INVITED ARTICLE

INTERSEX AND GENITAL AMBIGUITY

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ABSTRACT

Normal sexual differentiation in males and females is described. Discussion of disorders of abnormal sexual development is confined to those producing genital ambiguity. Genital ambiguity is further subdivided into disorders of gonodal development and disorders of fetal endocrinology.

Disorders of gonadal development with abnormal sex chromosome constitution include those with and without sexual ambiguity. Only those producing sexual ambiguity, true hermaphroditism and mixed gonadal dysgenesis are discussed further.

Disorders of fetal endocrinology are divided into female and male pseudo hermaphroditism. The main features of each are highlighted. A practical method of management of patients with ambiguous genitalia then follows.

Keywords: Sexual differentiation, Intersex, genital ambiguity.

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INTRODUCTION

The normal development, growth and function of the genital organs make a fundamental contribution to the balanced psychological and physical make-up of both males and females. A disturbance of the process of fetal sexual differentiation may result in malformation or even ambiguity of the genitalia.

EMBRYOLOGY OF SEXUAL DEVELOPMENT

Human genetic sex is established at conception; the homogametic state (XX) is considered female and the heterogametic state (XY) is considered male.

First, the sex chromosomes determine whether the indifferent gonad that develops in the urogenital ridge will differentiate into a testis or an ovary. Testicular differentiation is partly dependent on the presence of a threshold titre of H-Y antigen (H stands for histo-compatibility) that is secreted by Sertoli cells. Two X chromosomes are usually needed for normal ovarian development and maintenance. The testis is anatomically distinct some weeks before ovarian differentiation.

Second, Sertoli cells in the testis also produce a mullerian-inhibiting substance (MIS), a polypeptide protein that causes the mullerian (paramesonephric) ducts to regress. In the absence of this substance, the mullerian ducts develop passively to form the fallopian tubes, uterus and upper vagina. MIS has a local action, which inhibits development of the ipsilateral fallopian tube. To prevent development of the uterus and vagina, both testes must secrete adequate amounts of MIS. Thus, a patient with a testis and a contralateral streak, ovary, or ovotestis generally has a uterus and vagina and a single fallopian tube on the side with the streak or ovary.

Third, testosterone produced by the Leydig cells in the testis is required for the wolffian (mesonephric) duct to differentiate into epididymis, vas deferens and seminal vesicle. Testosterone acts locally on the ipsilateral wolffian duct. In the absence of a testis, inability of a testis to produce testosterone, or insensitivity of the wolffian duct anlage to testosterone, differentiation of the wolffian duct does not occur.

Fourth, development of male external genitalia and differentiation of the prostate are dependent on the local conversion of testosterone (the prohormone) to dihydrotestosterone (DHT), which is mediated by the enzyme 5-alpha-reductase. Dihydrotestosterone causes (1) the genital tubercle to enlarge and form the glans penis (2) the genital folds to enlarge and fuse to form the penile shaft, with migration of the urethral orifice along the lower border of the shaft to the tip of the glans, and (3) the genital swellings to fuse and form a scrotum.

Fifth, female internal organs and external genitalia develop in the absence of hormones secreted by the fetal ovary and differentiate even when gonads are absent. Unless interrupted by the regressive influence of MIS, differentiation of the mullerian ducts results in formation of fallopian tubes, a uterus and a vagina. In the absence of the masculinizing effect of DHT, the undifferentiated external genital anlage develops into the vulva. The genital tubercle develops into the clitoris, the genital folds into the labia minora, and the genital swellings into the labia majora. Thus, the infant with ovaries or streak gonads has female internal and external genitalia at birth.

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Thus, the sex of an individual can be identified by four anatomical characteristics: (1) sex chromosomes, (2) gonads, (3) internal genitalia, and (4) external genitalia. The psychological characteristics are usually related to the morphology of the external genitalia. Intersexuality results when there is a discrepancy in the genetic, gonadal or genital make-up of an individual. Disorders of sexual differentiation have traditionally been classified into three categories according to gonadal morphology. Female pseudohermaphroditism describes genital ambiguity resulting from abnormal virilization of the female fetus with normal ovaries. The male counterpart - male pseudohermaphroditism - is the result of incomplete virilization of the male fetus with normally differentiated testes. A third category consisting of subjects with abnormal gonadal differentiation includes the true hermaphrodite, who has both male and female gonadal tissue, and other syndromes of dysgenetic gonadal development.

Disorders of sexual ambiguity can be further divided into two major categories based on their aetiology: (1) disorders of gonadal development, in which the basic defect is usually a major chromosomal lesion which occurs by chance and is not hereditary, and (2) disorders of fetal endocrinology, in which the individual has normal chromosomes but usually has a genetic defect that in many instances is hereditary.

DISORDERS OF GONADAL DEVELOPMENT

Additions, deletions, or mosaicism of the sex chromosomes characterize individuals in this category. The appearance of the gonads is variable and ranges from the appearance of a streak gonad to a nearly female or male gonad.

The most common disorders of gonadal development, Klinefelter's Syndrome (47XXY) and gonadal dysgenesis (Turner's Syndrome and its variants) do not cause genital ambiguity.

Other disorders of gonadal development resulting frequently in sexual ambiguity are true hermaphroditism and mixed gonadal dysgenesis.

TRUE HERMAPHRODITISM

True hermaphroditism is defined as the presence of both testicular and ovarian tissue in a patient. The gonads may be ovary and testis separately or combined in an ovotestis.

The ovotestis is the most frequently encountered gonad in true hermaphroditism, followed by an ovary. The testis is least often encountered. The nature of the genital organ adjacent to a gonad in true hermaphroditism is dependent on the nature of the gonad. Thus, a fallopian tube is adjacent to an ovary and an epididymis or vas deferens is adjacent to a testis. Either a mullerian or a wolffian structure, but not both, is adjacent to an ovotestis. Most of the fallopian tubes adjacent to ovotestes have closed ostia. A uterus is nearly always present, but it is usually hypoplastic, unicornuate or otherwise maldeveloped.

Cryptorchidism is frequently present, together with some deficiency in labia-scrotal fusion. The external genitalia are generally more male than female, but at puberty about three-fourths of true hermaphrodites develop gynecomastia and more than half menstruate. The most common karyotypes in true hermaphrodites are 46XX, 46XY and mosaic, usually 46XX/46XY.

MIXED GONADAL DYSGENESIS

Mixed gonadal dysgenesis (MGD) or asymmetric gonadal dysgenesis is a syndrome characterized in most patients by a mosaic 45X/46XY karyotype, persistent mullerian duct structures, an abnormal testis, and a contralateral streak gonad. In contrast to true hermaphroditism, in MGD a fallopian tube is often adjacent to the gonad regardless of whether it is a testis or streak, confirming the dysgenetic nature of the testis.

MGD is detected in the neonate principally because of ambiguity of the external genitalia. Frequently, a palpable testis bulges through an indirect inguinal hernia or descends completely into the labio-scrotal fold, resulting in asymmetry of the genital swellings.

DISORDERS OF FETAL ENDOCRINOLOGY

The second major category, disorders of fetal endocrinology, can be subdivided into female pseudohermaphroditism with partial virilization and male pseudohermaphroditism with partial failure of virilization.

FEMALE PSEUDOHERMAPHRODITISM WITH PARTIAL VIRILIZATION

Female pseudohermaphroditism usually is due to congenital adrenal hyperplasia (CAH), although some forms have non-adrenal aetiology. CAH is the most frequent cause of ambiguous genitalia in the newborn. It is important to recognise this condition as the lack of specific adrenal steroids may threaten the life of the patient.

It is also the only type of intersex condition with the possibility of entirely normal sexual function, including fertility, as virilization involves only the external genitalia.

Although six different enzyme defects have thus far been reported as variants of CAH, only three - 21-hydroxylase deficiency, with or without salt wasting, 11-hydroxylase deficiency, and 3β-ol dehydrogenase deficiency - are associated with virilization of the external female genitalia. Deficiency of 11-hydroxylase is associated with hypertension. Deficiency of 3β-ol dehydrogenase, the least common is associated with the mildest virilization, but it usually is fatal because it results in severe adrenal insufficiency. These autosomal recessive disorders in turn cause lack of cortisol synthesis with a resultant increase in adreno-corticotrophic hormone (ACTH) production. The increased ACTH causes increased production of adrenal androgens, which masculinizes the external genitalia only. This is because the androgenic stimulus arrives too late to switch on the wolffian ducts. Because the androgen production can vary according to the enzymatic defect, the degree of virilization in these patients is variable and can range from clitoromegaly with minimal labial fusion to complete scrotal fusion with the urethra opening at the tip of the phallus. With the latter morphology, the infant may resemble a completely normal male with cryptorchidism. Therefore, the obstetrician should examine every newborn boy and palpate the scrotum. If no testes are palpable, CAH should be suspected and appropriate diagnostic tests performed. It is important to establish the diagnosis soon after birth because the 21-hydroxylase deficiency with salt wasting and the 3β-o1 dehydrogenase deficiency

may cause death. Once the diagnosis is suspected, it can be easily confirmed by testing for elevated levels of serum 17-hydroxyprogesterone.

Males with CAH have no evidence of genital ambiguity but may have an enlarged phallus and a hyperpigmented rugated scrotum.

The non-adrenal type of female pseudohermaphroditism is caused by excess exogenous or endogenous androgen stimulation of the fetus during pregnancy. Exogenous androgen can come from maternal ingestion of androgenic drugs, including oral contraceptives. Fetal virilization is very likely if a pregnant woman takes 19-nortestosterone derivatives between 14 and 18 weeks of gestation. Endogenous androgen can be produced by a virilizing ovarian tumour such as a luteoma. The degree of virilization does not progress with age.

MALE PSEUDOHERMAPHRODITISM WITH PARTIAL FAILURE OF VIRILIZATION

END-ORGAN DEFECTS:

The most common category is due to a defect in testosterone action. This most frequently is caused by a complete or partial defect of the androgen cellular receptor in the target cells (androgen insensitivity or testicular feminization syndrome.) As a result, neither internal nor external genital organs respond normally.

Testicular feminization is inherited as an X-linked trait and in the complete form, the external genitalia are phenotypically female. For this reason, the condition is rarely diagnosed before puberty unless an inguinal hernia or labial mass is encountered or unless the disease is known to be familial. The patient usually presents after puberty with primary amenorrhoea, scanty or absent body hair, absent internal genitalia and female external genitalia with a short or absent vagina. These individuals have to be differentiated from females with normal ovaries and congenital absence of the uterus. The latter have normal body hair.

About 10% of patients have partial expression of the androgen insensitivity syndrome, inherited as an X-linked recessive trait. In Type I patients, the clinical presentation of this disorder ranges from almost complete failure of virilization to essentially complete phenotypic masculinization. All develop breasts at puberty, and varying degrees of development of the male internal genitalia also are seen. Since virilization may accompany breast development at puberty, gonadectomy should be performed before puberty.

In Type II patients with incomplete androgen insensitivity syndrome (5-alpha reductase deficiency), target organs in this familial form of male pseudohermaphroditism cannot reduce testosterone, the prohormone to DHT, the hormone that masculinizes the indifferent urogenital sinus. In this condition, the abnormalities in the reproductive tract are confined to the external genitalia and prostate. The disorder is transmitted as an autosomal recessive. Affected males have ambiguous external genitalia at birth with bilateral undescended testes and a lack of a phallus (pseudo-vaginal perineoscrotal hypospadias). Puberty brings marked virilization, phallic growth and descent of the testes into the scrotum. The prostate, however, remains impalpable. Gynecomastia does not occur. In certain instances, individuals with this disorder can be raised as males, as they can ultimately have adequate sexual function. The appearance of virilization at puberty and the lack of breast development are in contrast to the complete form of testicular feminization and defects of testosterone synthesis.

GONADAL DEFECTS:

These conditions are associated with regression (destruction) of the gonads or their anlage during intrauterine life, specific enzymatic defects in testosterone synthesis or defects in elaboration or action of MIS.

Testicular Regression Syndrome. - Testicular regression is a concept that unifies a variety of separate conditions in which both testes have regressed during prenatal life. The various names given in the earlier literature to aspects of the syndrome (rudimentary testis, complex bilateral anorchia, Swyer's syndrome, vanishing testis) reflect the diverse findings in these patients. This heterogenous group of disorders is a manifestation of the variable timing of gonadal regression resulting in a slightly different phenotypic expression and spectrum of differentiation or atrophy of internal genital structures. At one end of the spectrum, the internal genitalia and gonads are absent and the external genitalia are female. At the other end of the spectrum which is close to the endpoint of normal genital development, the patients are phenotypic males, but gonadal tissue is absent. Intermediate in the spectrum are patients with genital ambiguity and various combinations of wolffian or mullerian duct development.

Persistent Mullerian Duct Syndrome - In this syndrome, a defect in MIS synthesis leads to males with bilateral testes and normal male internal and external genitalia; however, they also have a uterus and fallopian tubes. The latter are frequently present in an inguinal hernia (hernia uteri inguinalis).

Defects in Testosterone Synthesis - Patients with these defects have a 46XY karyotype, male gonads and ambiguous external genitalia, and they may develop breasts at puberty. The fetal testes differentiate normally and produce normal amounts of MIS, so no mullerian structures remain. But the inadequate testosterone production causes incomplete differentiation of the external genitalia; ambiguity results. The degree of ambiguity depends on the severity of the enzymatic defect. There are five basic steps in the biosynthesis of testosterone from cholesterol. Deficencies of those enzymes that are also necessary for cortisol synthesis constitute forms of the adrenogenital syndrome. The enzyme deficiencies occur in both the adrenal glands and the gonads, and inheritance is autosomal recessive. Only a few isolated patients have been reported with each of these genetic deficiencies.

MANAGEMENT OF THE PATIENT WITH AMBIGUOUS GENITALIA

The management of the patient who presents with ambiguous genitalia is in part dependent upon age. A newborn presenting with ambiguous genitalia represents a medical emergency and requires immediate attention and investigation. Regardless of the complexity of the anomaly, appropriate and rapid gender assignment at delivery, or soon thereafter at referral hospitalization, often will determine the success of the final outcome for the

child and the family. The goal in the management of such patients is to establish a diagnosis and to assign a sex of rearing that is most compatible with a well-adjusted life and sexual adequacy. The sex chromosome pattern and gonadal histology are entirely immaterial regarding gender assignment. Once the sex for rearing is assigned, the gender role is reinforced by the use of appropriate surgical, hormonal or psychological measures.

It is imperative that the parents be informed immediately in a non-traumatic manner. They should be told that the baby's sex organs are developed incompletely and that this birth defect precludes immediate gender assignment. However, diagnostic studies will commence at once to determine the gender of the baby. Until then, the sex of the child should not be announced and a birth certificate cannot be completed.

The newborn patient is considered to be at risk for the development of an adrenal crisis until the diagnosis of one of the forms of adrenal hyperplasia, associated with the impairment of glucocorticoid and mineralocorticoid production and ambiguous genitalia, is ruled out. Prompt diagnosis and institution of appropriate therapy are therefore essential. With early treatment, normal external genitalia and fertility can be achieved.

When examining the newborn with ambiguous genitalia, it is usually not possible to distinguish between male and female pseudohermaphroditism on the basis of appearance of the external genitalia. However, gonads that have descended to labial, scrotal or inguinal regions are almost always testes. Thus, the presence of one or two palpable gonads rules out virilization of an otherwise normal female, the most common form of ambiguous genitalia. Conversely, the infant born with ambiguous genitalia without palpable gonads most often represents virilization of a genetic female, usually as the result of CAH. Thus, determining the presence or absence of palpable gonads is the key in the initial evaluation.

The initial anatomical evaluation of the infant without palpable gonads is designed to establish whether a cervix and uterus are present. This is accomplished by ultrasonography and/or genitography. The presence of mullerian derivatives in an infant with ambiguous genitalia excludes male pseudohermaphroditism except for the cytogenetic forms resulting in gonadal dysgenesis. Infants with a cervix and uterus almost always will be assigned the female gender irrespective of phallus size, because they are either virilized genetic females with full reproductive potential (CAH, exogenous androgens, maternal virilizing disorders), individuals with mixed (asymmetric) gonadal dysgenesis, or true hermaphrodites. A careful search for the presence of other somatic anomalies is of great importance in the examination of the neonate.

For infants without a cervix and uterus their gender assignment often will depend on the adequacy of the phallic structure. Infants with an inadequate phallus and/or severe hypospadias are best assigned the female gender. Errors in testosterone action tend to preclude adequate virilization, and infants born with these disorders usually should be assigned the female gender. The same holds true for the most infants with 5-alpha-reductase deficiency.

When an infant does have palpable gonads, distinction should be made between an infant with unilaterally and one with bilaterally palpable gonads. A unilaterally palpable gonad may indicate asymmetric development of the internal genitalia and be consistent with either mixed gonadal dysgenesis or true hermaphroditism. A genito-urogram may show unilateral or complete mullerian duct development. Such infants are best assigned the female gender. Infants with ambiguous genitalia and symmetric labioscrotal or inguinal gonads usually represent cases of incomplete androgen insensitivity of Type 1 or Type 2 or defects in testosterone biosynthesis. No infant with bilateral palpable gonads will have a cervix or uterus. Again such infants are assigned the female gender.

It is unnecessary to obtain a karyotype before gender can be assigned. The karyotype is helpful only when it confirms the clinical and anatomical findings.

All intra-abdominal gonads or gonadal streaks in patient with intersex disorders and a Y chromosome have a relatively high potential for becoming malignant. The two most common tumours are dysgerminoma and gonadoblastoma. Tumour incidence markedly increases at about the time of puberty in all intersex disorders with a Y chromosome other than testicular feminization. Therefore, the gonads should be removed before puberty from individuals with these disorders and a Y chromosome. Tumours are uncommon before the age of 25 in individuals with testicular feminization. Because the gonadal secretion of these individuals induces normal pubertal feminization, including breast development, removal of their gonads may be delayed until after age 20 with relative safety. Intersex patients without a Y chromosome rarely develop gonadal tumours, so their gonads or streaks should not be removed.

Patients with ambiguous genitalia presenting after early infancy, or those who present in adolescence with pubertal failure, also require prompt medical attention and evaluation in a manner similar to that outlined for the neonate. A severe form of adrenal insufficiency, however, is essentially ruled out by later presentation, although milder forms must still be considered and investigation of adrenal function, along with gonadal function, is warranted.

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