Ambiguous genitalia: An approach to its diagnosis

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Authors: E. Doménech Abellán, C. Serrano García, A. Gilabert Úbeda, F. Valero García, D. Carbonell Ruiz, L. Serrano Velasco; Murcia/ES
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Purpose

To present the cases of ambiguous genitalia detected in newborn babies and breast-fed children in our hospital, showing the finds obtained in the exploration of the external genitals as well as the internal genitals through genitography and ultrasound.

Methods and Materials

We studied, through genitography and ultrasound, the newborn babies and breast-fed children with external ambiguous genitalia that had a consultation in our department from February 2006 to September 2007.

We used the classification of Shopfner through genitography. It classifies the intersexual states in six different levels.

ANATOMICAL CLASSIFICATION OF VIRILIZATION (PRADER). Figure 1 on page 7
I. Female external genitalia with clitoromegaly.
II. Clitoromegaly with partial labial fusion forming a funnel-shaped urogenital sinus.
III. Increased phallic size with complete labioscrotal fusion forming a urogenital sinus with a single opening.
IV. Complete scrotal fusion with the opening of the urogenital sinus at the base of the phallus.
V. Normal male external genitalia.

CLASSIFICATION BY GENITOGRAPHY (SHOPFNER). Figure 2 on page 8
TIPO I. Normal female urethral anatomy. A small common urogenital sinus.
TIPO II. Normal female urethral anatomy. A big common urogenital sinus.
TIPO III. Male type of urethra without seminal colliculus. A small common urogenital sinus.
TIPO IV. Underdeveloped vagina opening and uterus. Male type of urethra with seminal colliculus.
TIPO V. Undeveloped uterus.
INTRODUCTION
Disorders of sexual development (DSD), formerly termed intersex conditions, are among the most fascinating conditions encountered by the clinician.
The ability to diagnose these conditions 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 clinical and basic science research, which show that gender identity development likely begins in utero.
While the techniques of surgical genital reconstruction have been mastered, the understanding of the psychological and social implications of gender assignment has shifted the paradigm away from early reconstruction in some cases.

EMBRYOLOGY OF SEXUAL DIFFERENTIATION
Phenotypic sex determination begins with genetic sex and follows a logical cascade: chromosomal sex determines gonadal sex, which determines phenotypic sex.
The type of gonad present determines the differentiation/regression of the internal ducts (ie, müllerian and wolffian ducts) and ultimately determines the phenotypic sex.
Gender identity is determined not only by the phenotypic appearance of the individual but also by the brain's prenatal and postnatal development as influenced by the environment.

Gonadal differentiation
- During the second month of fetal life, the indifferent gonad is guided to develop into a testis by genetic information present on the short arm of the Y chromosome.
- When Testis-determining factor (TDF) is absent or altered, the indifferent gonad develops into an ovary.

Differentiation of internal ducts. Figure 3 on page 9
- Development of the internal ducts results from a paracrine effect from the ipsilateral gonad.
- When testicular tissue is absent, the fetus morphologically begins and completes the internal sex duct development and external phenotypic development of a female.
- When testicular tissue is present, two produced substances appear to be critical for development of male internal sex ducts and an external male phenotype, namely, testosterone and müllerian-inhibiting substance (MIS) or AMH.
EMBRYOLOGY OF SEXUAL DIFFERENTIATION

Differentiation of external genitalia
The external genitalia of both sexes are identical during the first 7 weeks of gestation.

- Without the hormonal action of the androgens testosterone and dihydrotestosterone (DHT), external genitalia appear phenotypically female.

- In the gonadal male, differentiation toward the male phenotype actively occurs over the next 8 weeks. This differentiation is moderated by testosterone, which is converted to 5-DHT by the action of an enzyme, 5-alpha reductase, present within the cytoplasm of cells of the external genitalia and the urogenital sinus.

DIAGNOSIS

History
Evaluation of a newborn with ambiguous genitalia requires a team effort. The most common disorder of sexual development (DSD), congenital adrenal hyperplasia (CAH), results in virilization of a 46,XX female and thus is classified under the heading of 46,XX DSD. The clinician's challenge is to distinguish CAH from other less common causes of ambiguous genitalia.
A detailed family history is essential and should include the following:
- A family history of genital ambiguity, infertility, or unexpected changes at puberty may suggest a genetically transmitted trait.
- A history of early death of infants in a family may suggest a previously missed adrenogenital deficiency.
- Maternal drug ingestion is important, particularly during the first trimester, when virilization may be produced exogenously in a gonadal female.
- Although extremely rare, a history of maternal virilization may suggest an androgen-producing maternal tumor (arrhenoblastoma).

Laboratory Studies
Chromosomal analysis.
Endocrine screening.
Serum chemistries/electrolyte tests.
Androgen-receptor levels.
5-alpha reductase type II levels.

Physical
EXTERNAL GENITALIA EXAMINATION.
. Note the size and degree of differentiation of the phallus, since variations may represent clitoromegaly or hypospadias.
. Note the position of the urethral meatus.
. Labioscrotal folds may be separated or folds may be fused at the midline, giving an appearance of a scrotum.
. Labioscrotal folds with increased pigmentation suggest the possibility of increased corticotropin levels as part of adrenogenital syndrome.

GONADAL EXAMINATION.
Documentation of palpable gonads is important. Although ovotestes have been reported to descend completely into the bottom of labioscrotal folds, in most patients, only testicular material descends fully.
- If examination reveals palpable inguinal gonads, diagnoses of a gonadal female, Turner syndrome, and pure gonadal dysgenesis can be eliminated.
- Impalpable gonads, even in an apparently fully virilized infant, should raise the possibility of a severely virilized 46,XX DSD patient with CAH.

RECTAL EXAMINATION.
- Rectal examination may reveal the cervix and uterus, confirming internal Müllerian structures.
- The uterus is relatively enlarged in a newborn because of the effects of maternal estrogen, permitting easy identification.

Procedures
Exploratory laparotomy/gonadal biopsy: Open exploration may help identify internal duct anatomy and allow gonadal tissue to be obtained for histologic characterization; however, many authors advocate laparoscopy for this purpose.

Diagnostic laparoscopy/gonadal biopsy: A laparoscope may be inserted just inferior to the umbilicus under general anesthesia, allowing rapid identification and delineation of the internal duct anatomy without the morbidity associated with open exploration. Biopsy of gonads may be performed laparoscopically by placing additional trocars.

Imaging Studies
ULTRASONOGRAPHY.
- Renal/bladder ultrasonography can be performed at the bedside in the neonatal ICU. Ultrasonography also helps identify müllerian structures. In a neonate, findings of ambiguous genitalia, enlarged adrenal glands, and evidence of a uterus are virtually pathognomonic for CAH. Ultrasonography usually allows visualization of a neonate’s adrenal glands, which may be enlarged in infants with congenital adrenal hyperplasia (CAH); however, normal
ultrasonographic findings in the adrenal glands do not exclude a diagnosis of CAH. When adrenal glands are enlarged in patients with CAH, the glands have a cribriform appearance.

GENITOGRAPHY.
Genitography helps determine ductal anatomy.
In a neonate with ambiguous genitalia, a catheter can be inserted into the distal urogenital sinus (urethra). Contrast is injected to outline the internal ductal anatomy. Findings may indicate normal urethral anatomy, an enlarged utricle, a müllerian remnant in a male, a common urogenital sinus, or an area of vaginal and urethral confluence in female neonates. It allows us to assess the internal genitalia (better the U.S. or MRI). Surgical planning: prove the union between the vagina and urethra.

MRI.
CT scanning and MRI are usually not indicated but may help identify internal anatomy. Undescended testes.
Vaginal Anatomy.

CLASSIFICATION
Recently, the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) have published proposed changes to the nomenclature and definitions of disorders in which the development of chromosomal, gonadal, or phenotypic sex is atypical.

Previous Revised
Female pseudohermaphrodite 46,XX DSD
Male pseudohermaphrodite 46,XY DSD
True hermaphrodite Ovotesticular DSD
XX male 46,XX testicular DSD
XY sex reversal 46,XY complete gonadal dysgenesis

TREATMENT
Medical Care.
Medical therapy for intersex conditions depends on the underlying cause and is indicated for the conditions associated with ambiguous genitalia, including congenital adrenal
hyperplasia (CAH). Supplemental hormone therapy may be implemented if gonadal function is compromised.

**Surgical Care.**
In a virilized female, the surgical procedure is termed feminizing genitoplasty and includes vaginoplasty and clitoroplasty.
Undervirilized males typically have hypospadias requiring surgical reconstruction. Gender reassignment may be considered in patients with male pseudohermaphrodisim and genital inadequacy.

**Images for this section:**
**Fig. 1:** ANATOMICAL CLASSIFICATION OF VIRILIZATION (PRADER).
Fig. 2: CLASSIFICATION BY GENITOGRAPHY (SHOPFNER).
Fig. 3: GENITAL DEVELOPMENT
Results

A total of 10 patients with ambiguous genitalia were studied, being ultrasound a fundamental tool for studying the internal genital anatomy as well as for the visualization of the suprarenal glands with the aim of ruling out a congenital adrenal hyperplasia (the most common cause of female pseudohermaphroditism).

Genitography allowed us to assess the urogenital sinus, the anatomy of the urethra, the vaginal cavity, the utricle and the outline of the cervix. It is also useful to determine the spatial relationship between the vagina and the urethra in the surgical planning.

Below are the most representative cases studied.

**46,XX disorders of sexual development (formerly termed female pseudohermaphroditism)**

ETIOLOGY
Overall, Congenital Adrenal Hyperplasia (CAH) is the most frequent cause of ambiguous genitalia in the newborn, constituting approximately 60% of all intersex cases. Excessive androstenedione production results in a gonadal female with a virilized phenotype. In 90% of patients with CAH, the block is at the 21-hydroxylation enzyme.

Although rare, female pseudohermaphroditism may be drug induced. Virilization of a female fetus may occur if progestational agents or androgens are used during the first trimester of pregnancy. Ovarian or adrenal tumors producing androgens.

CAH
Presents a spectrum of abnormalities, including the degree of phallic enlargement, the extent of urethral fold fusion, and the size and level of entry of the vagina into the urogenital sinus.

Although the degree of virilization seen in CAH can be extreme, internal müllerian structures are consistently present. In 90% of patients with CAH, the block is at the 21-hydroxylation enzyme. This leads to a mineralocorticoid deficiency and a buildup of androgenic byproducts, which causes masculinization of a female fetus. The result is a female infant with varying degrees of virilization. Biochemically, 75% of patients have salt-wasting nephropathy. Prior to common recognition of this condition, as many as one third of patients presented with evidence of vascular collapse.
Prenatal diagnosis is confirmed by noting an elevated amniotic fluid level of 17-hydroxyprogesterone (17-OHP) during the second trimester or by HLA typing of amniotic cells.

CAH is diagnosed more often following birth during evaluation of a 46,XX child with ambiguous genitalia, when rectal examination, retrograde genitography, or ultrasonography reveals evidence of an internal müllerian structure in the form of a cervix. Diagnosis is confirmed by an elevated serum level of 17-OHP. Remember that 17-OHP levels may be markedly elevated in the 11-hydroxylase form of CAH, as well as in the rare child with the 3-beta-hydroxysteroid dehydrogenase form of CAH.

Patients who have CAH with 11-hydroxylase block accumulate deoxycorticosterone (DOC) and 11-deoxycortisol. This form of the syndrome exhibits salt retention and hypertension because DOC is a potent mineralocorticoid.

**CASE 1** (Figure 1) on page 17

Child of one year with CAH descompensation and severe hyponatremic dehydration
KARYOTYPE: 46 XX
ABDOMINAL ULTRASOUND: No suprarenal mass. Presence of uterus and ovaries.
EXTERNAL GENITALIA EXAMINATION: Anatomical Classification of Virilization Grade III of Prader.
Both ovarian and testicular tissues are present in ovotesticular DSD, an uncommon cause of genital ambiguity, accounting for fewer than 10% of DSD cases.

**Ovotesticular disorders of sexual development (formerly termed true hermaphroditism)**

Appearance of the genitalia varies widely in this condition. While ambiguity is the rule, the tendency is toward masculinization.
The most common karyotype is 46,XX, although mosaicism is common.

Gonadal findings may be any combination of ovary, testis, or ovotestis.

An ovotestis is most common and is found in approximately two thirds of patients. When an ovotestis is present, one third of the patients exhibit bilateral ovotestes. A testicle, when present, is more likely to exist on the right (57%), and an ovary, when present, is more common on the left (62%). A palpable gonad is present in 61% of patients; of these, 60% are found to be an ovotestis. An ovary, when found, is situated most commonly in the normal anatomic intra-abdominal position. The least common gonad in ovotesticular DSD is the testis; when present, a testis is found approximately two thirds of the time in the scrotum, emphasizing that normal testicular tissue is most likely to descend fully.
Ovotestes may present with either a fallopian tube or a vas deferens but usually not both. If a fallopian tube has a fimbriated end, the end is closed in most patients, perhaps contributing to the usual lack of fertility. While rare, fertility has been reported. Gonadal tumors also are rare but have been reported.

Sex assignment should be agreed between parents and multidisciplinary team and various influencing factors:
. The weather in the diagnosis, late in our case.
. Cultural reasons that incline towards the male parents.
. The surgical difficulty, much greater in the case of allocation to male.
. Functionality and future fertility, lower for the male sex assignment.

Usually present ambiguous genitalia with small phallus, hypospadias, scrotal penis or perineum, urogenital sinus and lips fused and cryptorchidism.

**DIAGNOSIS:**
Ultrasound:
Identifies the uterus when is present, usually hypoplastic.
Menstruation at 50%. Spermatogenesis rare.
Guides gonadal biopsy.

**TREATMENT:**
Urethroplasty. Gynetoplasty.
Hysterectomy. Laparoscopic salpingectomy and oophorectomy.

**CASE 2 (Figure 2) on page 18**

Child of 1 month and 3 weeks who was admitted to study ambiguous genitalia.
Increased testosterone, cortisol, ACTH and basal aldosterone.
KARYOTYPE: 46 XX
ABDOMINAL ULTRASOUND: No uterus and left ovary. Gonad with morphology of testis in the right labium, with vas deferens. Presence of lower third vaginal.
EXTERNAL GENITALIA EXAMINATION: Anatomical Classification of Virilization Grade III of Prader.
Increased phallic size with a groove in the base.
Introit small with urethral outlet at that level.
Complete labioscrotal fusion.
Gonad palpable in the right labium.
Exploratory laparoscopy:

Left abdominal gonad undifferentiated with a rudimentary ovarian appearance. Uterus small. Gonad excision is performed.
Biopsy of left gonad: ovarian tissue with numerous well-formed primordial follicles and some follicular cysts. It is accompanied by well structured tube and some early structures resembling epididymis but not observed testicular tissue.

Biopsy of right gonad: testicular parenchyma with mild peripheral fibrosis. Are recognized spermatogonias and immature Sertoli cells.

**46,XY disorders of sexual development** (formerly termed male pseudohermaphroditism)

**Isolated deficiency of MIS.**
Isolated MIS deficiency is a rare syndrome and usually does not present in the newborn period because the genitalia appear to be those of a male with undescended testes. The most common presentation is a phenotypic male with an inguinal hernia on one side and an impalpable contralateral gonad. Herniorrhaphy reveals a uterus and fallopian tube in the hernia sac. Since the testis produces reference range levels of testosterone, a vas deferens presents bilaterally, usually running close to the uterus; therefore, damage to the vas is likely when excising müllerian remnants. At times, the vas deferens ends blindly. Appropriate surgical management attempts to bring the testes into the scrotum based on the rationale that testis tumors may occur later, emphasizing the need to remove any testicular tissue that cannot be palpated.

**Deficient testosterone biosynthesis.**
Production of testosterone from cholesterol involves 5 enzymatic steps, and defects have been identified at each step. During the newborn period, these patients present as 46,XY gonadal males with poor virilization and ambiguous genitalia. The genitalia respond to exogenously administered testosterone.

**Complete androgen insensitivity syndrome** (causing testicular feminization).
 Syndromes of androgen insensitivity involve a failure of the end organ (external genitalia and prostate) in a 46,XY gonadal male fetus to respond to appropriately produced levels of DHT. Inheritance appears to be X-linked. Complete androgen insensitivity presents in infancy only if the child has a shallow blind-ending vagina, reflecting the lack of internal müllerian development expected in an XY patient whose testes manufacture MIS at reference range levels. Inguinal hernias are common in testicular feminization, and an occasional case is detected during inguinal herniorrhaphy when a gonad is present in the hernia and a fallopian tube cannot be seen. Failure to identify an internal müllerian structure in a phenotypic female with an inguinal hernia should always raise the possibility of testicular feminization.
If not detected in this fashion, diagnosis usually is not made until puberty, when the patient presents with amenorrhea. Although these characteristics are not noted early in life, these girls exhibit a body hair deficiency as they age, and their breasts, although well formed, characteristically are deficient in stroma. Despite a 46,XY karyotype and gonads with the typical appearance of testes (perhaps altered similarly to those with cryptorchidism), a feminine gender assignment is unquestionable because of the completely feminine phenotype and because end-organ failure prevents endocrinologically produced masculinization. Confirmation of the diagnosis is crucial because the syndrome is associated with a significant incidence of gonadal malignancies (6-30%). Disagreement exists on the best timing for gonadectomy. Although a vaginoplasty later may be required, many of the girls have an adequate vagina, requiring no therapy or possibly only vaginal dilation.

**Partial androgen insensitivity syndrome:**
These patients demonstrate a spectrum of external genitalia ranging from very feminine (eg, Lubs syndrome) to increasingly masculine (eg, Gilbert-Dreyfus syndrome) to most masculine (eg, Reifenstein syndrome). A diagnosis of incomplete androgen insensitivity is suggested by elevated LH levels, with reference range levels of plasma DHT and 5-alpha-reductase activity in genital skin fibroblasts. Exogenously administered androgens do not cause adequate virilization. An early gonadectomy and feminizing genitoplasty are recommended in infancy.

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**5-Alpha-reductase deficiency:**
A 46,XY fetus with normal testes but lacking the enzyme 5-alpha reductase in the cells of the external genitalia and urogenital sinus cannot produce DHT. Therefore, the fetus is born with minimally virilized external genitalia (eg, pseudovaginal perineoscrotal hypospadias), although the fetus usually has a degree of phallic enlargement, reflecting the direct action of testosterone. The striking feature in these patients is the extreme virilization at puberty, presumably caused by direct action of testosterone on the phallus. At puberty, penile growth
is dramatic, and the individual develops a masculine voice and muscle mass. The only characteristics that do not develop are those that depend on DHT (eg, prostatic enlargement, facial hair, acne).

Diagnosis of 5-alpha-reductase deficiency can be confirmed in a patient with a 46,XY karyotype by the presence of a high ratio of serum testosterone to DHT. Urinary metabolites of testosterone and DHT can be used to establish the diagnosis in a similar fashion.

Gender assignment in these patients has been debated because of the major virilization that occurs at puberty.

Surgical results of a masculinizing operation in a mildly virilized infant are poor, and the burden to the child of growing up with inadequate genitalia hardly seems justified. Gonadectomy and feminizing genitoplasty.

**Partial gonadal dysgenesis**

Partial gonadal dysgenesis can be classified as either 46,XY DSD or sex chromosome DSD if there is mosaicism (45,X/46,XY). These represent a spectrum of disorders in which the gonads are abnormally developed. Typically, at least one gonad is either dysgenetic or a streak.

For example, in MGD, a streak gonad is usually present on one side and a testis (usually dysgenetic) on the opposite side.

In 1967, Federman used the term dysgenetic male pseudohermaphroditism (DMP) to describe patients with bilaterally dysgenetic testes and incomplete virilization of the internal sex ducts and external genitalia. Federman indicated the similarities in karyotype, gonadal histology, and phenotype that this group shares with patients with MGD and those with ovotesticular DSD.

A dysgenetic testis histologically demonstrates immature and hypoplastic testicular tubules in a stroma characteristic of ovarian tissue but that lacks oocytes. This stroma has the appearance of that seen in streak gonads and may help to explain the similarities of these syndromes.

Although the degree of virilization varies, all patients have a vagina and a uterus, and most have a fallopian tube, at least on the side of the streak.

Small urogenital sinus, testis on one side and ovary on the other side, hypertrophy of clitoris and lip-bifid scrotum.

There is the risk of gonadal malignancy (gonadoblastoma) (25%) when a Y chromosome is present in the karyotype.

Early gonadectomy appears wise because tumors have been reported to arise in the first decade in both syndromes.

Gender assignment for patients with DMP and MGD remains under debate.

**Pure gonadal dysgenesis**
This class of DSD, with bilateral streak gonads appearing as ovarian stroma without oocytes, usually goes unrecognized in newborns because the phenotype is typically completely female. Patients tend to present at puberty, at which point they do not undergo normal pubertal changes. Girls with Turner syndrome (45,XO) may be detected earlier by noting the characteristic associated anomalies of short stature, webbing of the neck, and wide-spaced nipples. Neither Turner syndrome nor the 46,XX type of pure gonadal dysgenesis appear to be associated with increased risk of gonadal malignancy.

Therapy in these children (from an intersex standpoint) is primarily limited to appropriate estrogen and progesterone support. The 46,XY type of pure gonadal dysgenesis poses a different problem because the bilateral streak gonads carry a significant potential for malignancy. Nearly one third of patients develop a dysgerminoma or gonadoblastoma; therefore, gonadectomy becomes important as soon as the diagnosis is recognized. Pure gonadal dysgenesis syndromes represent opportunities for genetic counseling.

Images for this section:
Fig. 1: Case 1
Fig. 2: Case 2
Conclusion

The birth of a newborn baby with ambiguous genitalia is a challenge for the medical team since a series of differential diagnosis must be considered quickly and in an orderly way.

The radiologist, through ultrasound and genitography, can study the internal organs, reach an early definitive diagnosis and minimize the anxiety that the lack of definition of the sexual identity of the newborn baby or breast-fed child causes to their family.

References


Personal Information