MALE PSEUDOHERMAPHRODITISM: ETIOLOGIC FACTORS, CLINICAL EVALUATION AND SURGICAL TREATMENT - CASE REPORT

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SUMMARY

A case of male pseudohermaphroditism with ambiguous external genitalia, surgically corrected in adulthood, with assignement of the phenotype to the female sex is described.

The syndrome is ascribed to defective enzymatic activity of the 17-ketosterol-reductase. Surgery was performed in order to obtain correction of the patient ambiguous genitalia to the female genitalia and relative adjustment to the phenotype.

Postoperatively, hormonal therapy was instituted initially with a sequential estroprogestinic treatment and afterwards with quinestrol and cyproterone acetate, to establish a feminine hormonal pattern. A period of approximately two years was required before any positive conclusion could be drawn from our gynecological intervention.

Surgical correction of ambiguous external genitalia and the phenotypes adjustment to his external genital sex tend to remove both anatomical and psychological obstacles and in several cases of male pseudohermaphroditism have allowed the patients to establish ordinary interpersonal relationship patterns. In particular, early surgery is best suited to those cases where a clitoral urethra is lacking: surgical castration ideally should be performed before puberty has been reached in order to avoid a male crisis at puberty. This solution however is uncommon in clinics as the gynecologist is often consulted at a later stage when puberal manifestations are already present.

This study involves the clinical evolution of one case of male pseoudohermaphroditism with ambiguous external genitalia treated surgically in adulthood and with the phenotype assigned to the female.

CASE REPORT

G. M., 31 years of age, assigned to the female sex at birth.

Height 168 cm, body weight 60 kgs, android morphotype, marked hypertrichosis and hirsutism over entire body; ambiguous external genitalia (hypertrophied, phalliform clitoris, urethral meatus and introitus vaginae with common orifice (fig. 1 a), absence of the vagina, pigmented labia majora, testes located in the inguinal canals (fig. 1 b), absence of Müllerian structures, normal psychic development with feminine psychosexuality, absence of the prostate, 46 XY karyotype.

The study of testosterone metabolism showed normal 5α-reductase activity. 4-^{14}C-testosterone obtained from N.E.D. (specific activity 53 mCi/mMol) in fibroblast culture was used in this study. Prof. T. Wienkler (Institut für Humangenetik und Anthropologie der Universität - Freiburg im Breisgau - Bundesrepublik Deutschland) carrier out this determination.

Hormonal findings are reported in table 1.

FSH and LH values were determined by double antibody radioimmunoassay ([1, 2]) (Biodata Serono, Rome); reference standard; 2nd I.R.P., h.M.G. and LER 907. The sensitivity of this method is approx. 1 m.I.U./ml.

The progesterone ([3]) values were determined by the RIA-PEG method (Biodata Serono, Ro-

Table. 1. — *Hormonal findings.*

			Normal values	
FSH	93	m.I.U./ml	(5-15	m.I.U./ml)
LH	64	m.I.U./ml	(5-15	m.I.U./ml)
Progesterone	0.46	ng/ml	(0.3-0.8	ng/ml)
17β-estradiol	35	pg/ml	(13-17	pg/ml)
Estrone	84	pg/ml	(22-48	pg/ml)
Androstenedione	412	ng/100 ml	(<160	ng/100 ml
Testosterone	29	ng/100 ml	300-900	ng/100 ml

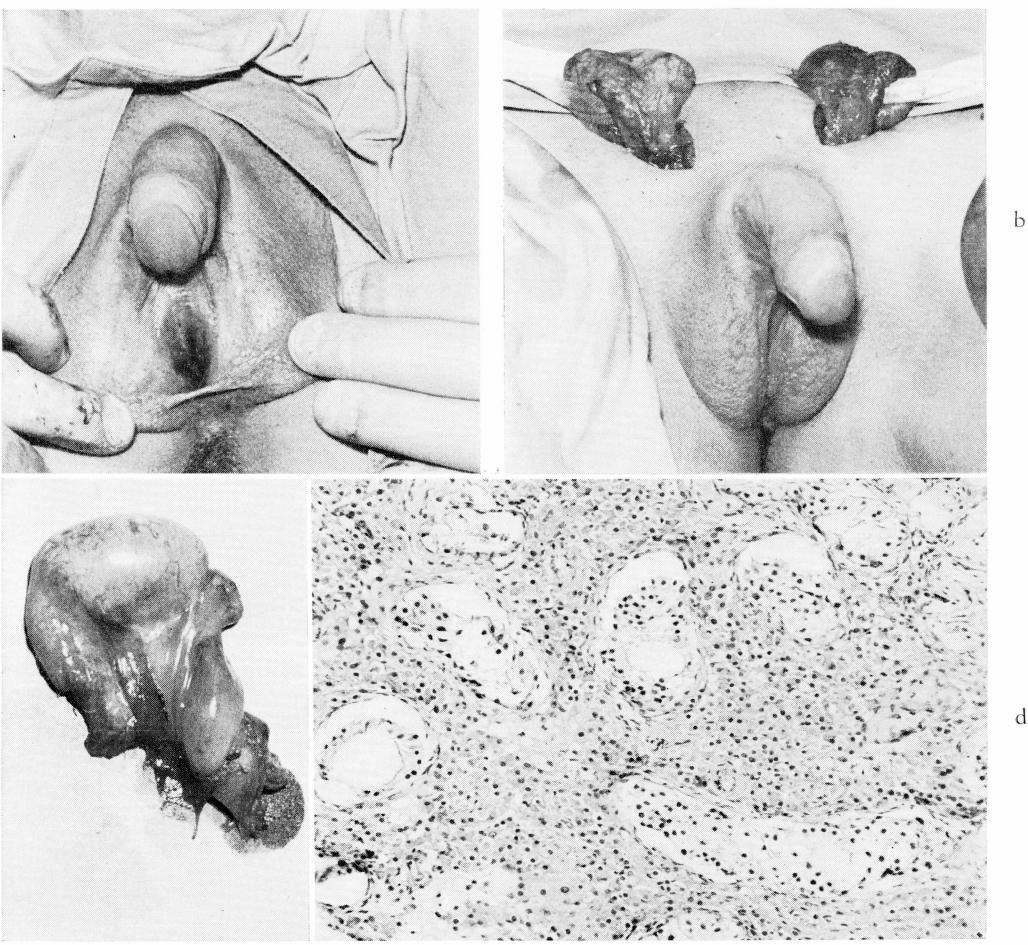


Fig. 1. — a) External genitalia with phalliform clitoris; introitus vaginae and urethral meatus with common orifice. b) Testes retained in inguinal canals. c) Right testis with epididimys and ductus deferens. d) Atrophied seminiferous tubules, without germinal cells, containing only Sertoli cells; hyperplasia of Leyding cells (E.E. 100×).

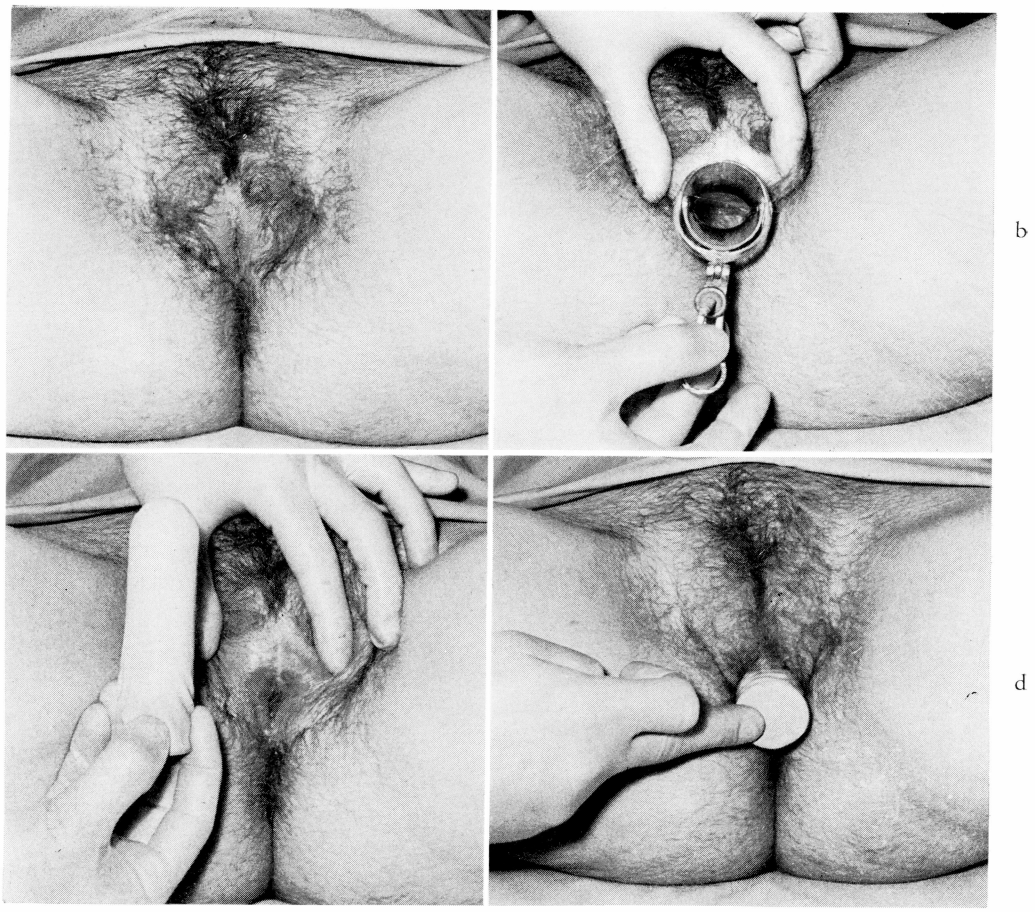


Fig. 2. — a) External genitalia after surgical correction. b) c) d) Devices evidencing neovaginal depth.

me) after ethyl ether extraction. The sensitivity of this method is approx. 5 pg/ml.

Prof. D. Knorr (Kinderklinik der Universität im Dr. von Haunerschen Kinderspital - München, Bundesrepublik Deutschland) carried out estrone ([4]), estradiol ([4]), androstenedione ([5, 6]) and testosterone ([6]) determinations.

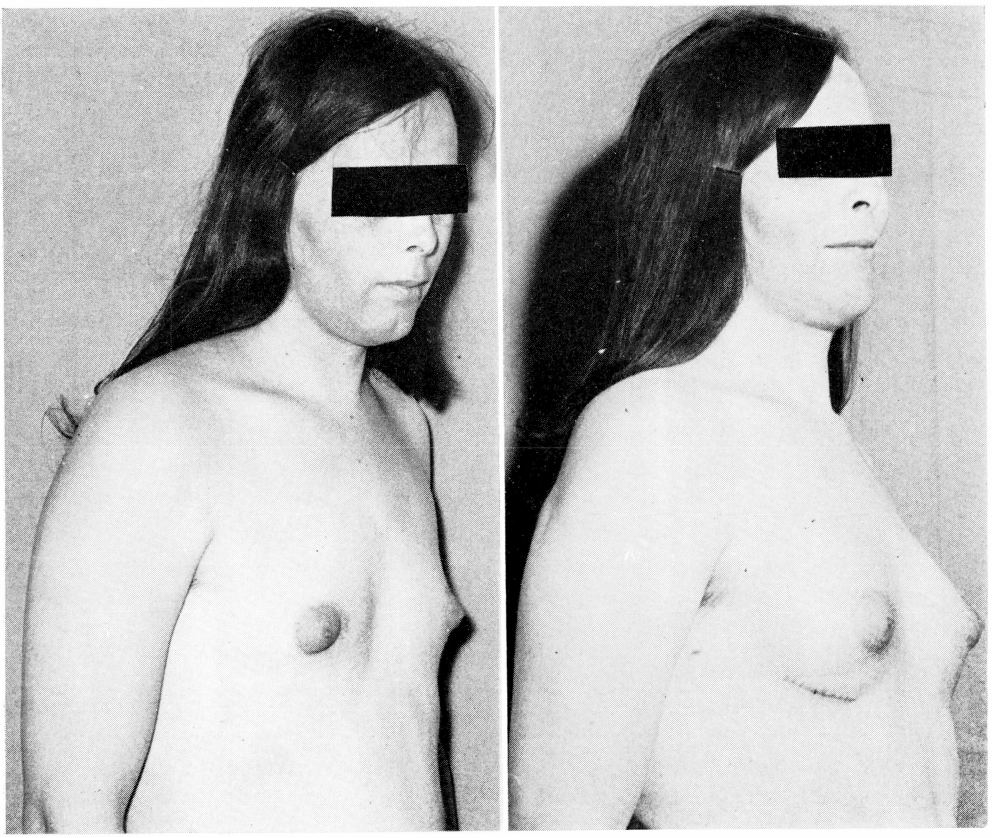
Estrone and estradiol were determined by radioimmunoassay using Sephadex L 20 chromatography. Androstenedione and testosterone levels were determined by gas chromatography using TLC.

Surgical treatment: bilateral inguinoplasty with removal of the testes (fig. 1 c), perineoplasty and reconstitution of introitus vaginae, amputation of the clitoris, neovagina according to Vecchietti's ([7]) method, bilateral mammary plastics using 145 ml silicon gel prothesis (fig. 3 a - 3 b). Surgery was performed in 3 stages. Histologic examination of the testes showed: tubular atrophy with thickened basal membrane absence of germinal cells, only Sertoli cells were present; hyperplasia of the Leydig cells with pseudoadenomatous aspect (fig. 1 d).

Postoperative hormonotherapy:

Initially:

- Mestranol 0.015 mg (1st to 7th day);
- Mestranol 0.050 mg (8th to 14th day);
- Mestranol 0.050 mg (15th to 21st day);
- Mestranol 0.075 mg (22nd to 28th day);
- Ethynodioldiacetate 1 mg (15th to 21st day);
- Ethynodiol diacetate 2 mg (22nd to 28th day).



a b

Fig. 3. — Breasts outline before (a) and after (b) bilateral mammary plastics with 145 ml silicon gel prothesis.

Afterwards:

- Quinestrol 1 mg/die and Cyproterone acetate 300 mg/die.

Clinical evolution: the neovagina proved to be well adapted to cohabitation (Fig. 2) by periodical training with a suitably shaped dilator. Hirsutism in the visible areas was treated by electrocoagulation of the hair follicles.

Hormonal anti-androgen treatment slowed down hair growth but did not reduce the areas of hair distribution.

The subject showed complete adjustment to the feminine phenotype after the first week of surgical treatment. There were neither depressive episodes nor psycholability manifestations.

Distribution of clearly masculine subcutaneous fat and muscular masses were not modified by treatment.

DISCUSSION

The clinical picture may well be ascribed to an enzyme deficiency syndrome in testosterone synthesis at the level of the Leydig cell's ([8, 9]). Hormonal determinations are suggestive of a transformation defect from Δ_4 androstenedione (Δ_4A) to testosterone (T), with raised estrone (E_1) values and normal estradiol (E_2). The 5α-reductase enzymatic activity controlling conversion of T to dihydrotestosterone (DHT) was also normal. The presumably defective enzymatic activity might be the 17-ketosteroid-reductase, essential to the transformation from Δ_4A to T and from E_1 to E_2 ([10, 11, 12]).

Hormonal values indicate that transformation deficiency is incomplete: this may be due to the fact that peripheral conversion from Δ_4A to T is maintained, with only the testicular one being blocked.

Behaviours of this type have been reported ([10, 11, 13]). Similarly, good preservation of the transformation of E_1 into E_2 in the gonads ([14]) was also reported. Virilization seems to be related to the peripheral receptors normal sensitivity to androgens. High LH and FSH levels appear justified by low androgens values, or perhaps, as far as LH is concerned, by positive estrogen feed-back.

Unfortunately this case of male pseudohermaphroditism came to us for assistance in his adulthood, in order to obtain correction of his ambiguous genitalia to female genitalia and relative adjustment to the phenotype. Italian law allows such operations as the patient was classified as female at birth and consequently reared as such. Moreover surgical castration seemed, in our opinion, definitely indicated to avoid the risk of heteroplastic degeneration, which can occur in cases of gonadal dysgenesis ([15]). Our intervention was not intended to be a sex conversion operation as carried out in male trans-sexuals since this type of surgery entails a radical change of the individual's image and not solely the adjustment of an anomalous phenotype to an already oriented psychic sex.

The absence of sexual ambivalence confirmed that the motivation for undergoing surgery was the result of a situational crisis centered on the external genitalia abnormality so much so that castration and the near certainty that no orgasms could ever be experienced were considered by the subject to be factors of secondary importance in his decisional choice ([16, 17]). Our only regret is that we were not consulted before puberal changes had occured.

It has been shown that an increase in androgens is especially important in bone growth and in the development of secondary sexual characteristics such as body hair distribution, size of the penis, and muscular mass distribution ([18, 19, 20, 21]).

This fact re-emphasizes the importance of surgical castration before the onset of puberty in order to attenuate the phenotype masculinization, even if the adrenarche effects have already taken place as was seen in this case where they were attenuated by the documented enzyme deficiency. It should be underlined that an early orchiectomy might have forestalled amputation of the clitoris as its phalliform hypertrophy could have been prevented: the abnormally hypertrophied clitoris did not allow clitoroplasty. Perineal plastic surgery and neovaginoplasty were not negatively influenced by age. With regard to the surgical technique adopted, the neovagina was created by employing Vecchietti's technique ([7]). This method entails the creation of a cleavage by retrograde laparotomy passing between the bladder and the rectum up to the pseudohymenal diaphragm. This is then perforated by means of a needle forceps introduced through the cleavage, fixing an acrylic olive in the pseudohymenal fovea by threads attached to the abdominal walls, on the outside of the recti muscles after shifting them, through the cleavage, towards the bladder sides in order to effect periodical tractions from outside for a few days.

We instituted a sequential estroprogestinic treatment both to prevent involutive disturbances following surgical castration and to establish a feminine hormonal pattern. In this way conditioning by the hormonal sex over the psychic sex was obtained, eliminating previous divergent interferences between gonadal sex and external genital sex.

The combined hormonal treatment acted concurrently with the estroprogestinic one and helped to control hypertrichosis and hair distribution in the typically masculine areas.

Psychotherapy was also extremely useful, particularly during the months following conclusion of all surgical stages.

Approximately two years were needed after the conclusion of all surgical procedures before we were able to fully assess the results of our performance. Correction of the external genitalia, the proven suitability of the neovagina to cohabitation and regression of the more evident masculinization phenomena contributed to the adjustment of the patient to the feminine pattern, so that he married a male subject, and allowed him to resume his previous working activities. This total adjustment to social life, in itself, justifies our management of the case, independently of the esthetic and functional outcome.

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