TESTICULAR FEMINIZATION SYNDROME*

(Report of A Case)

by

NIRMALA G. MOKADAM

and

RUKMINI KALAPPA

The problem of intersex is an old one and is said to be present when there is a contradiction of one or more of the following morphologic criteria of sex: chromosomal sex, gonadal sex, internal sex organs and external genitals, causing doubt as to the individual's gender. A form of male pseudohermaphroditism "Testicular Feminization" is a term suggested by Morris in 1953 for a hereditary syndrome which is characterised in its complete form by the absence of uterus and ovaries, scant growth of pubic and axillary hair and presence of testes in a phenotypic female. About 200 cases have been reported in literature so far with the above criteria and histologically proved testicles. However, with recent advances in chromosomal studies, when the patient is found to have a negative nuclear sex chromatin pattern and karyotype 46 XY, about 25 cases have been proved, both histologically and chromosomally. A case of "Testicular feminization" is being reported herewith proved both by histological means and chromosomal studies.

From the Dept. of Obst. & Gynec. Medical College, Nagpur.

Received for publication on 31-5-67.

Case Report

K. K. an unmarried girl of 15 years, was admitted on 1-12-1966 with the complaints of primary amenorrhoea and vague dull pain in the lower abdomen for six months.

Family history: She had an elder sister who was married but was forsaken by her husband for failure to reproduce and perhaps improper sexual relations. She was also a case of primary amenorrhoea but as she was working at Bombay she could not be examined by us.

Physical examination: General physical examination revealed a thin built feminine appearing individual, 5 feet two and a half inches tall, weighing 100 lbs, with a span of 5 feet 3½ inches. The blood pressure was normal. The breasts were well developed with normal areolae and nipples; there was no axillary hair and pubic hair was very scanty and sparse. General physical findings were normal except for tender masses 3 cm. in diameter in both inguinal canals. (Fig. 1).

Local examination: The external genitalia were those of a normal female, with normal clitoris and labia. The vagina was 1 cm. in length with normal mucous membrane. No cervix was visualised or palpable in the vaginal vault. On rectal examination no internal genitals were palpable.

Laboratory data: These revealed a haemoglobin level of 11.5 gms normal white blood cell count, slightly raised sedimentation rate, negative urine analysis, normal

intravenous pyelogram, negative nuclear chromatin pattern (buccal smear and peripheral smear). Chromosomal culture of bone marrow showed a male karyotype, 46 chromosomes with the sex chromosome pattern being XY.

Operative and post-operaitve course. Exploratory laparotomy was performed on 10-12-1966 by a Pfannenstiel incision. There was no evidence of uterus, tubes (Mullerian structures) or ovaries. The kidneys were of normal size and placed normally. Bilateral gonadectomy was done. Fig. 2. Microscopic examination of the gonads (testes) revealed presence of seminiferous tubules and Leydig cell hyperplasia. No structure resembling ovarian tissue was seen. (B66-8297-8300).

The patient was reviewed about a month ago (end of June 1967), and apparently the patient manifested a normal health with the same appearance as at the time of discharge.

Sex factors in patient K. K. (testicular feminization syndrome)

Sex factor	Patient K. K.
1. Genetic — Nuclearchromatin	Negative ♂
Chromosomal pattern	46-XY ♂
2. Gonad	Testes ♂
3. External genitals	Female ♀
4. Sex hormonal status	(not done usually ♀)
5. Sex of rearing	Female ♀
6. Sex role or phenotype	Female ♀

Discussion:

The most significant features of the testicular feminization syndrome as described by Morris are:

(1) Female habitus, breast development and other secondary sex characteristics.

(2) Scant or absent axillary or pubic hair in most cases.

(3) Female external genitals, with a tendency to under-development of labia and a blind vagina.

(4) Absence of internal genitals except for rudimentary anlage and gonads which may be located intra-abdominally or along the course of the inguinal canals.

(5) Gonads histologically consistent with undescended testes.

(6) Urinary excretion studies suggesting testicular secretion of oestrogens and androgens with elevated urinary gonadotropins occasionally.

Pathologic aspect: The histopathology of the gonad is similar to that of a cryptorchid testes. The seminiferous tubules are immature with little evidence of spermatogenesis and with a predominance of sertoli cells which are well developed and filled with abundant lipid and may be the source of oestrogenic secretion. The interstitial cells are also hyperplastic accounting for the increased urinary 17-ketosteroid excretion in some cases.

Non-specific fibrous stroma may be present in some areas resembling ovarian stroma which has hence led to the mistaken diagnosis of ovotestis (Morris, Novak and Cotte and Pallot). However, the term ovotestis should be reserved for those cases where there are more definite ovarian elements like follicles or their derivatives.

The incidence of malignancy in these gonads is difficult to evaluate but, from reports in literature (Jones, Morris, Goldberg et al) varies from 5 to 9 per cent, which suggests removal of the testes on attainment of puberty as by then their role in the development of the female secondary sex characteristics is over.

Hormonal aspect: Endocrine studies have shown the testes as the source of the oestrogen-like hor-

mones. Though no ovarian tissue has been found in the patients, the presence of normal female secondary sex characteristics, oestrogenic vaginal smear, normal levels of oestrogen excretion in urine with lack of masculinity suggesting the testes as the source of oestrogens proved by the disappearance of oestrogens in urine, rise in pituitary gonadotrophins and appearance of hot flushes on removal of the gonads as observed by Mishall, Morris, Goldberg and Maxwell.

Some cases of testicular feminization tend to show a slightly eunuchoid build with long extremities as observed in this case. Since the sex hormones play a role in the closure of the epiphyses the increased growth of the long bones reflects a failure of epiphyseal closure probably due to lack of inhibition of the pituitary growth hormone by the sex hormones. Morris' contenion is that some somatic factor in the bones themselves may play a role. The breasts, the bony pelvis, the long bones and other structures may be somatically "male" or "female" requiring only small amounts of the proper sex hormone for their development. But if the end organ is of the opposite sex even large amounts of hormone will produce a limited response.

The absence or scant growth of xillary or pubic hair has not been atisfactorily explained. The relavely normal hormonal values cannot explain the absence of sex hair n an endocrine basis. Probably here is a local defect of the hair follcles which do not respond to the ndrogens as suggested by Wilkins.

In spite of increased 17-ketosteroid values to 15 to 30 mg./24 hours or more in some cases, there is a lack of androgen effect which is explained by Morris as due to—

(1) An inability of the gonad to produce androgen of high biologic activity, such as testosterone due to the deficiency of enzymes such as 3 ß-ol dehydrogenase or 17 ß hydroxysetroid dehydrogenase.

(2) An accelerated conversion of androgens to inactive metabolites or oestrogens at peripheral sites, such as the liver and kidney.

(3) End organ failure to respond to androgens or androgen insensitivity as suggested by Wilkins.

Aetiology and hereditary aspect: The fact that this syndrome is hereditary in nature is suggested by the high familial incidence as observed by Morris, Thelliar *et al*, Zourlas and Jones etc. Tailard and Prader noted that the disease is transmitted by the female and occurs only in the male. The intersexes are of female phenotype, but male genotype and are always sterile. Though the exact aetiology is unkown the mode of inheritance may be explained by either a sex linked recessive gene or a sex limited autosomal dominant gene (Ashley, Morris, Grumbach and Baer, McKusick and Wilkins).

The lack of androgen effect is explained by the abnormal embryonic development as well as abnormal secondary sex characteristics.

In foetal life deficient androgen effect is noted by the fact that the development of the urogenital sinus is female and there is a failure of development of the Wolffian system. The foetal testicular hormones are responsible for the male development of these structures, but in their absence

they will be female as shown by the studies of Jost and others on the effect of castration of the male foetus in utero. The absence of the Mullerian derivatives indicates that the testes secretes the Mullerian inhibiting substance. Morris states that the non-action of the androgens plus the presence of the testicular Mullerian inhibiting factor may explain the foetal development, while the non-action of androgen plus testicular oestrogens may account for the female secondary sex characteristics. No secondary sex characteristics of the male type are developed at puberty as the testicular androgens are incapable of virilizing these patients in spite of the increased 17-ketosteroid values which are normal for males. Morris and Wilkins noted that administration of large doses of synthetic androgens failed to masculinize these patients suggesting that the defect may lie in the androgens.

Genetic aspect: The nuclear sex as determined by buccal smear is negative for sex chromatin suggesting the male genotype as observed by Barno, Zourlas and Jones, Morris etc. There is no chromosomal abnormality in these cases as reported by Jacobs and his associates, Walker *et al*, Puck *et al*, Jourlas and Jones, Morris etc. which is confirmed by our study. The chromosomal pattern is 46-XY as that of a genotype male.

Psychological aspect: Although the patient is genetically male the psychologic development and sex of rearing is female, hence no attempt should be made to alter this situation. On learning suddenly that 'she' belonged to the opposite sex would produce a profound mental trauma and an adverse effect on her morale making normal living difficult. The patient should be explained that (1) her uterus has not developed, (2) she may not menstruate, or conceive but (3) in all other aspects she would be no different from other women.

Summary

A case of "testicular feminization" syndrome has been described where in addition to the usual criteria of diagnosis like inspection of external genitalia and internal genitalia on laparotomy with histological examination of the gonads, nuclear sex chromatin determination and chromosomal analysis has been performed. The pathologic hormonal, genetic, aetiologic and hereditary and psychologic aspects of the syndrome have been discussed.

Acknowledgements

We wish to thank the Dean, Medical College and Hospital, Nagpur for permitting us to use the Hospital records and the staff of the Pathology Department for their co-operation regarding the histopathological examination and chromosomol analysis.

References

1. Ashley, D. J. P.: Quoted by No. 22
2. Barno, A.: Am. J. Obst. & Gynec 84: 710, 1962.
3. Bourne, A.: Claye, Sir Andrew British Obstetric & Gynaecologica Practice: ed. 3, London, 196 William Heinamann.
4. Goldberg, M. D. and Maxwell, M F.: Quoted by No. 14.
5. Grumbach, M. M. and Barr, M. L Quoted by No. 15.
6. Jacobs, P. A., Baikie, A. G., Cou

Brown, W. M., Forrest, H., Roy, J. R., Stewart, J. S. and Lennox, B.: Lancet. 2: 591, 1959.
7. Jones, H. W. Jr. and Wilkins, L.: Am. J. Obst. & Gynec. 82: 1142, 1961.
8. Jones, H. W. Jr. and Scott, W. W.: Hermaphroditism, Genital Anomalies and Related Endocrine Disorders, Baltimore, 1958, Williams and Wilkins, p. 170.
9. Jost, A.: Quoted by No. 11.
10. Kendall, B. and Loewenberg, L. S.: Obst. & Gynec. 20: 551, 1962.
11. Masani, K. M.: Textbook of Gynaecology: ed. 4, Bombay, 1963, Popular Prakashan.
12. McKusick, V. A.: Quoted by No. 22.
13. Mishell, D. R.: Quoted by No. 14.
14. Morris, J. M.: Am. J. Obst. & Gynec. 65: 1192, 1953.
15. Morris, J. M. and Mahesh, V. B.: Am. J. Obst. & Gynec. 87: 733, 1963.
16. Puck, T. T., Robinson, A. and Tjio, J. H.: Quoted by No. 20.
17. Stewart, J. S. S.: Lancet. 2: 595, 1959
18. Tailard, W. and Prader, A.: Quoted by No. 22.
19. Thelliar, G., Le Tessier, A. and Herrion, R.: Quoted No. 22.
20. Walker, P. C., Carney, P. and Earl, F. Gates: Am. J. Clin. Path. 41: 297, 1964.
21. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, 1957, C. C. Thomas, p. 276.
22. Zourlas, P. A. and Jones, H. W. Jr.: Obst. & Gynec. 25: 768, 1965.

Figs. on Art Paper XIV