TESTICULAR FEMINIZATION

by

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Testicular feminization is a term, used originally by Morris in 1953, to describe a hereditary syndrome characterised by an individual with testes who presents as a female phenotype. This has been further classified as complete and incomplete testicular feminization (Morris and Mahesh, 1963). The main clinical features of complete testicular feminization are:

1. Female habitus, sometimes showing eunuchoid tendencies.
2. Female distribution of hair with scanty or absent axillary and pubic hair.
3. Normal breast development with somewhat smaller nipples.
4. Normal or infantile external genitalia with no clitoral enlargement.
5. Blind vagina of small or normal length.
6. Absent uterus, cervix and ovaries.
7. Presence of labial, inguinal or abdominal testes.

In the incomplete type, in addition to the above characteristics, there is enlargement of the clitoris as well. Though both these conditions are hereditary, they, as a rule, do not occur in the same family tree.

The incidence of complete testicular feminization is difficult to determine as most of these patients have no symptoms other than amenorrhoea. Morris had reviewed the literature in 1953 and collected 82 cases of male psuedohermaphroditism who clinically fitted into this syndrome. He further studied 92 cases with female phenotype in 1963, in whom the secondary sex characters had already developed and there was histological proof of the testes.

In 1966, Teter *et al* found 7 cases of complete and incomplete forms of testicular feminization out of a series of 265 cases of primary amenorrhoea. Subsequently, more case reports have appeared in the literature (Zourlas and Jones 1965; Mokadam and Kalappa 1967 and Sunandabai, *et al,* 1968). Jogeillo and Atwell (1962) went through the records of 120 girls under the age of 15 years undergoing herniorrhaphy operation and they found one case of testicular feminization. Based on the prevalence of hernia in female and male children under the age of 12 years, he estimated the incidence of this syndrome as

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1 in 62,400 males. Hauser *et al* (1963) believed that it occurred 10 times more than Prader's (1963) estimate of 1 in 20,000 males. Netter *et al* (1963) found testicular feminization in 15-20% of all intersexual individuals.

The diagnosis of this syndrome is to be considered when a female child presents with inguinal hernia containing gonads in the hernial sac in cases of primary amenorrhoea with absent uterus and cervix, in patients with absent vagina with absence of axillary and pubic hair and in patients with germ cell tumour. Two cases of testicular feminization were seen at the Lady Hardinge Medical College and Hospital, New Delhi.

Case 1

G. K., aged 27 years, was admitted in the hospital with the history of primary sterility. There was nothing significant in the past and the family history. She gave a history of bleeding per vaginam for 5 days, at the age of 17 years, after which she never menstruated. She was married for 6 years and was leading a normal married life.

On examination, the patient was a stout young woman, 5 ft. 3 inches in height, weighing 152 lbs., with a pulse rate of 84/min. and B.P—120/90 mm. of Hg. Cardiovascular and respiratory systems did not reveal any abnormality. Breasts were well developed but there were no axillary or pubic hair. The abdomen was flabby and obese. A small swelling was felt on either side of the mons pubis. Vaginal examination revealed a blind vagina of 2½" length. A small nodule was felt at the vault and the cervix and uterus could not be made out. On rectal examination, the same nodule was felt anteriorly but the uterus could not be defined.

Investigations

Hb-9.5 gm%; urine analysis-N.A.D.; blood Urea-32.8 mgm%; I.V.P.—normal; vaginal smear showed groups of cornified and precornified cells. The buccal smear was chromatin negative. Excision of both the gonads was done by making oblique incisions parallel to the inguinal ligaments. The swelling on the right side was covered with thick tunica albuginea, which was incised and a mass, 2" x 2", was visualized, connected on one side with a longitudinal structure which looked like a fallopian tube. There was a cystic mass attached to the blunt end of the structure. On the other end of the mass there was a fibrous cord-like structure which looked like a ligament. Parallel to this was running a sheath of blood vessels. This fibrous cord was traced upwards upto the internal inguinal ring and the peritoneal cavity was opened and explored; there was no uterus or cervix palpable. The entire mass was excised at the level of the internal ring and the stump was transfixed and the peritoneal cavity was closed. The incision was stitched in layers. Gonadectomy was performed on the opposite side as well. Post-operative period was uneventful.

Gross appearance

Specimen consisted of an encapsulated piece of firm tissue, measuring 3 x 2 x 2 cm., with a cord like structure attached to it on one side. "Microsection (Fig. I) shows a variable picture of immature testes. At most of the places the seminiferous tubules are irregularly distributed in small groups while at other places it is in adenomatous form showing a foetal appearance (Fig I). These tubules are lined by immature sertoli cells in some places while in other areas sertoli cells appear normal. Occasional tubules in small groups show incomplete spermatogenic activity (Fig. II). Tubular walls are thin in the foetal nodule, while thick and collagenized at other places. Immature Leydig cells are seen in large aggregates enclosing a few tubules only (Fig. III).

Case 2

Mrs. C. K., aged 25 years, was admitted in the hospital with complaints of primary amenorrhoea, white discharge per vaginam for 7 years and pain in the lower abdomen for 1½ years. In the past she had epileptic fits and was admitted in a local hospital 8 years earlier for investigations and treatment. Family history was of no im-

portance. She was married for 1½ years and had no complaints regarding marital relations. On examination she was a fairly well nourished woman not anaemic, with a normal cardiovascular system, B.P.—120/80 mm. of Hg. and pulse rate of 74/min. Height 5 ft. 1 inch.; weight—90 lbs. Breasts were normal and pubic and axillary hair were scanty. Per abdomen—N.A.D. On vaginal examination, the fingers could be pushed in for 2½ inches into the blind vagina. Cervix and uterus could not be made out. On coughing a firm mass was palpable in both labia majora. Rectal examination showed a clear pelvis. A provisional diagnosis of labial testes was made.

Investigations

Hb—10 gm%; urine analysis—normal; blood urea—23.5 mgm%; I.V.P.—normal; vaginal cytology—few cornified and precornified cells were seen. Sex chromatin was negative. Bilateral gonadectomy was done.

Histo Pathological Report

Gross appearance—2 encapsulated masses, greyish white in colour, measuring 5 x 2 and 5 by 1 cm. in size. Cut surface showed a reticulated greyish brown appearance. Cord like structures were attached to either piece. Microsection showed structure of testes. The seminiferous tubules were lined by immature Sertoli cells, with no germ cells (Fig. IV). Small aggregates of immature Leydig cells were seen in between the tubules. There was no spermatogenic activity seen.

Discussion

Both these patients presented with a history of sterility and primary amenorrhoea. Although the first patient did give a history of having had one period, it could not be believed in the light of physical findings. Both patients were married and were leading a normal marital life. They had a female habitus, normal breast development with comparatively smaller nipples, absent and scanty axillary and pubic hair, inguinal and labial gonads, normal clitoris, a blind vagina but adequate for marital relationship and absent uterus and cervix.

Aetiology and genetics

Testicular feminization is a hereditary endocrine disorder. It is transmitted through the maternal line, either as X-linked recessive trait or as male-limited autosomal dominant. The karyotype is usually XY (Dewhurst 1967; Zourlas 1965 and Peris 1968), but other chromosome composition like XO/XX/XY mosaic and XXY have also been identified with the same syndrome (Morris *et al*, 1963). The carriers are usually normal females, but decreased pubic and axillary hair and delayed menarche have been noted in the mothers grandmothers, aunts and sisters of the affected individuals suggesting that a similar defect may to a certain extent be transmitted to the female. The affected individuals are of female phenotype, male genotype and are sterile.

Endocrine studies performed on these cases show plasma testosterone, de-hydroepiandrosterone and androsterone within the normal range for normal males (Peris 1968). Urinary excretion of 17-ketosteroids is normal or slightly elevated. Urinary oestrogens are within normal range for males and females, urinary gonadotrophins are normal or slightly elevated (Peris 1968, Morris and Mahesh 1963). These results substantiate the most current concept of the pathogenesis of this syndrome, i.e. the end organs insensitivity to the androgens in the body. The testicles in the foetus have a two-fold function; firstly, to secrete the androgens on which is dependent the develop-

ment of the male genital organs, and secondly to have an inhibiting effect on the müllarian duct development. Because of the non-action of the androgens present in the body, the male genital organs fail to develop and at the same time the müllarian duct development is inhibited.

The development of female secondary sex characters at puberty are explained by the non-action of the androgens along-with little action of the oestrogens. Absent or scanty axillary and pubic hair are again due to insensitivity of the end organs. On the other hand, normal or excessive breast growth may be due to hypersensitivity of the end organ to the circulating hormones.

Pathological aspect

The gonads in this syndrome have been described to be almost similar to those of undescended testes, although these can often be distinguished histologically. The tubules resemble those of the less mature testes than would be expected from that age of the patient. They are often like the tubules in tubular adenoma. They contain mature sertoli cells. There might be some germ cell development but spermatogenesis is extremely rare. Case 1 is one of the very rare types, where a section of the testes shows spermatogenic activity. The Leydig cells may be absent or replaced by collagenous tissue in some area, whereas they may form large aggregates in the other areas particularly near the hilus of the gonads. The undescended testes show a large number of Leydig cells but not such aggregates. There may be areas of non-specific fibrous stroma resembling ovarian stroma. No follicular derivatives are present, which distinguish it from ovo-testes. (Morris and Mahesh 1963). The ovarian like tissue is not present in the undescended testes. Frequently, cysts are reported in the epididymis or in the para-testicular structure. The rudimentary cord-like structures represent the fallopian tube or vas-deferens as seen attached to the gonads in Case 1.

Psychosexual aspect

From the psychosexual aspect, patients are definitely females. They are reared up as female children and it is only at puberty when they do not start menstruation, that some abnormality is suspected. There is a high incidence of psychosis and suicidal tendencies in these patients (Morris 1953). Their sex urges are the same as in other women and the desire for child-bearing is strong. Some married patients come to the gynaecologist for the treatment of sterility. These patients therefore, should be approached very gently and explained that they will not be able to bear children. It is unwise to inform the patient the true state of affairs. There should be no attempt to change their sex.

Treatment

Morris and Mahesh in 1963 collected 50 cases reported in the literature above the age of 30 years and found that 11 cases (22 per cent) had malignant tumours. In most of these patients the tumour itself was the indication for consultation. Other patients who had no symptoms might have gone undetected and unreported. Even allowing for this discrepancy, the incidence of malignancy is

high enough to advocate bilateral gonadectomy at least in all cases who have attained full development of secondary sex characters. Both our patients were in the late twenties and therefore the gonads were removed. Supplementation with oestrogens is advised in those cases who develop hot flushes and atrophy of breasts after gonadectomy.

Problem in the treatment only arises when this syndrome is diagnosed in childhood. It is observed that the patients fail to develop secondary sex characters if the gonads are removed in the childhood, as they form the main source of the hormone. It is therefore justifiable to leave the gonads intact till after the development of the secondary sex characters. For those patients who are married and have short vagina, artificial lengthening of the vagina may be recommended to enable them to lead a normal marital life (Jones and Wilkins 1961).

Summary

1. Two cases of complete testicular feminization are reported and the literature reviewed.

2. The first case is one of the very rare types showing spermatogenic activity which is a very rare feature of the syndrome.

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References

1. Dewhurst, C. J.: J. Obst. & Gynec. Brit. Comm. **74**: 353, 1967.
2. Hauser, G. A., Keller, M., Koller, T., Wenner, R. and Gloor, F.: Quoted by Morris et al 1963.
3. Jagiello, G. and Atwell, J. D.: Lancet. **1**: 329, 1962.
4. Jones, H. W. Jr. and Wilkins, L.: Am. J. Obst. & Gynec. **82**: 1142, 1961.
5. Mokadam, N. G. and Kalappa, R.: J. Obst. & Gynec. India. **17**: 741, 1967.
6. Morris, J. M.: Am. J. Obst. & Gynec. **65**: 1192, 1953.
7. Morris, J. M. and Mahesh, V. B.: Am. J. Obst. & Gynec. **87**: 733, 1963.
8. Netter, A., Lumbrosa, P., Yaneva, H. and Bellaish, J.: Quoted by Morris et al 1963.
9. Peris, Leon, A.: Clinical Obst. & Gynec. 1968.
10. Prader, A.: Quoted by Morris et al 1963.
11. Sunandabai, K., Gupta, U. and Mital, V. K.: J. Obst. & Gynec. India. **18**: 777, 1968.
12. Teter, J. and Boezkowski, K.: Am. J. Obst. & Gynec. **94**: 813, 1966.
13. Zourlas, P. A. and Jones, H. W. Jr.: Obst. & Gynec. **25**: 768, 1965.

See Figs. on Art Paper VI