Testicular feminization syndrome: a report of three Ethiopian patients and a brief review

EDEMARIAM TSEGA
M.D., D.C.M.T.(L), F.R.C.P.(C)

BELAI DAMTEW
M.D.

Department of Internal Medicine, Black Lion Hospital, Faculty of Medicine, Addis Ababa University

Summary

The clinical features of 3 Ethiopian patients presenting with the complete syndrome of testicular feminization are described. All 3 were seen because of primary amenorrhoea. At laparotomy, one patient had testes located intra-abdominally, a second lodged in the inguinal canals and a third as masses in the labia majora. Also, one of these patients had bilateral inguinal herniae, a usual feature of this syndrome. Since the incidence of malignancy is high among individuals with undescended testes, they were removed in 2 patients. In the third patient, however, the testes were not removed because of delay in development of secondary sex characteristics. The literature on testicular feminization is also briefly reviewed.

Introduction

The syndrome of testicular feminization, as originally described by Morris (1953), is characterized by a phenotypic female with typical female body build, well developed breasts, scanty or absent pubic and axillary hair, a small vagina ending in a cul-de-sac, absence of internal female structures and presence of testes intra-abdominally, in the inguinal canal or in the labia majora. Such patients are chromatin negative and have XY karyotypes. Genetically, therefore, they are males. The condition is transmitted as sex-linked recessive or a sex-limited autosomal dominant mutant gene. Thus, in an affected family, all of the females are normal while half of the males may be expected to be reared as females. The testes of the affected males produce Müllerian-inhibiting factor during fetal life resulting in absence of internal female structures (Jones and Wilkins, 1961). In spite of normal blood levels of testosterone and urinary 17-ketosteroids, male secondary sexual characteristics fail to develop at adolescence. The production of a normal level of testosterone for males, a failure to respond to exogenous testosterone and a variable level of oestrogen, low for normal female but usually high for normal male, suggest that the basic lesion in testicular feminization is abnormality in the response of target tissues to androgens (Morris and Mahesh, 1963; French et al., 1966; Chan and O'Malley, 1976) leaving the oestrogen unopposed for breast development and the appearance of other female secondary characteristics.

Patients with the complete syndrome of testicular feminization have a normal or small clitoris. There are some patients, however, with clitoral enlargement and unpredictable secondary sex characteristics. It has been suggested that patients with an enlarged clitoris should be differentiated from the complete form as 'incomplete', ‘partial’ or 'genitalia ambiguous' (Teter and Boczkowski, 1966). In this communication 3 cases of testicular feminization in Ethiopians are presented and the literature is briefly reviewed.

Case reports

Case 1

A 20-year-old patient was seen with complaints of amenorrhoea and infertility. She had always been identified as a female since childhood. She claimed a normal sexual relationship with her husband whom she had married 3 years previously. The only disappointment had been infertility.

She is the fourth child of a normal family. Two of the siblings are male and one, who could not be traced, is female.

Physical examination revealed a tall, slender girl with a feminine voice and body build. There was strabismus but colour vision was normal. The neck was not webbed. The thyroid gland was not enlarged. The breasts were well developed with wide areolae and small nipples. Axillary as well as the suprpubic hair was absent. The labia majora were prominent and each labium contained a firm elliptical, non-tender and freely mobile mass measuring 4×7 cm. The clitoris and labia minora were small and the vagina was a short pouch ending in a
cul-de-sac and without palpable or visible cervix (Fig. 1).

The buccal smear was negative for sex chromatin. Karyotyping and hormones could not be determined.

At laparotomy, no uterus or related gonadal tissues were found. However, there were testes, one on either side of the labia majora and associated with indirect inguinal herniae. Both testes were removed and the herniae repaired. She was discharged on stilboestrol and was lost to follow-up.

Case 2

A 19-year-old student was admitted to hospital because of amenorrhoea and poor development of secondary sex characteristics. The patient grew up as a 'female' and was always healthy. Both parents are alive and well. The mother had her menarche at a late age 12 years after marriage. The patient has 2 brothers and 2 sisters. Both sisters are known to have a normal menstrual history.

Physical examination revealed infantile breast and absence of axillary and pubic hair. The labia were small and the vagina was very shallow (only about 2 cm long) ending in a cul-de-sac. There was no inguinal or labial mass. The rest of the physical examination was normal.

At laparotomy, the uterus was absent and 2 gonads were found intra-abdominally. A biopsy taken from the right gonad showed it was malformed with disorganized tubules. There was no spermatogenesis and Leydig cells were not conspicuous. Connective tissue cells were chromatin negative (Fig. 2). Karyotyping and hormone levels were not determined. The patient was lost to follow-up.

Case 3

A 19-year-old girl was admitted to hospital with a complaint of bilateral swelling in the groins since childhood. She had never menstruated but had a satisfactory sexual relationship with her boy friend. She had 2 brothers, and one sister who is <6 years old.

Physical examination revealed a slender, tall and well developed girl. Colour vision was intact. There was no webbing of the neck. The thyroid gland was not enlarged and there was no lymphadenopathy. The breasts were big with wide areolae and small nipples. The respiratory and cardiovascular systems were normal. There was no hepatomegaly. There was no inguinal hernia. Axillary and pubic hair was absent. The vulva revealed a small clitoris and labia minora. The vagina was very short ending in a cul-de-sac. There was no palpable cervix or uterus.

The buccal smear showed absence of sex chromatin. Hormone levels and karyotype were not determined. At laparotomy, no uterus or other female gonadal tissues could be found. The 2 inguinal masses were removed. Macroscopically, both masses were covered with adipose tissue and the cut surface showed seminiferous tubules. Microscopically, the seminiferous tubules were atrophic and there were Sertoli cell 'adenomas'. There was no spermatogenesis (Fig. 3).

The patient was informed that she would never menstruate and should not expect children. She was discharged on oral stilboestrol 1·5 mg daily. After being lost to follow-up for nearly 30 months, during which time she had stopped taking stilboestrol, she complained that she had lost half of the volume of her breasts. There was no other secondary sex characteristic change. She was restarted on oral stilboestrol 1·5 mg daily and seems to be pleased with the result of her treatment 6 months later.
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Fig. 2. Case 2. Testicular tubules with masses of luteal cells between them and the capsule and without spermatogenesis (×160).

Fig. 3. Case 3. Testicular tubules show Sertoli cells only. There is no spermatogenesis. The edge of Sertoli cell 'adenoma' is on the left (×280).
Discussion

Since the first description of 82 cases by Morris in 1953, over 350 patients with testicular feminization had been reported by 1966 (Morris, 1953; Morris and Mahesh, 1963; Teter and Boczkowski, 1966). Out of 265 cases of primary amenorrhoea seen in an obstetrics and gynaecology clinic in Warsaw, Poland, during a period of 12 years, 7 were noted to be cases of testicular feminization (Teter and Boczkowski, 1966). Therefore, this condition, although uncommon, is not very rare. However, so far as the authors know, there are no reports of the syndrome from the African continent.

The incidence of inguinal herniae is high among these patients. In nearly 50% of the reported cases, herniae and inguinal gonads have been described (Morris and Mahesh, 1963). The reason for the failure of the closure of the inguinal ring is probably the lack of androgen effect. Case 1 had bilateral inguinal herniae and gonads in the labia majora. Since inguinal herniae are significantly less common in young girls than in boys, girls presenting with primary amenorrhoea and inguinal herniae must be suspected of having the syndrome of testicular feminization, especially if the axillary and pubic hair is scanty or absent, the vagina is small and the uterus cannot be palpated. Another curious but not uncommon finding among these patients is colour blindness, the cause of which is unknown. None of the 3 patients described in this paper is colour blind.

Case 1 and 3 presented with female phenotype, well developed secondary sex characteristics and satisfactory sexual relationship with their partners. Both were chromatin negative. The external genitalia were of the adult female type but with short vagina, small clitoris and labia minora. The axillary and pubic hair were absent. The breasts were fully developed with wide areolae but small nipples. The uterus was absent and the testes were removed from the labia majora (Case 1) and inguinal canals (Case 3).

Case 2, who is also phenotypically female but not married, presented with much less developed breasts, and an infantile vagina as well as total absence of pubic and axillary hair. The sex chromatin was negative. The uterus was absent and the gonads were located intra-abdominally. It appears that there was a delay in the development of secondary sex characteristics in this particular patient.

The syndrome of testicular feminization is genetically transmitted through the maternal line affecting only genetic males. Observations on pedigrees of previously reported cases suggest a sex-linked recessive or a sex-limited autosomal dominant mutant gene as a transmitter of this condition. Late menarche and decreased pubic and axillary hair have been noted in mothers, grandmothers, aunts and sisters of patients with testicular feminization (Morris and Mahesh, 1963). The phenotypic expression in about 50% of genetic males, with negative sex chromatin and XY chromosome, is a result of lack of androgen effect on target tissues. In fetal life, the Wolffian duct system fails to develop because of androgen insensitivity and the external genitalia fail to develop along male lines because of absent response to androgens (Jost, 1958). Although androgenic steroids do not appear to inhibit the development of the Müllerian system, the absence of Müllerian derivatives (ovaries, fallopian tubes and uterus) in the syndrome of testicular feminization is best explained by a Müllerian-inhibiting factor originating from the testes. Again, at puberty, absence of development of male secondary sex characteristics in the complete syndrome is a result of lack of androgen effect.

Administration of large doses of androgen to these patients does not produce virilization or change in the secondary sex characteristics. This is not entirely true in the ‘incomplete’ form (Morris and Mahesh, 1963). After castration, there is a tendency for ketosteroid and oestrogen levels to fall resulting in a decrease in vaginal cornification and some changes in secondary sex characteristics. This is best exemplified by Case 3 who complained that she had lost 50% of the size of her breasts after stopping her stilboestrol for 30 months.

The anatomical location of the testes in these cases varies from individual to individual. The 3 cases presented here revealed the 3 possible sites: In Case 1 the testes were located in the labia majora, in Case 2, it was intra-abdominal while in Case 3 it was in the inguinal canals. The incidence of malignancy (usually as germinomas, tubular adenomas, Sertoli cell tumours or cysts) in these organs after the age of 30 years is about 22% (Morris and Mahesh, 1963; Manuel, Katayana and Jones, 1976; Richardson and Robboy, 1977). Therefore, after the full development of secondary sex characteristics, removal of the testes with oestrogen replacement therapy is indicated. Cases 1 and 3 were discharged on an oestrogen preparation after castration but follow-up, as is always the case in Ethiopia, was unsuccessful. Case 2 was also lost to follow-up for nearly 2 years. Considering the cultural and educational backgrounds of these patients, no attempt was made to announce their true sex; however, they were informed that they would never menstruate and hence should not expect children.

References
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E. Tsega and B. Damtew

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