Personal practice

Intersex problems

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Paediatricians are familiar with the grief and anxiety which follow the birth of a child with a congenital malformation. When this involves the genitalia and there is doubt about the true sex of the child, sorrow is accompanied by embarrassment and dismay, leading to questions which cannot be ignored but which may be difficult to answer. We believe that it is important for parents in this situation to be told that urgent investigation will be carried out to define their baby's problem, and that they are left in no doubt that it will be possible to make an appropriate assignment of gender. The temptation to give a 'provisional' opinion must be avoided and in some cases it will be necessary to ask the local Registrar of Births and Deaths for permission to defer registration until the more appropriate sex for the child has been decided.

Initial assessment

In general, two different types of genital malformation are possible. In one, the appearance is of extreme underdevelopment of otherwise normal male genitalia, with micropenis but no hypospadias. Fetal gonadotrophin deficiency, other forms of hypopituitarism, 'rudimentary testes', and Klinefelter's syndrome are the best recognised causes of this type of anomaly. In the other variety, the genitalia may show a pattern which is intermediate between the normal male and female appearances, and it is not clear whether the patient is a boy with severe hypospadias or a girl with cliteromegaly and fusion of the labial folds. In these patients the presence or absence of palpable gonads is an important physical sign. Bilateral inguinal gonads suggest that the patient is a poorly virilised male (male pseudohermaphrodite), or possibly a hermaphrodite with ovotestes. The presence of a unilateral gonad suggests several possibilities, including for example a male pseudohermaphrodite, a patient with a testis and a contralateral dysgenetic gonad as a result of 46

XY/45 X mosaicism ('mixed gonadal dysgenesis'), or even a true hermaphrodite with one gonad within the abdomen. Absence of a palpable gonad suggests that the patient is a virilised female (female pseudohermaphrodite), when the most likely diagnosis is congenital adrenal hyperplasia. In this condition the external genitalia may occasionally be almost completely masculinised and the only clue to the diagnosis may lie in the apparent bilateral cryptorchidism of an otherwise normal boy.

Investigation

Laboratory investigation of patients with intersex disorders has been reviewed in several recent publications^{1 2} and will only be discussed briefly. With few exceptions, we believe that full chromosome analysis is needed in children with ambiguous genitalia: while examination of a buccal smear for nuclear chromatin *can* give a rapid result, the findings may be misleading, particularly in patients with abnormal sex chromosome patterns such as 45 X/46 XY mosaicism.

If congenital adrenal hyperplasia seems the most likely diagnosis, estimation of plasma 17 α -hydroxyprogesterone and 11-deoxycortisol have greatly facilitated the diagnosis of the 21-hydroxylase and 11-hydroxylase types of the disorder and have largely replaced analysis of urinary steroids.

In patients with bilateral gonads and a 46 XY karyotype, investigation of plasma testosterone, dihydrotestosterone, and androgen precursors before and after stimulation with human chorionic gonadotrophin (1000 IU) given daily for three days will help to decide whether the patient has a defect of testosterone (or dihydrotestosterone) synthesis, or whether testosterone production is normal and the basic problem is one of impaired sensitivity of the genital tissues to androgen. This latter type of case still poses one of the greatest challenges in

paediatric endocrinology. While it is now possible to determine whether the impaired response is related to an abnormality of the androgen binding receptors in tissue cultures of genital skin, as yet these methods do not allow a clear prediction of the degree of genital development which will take place at the time of puberty. We sometimes give such patients a brief course of low doses of depot-testosterone, for example 25 to 50 mg for a total of three injections given at four week intervals, to try to determine the likely extent of development at puberty. Unfortunately, the degree of enlargement of the phallus in response to treatment is often difficult to assess accurately, particularly as noticeable chordee is usually present. A therapeutic trial of testosterone may be more successful in patients with micropenis, many of whom respond well with good growth of the phallus.

Radiographic investigation using contrast media to visualise the urethra or vagina may be of value, particularly in patients who are likely to be raised as girls and who may require vaginoplasty at a later date.

In some patients laparotomy or laparoscopy with gonadal biopsy is indicated: this is particularly the case in those with asymmetric gonadal development or patients who show a discrepancy between the clinical findings and the karyotype—for example, no palpable gonads in a patient with a 46 XY karyotype or bilateral gonads in a patient with a 46 XX karyotype. In the former the biopsy may show the presence of gonadal dysplasia; in the latter, testicular and ovarian tissue indicating true hermaphroditism. In general, laparotomy and gonadal biopsy are not indicated in girls with congenital adrenal hyperplasia or in patients with bilateral gonads and a 46 XY karyotype.

Assessment of gender in the newborn

There are three important factors to be taken into consideration when deciding the more appropriate gender for an intersex patient. Firstly, the anatomy of the genitalia must be assessed to define the ease or difficulty of the surgical procedures which will be needed to construct functional male or female external genitalia. Secondly, the pattern of pubertal change which can be expected at the time of adolescence must be considered; will there be spontaneous virilisation or feminisation, and will such changes be fairly complete or will treatment with androgens or oestrogens be needed? Reproductive potential is only an important consideration in girls with congenital adrenal hyperplasia or hormone-induced female pseudohermaphroditism who are potentially fertile; most of the other

intersex disorders are associated with infertility in adult life although a few true hermaphrodites have been reported as fertile.³ Thirdly, the views of the parents on the most appropriate sex for their child must be taken into account. The race and cultural background of the family may be very important, especially when they are from societies where men occupy much more prestigious positions than women.

A newborn female child with congenital adrenal hyperplasia or hormone induced masculinisation will almost always be brought up in the female role, regardless of the degree of masculinisation, which can be corrected surgically. The extent to which ambiguous genitalia can be made into functioning male organs is an important and often more difficult consideration in other cases; if this cannot be done with any reasonable hope of success, the female role should be chosen since it is always possible to achieve this by surgical correction.

Presentation in later childhood or at puberty

In some instances, the presence of an intersex disorder will not become apparent until later childhood. For example, precocious puberty in a supposedly cryptorchid boy may bring to light the presence of congenital adrenal hyperplasia in severely masculinised girl, or perhaps more commonly, virilisation at adolescence in an otherwise normal girl may occur as a result of undiagnosed male pseudohermaphroditism.

In this situation, assignment of gender is concerned with the suitability of the external genitalia for life in the gender role in which the patient is already living and the orientation of the patient to that role. If, as is usually the case, the external genitalia are appropriate to the gender in which the patient has been living and is well adjusted, this role would be maintained and underscored by any surgical or hormone treatment which might be required. The most difficult cases are those in which the patient, although well adjusted to the male role, has poor external genital development which might make sexual life as a male unsuccessful. One is faced with the very difficult decision whether to leave such a patient in the gender to which he is adjusted, but in which he cannot perform sexually, or to re-register in the opposite role and risk hopeless psychological confusion.

Surgical management

Mention must be made of the different surgical procedures which may be necessary, with particular reference to their timing.

In a girl with congenital adrenal hyperplasia two procedures may be necessary, reduction in size of the phallus and enlargement of the constricted vaginal introitus. Our preference is for reduction of the clitoris during early infancy, and surgery can be performed in the neonatal period as soon as the congenital adrenal hyperplasia has been controlled. The advantage of this timing is that it allows the child to be discharged home without any visible sign of masculinisation.

Techniques exist for removing the corpora cavernosa yet retaining the sensitive glands,⁴ and good results are usually obtained. Enlargement of the vaginal introitus is often a more difficult procedure and is better left until later, usually until after puberty. In the rare circumstance of an older girl with congenital adrenal hyperplasia being brought up as a boy and being well adjusted to that role, hysterectomy and oophorectomy should be performed before puberty to permit continued life as a male. At a later date testosterone treatment can be given, and testicular prostheses inserted.

A genetic male or mosaic with a Y chromosome who is being raised as a girl will require gonadectomy because of the increased risk of malignancy. The risk of this happening at some time in a frankly dysgenetic gonad may be of the order of 30%,⁵ while in the well formed gonads of patients with androgen insensitivity the risk might be of the order of 5%.^{6,7} In patients who are raised as girls but who show some genital masculinisation, it is our practice to remove the testes during childhood to eliminate the risk of further masculinisation at puberty. In androgen insensitive patients who show no masculinisation and in whom spontaneous feminisation can be expected at puberty, orchidectomy can be carried out when breast development is complete.

In some 46 XY patients raised as girls construction of a vagina may be required but this is usually best deferred until adolescence or later.

A male intersex patient who is being brought up as a boy will require surgical correction of his hypospadias and associated chordee. Most urologists would aim to complete surgery by the age of 3 to 4 years. Orchidpexy is very often also required. In patients with 46 XY or 45 X mosaicism any obviously dysgenetic gonadal tissue should be removed because of the high risk of malignancy. Macroscopically normal testes are placed in the scrotum whenever possible as they usually produce some spontaneous virilisation at the time of puberty. Because of the risk of cancer, however, they may be best removed when adolescence is complete.

In a true hermaphrodite the inappropriate gonad—testis or ovary, depending on the sex of

rearing—should be removed; if the male role has been chosen, hysterectomy will also be required. In either role external genital surgery may be necessary.

Management at puberty

In congenital adrenal hyperplasia, close control of the disorder will permit the development of secondary sexual characteristics and menstruation, although menarche often occurs a year or two later than usual. Fertility in these patients is probably somewhat reduced, but many have had normal pregnancies and given birth to normal infants, usually by caesarean section.

Intersex patients who have had their gonads removed require hormone replacement treatment at the usual time of puberty. In a patient growing up as a female who has a uterus and who can be expected to have menstrual bleeding, it is our practice to give ethinyl oestradiol 10 to 20 µg daily for three weeks in four. When withdrawal bleeding occurs a progestogen can be given in the form of norethisterone 5 mg between days 12 and 21, in addition to the oestrogen. This regimen generally gives good secondary sexual development and regular withdrawal periods. When the uterus is absent, the hormone replacement treatment can be continuous, and it is doubtful if a progestogen needs to be used.

To achieve masculinisation in patients brought up as boys, we use injections of depo-testosterone, initially at a dose of 100 mg every six to eight weeks and subsequently at a dose of 250 mg every three to six weeks. Some patients, however, show a poor response to this treatment, particularly those with tissue insensitivity to androgens.

Family guidance

Most parents are at a loss as to how they can best explain the nature of the medical condition to their child without implying that 'she really is a boy' or that 'he started off as a girl'. We usually suggest that the patient is told that the 'ovaries' or 'testes' had to be removed because they were unhealthy or were producing 'the wrong balance of hormones', that hormone treatment will be needed to bring on the correct changes of puberty, and that fertility is not possible. In patients with male pseudohermaphroditism raised as girls it is also necessary to explain that they were 'born without a uterus' and that menstruation will not occur. While these explanations are probably adequate, at the time of adolescence it is likely that at least some of these patients will ultimately guess the true nature of their condi-

tion and may welcome a chance to discuss it frankly with their doctor, or even their parents.

May we end with a reassuring anecdote? One of us (JD) treated a masculinised girl who was changed from male to female at the age of 4 years.⁸ She was told that an error in assignment had been made and she had always been female. Over 20 years later, now a happily married woman, she presented again because of difficulty in conceiving. She is now pregnant.

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