BRIEF REVIEW
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Intersex
Abnormal sexual differentiation*

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Παθολογική σεξουαλική διαφοροποίηση

Περίληψη στο τέλος του άρθρου

One of the most challenging problems a urologist has to face is the diagnosis and management of patients with sexual differentiation disorders.

Such disorders most often manifest themselves by the abnormal appearance of the external genitalia when the baby is born, casting doubt on the baby's gender and causing a lot of anxiety on the part of the family.

Problems of ambiguous genitalia should, in principle, be managed by a team of specialists in order to reach a prompt and correct diagnosis. Urologists have an important role is this group and should work in close cooperation together with neonatologists, pediatric endocrinologists and geneticists, in order to achieve the best possible management of these patients.

CLASSIFICATION OF INTERSEX STATES

The anatomy and physiology of differentiation of the internal and external sexual organs in the fetus is quite complex, being regulated by factors at three different levels (fig. 1). Thus, normal chromosomal sex is, in the first place, essential for the normal development of the gonads. With very few exceptions, a normal 46XX or 46XY karyotype leads to normal sex determination and gonadal differentiation. The presence of the sex-determining region Y gene, the so-called SRY gene, on the distal part of the short arm of the Y chromosome leads to differentiation of the initially undifferentiated fetal gonad into a testis.[1,2]

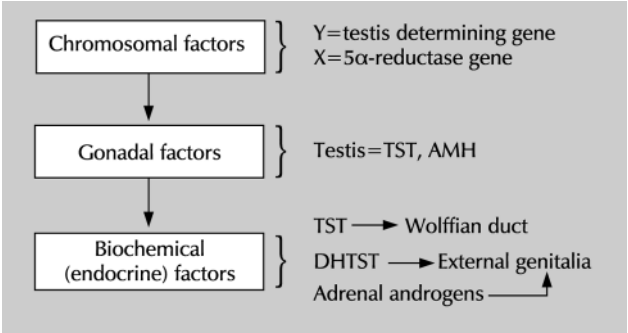

Figure 1. Factors involved in normal sexual differentiation.

In the presence of two normal X chromosomes the undifferentiated gonad should become an ovary. The absence of one X chromosome (i.e. 45 XO) will lead to early loss of gonadal germ cells and ovarian fibrous degeneration.[3]

The normally functioning fetal testis is in the position to induce further somatic male differentiation by means of the two hormones it produces (a) the anti-Mullerian hormone (AMH), secreted by the Sertoli cells, which is responsible for Mullerian duct regression, and (b) testosterone (TST) secreted by the Leydig cells, which is responsible for the maintenance and male differentiation of the Wolffian ducts and virilization of the urogenital sinus and external genitalia (genital tubercle). The virilising action on the urgenital sinus and external genitalia is achieved after local (intracellular) conversion of TST to dihydrotestosterone (DHTST) by the enzyme 5α-reductase[3] (fig. 2).

* The views expressed in this article have been proposed by the author to the Health Care Office of the European Association of Urology as guidelines for the management of intersex patients.

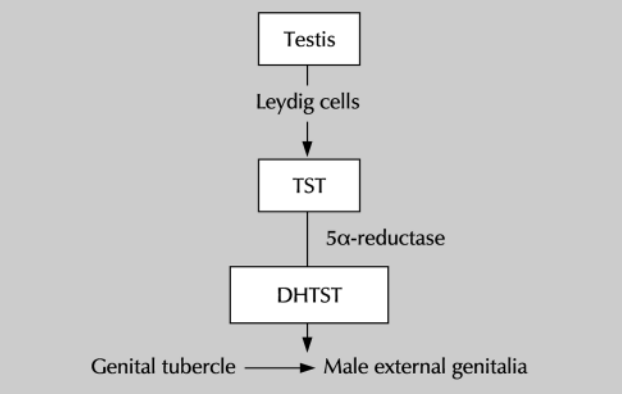

Figure 2. Somatic male differentiation via testicular hormones.

In addition, both AMH and DHTST require the presence of their respective cellular receptors in order to exercise their effects. It must be noted that the AMH-receptor gene has been mapped on chromosome 19, while the androgen-receptor gene is localized on the X chromosome. It is apparent that disorders of AMH or TST (DHTST) biosynthesis or dysfunction at the final (biochemical) level of sexual differentiation may lead to intersex states. Lack of AMH leads to the retention of Mullerian duct structures (tabl. 1), and lack of TST and DHTST leads to incomplete or absent virilization, while the opposite, i.e. overproduction of TST results is abnormal virilization. The fact that the androgen-receptor gene lies on the X chromosome explains the virilization of the female fetus in cases of androgen overproduction as in the adrenogenital syndrome.[3]

Classification of intersex states is neither easy nor uniform but a basic outline of these disorders is helpful to clinicians in their efforts to orient their thoughts for sorting out such cases. The classification proposed by Allen in 1976,[4] based on gonadal histology with subclassifications made primarily according to etiology, has stood the test of time. It has the advantage that gonadal histology is less uncertain in its interpretation than is dependence on the karyotype or the morphology of the external genitalia (tabl. 2). According to this method of classification, there are five major categories of intersex patients:

Table 1. Effects of inadequate biosynthesis or dysfunction of AMH, TST, DHTST.

– AMH ↓	⟶	Retention of Mullerian structures
– TST ↓	⟶	Inadequate differentiation of Wolffian duct structures (i.e. epididymis, vas deferens, seminal vesicles)
– DHTST ↓	⟶	Inadequate differentiation of genital tubercle → inadequate masculinization of external genitalia (severe hypospadias, microphallus)

Table 2. Classification of intersex states (modified from Allen, 1976).[4] Major categories grouped by gonadal histology, subclassification by etiology.

I. Ovary only: female pseudohermaphrodite → karyotype 46XX
  A. Secondary to endogenous androgens (CAH)
    1. 21-hydroxylase deficiency
    2. 11β-hydroxylase deficiency
    3. 3β-ol-dehydrogenase deficiency
  B. Secondary to maternal androgens (exogenous ingestion-endogenous production)

II. Testis only: male pseudohermaphrodite → karyotype 46XY
  A. Secondary to inadequate androgen (TST) production
    1. 20α-hydroxylase deficiency
    2. 3β-ol-dehydrogenase deficiency
    3. 17α-hydroxylase deficiency
    4. 17,20-desmolase deficiency
    5. 17-ketosteroid reductase deficiency
  B. Secondary to inadequate conversion of TST to DHTST → 5α-reductase deficiency
  C. Secondary to inadequate androgen (TST/DHTST) utilization (androgen receptor deficiency)
    1. Incomplete
    2. Complete (testicular feminization)
  D. Secondary to deficient AMH → hernia uteri inguinalis

III. Testis plus ovary: true hermaphrodite karyotype 46XY, 46XX, mosaic

IV. Testis plus streak: mixed gonadal dysgenesis → karyotype most often 45XO/46XX

V. Streak plus streak: pure gonadal dysgenesis → karyotype 45XO (Turner's syndrome), 46XX, 46XY

VI. Miscellaneous (?dysgenetic testes, ?teratogenic factors)

1. *Ovary only: female pseudohermaphrodite.* This is a 46XX patient with two normal ovaries and a uterus, with virilised external genitalia due to the endogenous overproduction of androgens by the fetal adrenal glands: congenital adrenal hyperplasia (CAH), adrenogenital syndrome (AGS). These patients account for approximately two thirds of intersex states in clinical practice.

2. *Testis only: male pseudohermaphrodite.* This is a 46XY patient with inadequate virilization of the external genitalia of a varying degree due to deficient biosynthesis of TST, inadequate conversion of TST to DHTST (lack of 5α-reductase) or inadequate androgen (TST/DHTST) utilization (lack of androgen receptors). This category also includes patients with AMH deficiency who exhibit adequate male external genitalia with retained Mullerian structures, i.e. tubes and uterus (hernia uteri inguinalis).

3. *Testis plus ovary: true hermaphrodite.* In this disorder the patients possess both ovarian and testicular tissue in various combinations. Their karyotype also varies, i.e. 46XX, 46XY or mosaic 46XX/46XY. True hermaphrodites make up approximately 10% of intersex cases.

4. *Testis plus streak gonad: mixed gonadal dysgenesis.* This is the second most common category of intersexuality. The most common karyotype of these cases is

45XO/46XY mosaicism. The existing dysgenetic testis is infertile and Mullerian structures may be present on both sides. There is a high risk of neoplastic degeneration (gonaboblastoma) of the existing testis after puberty.

5. *Streak plus streak: pure gonadal dysgenesis.* This group of phenotypic females with bilateral gonadal streaks comprises three separate sub-groups based on their karyotypes: 45XO (Turner's syndrome), 46XX and 46XY. The latter sub-group is particularly prone to malignant degeneration of the streak gonads.

CLINICAL MANAGEMENT

The neonatal emergency

The management of the neonate presenting with ambiguous genitalia is one of the most challenging problems a urologist has to face. Within a very short time the team of specialists dealing with such cases must reach the correct diagnosis of the underlying disorder and propose the most appropriate management regarding gender assignment and subsequent medical or surgical therapy.

The first step of action is to explain the situation to the parents fully and kindly and delay registering and naming the newborn as long as this is necessary. A careful family history must be taken, noting the occurrence of any similar cases or the history of sudden neonatal death of earlier babies (possible CAH) (tabl. 3).

The bady is then examined carefully, and apart from a general assessment for other dysmorphic features or malformations the following items are noted concerning the external genitalia:

- The size of the phallus and the amount of corpus cavernosum present
- The position of the urethral meatus and whether there is a separate vaginal opening or a urogenital sinus
- The presence of palpable inguinal masses, i.e. gonads. It must be remembered that if a gonad can be felt it is almost certainly a testis, which virtually excludes female pseudohermaphrodites (i.e. CAH)
- Abnormal genital (and areolar) pigmentation suggestive of ACTH overproduction, hence CAH
- The presence of a palpable uterus on digital rectal examination.

The following laboratory investigations are then mandatory:

- Buccal smear (if available with accuracy)
- Plasma 17-OH-progesterone assay
- Plasma electrolytes.

These three investigations will provide definitive evidence of CAH, which is the most frequent intersex disorder, in which case no further investigation is needed. Otherwise the laboratory work-up will proceed as follows:

- Karyotype
- Plasma LH, FSH and TST assay pre- and post-hCG administration. The hCG stimulation test is particularly helpful in differentiating the main syndromes of male pseudohermaphrodites (tabl. 4) and in evaluating the Leydig cell potential and the potential for phallic growth which is essential if the baby is to be assigned male sex
- Abdominal ultrasound (U/S) to visualise possible internal genital organs
- A contrast medium genitogram to visualise urethral or urogenital sinus morphology
- Urethral or urogenital sinus endoscopy under general anesthesia, provided the examiner is experienced in interpreting the findings.

Once the necessary examinations are completed the following rules of thumb can be applied regarding a precise diagnosis:[5]

Table 3. Diagnostic work up of neonates with ambiguous genitalia.

Good history (family, maternal, neonatal)
Parental consanguinity
Previous intersex disorders or genital anomalies
Previous neonatal deaths
Primary amenorrhea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or sinus urogenitalis
Size of phallus
Palpability, symmetry of gonads
Blood pressure
Investigations
Buccal smear
Blood: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST cortisol, ACTH
Urine: adrenal steroids
Karyotype
Ultrasound
Genitogram
hCG stimulation test
Androgen binding studies

Table 4. hCG stimulation test in male pseudohermaphrodites.

1. Normal increase in both TST and DHTST=androgen insensitivity syndrome
2. Subnormal increase in both TST and DHTST with increase in androgen precursors=TST biosynthetic block
3. Normal increase in TST but subnormal increase in DHTST=5α-reductase deficiency

– Positive buccal smear test and no palpable gonads: CAH or female pseudohermaphrodite due to maternal exposure to androgens. In the case of CAH immediate medical therapy must be instituted (corticosteroid substitution, electrolyte and BP monitoring).
– Buccal smear test negative and one or two gonads palpable (more often inguinal); if there are Mullerian duct structures then the diagnosis is gonadal dysgenesis or true hermaphroditism; if there are no Mullerian duct structures the anomaly is that of a male hermaphrodite due to either abnormal TST biosynthesis, inadequate conversion of TST to DHTST (5α-reductase deficiency) or receptor anomaly (androgen insensitivity syndrome).

The decision for appropriate sex assignment is then made taking into account the precise etiological diagnosis and the functional potential of the genitalia. Schematically the following practical outline can be applied:[1,4,6]

– Female pseudohermaphrodites (i.e. CAH) should be reared as females since genitoplasty can correct virilization, and spontaneous puberty, sexual intercourse and fertility are to be expected.
– Male pseudohermaphrodites with an inadequate phallus should be given androgenotherapy, i.e. systemic TST, and those with a poor clinical response should be reared as girls. The only exception is that of 5α-reductase deficiency patients, if recognised, in whom a masculine puberty is expected, and they may be reared as male.
– True hermaphrodites are preferably reared as girls as they have adequate Mullerian structures, i.e. vagina.
– Mixed gonadal dysgenesis patients with an inadequate phallus and intraabdominal testes are usually preferably reared as girls. Male sex may, however, be chosen when the phallus is of adequate size with corpus cavernosum, and the testis is palpable, inguinal or scrotal.
– Pure gonadal dysgenesis patients are reared as girls.

Late diagnosis and management

Despite meticulous diagnostic work-up and treatment during the neonatal period, there will inevitably be certain cases with disordered sexual differentiation, who are brought for urological consultation during late childhood or adolescence. Problems arise when these individuals fail to conform to their sex of rearing when they cannot perform sexually or if they still have gonads with neoplastic potential.

Female patients with CAH may complain at puberty of difficulties during intercourse because of a narrow introitus and inadequate vaginal canal. These patients should be carefully examined, if necessary under general anesthesia, and a gynecological assessment made on the need for revision vaginoplasty.

Male patients with CAH (especially those who are non-salt losers) may present with signs of excess androgen production such as rapid growth, hirsutism and precocious puberty. Appropriate work-up will disclose the underlying disorder and steroid treatment will delay puberty and prevent premature closure of the epiphyses.

Male pseudohermaphrodites with 5α-reductase deficiency who are reared as girls develop at puberty the secondary characteristics which are dependent on TST.[7] They become aggressively male in behavior, the "clitoris" grows, the voice breaks, and the body habitus becomes obviously male, while there is no acne or facial hirsutism. A careful examination at this stage will reveal high lying testes. The question of gender reassignment may then become the epicenter of prolonged discussions. Before any definite decision is taken, evaluation by a team of specialists, including a psychiatrist, is mandatory.[7,8]

SPECIAL ISSUES

Genitoplasty

Correction of the external genitalia according to the sex of rearing is very important and helps to confirm the child's sex for the whole family.[1,3]

Masculinizing genitoplasty incorporates the following stages:

a. Androgenotherapy, i.e. administration of TST, the goal of which is to restore, if possible, a normal penile size, hence it should be used in the first months of life. TST can be administered systemically or locally, but the latter mode involves the mother in the treatment.
b. Excision of Mullerian duct structures: firstly because subsequent urethroplasty may increase urethral resistance and cause urine retention and infection within a persisting vaginal structure (pseudocolpos), and secondly because casual discovery of a retained Mullerian structure later in life may cause the patient to question his gender.
c. Urethroplasty with release of chordee and correction of scrotal deformities.
d. Orchidopexy of ectopic testes which are to be retained.

Feminizing genitoplasty in CAH should be performed once the patient's general status, blood pressure and electrolyte balance have been stabilised by systemic steroid substitution. This is usually achieved around the 2nd–3rd month of life.

The family should be cautioned, however, that re-evaluation of the vaginal opening and possibly a revision vaginoplasty may be needed at puberty.[1,3,4]

Indications for the removal of gonads

The gonads of intersex patients should be removed in the following cases:[9–11]

a. Inappropriate gonadal type for the sex of rearing, as in male pseudohermaphrodites who are to be reared as girls or true hermaphrodites where discordant gonadal tissue is not needed. This type of surgery should be performed as early as possible in the neonate.

b. High risk of malignancy (gonadoblastoma/dysgerminoma). This applies particularly to patients with mixed gonadal dysgenesis, those with true gonadal dysgenesis and 46XY karyotype and, to a lesser extent, for male pseudohermaphrodites with androgen receptor insensitivity and true hermaphrodites with 46XY karyotype. The risk for gonadal tumor is real after puberty, hence this type of surgery can be postponed till that age.

ΠΕΡΙΛΗΨΗ

Παθολογική σεξουαλική διαφοροποίηση

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Οι διαταραχές της σεξουαλικής διαφοροποίησης εκδηλώνονται κατά κανόνα με την εικόνα έξω γεννητικών οργάνων αμφίβολου φύλου. Η ακριβής διάγνωση και ορθή αντιμετώπιση της υποκείμενης ανωμαλίας, που θα βοηθήσει μετέπειτα την ομαλή σεξουαλική και κοινωνική εξέλιξη του πάσχοντος, αποτελεί μεγάλη πρόκληση για τον ουρολόγο. Η γνώση των βασικών παραγόντων που εμπλέκονται στην ομαλή σεξουαλική διαφοροποίηση και οι διαταραχές που προκύπτουν από την απουσία ή ανεπαρκή δράση τους βοηθά σημαντικά στην επίλυση των προβλημάτων αυτών. Οι κύριες φάσεις διαγνωστικής και θεραπευτικής παρέμβασης είναι (α) η νεογνική περίοδος, όπου με την προσεκτική λήψη ιστορικού, την επιμελή κλινική εξέταση και τη χρήση γενετικού, βιοχημικού και απεικονιστικού ελέγχου επιβάλλεται ταχέως ο προσδιορισμός του πραγματικού φύλου και της υποκείμενης διαταραχής, ώστε να ακολουθήσει η πρόταση για την επιλογή του φύλου, που θα καλύπτει μελλοντικά τον ασθενή κατά τον πλέον επαρκή τρόπο, (β) η περίοδος της ήβης, όπου μπορεί να γίνουν αντιληπτά προβλήματα που δεν διαγνώστηκαν αρχικά, οπότε θα πρέπει να ληφθούν αποφάσεις όσον αφορά την ενδεχόμενη αναθεώρηση του φύλου του πάσχοντος. Η σπανιότητα αλλά και τα σύνθετα ανατομικά προβλήματα των ατόμων αυτών επιβάλλουν την παραπομπή τους σε ειδικά κέντρα, όπου τόσο την υποστήριξή τους όσο και τη χειρουργική αντιμετώπισή τους αναλαμβάνουν εξειδικευμένοι στα θέματα αυτά επιστήμονες.

Λέξεις ευρετηρίου: Αμφιβόλου φύλου έξω γεννητικά όργανα, Σεξουαλική διαφοροποίηση, Ψευδερμαφροδιτισμός

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