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ENDOCRINE STUDIES
AND SUCCESSFUL TREATMENT IN A PATIENT WITH TRUE HERMAPHRODITISM

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ABSTRACT

A 12-year old, 46 XX true hermaphrodite born with genital ambiguity was studied and successfully treated. The serum LH and FSH profile resembled that of a pubertal normal individual, and LH-RH administration induced a normal LH response. Baseline testosterone serum levels were within the range for normal children. Exogenous HCG stimulation induced a significant serum testosterone increase up to values similar to those observed in normal post-pubertal males. Surgical examination disclosed the presence of bilateral ovotestis, normal Mullerian derivatives, epididymis, and vas deferens. A complete ovotestis with testicular predominance and the testicular portion of the contralateral ovotestis as well as the Wolffian derivatives, were removed. A further HCG stimulation 3 months after surgery, failed to induce serum testosterone increase. Spontaneous menarche was observed 6 months after surgery and ovulation was well documented. At present the patient has several characteristics of female sex including those of chromosome complement, gonad, internal and external genitalia, hormone levels and gender identity, thus demonstrating that treatment was successful and that reproductive function could be obtained. The finding of spontaneous ovulation following removal of the testicular portion suggests normal cyclic gonadotrophic release implying a difference between animal models and man in regard to hypothalamic virilization.

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The cytogenetic and anatomical features of true hermaphroditism have been well established (Clayton et al. 1958; Rosenberg et al. 1963; Mori & Mitzutani 1968; Kasdan et al. 1973). A variety of chromosome complements in sporadic and familial cases of true hermaphroditism has been reported (Blanck et al. 1964; Hung et al. 1966; Jones & Scott 1971; Van Niekerk 1976). It is well known that in true hermaphroditism the most frequent chromosome complement found is 46 XX. The development of testicular tissue in these circumstances has not yet been satisfactorily explained; however the assessment of H-Y antigen in leukocytes of 46 XX true hermaphrodites strongly suggests that this determinant of testicular differentiation is present (Wachtel et al. 1975; Saenger et al. 1976). Since there is limited information on endocrine studies (Armendares et al. 1975; Gallegos et al. 1976) as well as on results of surgical treatment in these patients, we felt it was of interest to report the hormone profile of a 46 XX patient with true hermaphroditism before and after successful surgical treatment. The results demonstrated that cyclic ovarian function was achieved after surgery, suggesting that testicular androgens do not induce hypothalamic male imprinting in man in terms of gonadotrophin secretion.

MATERIAL AND METHODS

Clinical summary

A 12 year-old phenotypically female patient presented because of genital ambiguity. The patient was the eleventh child in a family of 12, born by normal full-term delivery after an uneventful pregnancy. At birth genital ambiguity including a 3 cm phallus, labia majora and a common urethral and vaginal opening was noted. Rearing sex was male until age 5 when it was reversed to female sex. At this age, an exploratory laparotomy was performed and bilateral gonadal biopsies were taken and the phallus removed. Histological examination of gonadal biopsies demonstrated the presence of bilateral ovotestis. At age 11 thelarche and pubarche were observed. The family history was unremarkable. Physical examination revealed a normal upper/lower segment ratio. Vital signs were normal. Mammary gland development was similar to that observed in age-matched normal girls and normal axillary and pubic hair were observed. Gynaecological examination disclosed the presence of normal labia majora, underdeveloped labia minora, a common urethral and vaginal opening, and a normal sized uterus. Sex chromatin was positive and the chromosome complement was 46 XX. Adrenal function as evaluated by measuring the urine excretion of 17-OHCS and 17-KS was within normal limits. X-ray films revealed normal bone age, normal urography, and normal vagina, uterus, and permeable Fallopian tubes. The patient was then submitted to endocrine evaluation and laparotomy.

Methods

Reagents for LH and FSH radioimmunoassay (RIA) were obtained from the NIAMDD, NIH (Bethesda, Maryland). Antirabbit gamma globulin, used as second antibody, as well as testosterone (T) antisera were prepared in our laboratories. Syn-
thetic LH-RH was obtained from Hoechst Farbwerke, A.G. and HCG was a gift from Organon Mexicana.

Serum LH and FSH were measured by double-antibody radioimmunoassays (RIA) as previously described (Mendoza et al. 1972; Scaglia et al. 1976). Results were expressed as mIU/ml according to the 2nd IRP-HMG. Baseline levels of serum gonadotrophin were determined in blood samples drawn from the antecubital vein through an indwelling catheter. Samples were obtained every 15 min for 60 min. Pituitary reserve and responsiveness were evaluated by giving an iv bolus of synthetic LH-RH (100 μg), and measuring LH and FSH after the decapptide injection. Serum T and progesterone were measured by hapten-RIA without chromatographic purification as previously described (Febres et al. 1975). Results were expressed as ng/ml. Testicular endocrine function was assessed by the im administration of HCG 5000 IU/day for 7 consecutive days. Urine pregnanediol, 17-OH corticosteroids and 17-ketosteroids were measured by conventional procedures. X chromatin and karyotype were determined by standard methods.

**RESULTS**

Mean serum baseline levels (± sd) of LH and FSH were 12 ± 2.4 and 12 ± 0.89 mIU/ml, respectively, and the administration of LH-RH resulted in a 3.9-fold increase of the LH serum levels, without a concomitant increase of the FSH serum levels (Fig. 1).

![Fig. 1. Baseline serum levels of LH and FSH, and pituitary responsiveness to exogenous LH-RH iv stimulation.](image-url)
Mean serum baseline (± sn) T levels were 0.4 ± 0.18 ng/ml in blood samples drawn at frequent intervals. Exogenous HCG administration resulted in a significant increase of the T serum levels up to 4.3 ng/ml (Fig. 2). The karyopinotic index value, as assessed in serial vaginal smears was 50, indicating an adequate oestrogen activity.

At laparotomy bilateral intra-abdominal ovotestis were found. The right gonad consisted of clear cut separated ovarian and testicular portions, with testicular predominance (80 %) and it was totally removed. The left ovotestis had an ovarian predominance (80 %) and in a similar manner to the contralateral gonad the ovarian and testicular components were arranged in end-to-

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

Fig. 2.
Baseline serum testosterone levels (A), testosterone response to HCG stimulation before (B), and 3 months after removal of testicular tissue (C).
Fig. 3.
Histological appearance of the right (A) and left (B) ovotestis, showing ovarian stroma with primordial follicles, immature seminiferous tubules and epididymis is noted in the right gonad.
end fashion, thus both components were clearly visible. It was decided to remove the testicular portion only including a thin portion of surrounding ovarian tissue. Histological examination of the removed gonadal tissue confirmed the macroscopic data (Fig. 3). As expected from the X-ray studies, a normal uterus and bilateral Fallopian tubes were found. In addition a right epididymis and a vas deferens on the right side were found and removed (Fig. 3).

Three months after surgery a testicular HCG stimulation performed in an identical fashion to that done previously, failed to induce an increase in the T serum levels as shown in Fig. 2. Six months after surgery spontaneous endometrial bleeding was noticed and it was followed by periodic and regular menses. Simultaneously, adequate breast development and sexual hair growth were observed. In order to assess the existence of cyclic ovarian function, the urinary excretion of pregnanediol and the serum progesterone levels were studied throughout a complete menstrual cycle. Fig. 4 shows a biphasic pattern of both serum progesterone and urine pregnanediol, demonstrating the occurrence of ovulation. Normal serum LH and FSH levels during follicular (mean 8.3 and 6.0 mIU/ml, respectively) and luteal phase (mean 5.7 and 5.1 mIU/ml, respectively) were observed.

**DISCUSSION**

The patient reported is a typical case of true hermaphroditism with genital ambiguity and a 46 XX chromosome complement. It belongs to the group 2 (bilateral ovotestis) according to Jones' classification (Jones & Scott 1971).
Although initially the sex of rearing was male, at age 5 the patient was both surgically and psychologically oriented towards the female sex.

We began our studies when she was at the onset of puberty, when she had already initiated breast development and sexual hair growth. Serum immunoreactive levels of both LH and FSH resembled those observed in normal boys and girls of corresponding age at the onset of puberty (Faiman & Winter 1974). Pituitary responsiveness as evaluated by LH-RH stimulation disclosed a significant rise of LH levels without a concomitant FSH increase. Therefore it was concluded that the hypothalamic-pituitary gonadotrophin function corresponded to an individual at the onset of puberty although an unexpected lack of FSH response to LH-RH was observed. Since female sexual characteristics such as breast development, sexual hair growth, and oestrogenic activity in vaginal smears in the absence of signs of virilization were present at the time of study, it was thought that the endocrine ovarian function had already started, while the endocrine testicular activity had not. The testicular function was studied before and after exogenous gonadotrophin stimulus. Baseline T were in the range of normal pre-pubertal boys, and after stimulation a significant rise on T levels was noted, thus demonstrating the presence of stimulable testicular tissue although the spontaneous endocrine function of the male gonad had not yet been initiated.

The earlier occurrence of ovarian hormonal production as compared with the endocrine testicular activity observed in this hermaphrodite individual is in line with the observation that ovarian function in normal girls, usually precedes the gonadal function in normal boys (Reiter & Root 1975).

The finding of bilateral ovotestis confirmed the diagnosis of true hermaphroditism type 2 in this patient. On the basis of a clear anatomical separation of the ovarian and testicular portions of the left ovotestis, the high predominance of ovarian tissue, the anatomical integrity of Mullerian derivatives as well as the phenotypic and behavioural characteristics, it was decided to remove the testicular portion of the left ovotestis, the whole contralateral ovotestis with testicular predominance, and the Wolffian derivatives.

Although it was felt that no testicular tissue was left in the abdominal cavity, three months later a second testicular stimulation test was performed. Lower baseline T and a complete lack of testicular response to exogenously administered HCG was observed, thus ruling out the presence of functional testicular tissue. The validity of this procedure in the detection of small amounts of male gonadal tissue has been described by Parks et al. (1974) and Kirschner et al. (1970) in the study of XY agonadal patients. We are aware, however, of the potential malignancy of intra-abdominal testicular tissue, therefore periodic HCG stimulation tests have been scheduled for the patient.

Although the development of Mullerian structures (uterus, permeable Fallopian tubes, and vagina) in the presence of bilateral ovotestis in the patient
suggests a lack of either synthesis or action of the Mullerian inhibitor factor, an adequate explanation can not be given. Recently a case with similar findings has been described (Duck et al. 1973). After surgery a normal cyclic ovarian function was observed as assessed by regular cyclic menses and ovulation confirming and extending previous morphological observations. In fact in most cases the ovarian portion of ovotestis is histologically normal and 50% presented histological evidence of ovulation (Van Niekerk 1976). These findings demonstrated that in spite of an active testicular function during intrauterine life in this patients a cyclic female pattern of hypothalamic, pituitary, and ovarian function was started under appropriate hormonal environment, suggesting that the androgen-induced hypothalamic virilization phenomenon described in other species (Gorski 1971) did not occur. Barraclough & Gorski (1961) demonstrated that administration of aromatizable androgens or oestrogens to neonatal female rats induced a tonic gonadotrophin secretion profile at puberty similar to that observed in male rats. Therefore it appears that there is a difference between animal models and man in terms of hypothalamic androgen imprinting. The overall data were interpreted as demonstrating that treatment was successful since now the patient is a normal female in terms of chromosomal complement, gonad, internal and external genitalia, phenotype, and gender identity, and that reproductive function can be obtained.

REFERENCES


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