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Ambiguous genitals and the choice of gender

by

P. Kiss, Magda Osztovics and P. Szőnyi

Apáthy Children's Hospital; Laboratory of Cytogenetics, National Institute of Public Health; and Heim Pál Children's Hospital, Budapest

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In 8 children with ambiguous external genitals, sex chromosome, hormonal and histological examinations were performed. On this basis the registered sex and the surname of the child were changed from the registered male to female in 3 cases and from female to male in one case. Diagnosis and the decision about the gender are urgent tasks, since prolonged waiting may have serious consequences in psychosexual development.

The two main types of sex chromosomal anomalies, the 45,X (Turner) syndrome and the 47,XXY (Klinefelter) syndrome display well-defined clinical patterns [6, 7]. In these patients with few exceptions, the choice of gender at birth does not cause any difficulty, and later it is not necessary to alter the registered sex. On the other hand, in newborns with uncertain, ambiguous external genitals the choice of gender at birth is not a simple task. An erroneous registration leads, apart from administrative complications, to considerable disturbances in psychosexual development and in the life of the whole family. Procrastination, transitory solutions are not admissible since the examinations needed can be performed during the first days of life [3].

The present work has the aim to call attention to the diagnostic problems on the basis of 8 cases, principally from the aspect, when it seems necessary to alter the registered sex (Table I).

Case reports

Case 1. U. T; a newborn, the second child from a second pregnancy.

External genitalia: labioscrotum; massive, penis-like clitoris. The urethra opens below the apex. A probe is easily introduced into the vagina which is adequately wide and long. The labia majora contain no testicles. Rectally, a normal uterus is palpated.

Laboratory data

Female sex chromatin positive. Karyotype in peripheral lymphocyte and skin fibroblast cultures: 46,XX.

17 ketosteroid,4.8 mg/day
ketogen steroid,7.2 mg/day
serum sodium,123 mval/L
serum potassium, 7.12 mval/L
serum chlorine,92 mval/l

Diagnosis: salt-losing adrenogenital syndrome. Cortisol and DOCA substitution was successful.

Remark: The registered sex and surname of the newborn were changed to female.

Case 2. E. T., third child of the sixth pregnancy, two sisters are healthy. At birth the child was registered as female but 1 month later the registration was corrected for male.

TABLE I
Data of patients

Case No.	Registered sex (surname)	Gonadal structure	Morphology of genitalia: external	Morphology of genitalia: internal	Karyotype in cultures: lymphocyte	Karyotype in cultures: fibroblast	Diagnosis	Necessity of change of surname
1.	male	female	ambiguous	female	XX	XX	adrenogenital syndrome (salt-losing)	Yes
2.	female then male	female	ambiguous	female	XX		adrenogenital syndrome	Yes
3.	male	female	ambiguous	aplasia	XO		Turner syndrome	Yes
4.	female	—	female	—	XY	XY	agonadism	No
5.	male	male	ambiguous	male	XO/XY		hypospadias	No
6.	female	mixed	ambiguous	mixed	X/XY/XYY	X/XY/XYY	gonadoblastoma	No
7.	female	mixed	ambiguous	mixed	XY	XY	male pseudohermaphroditism	Yes
8.	female	mixed	ambiguous	male	XY	XY	testicular feminization	No

Status at the age of 4 years and 6 months: tall, slender child, making the impression of a boy. Developed pubic hair, penis-like clitoris, labioscrotum; no testicles could be palpated.

Laboratory data

Female sex chromatin positive. Karyotype,46,XX

17 ketosteroid,15.2 mg/day

ketogen steroid,27.5 mg/day

pregnanetriol,1.98 mg/day

Diagnosis: adrenogenital syndrome, not salt-losing (partial 21-hydroxylase deficiency). Cortisol substitution was effective.

Remark: new registration, now finally as female.

Case 3. J. R.: second pregnancy; 2,400 g birth weight. Registered as male. From the first pregnancy a healthy boy was born.

During the newborn period, no oedema was observed. The phenotype demonstrated no particular differences. At the age of 7 days, owing to anomalies of the external genitalia, sex chromatin examination of the buccal mucosa was performed; since the result was negative, the child was considered to be a male.

Admission at the age of 3 months: the organs are negative. Minor anomalies: larger than normal prominent ears, deep muchal hair line. Intravenous urography: normal kidneys on both sides. Miction cystography: on the right side vesicoureteral reflux; urinary bladder normal in size and shape.

External genitalia: the vaginal orifice is not visible, the probe fails to enter. Instead of labia majora a structure making the impression of a fissured scrotum can be seen (Fig. 1). Neither here, nor in the inguinal canal can testicles be palpated. At the site of the clitoris an about 2 cm large phalliform formation is found with perineal hypospadias (Fig. 2). The external genitalia correspond to pseudohermaphroditism.

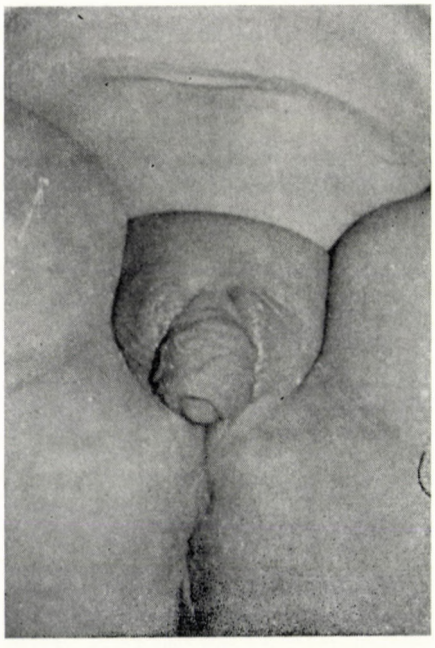

FIG. 1. Case No. 3. Penis-like clitoris and scrotal fissure in a 6-month-old child with Turner syndrome

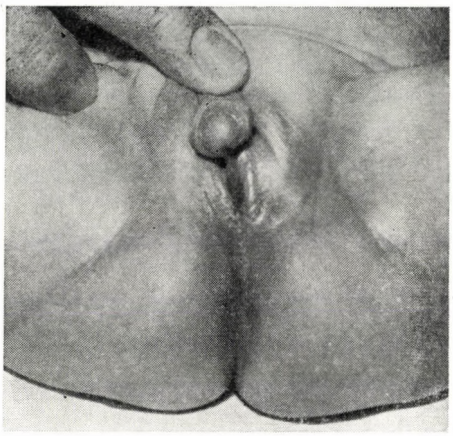

FIG. 2. Case No. 3. Penis-like clitoris with perineal hypospadias

Adrenogenital syndrome could be excluded on the basis of normal urinary 17 ketosteroid (0.3 mg/day) and pregnanetriol (traces) excretion.

Karyotype: 45,X; no suspicion of mosaicism.

Remark: based on the chromosomal examination, the diagnosis of Turner syndrome was confirmed and the registered surname and sex have been changed to female. The necessary correction and plastic surgery will be performed at later age.

Case 4. U. M., a child of female phenotype was born from the second pregnancy.

Status: dystopic sacral kidney on the left side (Fig. 3), bilateral coloboma of iris, dextroposition of the heart, pectus carinatum.

External genitalia: clitoris larger than usual (Fig. 4); the vaginal orifice is closed by a formation resembling an imperforate hymen. Rectally no uterus can be palpated; testicle-like formations are absent. The opening of the urethra is at the usual place; cystography reveals normal conditions.

Laparotomy at the age of 5 years: in the abdomen no gonad was found.

Karyotype: 46,XY in both peripheral lymphocyte and skin fibroblast cultures.

Diagnosis: total agonadism.

Remark: despite the difference between the chromosomal sex and the registered sex, it was recommended to bring up the child as a girl.

Case 5. K. I., the child was born from the second pregnancy of the 19-year-old mother. The first pregnancy ended with an artificial abortion. At birth the external genitalia were conspicuously anomalous.

Status: labioscrotum, bilateral cryptorchidism, balanic hypospadiasis.

Laboratory data:

Karyotype of the child: 45,X/46,XY

Karyotype of the mother: 46,XX/47, XXX

Remark: the anomalies of the external genitalia have been ascribed to the sex chromosomal abnormality due to the maternal mosaicism. Leaving the registered sex unchanged the child may be regarded as male.

Later the mother had two further pregnancies, which ended with spontaneous abortion in the 2nd and 3rd months, respectively. We had no possibility to examine the aborted fetuses.

Case 6. G. K., This 18-year-old girl was examined because of primary amenorrhoea (8).

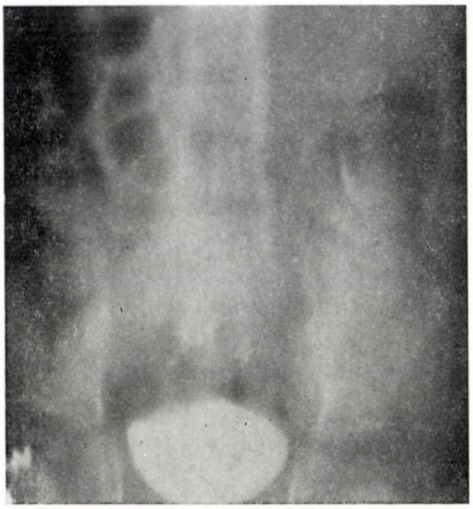

FIG. 3. Case No. 4. Dystopic left kidney in 10-month-old XY girl with total agonadism

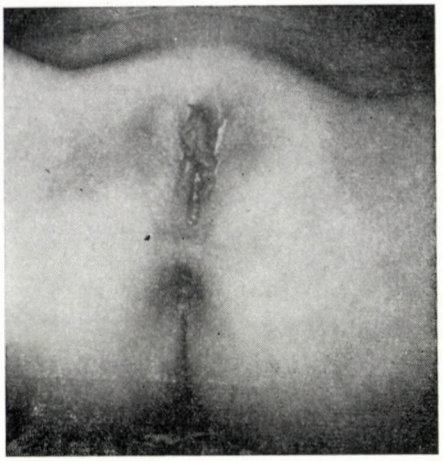

FIG. 4. Case No. 4. External genitalia in total agonadism at the age of 5 years

Status: body height 156 cm; undeveloped breasts; lacking axillary hair; pubic hair of masculine type. Hirsutism on face and extermities. Masculine appearence and character. The external genitalia are of feminine character; the clitoris is enlarged.

Laparotomy: in the right side of the pelvis a small uterus and tubae without ovaries, on the left side a bean-sized testicle-like formation were found. Histological examination of the latter revealed a gonadoblastoma.

Karyotype: 45,X/46,XY/47,XYY mosaicism in both the peripheral lymphocyte culture and in the removed gonadal tissue.

Diagnosis: gonadoblastoma. In view of the present psychosexual condition it was decided to maintain the feminine sex.

Case 7. T. Z., the 3-month-old infant, registered as a female, was operated upon in view of the external genitalia being ambiguous (Fig. 5), and the presence of a swelling (incarcerated hernia?) in the left inguinal region. In the 4 cm wide neck of the hernia, formations corresponding to an uterus and adnexa were found. The left adnexa were connected with a bean-sized gonad; the histological picture showed an undeveloped testis. No gonad was connected with the right adnexa.

Laboratory data: female sex chromatin negative. Karyotype: 46,XY in peripheral lymphocyte and skin fibroblast cultures.

Diagnosis: male pseudohermaphroditism.

Remark: the operational findings as well as the chromosome examination indicated the dominance of male sex character. The registered sex and surname were changed for male.

Case 8. B. E.; a 12-year-old girl was examined owing to unusual external genitalia. A reliable family history could not be obtained; a sibling of the mother was said to have similar genitals.

Status: well-proportioned figure, puerile breasts; axillary and pubic hair is absent. Penis-like clitoris (Fig. 6). The labia minora can be recognized; they surround the urethra at the vaginal entrance. Rectally no uterus could be palpated.

Gonadal exploration: histological examination of the testicle-like formations pal-

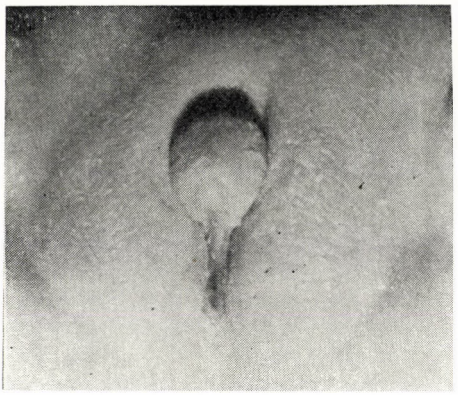

FIG. 5. Case No. 7. External genitalia of a 3-month-old child with male pseudohermaphroditism

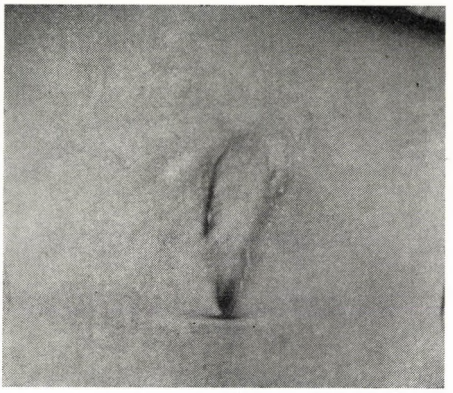

FIG. 6. Case No. 8. External genitalia of a 12-year-old child with testicular feminization

pated inguinally on both sides demonstrated rudimentary testicular tissue.

Karyotype: 46, XY, q + in both lymphocyte and fibroblast cultures.

Diagnosis: testicular feminization, somewhat supported by the supposed familial occurrence.

Remark: it was recommended to maintain the registered female sex.

DISCUSSION

According to Jones and Scott [4] the criteria of sexual gender are decided by the

1) sex chromosomes
2) gonadal structure
3) morphology of external genitalia
4) morphology of internal genitalia
5) hormonal state
6) sex of rearing
7) gender role of individual

To these should be added the registered sex, thus the chosen surname of the newborn. Luckily, there is usually a coincidence of the criteria mentioned above.

In the newborn the gender is usually established by the appearence of the external genitalia, and this will decide the gender once and for all. If, however, the external genitalia are ambiguous, the decision rests with the obstetrician and, if the decision is erroneous, a long series of damaging consequences has to be reckoned with.

In children born with ambiguous genitalia the change of the registered sex (surname) means the slightest difficulty; much more difficult is the reconstruction of the altered morphological structures, and even more so are the psychical habilitation and rehabilitation.

Most difficulties can be prevented by due examinations done as early possible. No delay is permissible, especially as in certain cases the early diagnosis is life-saving (see Case No. 1). In our experience (see Cases Nos 1, 2, 3 and 7) the necessary change of the surname causes no difficulty and the changed name signifies also the change

of sex. Just therefore the decision must be based on a careful and detailed series of examinations.

The change of name and sex in early infancy will ensure the right psychosexual development. In older children, particularly after puberty, the previous psychosexual situation and behaviour have, however, to be taken into consideration.

Human sexual behaviour is not fully dependent on the genetical code, since environmental influences such as clothes, plays, and especially the approach of the family have a considerable influence on psychosexual consciousness [9]. This is well demonstrated by the XY karyotype children raised as girls (see Cases Nos 4, 6 and 8). In other cases, owing to the anatomy of the external genitalia (Case No. 7) or due to the sex gender and psychosexual consciousness developed during a number of years, the registered sex will have to be changed [1, 2]. In the choice of gender the anatomical condition has to be considered in the first place, and the only support has to be expected from the chromosomal examination.

Finally, the problems of genetic counselling should be mentioned. The parents of the children presented in newborn and infant age would like to know the degree of risk in the next child. This too underlines the importance of early and reliable diagnosis.

Virilizing congenital adrenal hyperplasia (adrenogenital syndrome) is a recessively inherited enzyme defect. The androgen hyperproduction induces a masculinization of the female fetus so that the male character of external genitalia will occur but the internal gonads will remain female. The diagnosis rests on the urinary ketosteroid and pregnanetriol excretion [5]. If the condition is associated with salt loss, the diagnosis is life-saving. Cortisol substitution will ensure normal development in the female direction even in cases of considerable masculinization. Despite the 25 % risk of recurrence we recommend acceptance of the next child, since early diagnosis and cortisol substitution will always ensure a normal course of life.

In Turner and Klinefelter syndromes without mosaicism or in the case of XY girls or XX boys the occurrence is sporadic, therefore no recurrence has to be feared. In cases of sex chromosome mosaicism, however, chromosome analysis of the parents will only clarify the situation. In symptom-free carriers of mosaicism the risk of recurrence is high, but owing to the well-known diagnostic difficulties of mosaicism, a prenatal choromosome examination will not supply reliable support to early (prenatal) diagnosis. The only change which has to be reckoned with from the point of view of recurrence, is testicular feminization.

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P. Kiss, M. D.
Ilka u. 57
H-1143 Budapest, Hungary