history, we found that her calorie intake was adequate. Mid-parental height was within normal limits, there was no

significant past history; other sibling who was a male was normal. Her IQ was appropriate for the age.

She was of average build, with weight 31.7 kg and height 130 cm (<3rd centile). General physical examination including blood pressure was normal. Clitoromegaly and significant hirsutism (Ferriman Gallaway score 12) was present. She was prepubertal as evidence by Tanner staging (B1A1P1). Menarche was not attained. Genital examination revealed female phenotype with clitoromegaly. There were no palpable gonads. However separate urethral, vaginal and anal openings were present.

Her hemogram and serum electrolytes were normal. Stimulated serum cortisol by aqueous ACTH was normal (serum cortisol basal 6.6 µg/dL, 60 minutes after stimulation 20 µg/dL). Plasma ACTH at 8 am was normal (24.0 pg/mL, normal 20-100 pg/mL). Serum DHEAS and testosterone were high for age (S.DHEAS 48 µg/dl; normal 10-16 µg/dL, serum testosterone 1.5 ng/ml; normal 0.1-1 ng/mL). Other investigations - serum estradiol (55 pg/ml), serum estriol (< 0.1 mg/dL), and urinary ketosteroids were normal. Her bone age was corresponding to the chronological age. Pelvic sonography revealed a small uterus 3.3 x 2 x 1.8 cm, normal contour and echo-structure. A thin linear endometrial echostructure was seen. The left gonad was seen with much difficulty and was small (1.5 x 1 cm). The right gonad could not be seen. The Pouch of Douglas was clear and no pelvic collection was seen. CT scan of abdomen and pelvis were normal. Her Karyotyping was 46, XY.

Exploratory laprotomy was performed. Testis was present on the left side and a streak or an absent gonad on the right side. Both the gonads were removed in view of her 46xy

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karyotype since the presence of Y chromosome increases the chances of gonadoblastoma. Gonadal histopathology showed testicular remnants. Hence a diagnosis of mixed gonadal dysgenesis was confirmed.

The parents as well as the child were counseled separately. The girl and the parents understood the facts and, with their consensus it was decided that the child would be reared as a girl, which was the child's demand also. Her clitoroplasty was done and she is on cyclic hormonal replacement therapy for the last one year. She is doing well psychologically with regular menstrual periods.

Case 2: A three-month-old child was brought by her parents, for ambiguity of sex observed since birth. The child was a product of full term normal delivery (birth weight 3 kg) from a non-consanguineous marriage. She was the second child of her parents, the first one being a 3-year-old normal female. There was no history of abortion. Neonatal period was uneventful with normal growth and developmental milestones. On direct questioning regarding history of the drug intake during pregnancy, the mother confessed that she received three injections of some male hormone for three consecutive days during the first trimester of pregnancy to get a male child.

On physical examination, the weight was 5.5 kg, length 55 cm and circumference of the head 40 cm. She was fully nourished and well developed; she could smile and hold her neck. On general examination, anterior fontanelle was open, skin was normal with no pigmentation. Her vitals were normal with systolic blood pressure 65 mm Hg.

Examination of external genitalia revealed ambiguity – clitoris was enlarged with posterior fusion of the labia majora. Urethral orifice was seen just posterior to the clitoris. A large orifice, urogenital sinus, was seen just behind the clitoris. A separate anal opening in a further posterior position was visible. No gonads were palpable in the labia.

Investigations revealed Hb of 13 g/dL with total count of $11,000/\text{mm}^3$ (N40, L55, M3, E2). Routine urine examination was normal. Chest X-ray was normal; bone age was normal for age. Abdominal sonography revealed a small infantile uterus with both ovaries into the pelvis.

Karyotyping revealed normal pattern with 46,XX. Endocrine evaluation revealed normal serum cortisol (stimulated), 17-hydroxy-progesterone, ACTH, DHEA, testosterone, estradiol and estriol. Urinary 17 ketosteroids was also normal. It was therefore, concluded that the baby was female with ambiguous genitalia as a result of androgens taken by the mother during embryogenesis.

The parents were counseled for surgical separation of the posterior part of the fused labia majora and corrective surgery

of the urogenital sinus at a second stage. But they are not willing for admission and surgery.

Discussion

Two cases with ambiguous genitalia as a result of androgen excess are discussed here, where case I was a type of ambiguous genitalia known as mixed gonadal dysgenesis where a genetically male (46XY) child was reared as female. Androgens produced by her gonads resulted in a picture of pseudohermaphroditism. She was to be reared as a female since the diagnosis could be made only at adolescence.

Mixed gonadal dysgenesis (MGD) is a syndrome characterized by a 46,XY or a mosaic 45,X/46,XY karyotype, the presence of a testis on one side and a streak or an absent gonad on the other, persistence of Müllerian duct structures, and a variable degree of genital ambiguity¹⁻⁴. Although most patients with MGD present as ambiguous genitalia at birth, a small number may exhibit normal external genitalia, often male in appearance⁵. Dysgenetic gonads are morphologically and functionally abnormal. They produce an inadequate amount of testosterone, which causes incomplete masculinization of the genitals and poor development of the Wolffian duct structures. Moreover, an insufficient or delayed production of Müllerian inhibitory factor causes the persistence of Müllerian structures⁴⁻⁵.

Gender assignment for patients with MGD remains under debate. Glassberg⁶, citing that no case has been reported of a tumor developing in a fully descended testis in a patient with either type of MGD argues for assigning of the male gender to patients who are sufficiently virilized. Rajfer et al⁷ prefer an elective feminine gender assignment for patients with MGD because the uterus and vagina are always present and one half of patients are markedly short and have a high incidence of inadequate external virilization. In both types of MGD, male gender assignment is considered only for the most significantly virilized patients with a completely descended testis.

It is interesting that an individual with 46,XY karyotype is being reared as female with the help of medical and surgical treatment and is now phenotypically female. But two questions still remain to be answered. Should she get married? And can she bear a child?

The detailed prognosis has to be explained to parents regarding normal sexual life but normal reproductive outcome may not be possible.

The second case was genetically female (46XX) while parents wanted to rear her as a male. The androgens consumed by the mother during embryogenesis possibly resulted in ambiguous sex. Female pseudohermaphroditism in this case was drug induced. Virilization of a female fetus may occur if androgenic progestational agents or androgens are used during

the first trimester of pregnancy. After the first trimester, these drugs cause only phallic enlargement without labioscrotal fusion. The incriminated drugs were formerly administered to avoid spontaneous miscarriages in patients who had a history of habitual abortion⁸. In this case the drug was given to get a male child. A sincere effort to remove the gender bias is needed in order to check such hazards.

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